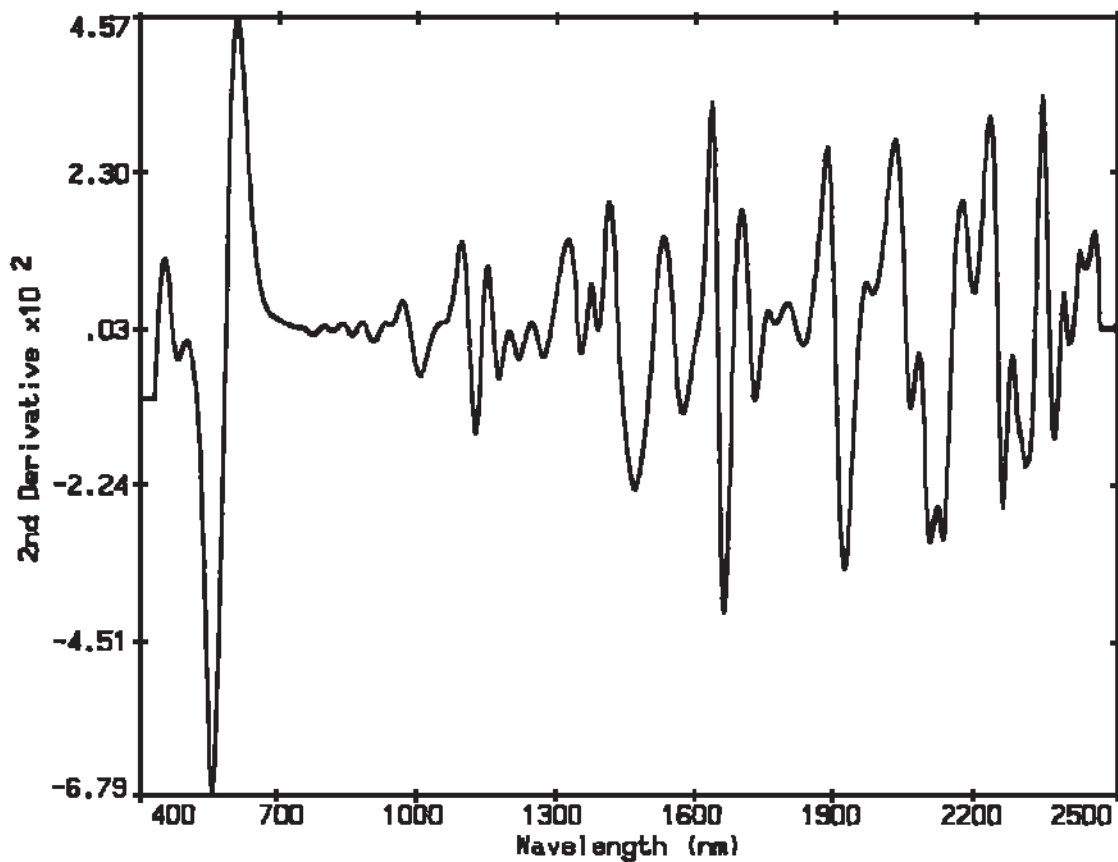


Following the progress of pharmaceutical mixing studies using near-infrared spectroscopy



This Application Note shows the possibility to apply near-infrared spectral information for monitoring the pharmaceutical mixing process.

Method description

Introduction

One of the most arduous, yet important steps in solid dosage form development is the mixing study. In most dosage form development standard operating procedures (S.O.P.s), the mixer is charged (loaded with the excipients and actives), then mixed for a set time (5, 10, 15 minutes). The mixer is opened and a "sample thief" is used to obtain "grab" samples from various locations and depths throughout the mixer. The mixer is closed and operated for the next time period. A series of samples representing the uniformity of the mixer's contents is collected and sent to the analytical lab for analysis.

The samples are usually extracted and assayed for the active(s) by either UV-Vis or HPLC. While it is important to have a well-distributed drug substance, all other ingredients are also salient. Typically, a tablet mix will also contain a lubricant, a binder, a disintegrant, some colorant(s), and an antioxidant. Rarely are any of these tested in a normal mixing study.

For many near-infrared (NIR) applications, the matrix is considered a problem because most organic and many inorganic species tend to absorb in the NIR spectral region; however, in this case, NIR absorption is a plus. The mixture may now be checked for homogeneity in two ways; either visual comparison, or using qualitative spectral algorithms.

Experimental

A Foss NIRSystems Model 6500 NIR Spectrophotometer with a sample transport system was used for this study. A standard sample cup was used to introduce the samples. Since this instrument is not available anymore, the NIRS XDS RapidContent Analyzer is recommended. Pharmaceutical grade lactose and talc were employed as excipients in this study. Aspirin and vitamin B-12 were the actives. The pure substances were scanned and labeled under their actual names. Fifty (50) grams of each was placed in a 250 mL Erlenmeyer flask labeled A, B, C, and D. For the first "mix", about five (5) grams of A was transferred to B, C, and D. Five (5) grams of B was transferred to A, C, D, et cetera. The samples were mixed and scanned as mix 1A, 1B, 1C, and 1D.

The second mix was performed in the same manner, with the samples named 2A, 2B, etc. This procedure was repeated six times, with the sixth mixture actually being a uniformly mixed sample of all the flasks together (6A, 6B, 6C, and 6D).

Prior to NIR analysis of the samples, each container was mixed to provide a representative sample for NIR analysis.

The sample was placed in a standard sample cup and scanned 32 times from 400 to 2500 nm in the reflectance mode. The second derivative spectra were calculated to obviate any slight baseline differences due to particle size variations.

Results and discussion

Method 1: The spectra from each set of mixing samples (mix 1, mix 2, etc.) were visually compared. When the spectra overlay to the best approximation, the mix may be considered "complete." Figures 1 and 2 show an early and later mix of aspirin, salicylic acid, talc, and lactose. This approach is satisfactory for a fast screening work.

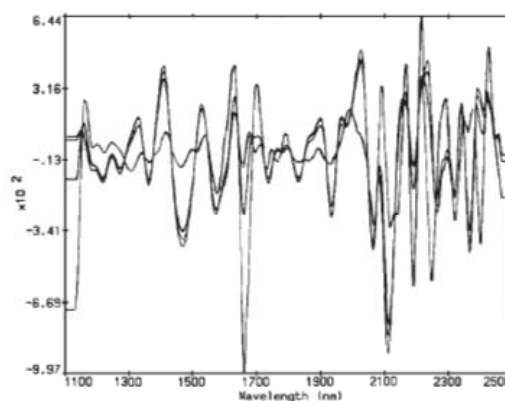


Fig. 1. First mix; 2nd derivative

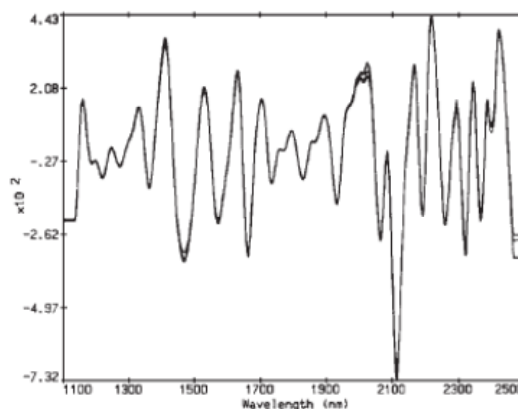


Fig. 2. Sixth mix; 2nd derivative

Method description

Method 2: A more accurate approach involves the use of a spectral matching algorithm. In spectral matching, a spectrum of an unknown sample is treated as a vector. This vector is compared with similar vectors of the "proper mix" spectra via a dot-product, producing the cosine of the angle between them. (The vectors are normalized to eliminate magnitude differences.) If there is no difference, or a zero angle, the cosine is 1.0000. As the vectors approach a cosine of 90 degrees, they are orthogonal, or totally independent of each another. The match index can vary from -1.0000 to 1.0000, where -1.0000 would be a negative match.

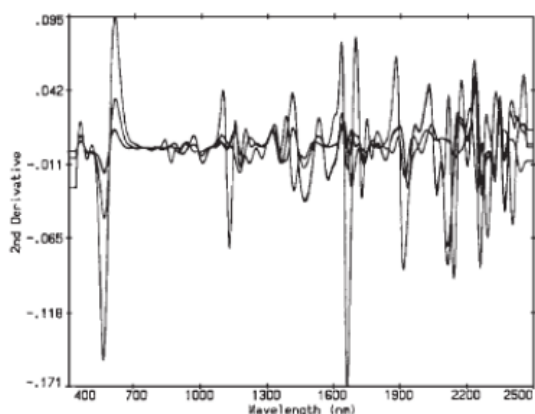


Fig. 3. Early mix samples

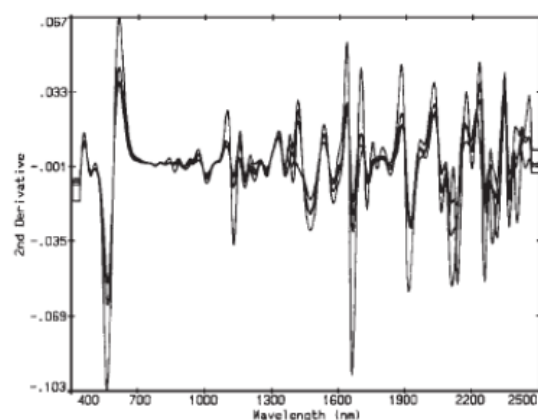


Fig. 4. Middle mix samples

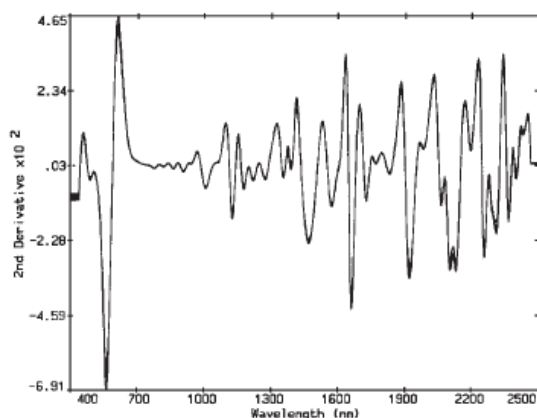


Fig. 5. Penultimate mix samples

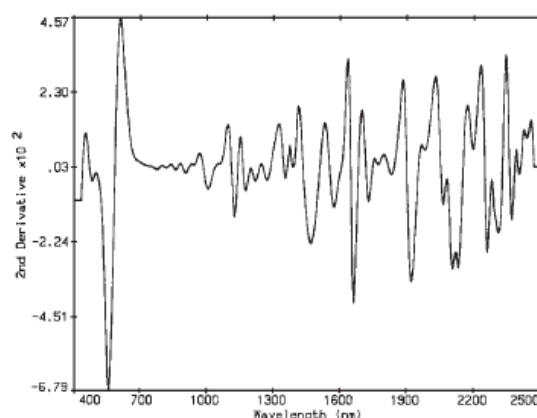


Fig. 6. Final mix samples

Fig. 3 through 6 show the earliest, middle, penultimate, and final mixtures of the run, respectively. The correlation improves with each mixing test point. The endpoint of the mixing study must be determined by the analyst as the mixture best correlating with the "standard mixture."

Conclusions

It is apparent from the data that the use of a spectral matching algorithm can save hundreds of hours in a routine mixing study. For regulatory reasons, however, several samples of the final and penultimate materials must be assayed for content uniformity. Despite these required tests, a significant amount of early testing time may be avoided in future mixing studies.