Acoustic-resonance Spectrometry as a Process Analytical Technology for the Quantification of Active Pharmaceutical Ingredient in Semi-solids

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ABSTRACT

The purpose of this study was to demonstrate acoustic resonance spectrometry (ARS) as an alternative process analytical technology to near infrared (NIR) spectroscopy for the quantification of active pharmaceutical ingredient (API) in semi-solids such as creams, gels, ointments, and lotions. The ARS used for this research was an inexpensive instrument constructed from readily available parts. Acoustic-resonance spectra were collected with a frequency spectrum from 0 to 22.05 KHz. NIR data were collected from 1100 to 2500 nm. Using 1-point net analyte signal (NAS) calibration, NIR for the API (colloidal oatmeal [CO]) gave an r^2 prediction accuracy of 0.971, and a standard error of performance (SEP) of 0.517%CO. ARS for the API resulted in an r^2 of 0.983 and SEP of 0.317%CO. NAS calibration is compared with principal component regression. This research demonstrates that ARS can sometimes outperform NIR spectrometry and can be an effective analytical method for the quantification of API in semi-solids. ARS requires no sample preparation, provides larger penetration depths into lotions than optical techniques, and measures API concentrations faster and more accurately. These results suggest that ARS is a useful process analytical technology (PAT).

KEYWORDS: creams, gels, lotions, net analyte signal, ointments, process analytical technologies (PAT), sound.

INTRODUCTION

Colloidal oatmeal (CO) is used as an ingredient in some pharmaceutical lotions, cosmetics, and toiletries. While listed as inert in some lotions but active in others, CO is one of many examples in cosmetics and other household products that fall into a gray area for the US Food and Drug Administration (FDA). Between November 2002 and March 2004, there were over 20 FDA recalls on household cosmetic products including shampoos, sprays, hand soaps, toothpastes, and lotions.[1] These recalls, resulting from mislabeling and active pharmaceutical ingredient (API) concentration errors, caused companies considerable unnecessary expense. A rapid and accurate in-process assay, capable of testing and validating individual samples, would obviate the need for the disposal of entire lots of problem products. The FDA process analytical technology (PAT) initiative calls for the development and implementation of manufacturing processes to guarantee a predefined quality of pharmaceutical materials as warranted by risk analysis.[2] These processes include multivariate data acquisition and analysis tools, and in-process and end point monitoring tools. The development of acoustic resonance spectrometry as an in-process and end point monitoring device is in harmony with the PAT initiative.

Current assays for analyzing API in various topical lotions are based on high-performance liquid chromatography (HPLC) with UV/visible detection,[3,4] Fourier transform infrared (FTIR) spectroscopy,[5] and NIR spectroscopy.[6] These conventional assays require both more sample preparation and more time for each scan than ARS. Sometimes lotions do not exhibit an optical chromophore,[7] so they must be fixed with labeled isotopes.[4] In addition, optical methods provide poor penetration through semi-solids in comparison to acoustic methods.

Acoustic resonance spectrometry (ARS) is typically much more rapid than HPLC and NIR. It is nondestructive and requires no sample preparation as the sampling waveguide can simply be pushed into the lotion. To date, the AR spectrometer has successfully differentiated and quantified sample analytes in various forms: tablets,[8] powders,[9-11] and liquids.[12-14] It has been used to measure and monitor the progression of chemical reactions, such as the setting and hardening of concrete from cement paste to solid.[15] Acoustic spectrometry has also been used to measure the volume fraction of colloids in a dispersion medium, as well as for the investigation of physical properties of colloidal dispersions, such as aggregation and particle size distribution.[16,17] Typically, these experiments are performed with sinusoidal excitation signals and the experimental observation of signal attenuation. From a comparison of theoretical attenuation to experimental observation, the particle size distribution and aggregation phenomena are inferred. In place of a sinusoidal excitation signal sweeping across the desired frequency range, this research makes use of broadband white noise and standing resonance waves. To our knowledge, this

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research presents the first application of a broadband white noise excitation signal to a resonant system for quantification of colloidal particles in a dispersion medium.

It must be noted that a description of colloid aggregation and particle-particle interaction is beyond the scope of this research. Colloidal oatmeal is a lyophilic colloid, and it is readily hydrated and dispersed evenly through a solution. Therefore, the resonant acoustic signal received at the detector is taken to be an approximate representation of the bulk of the sample, regardless of microscopic differences between individual colloids. As with other acoustic studies, the individual colloid particles are considered to be spherical and uniform, thus each particle produces a uniform effect on the bulk physical properties of the surrounding medium.[16]

Figure 1 provides a simple schematic of the AR spectrometer for the following discussion. The AR spectrometer used in this research was built in the near-field configuration, where the wavelength of the excitation signal is much larger than the quartz rod or the sample that is applied to the rod. An acoustic signal is applied to one of the piezoelectric transducers (PZTs) and received at the other. The sample, which is in mechanical contact with the vertex of the quartz rod, constitutes a load on the resonant system. With no sample in mechanical contact with the waveguide connecting the PZTs, little excitation signal is lost and the acoustic signal received at the detector is the sum of an ensemble of standing waves. The typical AR spectrum results from the pattern of constructive and destructive interference between the 2 sound paths; one that travels down the quartz waveguide and through the sample and back on the way to the collecting PZT, and the other that stays in the quartz rod and has no sample interaction. The excitation signal is a broadband white noise source as illustrated in Figure 2, where all frequencies between 0 and 22.05 KHz

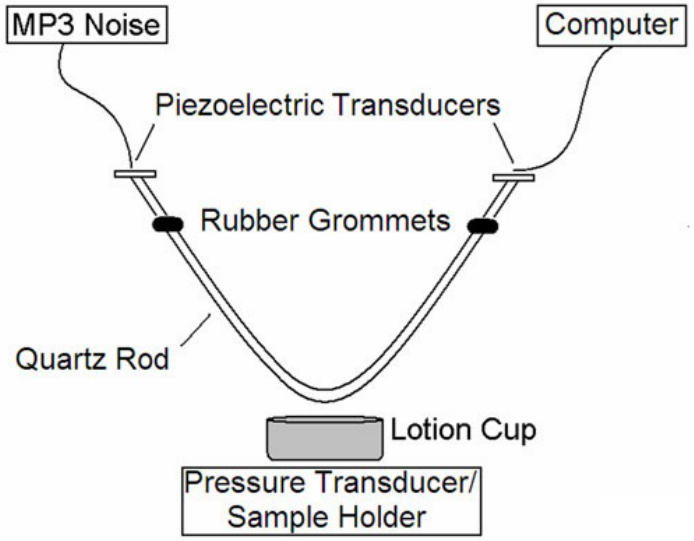

Figure 1. A schematic diagram of the ARS instrument.

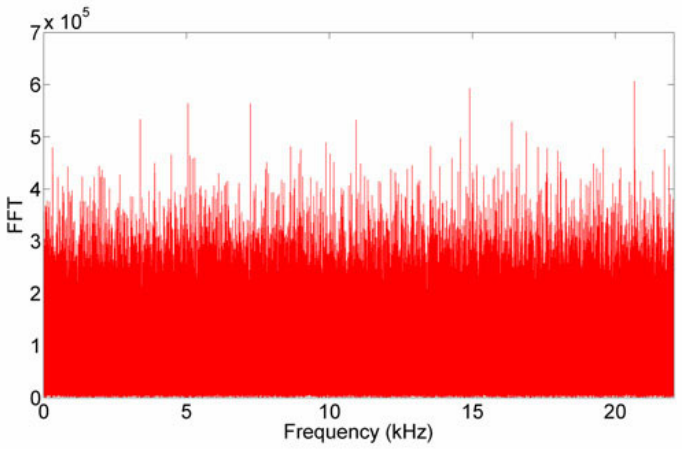

Figure 2. Frequency domain representation of the white noise excitation signal source delivered from an MP3 player to the PZT. All frequencies between 0 and 22.05 KHz are excited simultaneously.

are excited simultaneously. However, the wave collected at the detector is primarily composed of 3 large resonance structures as illustrated in Figure 3 (2.35-2.7 KHz, 9.6-11.2 KHz, and 14.15-17.0 KHz). When a sample is placed in contact with the vertex of the waveguide, acoustic waves escape and propagate through the lotion/quartz interface and into the sample holder. The added mass effect causes a shift in the resonant frequency of the system, while the frictional or viscous drag force causes a reduction in peak amplitude. This pattern gives rise to the characteristic AR spectrum for any given analyte. In some cases, a third transmitting transducer beneath the sample may increase the analytical signal,[8] although it was not required in this research.

Because the propagation of an acoustic wave is based on longitudinal compressions and rarefactions of the medium through which the sound propagates, each analyte responds differently to the frequency and amplitude of the applied

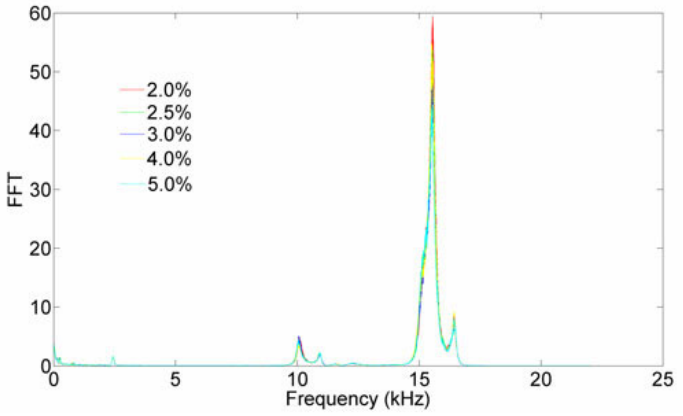

Figure 3. Three large resonance structures are prevalent for this design of the ARS despite excitation with a broadband white noise source. This figure illustrates AR scans of the different colloidal oatmeal concentrations in lotions.

acoustic signal. Acoustic spectra are the direct manifestation of the physical differences between samples such as density, viscosity, acoustic velocity, the degree to which samples and analytes compress and expand in response to an applied acoustic excitation, as well as depth of penetration, and the contact pressure between the resonator and the sample.[18-20] These effects are seen in the acoustic spectra as a shift in the resonant frequency of the system, a reduction or an increase in the peak amplitude, or a mixture of both effects. Chemical changes in samples affect the physical properties measured in acoustic spectra. Figure 4 illustrates the shifts in resonance frequency and changes in peak height between acoustic spectra from 4 different analytes: water, air, metal, and lotion. The forces acting on the standing acoustic wave come from the inertial effect as the sample is moved by the vibrating quartz rod, and from the dissipative effect owing to the viscous drag force. The quartz rod was chosen as the waveguide because of its high characteristic sound velocity and because quartz is an electrical insulator, which prevents electromagnetic standing waves in the waveguide. The velocity keeps acoustic impedance to a minimum according to $Z_{ac} = P/vA$, where Z is acoustic impedance, P is sound pressure, v is sound velocity, and A is cross sectional area.[21,22]

Chemometrics

This research compared 2 different calibration methods, net analyte signal (NAS) and principal component regression (PCR). PCR has been described previously.[23] For NAS calibration, a vector of instrumental responses r_k is the sum of 2 independent signals, the signal from all interferences $r_k^{=}$, and the signal from the analyte of interest $r_k^{\perp}$, which is orthogonal to the contribution from the interferences.[24] This orthogonal portion is termed the NAS and is the portion of the signal used for multivariate calibration. A matrix R $(J \times I)$ without the analyte of interest must be available, where J is the number of wavelengths and I is the number of samples. A projection matrix $P_k^{\perp}$ can be calculated according to Equation 1.

$$P_k^{\perp} = (I - R_{-k}R_{-k}^{+}) \tag{1}$$

where I is the identity matrix, and the '+' superscript indicates the Moore-Penrose pseudo-inverse. Using 1-point calibration with spectrum r_{cal}, the NAS vector $r_{cal}^{\perp}$ can be calculated with Equation 2.

$$r_{cal}^{\perp} = P_k^{\perp} r_{cal} \tag{2}$$

This vector is then normalized to length 1 with Equation 3.

$$r_k^{NAS} = \frac{r_{cal}^{\perp}}{\|r_{cal}^{\perp}\|} \tag{3}$$

The slope of the calibration line is calculated from Equation 4.

$$s = \frac{\|r_{cal}^{\perp}\|}{c_{cal}} \tag{4}$$

where s is the slope and c_{cal} is the analyte concentration of the calibration spectrum. The first step of NAS calibration

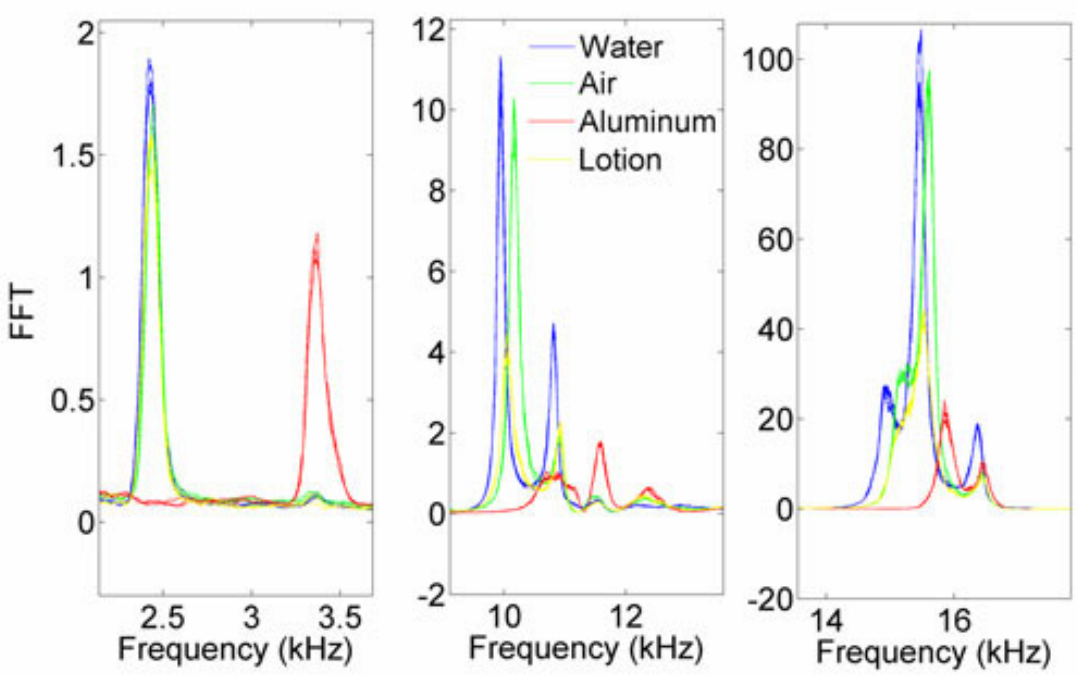

Figure 4. A zoomed view of the 3 large resonance peak structures considered in this study.

includes using Equations 2 to 4 to find the NAS direction and determine the length of the NAS vector. When the NAS direction and magnitude are known, the unknown spectrum r_{un} can be projected in the NAS direction with Equation 4 and its magnitude compared with the calibration magnitude.

$$y_{un}^{NAS} = r_{un}^{T} r_{k}^{NAS} \tag{5}$$

Equation 6 can now be used to calculate c_{un}, the unknown analyte concentration.

$$c_{un} = \frac{1}{s} y_{un}^{NAS} \tag{6}$$

The NAS approach allows for the calculation of figures of merit from multivariate data sets. In severely overlapping spectra, it has historically been difficult to quantify selectivity, sensitivity, and signal-to-noise (S/N) because of the inability to distinguish between interferences and the analyte of interest.[25,26] With the NAS, these quantities can be measured directly. Selectivity is defined as the scalar degree of overlap, α, between the NAS vector and the calibration spectrum according to Equation 7.

$$\alpha = \frac{\|r_{cal}^{\perp}\|}{\|r_{cal}\|} \tag{7}$$

The selectivity is a measure from 0 to 1 indicating how unique the analyte of interest is compared with the interferences. The sensitivity is a measure of the analyte variation in response to a change in concentration. This quantity can be expressed as Equation 8.

$$s_k = r_k^{NAS}/c_k \ , \tag{8}$$

where c_k is the concentration of the k-th analyte. Sensitivity should be the same for each concentration and each NAS vector.[27] The S/N ratio can be expressed as Equation 9.

$$S/N = \frac{c_k \|r_k^{NAS}\|}{\|\varepsilon\|} \tag{9}$$

where ε is the random instrumental error.

Integrated Sensing and Processing Acoustic Resonance Spectrometry for Process Analytical Technology

Integrated sensing and processing (ISP) is a paradigm for instruments in which large physical fields of data are reduced to high-level information as the data are sensed, before the data are passed to a computer.[28] In many cases, the signal transmitted from the detector to the computer is directly proportional to the analyte concentration, or is a classification that represents the sample identity. Using ISP, little or no postcollection data processing is required, making analyses significantly faster and perhaps even more accurate. An imminent AR spectrometer, already under construction and validation, employs ISP by encoding a special excitation signal to resemble the spectral features required for the quantification of CO in lotion, so the signal received at the detector is directly proportional to the analyte concentration without further processing. ISP-ARS has great potential as a PAT for sensing in the pharmaceutical industry. The excitation can be specifically tailored to meet the needs of demanding analytical challenges. For example, if the need is to differentiate between 1% and 5% CO creams, an ISP waveform created for this purpose could be easily downloaded from an online database in the form of an .MP3 file. The hardware of the ISP-ARS comprises inexpensive commercial off-the-shelf (COTS) components, simplifying its manufacture and deployment.

Materials and Methods

Sample Preparation

CO samples were prepared using Gold Bond Sensitive Lotion (Lot No. 03518, Chattern Inc, Chattanooga, TN). Lotion was weighed into an 800-mL beaker. Five concentrations (2.0%, 2.5%, 3.0%, 4.0%, and 5.0%) of CO were prepared by gravimetric addition of CO to the lotion samples for a total sample mass of 350 g. Samples were heated to 50°C on a hot plate, while mixing with a paddle blade. When lotions reached 50°C, the CO (Vendor lot No. 22915, Chattern Inc, Chattanooga, TN) was added and the sample was mixed (Heidolph RZR 50, Frankfort, Germany) at a sufficient rpm to create a gentle vortex. The heat was then turned off and samples were mixed until they cooled to 35°C.

Acoustic Resonance Spectrometry Data Collection

Rubber grommets were positioned on the rod, so that they firmly held it in place but dampened the signal minimally. Previous investigations with a similar ARS model made use of a third transducer beneath the vertex of the rod, which acted as an interferometer.[29] Our investigation indicated that the interference pattern inherent to the 2 sound paths and its effects on the resonance frequency and peak amplitudes was sufficient to negate the need for an additional transducer. A white noise signal played through an ordinary MP3 player was used as the source of random noise across the range from 0 to 22.05 KHz. The ARS instrument was designed to output a voltage signal to a computer sound card (Realtek AC97, Realtek Semiconductor Japan Corp, Yokohama, Kanagawa, Japan), operated with a graphic user interface in Matlab 7.0.1 (The Mathworks Co, Natick, MA). Lotion

samples were placed in a small plastic cup and the vertex of the quartz rod was plunged into the cup, so the 2 were in mechanical contact for the duration of the scan. The penetration depth of the rod into the lotion was kept constant at 5 mm. All data were collected for 3 seconds at a sample rate of 44.1 KHz. Data were transformed from the time domain into the frequency domain by a fast Fourier transform (FFT), resulting in a signal-to-noise ratio of 110/1. Because the data set dimensions are a product of the sample rate and duration of the collection, each spectrum collected with these instrument parameters was 132 300 data points long. A 20-point moving boxcar average was performed on the frequency domain data as a smoothing function. In its current configuration, there are significant resonance peaks at 2.35 to 2.70 KHz, 9.6 to 11.2 KHz, and from 14.5 to 17.0 KHz. All data analysis was performed on these 3 frequency regions for the duration of the experiment.

Near Infrared Data Collection

A layer of lotion ~1-mm thick was spread on a single-well depression microscope slide (Gold Seal Products, Portsmouth, NH). NIR scans were collected with a scanning monochromator NIR instrument described previously.[30] Scans were collected from samples inside light-proof chamber in a darkened room to eliminate stray light interference. Samples were scanned in random order to eliminate the effects of drift over time on the results. All data were exported to Matlab 7.0.1 for all processing.

Data Analysis

The objective of this experiment was to test ARS in lotion analysis and compare the results with NIR spectrometry for the measurement of concentration change of API in lotion. NIR data were multiplicative scatter-corrected to eliminate baseline variations caused by path-length differences.[31] One-point NAS calibration was compared with PCR[23] for the measurement of CO from ARS and NIR spectra. Detection limits were estimated by a bootstrap error-adjusted single sample technique (BEST) multidimensional population translation of 1 cluster toward another.[32] The clusters used in the translation were unprocessed AR FFT spectra and PC scores. Other figures of merit such as selectivity, sensitivity, and signal-to-noise ratio were calculated using the NAS. All algorithms were written by the authors.

Results and Discussion

Acoustic Resonance Spectrometry Versus Near Infrared Spectrometry

The results from the calibration models are summarized in Table 1. NAS calibration outperformed PCR for both NIR and ARS. NIR for the measurement of CO gave an r^2 prediction accuracy of 0.971, and a standard error of performance (SEP) of 0.517%CO. ARS for the API resulted in an average $r^2 = 0.983$, calculated by averaging the r^2 from the 3 resonance peaks, and an SEP of 0.317%CO. Each NIR scan took almost 90 seconds to complete (the long integration time was selected to get an S/N competitive with ARS), while each ARS scan required only a maximum of 3 seconds to achieve similar sample predictive ability.

Acoustic Resonance Spectrometry Detection Limits

ARS spectra collected at n frequencies can be reduced to a single point in an n-dimensional hyperspace using the BEST. The resulting points usually form complex Lissajous patterns (or curved portions thereof) in hyperspace as analyte concentrations change because of the nonlinear nature of acoustic interactions.[33] BEST is a nonparametric cluster analysis algorithm based on the premise that spectra from similar samples tend to cluster in the same region of multidimensional hyperspace.[34] In order to demonstrate clustering quantitatively, multidimensional standard deviations (MSDs) can be used to measure the separation between clusters of different samples.[29,32,35] Using the BEST, intercluster MSDs greater than 3 indicate distinct cluster populations, while clusters less than 3 MSDs apart are inseparable with statistical significance. A multidimensional translation operation can be performed with this algorithm to estimate the theoretical detection limits of the instrument.[32] The translation operation is based on the principle that clusters from pure component spectra form distinct and separate populations, and a translation of one toward the other corresponds to a mixture of the 2 components when Beer's Law holds.

To estimate the theoretical detection limits for dynamic range calculations, intragroup spectra from the 2 lotion populations (P_1 and P_2) were used as $m \times n$ matrices.[32] The columns of the matrices were averaged by Equations 10 and 11, giving two $1 \times n$ vectors.

$$P_1 = \frac{1}{m} \sum_{i=1}^{i=m} P_{1i} \tag{10}$$

$$P_2 = \frac{1}{m} \sum_{i=1}^{i=m} P_{2i} \tag{11}$$

A difference spectrum X was calculated from $P_2 - P_1$. One population was spatially translated toward the other, $P_A = yX + P_2$, where y (defined on the interval $[0 < y \leq 1]$) started at zero and increased in increments of 0.01 until P_1 and P_A were inseparable by the BEST metric. The

Table 1. Three Seconds of Data Collection Gave the Highest r^2 and the Lowest RMSEP for Each Frequency Range and Both Chemometric Models*

Method			NAS		PCR	
ARS	Frequency (KHz)	Analysis Time (s)	r^2	RMSEP (% CO)	r^2	RMSEP (% CO)
	2.35-2.70	1	0.892	1.532	0.926	0.306
		2	0.985	0.787	0.943	0.260
		3	0.991	0.504	0.946	0.265
	9.60-11.20	1	0.962	0.491	0.855	0.427
		2	0.973	0.299	0.879	0.391
		3	0.983	0.251	0.948	0.255
	14.5-17.0	1	0.968	0.398	0.813	0.511
		2	0.979	0.262	0.816	0.495
		3	0.991	0.180	0.855	0.488
NIR	1100-2500 nm	120	0.971	0.517	0.956	0.314

*RMSEP indicates root mean squared error of prediction; NAS, net analyte signal; PCR, principal component regression; CO, colloidal oatmeal; ARS, acoustic resonance spectrometry; and NIR, near infrared.

detection limits were estimated by the BEST multidimensional translation experiment using raw AR spectra in the selected frequency regions and PC scores calculated from the selected frequency regions. The limits were calculated using translation of 2 clusters, the translation from 2%CO to 2.5%CO, and the translation from 2%CO to 5%CO; all results are summarized in Table 2. The best detection limits were seen using PC scores rather than raw AR spectra. This is an expected result as PC scores are inherently the representation of the largest difference between spectral groups. Therefore, separation has been optimized prior to estimation of the detection limits by PC scores.

Speed of Acoustic Resonance Spectrometry Method

To assess the maximum speed at which the ARS is still capable of quantifying CO, the FFT was calculated for progressively shorter blocks of time rather than calculating the FFT from the time domain data in its entirety. For example, the FT was calculated for 3 seconds, 2 seconds, and 1 second. NAS calibration and a PC regression were performed on the FFT. The speed of method results are presented in Table 1. These results suggest that longer periods of data collection offer an advantage in quantification, though it is not necessary to collect more than 1 second for a high predictive ability. There is a trade-off between scan time and performance. If the experimenter can spend the time to collect only 1s of data, the process is much faster but the predictive ability of the instrument suffers slightly.

Selectivity, Signal to Noise Ratio, and Sensitivity of Acoustic Resonance Spectrometry

Estimation of figures of merit is a straightforward task when the measured response is a scalar, such as in zero-order calibration methods. The measured response in zero-order methods is simply the contribution of the analyte plus a constant instrumental background or constant interference. However, in first-order data, where the measured response is a vector of scalars, the total instrument response is not sufficient to determine the figures of merit. The presence of multiple chemical and instrumental interferences varying simultaneously requires an extra step for multivariate calibration. Therefore, the portion of the signal orthogonal to the interfering chemical species and background, termed the NAS, must be determined prior to calculation of figures of merit.[24-27] Because the ARS functions by the interference between the analyte acoustic signal and a standing wave, there is usually a substantial instrument response even in the absence of a sample. For this reason, calculation of the NAS with acoustic data tends to behave much like an additional smoothing function. The NAS and figures of merit were

Table 2. Translations Were Performed With the 2 closest Concentrations and the 2 Most Distant Concentrations*

	Raw AR Spectra (Detection Limit %CO)		PC Scores (4 PCs) (Detection Limit %CO)	
Frequency (KHz)	2% → 2.5%	2% → 5.0%	2% → 2.5%	2% → 5.0%
2.35-2.70	0.210	1.26	0.100	0.150
9.0-11.20	0.175	1.23	0.050	0.210
14.5-17.0	0.235	1.41	0.160	0.090

*BEST indicates bootstrap error-adjusted single sample technique; AR, acoustic resonance; PC, principal component; and CO, colloidal oatmeal.

calculated according to Equations 7 to 9. Selectivity is a unit-less scalar ratio, indicative of the degree of overlap between the 2 vectors and was calculated to be 0.5963. The S/N was 110/1. The sensitivity of the ARS for CO in lotion is 0.230, given in instrumental response per unit concentration change.

Versatility and Flexibility

In addition to being rapid, effective, and inexpensive, the ARS has also proven to be an extremely versatile instrument. The same instrument and chemometrics can be applied to multiple analytes including tablets,[8] powders,[9-11] and liquids.[12-14] Because the system is set up such that a standing wave forms in the quartz rod in the absence of a sample, the addition of an analyte to the vertex of the rod acts as a load on the resonance of the system and necessarily disrupts the path length of sound in the waveguide. While the excitation frequencies passing through the rod and the analyte are the same, because of the large differences in their velocities, the wavelengths are usually longer in the quartz than in the sample. As a result, regardless of the colloid size, shape, and concentration, the waveforms from the waveguide and the sample will never be perfectly in-phase as they recombine at the vertex of the rod. This phase change will result in a characteristic pattern of constructive and deconstructive interferences for every analyte because of differences in physical properties.

Freedom From Interferences

The main sources of interferences for the ARS in this configuration are (1) acoustic waves propagating through the support structure of the instrument, (2) radiofrequency (RF) cross-talk directly between PZTs, and (3) inconsistent analyte and quartz rod alignment because of a manual loading procedure. Each of these points is addressed in the following discussion. (1) The quartz rod was mounted on a frame of wood, which is made up of a cellular network of pores that convert sound energy into heat by frictional and viscoelastic resistance.[36] The cellular pore network creates high internal friction, thus wood has more sound-dampening capacity than most structural materials. Because the mounting framework is constructed from wood, there is less sound traveling through the beams, and any sound that may get through is dampened owing to the placement of the rubber grommets holding the quartz rod in place. It should be noted that the wood construction for the purposes of this experiment was the low cost alternative to other potential materials. For example, if this instrument were needed in a current good manufacturing practices (cGMP) environment for PAT, it could just as easily be constructed from other acoustic dampening materials such as concrete and rubber. (2) To assess direct RF cross-talk, a PZT was suspended 10 cm from the epoxy-fastened receiving PZT. A white noise signal was generated with the suspended PZT and collected with the epoxy-fastened PZT. No signal was recorded with the sound card, suggesting that when the PZTs are fastened with epoxy to the quartz, they do not move unless driven by the excitation signal through mechanical contact. (3) More than 90 lotion samples have been scanned without an anomalous spectrum owing to manual loading. Because the position of the quartz rod is regulated by a vertical translation stage, the depth of penetration into the lotion is consistent, therefore spectra are reproducible, demonstrating the durability of the ARS.

CONCLUSION

This research demonstrates that ARS is faster, less expensive, and outperforms NIR spectroscopy for the quantification of CO in lotion. Therefore, it has demonstrated its potential as a PAT for the quantification of active pharmaceutical ingredient in semi-solids.

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REFERENCES

1. NIH NLM Specialized Information Services. Food and Drug Administration Actions: Recalls and Field Corrections 2002-May 12, 2004. *National Institutes of Health Web site.* Available at: http://householdproducts.nlm.nih.gov/NLM_FDARecalls.htm#rayblock1. Accessed: April 1, 2005.

2. USDA. Process Analytical Technology (PAT) Initiative. *US Food and Drug Administration Web site.* Available at: http://www.fda.gov/cder/OPS/PAT.htm. Accessed: April 1, 2005.

3. Mariani E, Villa C, Neuhoff C, Dorato S. Derivatization procedure and HPLC determination of 2-ethoxyethanol in cosmetic samples. *Int J Cosmet Sci.* 1999;21:199–205.

4. Westgate E, Sherma J. Determination of the sunscreen oxybenzone in lotions by reversed-phase HPTLC with ultraviolet absorption densitometry. *J Liq Chromatogr Relat Technol.* 2000;23:609–615.

5. Sabo M, Gross J, Rosenberg I. Quantitation of dimethicone in lotions using Fourier transform infrared spectral subtraction. *J Soc Cosmet Chem.* 1984;35:273–281.

6. Grunewald H, Kurowski C, Timm D, Grummisch U, Meyhack U. Rapid non-destructive raw material identification in the cosmetic industry with near-infrared spectroscopy. *J Near Infrared Spectrosc.* 1998;6:215–222.

7. Alltech Associates. Dimethicone. *Alltech Associates Inc Web site.* Available at: http://www.alltechweb.com/productinfo/technical/app/0048E.pdf. Accessed: April 15, 2005.

8. Buice R, Pinkston P, Lodder R. Optimization of acoustic-resonance spectrometry for analysis of intact tablets and prediction of dissolution rate. *Appl Spectrosc.* 1994;48:517–524.

9. Serris E, Perier-Camby L, Thomas G, Desfontaines M, Fantozzi G. Acoustic emission of pharmaceutical powders during compression. *Powder Technol.* 2002;128:296–299.

10. Reynaud P, Dubois J, Rouby D, Fantozzi G. Acoustic emission monitoring of uniaxial pressing of ceramic powders. *Ceramics Int.* 1992;18:391–397.

11. Martin LP, Poret JC, Danon A, Rosen M. Effect of adsorbed water on the ultrasonic velocity in alumina powder compacts. *Mater Sci Eng A.* 1998;252:27–35.

12. Kaatze U, Wehrmann B, Pottel R. Acoustical absorption spectroscopy of liquids between 0.15 and 3000 MHz. I. High resolution ultrasonic resonator method. *J Phys [E].* 1987;20:1025–1030.

13. Bolotnikov M, Neruchev Y. Speed of sound of hexane + 1-chlorohexane, hexane + 1-iodohexane, and 1-chlorohexane + 1-iodohexane at saturation condition. *J Chem Eng Data.* 2003;48:411–415.

14. Lévêque G, Ferrandis J, Van Est J, Cros B. An acoustic sensor for simultaneous density and viscosity measurements in liquids. *Rev Sci Instrum.* 2000;71:1433–1440.

15. Ferrandis JY, Leveque G. In situ measurement of elastic properties of cement by an ultrasonic resonant sensor. *Cement Concrete Res.* 2003;33:1183–1187.

16. Dukhin AS, Goetz PJ. Acoustic spectroscopy for concentrated polydisperse colloids with high density contrast. *Langmuir.* 1996;12:4987–4997.

17. Dukhin AS, Goetz PJ. Characterization of aggregation phenomena by means of acoustic and electroacoustic spectroscopy. *Colloids Surf A: Physicochem Eng Aspects.* 1998;144:49–58.

18. Ramdani A, Cros B, Sidki M, Ferrandis J. Acoustic near field technique for characterization of liquids, bitumen and cement setting. *Eur Phys J AP.* 2001;15:69–76.

19. Patois R, Vairac P, Cretin B. Near-field acoustic densimeter and viscosimeter. *Rev Sci Instrum.* 2000;71:3860–3863.

20. Prugne Ch, Van Est J, Cros B, Leveque G, Attal J. Measurement of the viscosity of liquids by near-field acoustics. *Meas Sci Technol.* 1998;9:1894–1898.

21. Mills TP, Jones A, Lodder RA. Identification of wood species by acoustic-resonance spectrometry using multivariate subpopulation analysis. *Appl Spectrosc.* 1993;47:1880–1886.

22. Lai E, Chan B, Chen S. Ultrasonic resonance spectroscopic analysis of microliters of liquids. *Appl Spectrosc.* 1988;42:526–529.

23. Medendorp J, Yedluri J, Hammell DC, Ji T, Lodder RA, Stinchcomb AL. Near infrared spectrometry for the quantification of dermal absorption of econazole nitrate and 4-cyanophenol. *Pharm Res.*

24. Boelens H, Kok W, Noord O, Smilde A. Performance optimization of spectroscopic process analyzers. *Anal Chem.* 2004;76:2656–2663.

25. Lorber A. Error propagation and figures of merit for quantification by solving matrix equations. *Anal Chem.* 1986;58:1167–1172.

26. Booksh KS, Kowalski BR. Theory of analytical chemistry. *Anal Chem.* 1994;66:782a–791a.

27. Lorber A, Faber K, Kowalski BR. Net analyte signal calculation in multivariate calibration. *Anal Chem.* 1997;69:1620–1626.

28. Medendorp JP, Lodder RA. Applications of integrated sensing and processing in spectroscopic imaging and sensing. *J Chemometr.* 2006;19:533–542.

29. Buice R, Lodder RA. Determination of cholesterol using a novel magnetohydrodynamic acoustic-resonance near-IR (MARNIR) spectrometer. *Appl Spectrosc.* 1993;47:887–890.

30. Fountain W, Dumstorf K, Lowell AE, Lodder RA, Mumper RJ. Near-infrared spectroscopy for the determination of testosterone in thin-film composites. *J Pharm Biomed Anal.* 2003;33:181–189.

31. Geladi P, MacDougall D, Martens H. Linearization and scatter-correction for NIR reflectance spectra of meat. *Appl Spectrosc.* 1985;39:491–500.

32. Lodder R, Hieftje G. Detection of subpopulations in near-infrared reflectance analysis. *Appl Spectrosc.* 1988;42:1500–1512.

33. Lodder R. CD/MP3 Acoustic Resonance Spectrometer. *Analytical Spectroscopy Research Group Web site.* Available at: http://www.pharm.uky.edu. Accessed: April 5, 2004.

34. Jolliffe IT. *Principal Component Analysis*. New York, NY: Springer; 2002.

35. Hamilton S, Lodder R. Hyperspectral imaging technology for pharmaceutical analysis. *Proc Soc Photo-Opt Instrum Eng.* 2002;4626:136–147.

36. Bear Creek Lumber. Western Red Cedar Physical Properties. *Bear Creek Lumber Web site.* Available at: http://www.bearcreeklumber.com/generalinfo/onlineliterature/technicalinfohtml/wrcphysicalproperties.html. Accessed: March 1, 2005.