

Optimization of Acoustic-Resonance Spectrometry for Analysis of Intact Tablets and Prediction of Dissolution Rate

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Acoustic-resonance spectrometry (ARS) provides a means of identifying and quantifying materials. A new ARS instrument incorporates a three-transducer design that increases sensitivity through interferometry and uses polyvinylidene fluoride piezoelectric films instead of ceramic transducers to give high output voltages, broader bandwidth, and lower cost. The operating parameters of the ARS are optimized with a widely applicable technique named Universal Numerical Optimization (UNO). The UNO technique allows refinement of instrumental parameters on the basis of distances in hyperspace between sample sets. The new ARS is able to identify different intact tablets and predict the percent dissolution of intact carbamazepine tablets at one hour in a standard apparatus to within 4.6% at a fraction of the cost of traditional or even near-IR methods.

Index Headings: Ultrasonic; Dissolution test; Optimization; Pharmaceuticals.

INTRODUCTION

When a new spectrometric method is introduced in the literature, the method is investigated initially with instruments with a number of different designs. Each new application of the spectrometric method requires a set of trial experiments to optimize the instrumental parameters. Eventually the different applications and instrumental designs assist in establishing the fundamental advantages and limitations of the spectrometric method.

The requirement for trial experiments and optimization extends to existing instruments that are used in a manner that deviates significantly from the literature. In cases where the spectrometric method and physics are not well defined, such as ultrasonic-resonance spectroscopy,¹ it may be difficult to predict the effects of instrumental modifications in an application. For example, a change that increases the sensitivity of an instrument to ultrasonic absorbance in a sample may decrease sensitivity to variations in ultrasonic velocity in the same sample. Trade-offs must be made, often between parameters with different and apparently incompatible units (such as absorbance and velocity). The Universal Numeric Optimization (UNO) introduced in this report allows simultaneous optimization of different parameters (even parameters with different units) by means of a nonparametric multivariate algorithm.

The first reported ultrasonic-resonance spectrometer consisted of a V-shaped quartz rod with two identical ceramic piezoelectric transducers (one transducer for

transmitting ultrasound and one for receiving ultrasound) glued to the ends.¹ Ultrasonic waves launched from the transmitting transducer interacted with a sample in contact with the vertex of the rod, producing resonance peaks detected at the receiving transducer where a standing wave could be established in the system. Qualitative identification of liquids with very different viscosities and densities, such as distilled water and glycerin, were made through visual interpretation of complex peaks on a strip-chart recorder. The report on ultrasonic-resonance did not discuss quantification of analytes in multicomponent mixtures or determination of the error associated with the identification of analytes.

UNO requires the collecting of spectra from samples to form calibration and test sets. Using the BEAST algorithm to measure the probability distributions of the test and calibration sets,^{2,3} UNO returns a distance in asymmetric multidimensional standard deviations between each point in the test set and the center of the calibration set. The optimization maximizes the average distance in standard deviations between different samples of the analytes one seeks to determine. The application of UNO to the ultrasonic-resonance spectrometer produced an instrument with many hardware improvements that allow both qualitative and quantitative measurements to be made. The new instrument operates at audible and ultrasonic frequencies; it is called the acoustic-resonance spectrometer (ARS).

The ARS has many potential industrial applications because of its rapid scanning ability and the nondestructive nature of its scans. For example, it has been shown that carbamazepine tablets can lose their effectiveness through exposure to humidity.⁴ The exposure of tablets to water vapor has resulted in a decreased dissolution rate of carbamazepine tablets both *in vivo* and *in vitro*. Several seizures and two deaths have been linked to carbamazepine tablets that did not dissolve properly.⁵ The use of ARS as a process control device could guarantee that all tablets leaving the production line would meet dissolution standards. ARS could also be used to prevent products from being loaded into the wrong containers, as well as to identify contaminated samples. In this work, the ARS has been optimized by UNO for the analysis of intact tablets and used to predict the dissolution rate of carbamazepine. The ARS is able to predict the dissolution rate of intact tablets much less expensively than the dissolution tests currently available, which destroy the tablet being tested. The results suggest that acoustic-resonance

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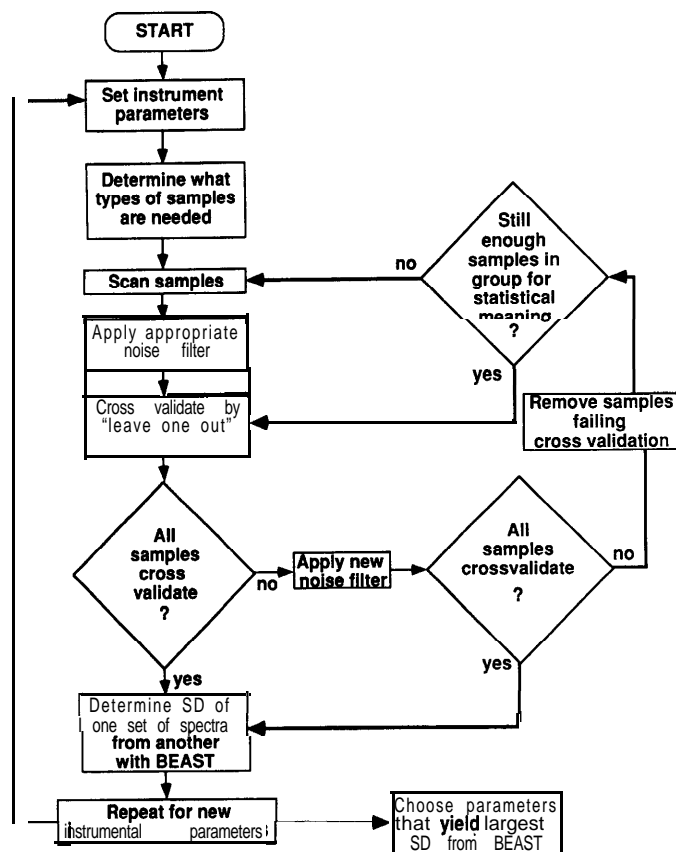


FIG. 1. Flow chart of the principal steps involved in the universal numeric optimization (UNO) technique.

spectrometry may be an ideal method for process control on pharmaceutical production lines.

THEORY

A flow chart of the universal numeric optimization technique is shown in Fig. 1. The instrumental parameters are set together as a group, and samples are chosen to cover the domain of each analyte targeted for determination. Each sample is scanned alternately with those from other analyte groups to eliminate error due to loading and instrumental drift. A noise filter is usually applied to eliminate one or more sources of random or nonrandom noise. The calibration sets (one for each analyte targeted for determination) are then analyzed with cross-validation by "data splitting" (if sufficient numbers are available) or "leave-one-out" methods. UNO requires that all sample sets representing all analytes pass cross-validation. Samples that fail to cross-validate are removed from calibration sets or test sets, and the cause of the failure is determined by some other reference method prior to inclusion in a calibration or test set. The BEAST algorithm on which UNO is based requires at least 10 samples for reproducible results.² Once all samples in each calibration set pass cross-validation, the BEAST algorithm is applied.

Analysis of data with the BEAST begins with a population P in hyperspace R that represents the universe of possible spectrometric samples of that analyte (the rows of P are the individual samples, while the columns are

independent information vectors, such as wavelengths or energies). P^* is a discrete realization of P based on a calibration set T , which has the same dimensions as P^* and is selected only once from P to represent as nearly as possible all the variations present in P .

P^* is calculated with the use of a bootstrap process by an operation $K(T)$, and P^* has parameters B and C , where $C = E(P)$ and B is the Monte Carlo approximation to the bootstrap distribution. The expectation value, $C = E(P)$, is a row vector with as many elements as there are columns in P .

Each new sample spectrum X is analyzed by an operation $\Psi(T, B, X, C)$, which projects a discrete representation of the probability density P in hyperspace onto the vector connecting C and X . X and C have identical dimensions. The directional standard deviation (SD) σ is found from the projected probability density:

$$\left\{ \sigma \left| \frac{\int_0^\sigma \left(\int_R P^* \rightarrow \vec{CX} \right)}{\int_R P^* \rightarrow \vec{CX}} = 0.68 \right. \right\}. \quad (1)$$

The integral over the hyperspace R is calculated from the center of P outward. The calculation of a skew-adjusted σ is based on a comparison of the expectation value $C = E(P)$ and $C_T = \text{med}(T)$, the median of T in hyperspace (with the same dimensions as C) projected onto the hyperline connecting C and X .

$$(C - C_T) \rightarrow \vec{CX}. \quad (2)$$

The result of the corrected projection is an asymmetric σ that provides two measures of the standard deviation along the hyperline connecting C and X :

$$\left\{ \begin{array}{l} \rightarrow \\ +\sigma \end{array} \left| \frac{\int_0^{+\sigma} \left(\int_R P^* \rightarrow \vec{CX} \right)}{\int_R P^* \rightarrow \vec{CX}} = 0.34 \right. \right\} \quad (3)$$

in the direction of X in hyperspace and

$$\left\{ \begin{array}{l} \rightarrow \\ -\sigma \end{array} \left| \frac{\int_0^{-\sigma} \left(\int_R P^* \rightarrow \vec{CX} \right)}{\int_R P^* \rightarrow \vec{CX}} = 0.34 \right. \right\} \quad (4)$$

in the opposite direction along the hyperline connecting C and X . To reduce the effects of nonrandom acoustic noise pulses on the measurements in hyperspace, one calculates each row of P^* as the median of three spectra of an individual tablet. Skew-adjusted SDs are used to calculate mean distances between spectra of different samples. The SDs between all sample sets are obtained for a given set of parameters with the use of all samples as both test and calibration sets. The BEAST process is repeated for many sets of parameters. The set of parameters that gives the largest BEAST SDs between sets of spectra from all the analytes is the optimum set of parameters for the given analytes.

EXPERIMENTAL

Materials. Figure 2 shows the sample compartment of the acoustic-resonance spectrometer, which contains a V-shaped quartz tube (6-mm o.d., 4-mm i.d., 220-mm length) with polyvinylidene fluoride piezoelectric films (Atochem Sensors, Norristown, PA) attached at both ends of the tube with aluminum plates and bushings. A third piezoelectric film was placed beneath the sample to create an interferometric effect and thereby increase the sensitivity of the system. The piezoelectric films have several advantages over ceramic transducers, including high output voltage, broader bandwidth, and lower cost. The piezoelectric films were mounted to the plates with a fast-setting epoxy. The sample was placed at the vertex of the tube. A sinusoidal voltage created by a sweep generator (Escort EFG22 10) in the frequency range of 0 to 58 kHz was applied to the piezoelectric film at the left end of the tube and to the piezoelectric film at the vertex.

A complex pattern of resonances is created by acoustic waves traveling through the air in the tube, and through the glass in the tube, and by interference from the sound waves passing through the sample from the third piezoelectric film into the vertex of the tube. These resonances are either diminished or enhanced by the acoustic absorbance spectrum and acoustic velocity of certain samples, giving the ARS its analytical power. The resonances are detected as sound intensities by the right piezoelectric film. Both the left and right transducers are shielded by grounded aluminum boxes to prevent rf interference. The quartz tube is secured by two rubber grommets that are mounted in holes in each aluminum box.

The signal received by the right transducer is amplified by a four-stage operational amplifier with a gain of 10^4 . The signal is then fed into a high-speed full-wave bridge rectifier and integrator circuit and into an Acro 400 analog-to-digital converter (Acrosystems, Beverly, MA). The spectra are collected on a Macintosh IIfx personal computer (Apple Computer, Cupertino, CA) with software written in QuickBASIC (Microsoft, Redmond, WA). The time required to complete a scan is determined primarily by the A/D and D/A and associated electronics. Present instrumentation (Industrial Computer Source Model ML 16P, San Diego, CA) in the laboratory permits a complete scan to be obtained with adequate resolution in as little as 20 ms.

The initial optimization of the ARS was performed with UNO with the use of replicate scans of thiamine (vitamin B₁, Nature Made, Los Angeles, CA) and pyridoxine (vitamin B₆, Walgreen's, Deerfield, IL) tablets as the test and calibration sets. The two vitamin tablets were both 100 mg in mass and were identical in size and shape to ensure that the spectral differences observed were due to the presence of different chemicals in the tablets and not merely to spectral resonances created by tablets of different size or shape. Only one tablet of each vitamin was scanned so that the samples remained constant and could be treated as standards in order to study the variations that arise in the instrument. Each tablet was placed under the vertex of the tube and held with 100 g of pressure by a lab jack and scale. Three replicate spectra were taken, and the tablets were exchanged until a total of 60 spectra were obtained for each tablet.

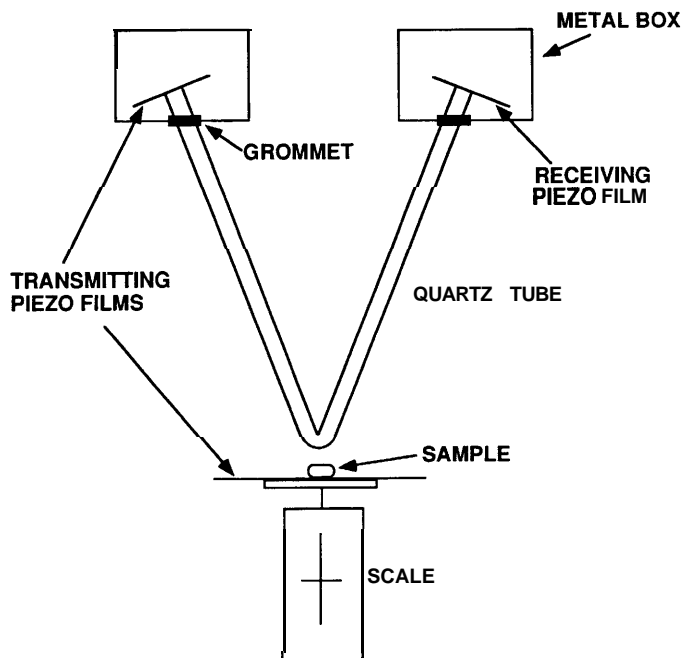


FIG. 2. Diagram of the sample compartment in the acoustic-resonance spectrometer (ARS).

Data analysis was performed with an IBM 3090-6005 vector supercomputer (International Business Machines). The IBM 3090-6005 ran software written in Speakeasy IV Zeta (Speakeasy Computing Corporation, Chicago, IL).

The dissolution medium for the carbamazepine tablets consisted of 1% sodium lauryl sulfate (95% pure, Sigma) and 1% methanol (HPLC grade, Fisher) in distilled water. Brand-name commercially available sources of carbamazepine tablets were used (Tegretol, Ciba-Geigy, Lot No. IT130122).

The atmospheric conditions surrounding the carbamazepine tablets were controlled with the use of a hydrator, which consisted of a glass desiccator in which the desiccant was replaced with distilled water. The tablets were exposed to moisture by placing them in uncapped scintillation vials and placing the vials inside the hydrator.

A VanderKamp 600 six-spindle dissolution tester (VanKel Industries, Edison, NJ) was used to conduct the dissolution test. Apparatus IT was used according to the USP dissolution guidelines for carbamazepine,⁶ with the exception that the dissolution medium consisted of no more than 1% methanol. The solutions were maintained at 37°C. The paddles rotated at 75 rpm. An ultraviolet (UV)-visible recording spectrophotometer (Shimadzu UV2 100, Columbia, MD) was used in this study for direct measurements of dissolved carbamazepine. Carbamazepine has a λ_{\max} at 287 nm.

Procedure. Thiamine and pyridoxine tablets were scanned, and the UNO technique was applied in order to optimize the ARS hardware for scanning intact tablets. The instrumental parameters optimized by UNO included the presence or absence of a conical holder for the tablet and the determination about whether to apply a signal to the transducer under the sample at the vertex of the quartz tube. The instrumental parameters were set, and each tablet was scanned three times and then swapped

for the other sample in order to cancel out error due to loading variations.

Carbamazepine tablets were utilized in the experiment to predict tablet dissolution rate. Twenty-four carbamazepine tablets were stored in the hydrator described earlier. Twenty-four carbamazepine tablets were also stored in a desiccator, and three tablets were scanned each day and returned immediately to the desiccator (to estimate how much moisture was already in the carbamazepine tablets when they were received from the distributor). The acoustic-resonance spectrum and the extent of dissolution at one hour in a standard dissolution apparatus were determined daily for three carbamazepine tablets from the hydrator. The day 0 spectra were obtained from dry tablets stored in a normal desiccator. The total time out of the hydrator or desiccator for each tablet for near-IR scanning was approximately 90 s. Then the three tablets were transferred from the hydrator to the dissolution apparatus, and the dissolution test was conducted as previously described. Three-milliliter samples were taken from each vessel at intervals of 5, 10, 20, 30, 40, 50, and 60 min. The dissolution medium removed was replaced by fresh medium to maintain a constant volume. The concentration of each solution was determined spectrometrically. Each solution was analyzed in duplicate. The average of the two values was used for regression analysis. Solutions were diluted by a factor of 10 when necessary (when solution absorbance was greater than 1.5 absorption units). The acoustic-resonance spectrum and the corresponding dissolution rate for each tablet were collected together on the computer. Principal component regression (PCR) was performed on the spectra to predict the tablet dissolution rate.⁷

RESULTS AND DISCUSSION

Construction of the Acoustic-Resonance Spectrometer. Ad hoc experiments were conducted with the UNO technique to ascertain which components should be changed to improve the instrument described in Ref. 1. These ad hoc experiments showed that a hollow quartz tube gave larger BEAST SDs in liquid samples (ethanol, water, ethylene glycol, and glycerin) than a solid quartz rod. This approach also demonstrated that brittle fast-setting epoxies were preferable to slow-setting epoxies and other cyanoacrylate glues for attachment of the piezoelectric films to the aluminum plates at the ends of the tube.

The output of the receiving piezoelectric film was amplified by a factor of 10,000 to digitize the signal on the A/D. Two amplifier circuits were tested: (1) a four-stage amplifier (with 10^1 gain at each stage) based on LM74 I integrated circuits, and (2) a two-stage amplifier (with 10^2 gain at each stage) based on the same integrated circuits. UNO experiments demonstrated that the four-stage amplifier produced larger distances between tablet spectra in SDs, and indicated that the four-stage amplifier was best for analyzing tablets by ARS. Later experiments demonstrated that the improved performance of the four-stage amplifier was due to the fact that the two-stage amplifier did not amplify signals above 20 kHz as well as the four-stage amplifier. The UNO testing of the two amplifiers also demonstrated the use of UNO to optimize a hardware parameter even though the reason for opti-

mizing the parameter was as yet unknown. In this case, UNO provided an observation that led to new experiments that explained the effect of the parameter on the ARS.

A similar application of the UNO technique revealed superior performance (i.e., larger distances between standards in SDs) by an amplifier circuit design in which the inverting inputs were connected and the noninverting inputs were grounded through resistors. (Connecting the inverting inputs in series instead of the noninverting inputs keeps the op amp outputs from floating with reference to ground.)

Optimization of the Acoustic-Resonance Spectrometer.

As the temperature of the ARS stabilized with each successive scan, the baseline drifted upward slightly. Multiplicative scatter correction was applied to all data sets to correct the baseline drift by removal of additive and multiplicative factors (if present).⁸ Figure 3A shows 15 individual scans of thiamine obtained on an ARS with quartz tube endplates and no bushings after multiplicative scatter correction. The peaks correspond to the resonances of the spectrometric system, including the sample. Most resonances exist even if no sample is present at the vertex of the quartz tube (see Fig. 3B). Addition of a sample selectively enhances or diminishes certain resonances, which are shown clearly in Fig. 3C. The pattern of peak enhancement or diminishment permits qualitative and quantitative analysis of samples. The analytical power of ARS is increased by increasing the number of resonances in the system because more peaks permit more complex patterns to be represented in the spectra. The tablets were scanned over the 0-58 kHz range (the maximum range allowed by the A/D, amplifier, and integrator electronics). The peak heights were generally inversely proportional to peak frequency, reflecting the same limitation of the electronic circuits.

After the ARS was constructed as described above, the ARS still needed to be optimized for new types of samples. The calibration and test samples were all intact tablets when the ARS was optimized for tablet scanning. Thus, a major instrumental parameter was the mechanism for holding the tablet during the analysis. Thiamine and pyroxidine tablets were scanned with the use of the following four holding mechanisms: (1) the tablets were scanned by placing them directly on the pressure scale, with the sample transducer located at the vertex turned off (these sets were labeled as B1 and B6); (2) the tablets were scanned by placing them directly on the scale, with the sample transducer on (these sets were labeled B1P and B6P); (3) the tablets were scanned with the sample transducer off, with the use of a conical holder constructed from aluminum to prevent the tablet from moving during or between scans (these sets were labeled B1H and B6H); and (4) the tablets were scanned in the same conical holder, with the piezoelectric transducer on (these sets were labeled B1PH and B6PH).

The optimization of the ARS tablet holder was carried out by determining the distance between the thiamine and pyroxidine sample sets scanned with the same holder arrangement. Thiamine and pyroxidine tablets were each used as a test and a calibration set for each holder arrangement. Figure 4 shows the distance in SDs obtained with the use of the labeled group as a calibration set and

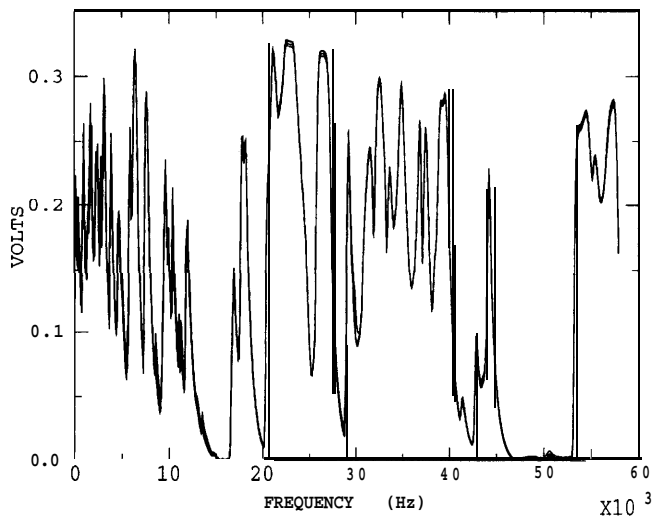


FIG. 3A. Fifteen superimposed spectra of thiamine tablets collected without activating the sample transducer at the vertex of the tube.

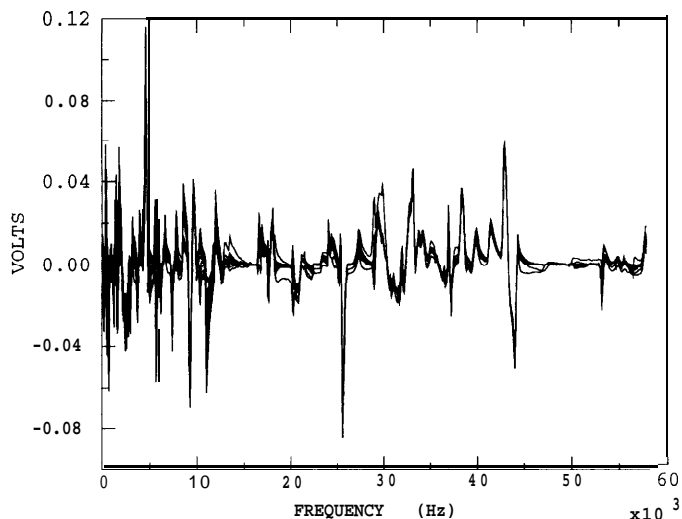


FIG. 3C. Fifteen superimposed spectra of the differences between the spectra in Fig. 3A and Fig. 3B.

the other sample (in the same holder arrangement) as the test set. The distances shown in Fig. 4 are normalized across the two tablet types by z-scoring to the calibration set size in BEAST SDs.

A glance at Fig. 4 shows that the optimum instrumental arrangement for differentiating pyroxidine tablets from thiamine tablets scans the pyroxidine using no holder, with the sample transducer activated. B6P produced the largest distance in SDs (with both of the spectral filtering methods discussed below). A tablet manufacturer producing a run of pyroxidine could use this ARS calibration set of pyroxidine tablets to prevent accidental substitution of thiamine into bottles in the pyroxidine run. However, B6P must be used as the calibration set because B1P produced a distance in SDs of less than 3.0, which indicates that the test set spectra (B6P) are indistinguishable from the training set (B1P). A tablet manufacturer producing a run of thiamine would have to use the ARS calibration set of thiamine tablets in B1H (with a conical tablet holder and the sample transducer inactivated) to

prevent accidental substitution of pyroxidine into bottles in the thiamine run. The difference in distance arises because the B1P group is much larger in volume in hyperspace than the B6P group; therefore SDs measured from the center of B1P (a large group) to the points of B6P (a small group) are much smaller than the SDs measured from the center of B6P to the points of B1P. The relative sizes of the groups are easily visualized on a graph of the principal component scores of the spectra (see Fig. 5).

The source of the difference in group size is evident in the acoustic-resonance spectra. Figures 6 and 7 show the acoustic spectra (after multiplicative scatter correction) for B1P and B6P, respectively. The region from 5 to 11

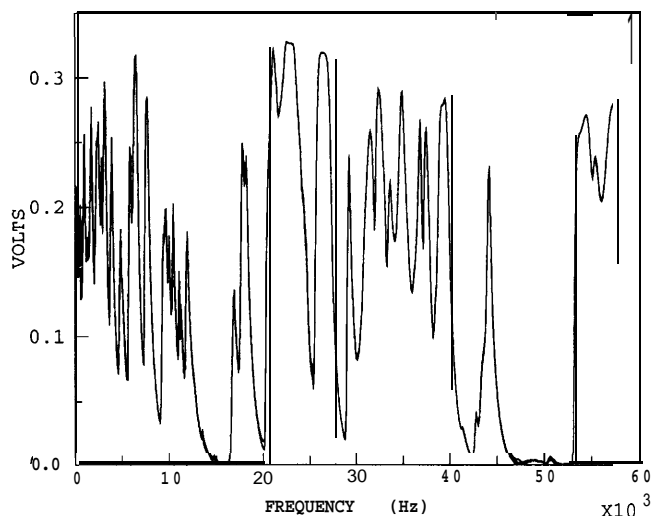


FIG. 3B. Fifteen superimposed spectra of the blank tube collected without activating the sample transducer at the vertex of the tube.

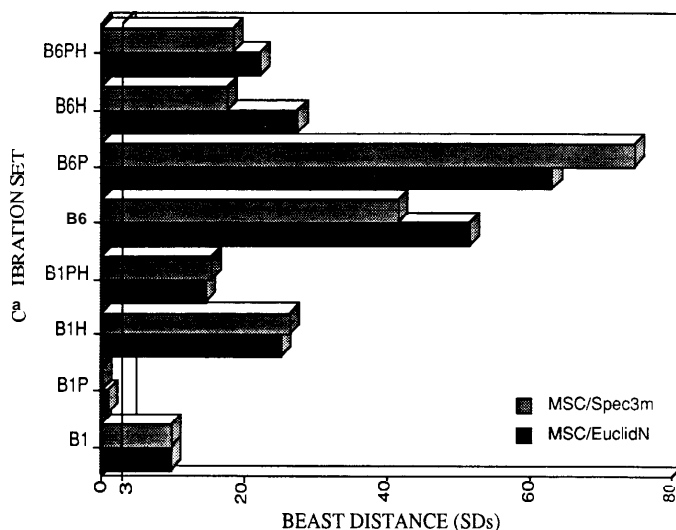


FIG. 4. A bar chart showing the average BEAST standard deviations obtained in UNO by calibrating with either thiamine (B.) or pyroxidine (B.) and testing the distance to the other vitamin sample spectra. "P" indicates that a piezoelectric transducer was placed beneath the tablet at the vertex of the tube. "H" indicates that an aluminum holder was used to secure the tablet at the vertex of the tube. A vertical line marks the 3σ limit for the calibration set.

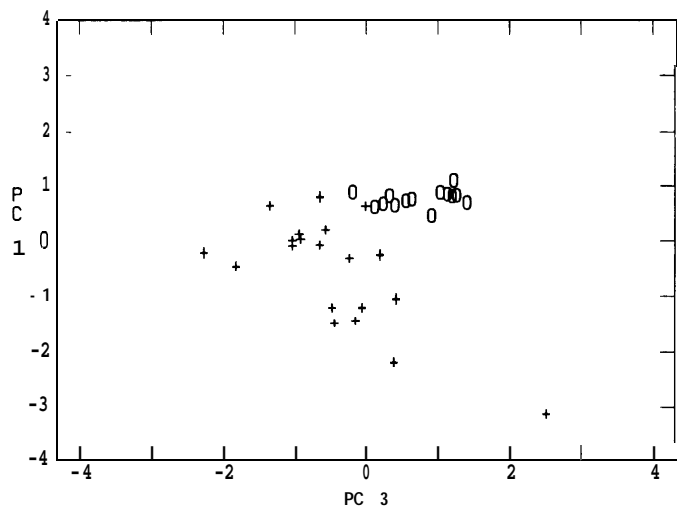


FIG. 5. The spectra of thiamine tablets (pluses) are more variable than the spectra of pyroxidine tablets (circles) and form a group in hyperspace that occupies a larger volume.

kHz shows a great deal of variation in B1P (thiamine), while the spectra of B6P (pyroxidine) are more uniform. The difference in spectral set volumes is reflected throughout Fig. 4. The B1 groups tend to be larger than the B6 groups when no holder is utilized and about the same size or smaller when the conical holder is used. Figure 4 also indicates that activation of the transducer beneath the sample tends to exaggerate differences in spectral set volumes. One possible explanation for the effect of the third transducer lies in a complex mechanism of constructive and destructive interference inside the spectrometer/sample system. The mechanical system coupling sound waves and sample is altered slightly by (1) changes in the acoustic absorbance, which is frequency-dependent; (2) changes in the wave velocity in the sample; and (3) changes in the position of the tube on the tablet, which changes acoustic pathlength. These changes can generate a spectral response ranging from complete signal

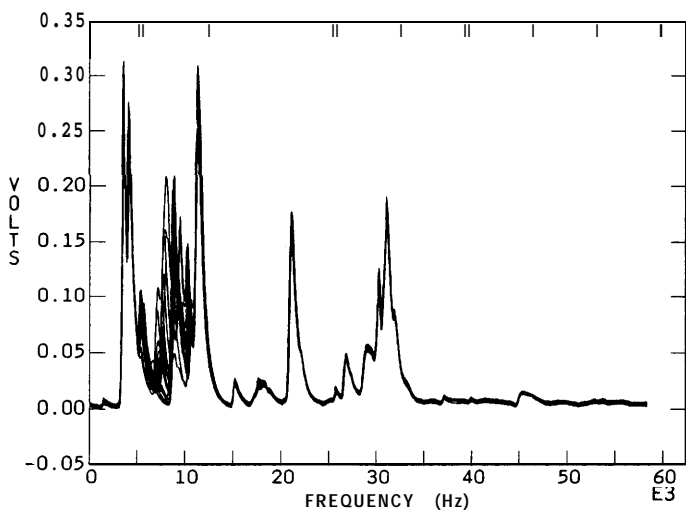


FIG. 6. Fifteen superimposed spectra of thiamine tablets collected with a piezoelectric transducer activated beneath the sample tablet. These spectra demonstrate that the increased variability occurs in a definite region of the spectra (5-11 kHz) and occurs only when the transducer beneath the sample is activated.

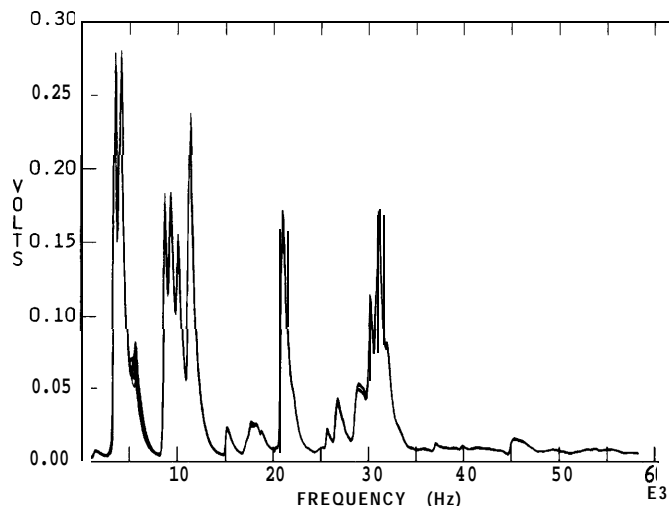


FIG. 7. Fifteen superimposed spectra of pyroxidine tablets show that activation of the transducer beneath the sample tablet does not cause increased spectral variability.

destruction to complete addition of the signal at nearly any given frequency. If the interference occurs at a frequency where no resonance exists, then the interference effect will not be observed in the spectra (as in B6P). Principal component analysis weighted the region from 5 to 11 kHz more heavily than some other regions. This weighting indicates that the region adds to the ability of the ARS to distinguish between the B1P and B6P spectra, although other sections of the spectrum are more important to the analysis.

Figure 4 also shows the effect of two different spectral noise filters on the tablet data. When multiple spectra are obtained from a single tablet, the spectra appear very similar and project close to one another in hyperspace. However, in an academic laboratory environment, a door may occasionally slam or someone may speak near the instrument as samples are being scanned. These infrequent noises create large artifact peaks (glaringly displaced points in hyperspace) that must be removed by hand or by computer algorithm prior to spectral analysis. Spec3m creates a new spectrum from the median value at each frequency of three scans of a sample to remove noise spikes. EuclidN projects three spectra into hyperspace as three points, finds the spectrum that is farthest from the other two, eliminates that spectral point as an outlier, and averages the remaining two spectra. When the noise on replicate spectra is random (e.g., when no doors slam) both filters introduce a tiny bias (very much smaller than the spectral difference between tablets) into the recorded spectrum. The tiny bias introduced by correcting artifact peaks by these algorithms is far more tolerable than the alternative of leaving the peaks in the spectra or manually editing and concatenating disk files of spectra to remove the artifacts. The performance of one noise filter is not consistently better than the other in any particular category of instrumental parameter.

Figure 4 shows that the best results were obtained by calibrating on the B6 samples scanned with the sample transducer activated and the tablet sitting directly on the transducer without a holder. One might expect that the use of a holder would improve the results by preventing errors due to tablet movement; however, the use of a

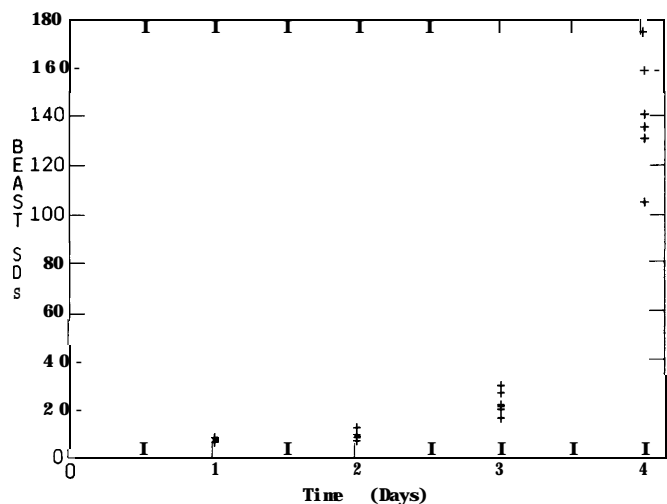


FIG. 8. A plot showing the increasing distance in standard deviations of test tablets (day 0) from calibration tablets (days 1-4) as the tablets absorb water in the hydrator.

tablet holder (B6H, B6PH) produced a distance in SDs that was less than that produced when no holder was used (B6, B6P). When the holder was used, the distances produced were much more similar for the groups (i.e., all spectral sets occupied a similar volume in hyperspace).

When a tablet holder was used, a more complicated system of interference seemed to exist, with most of the wave interference taking place inside the holder rather than inside the sample. In such a case, differences in the wave interference in the samples would be less important, and the test and calibration sets would appear to be similar in volume (B6PH, B 1 PH). When no tablet holder was used, most of the wave interference appeared to take place within the sample tablet, enabling the test and calibration sets to differ greatly in the volume of hyperspace they occupied (B6P, B 1 P).

The activation of the piezoelectric film transducer at the vertex of the tube, beneath the sample, further complicated the wave interference and exaggerated the differences between the test and calibration set volumes when no tablet holder was used (B1P, B6P). When a tablet holder was used with the sample transducer, the group sizes became more similar (B 1PH, B6PH). This trend existed only for the groups treated with the EuclidN noise filter. Because EuclidN tended to average random noise while eliminating spikes as outliers, perhaps a random noise was in the system that Spec3m could not eliminate.

Prediction of the Dissolution Rate of Carbamazepine. For carbamazepine tablets exposed to moisture in the hydrator for 0, 1, 2, 3, and 4 days, the average percent dissolution for three tablets after 1 h in a standard dissolution apparatus was found to be 108.56, 83.16, 72.35, 64.18, and 6.37%, respectively.

Each day, the carbamazepine tablets were scanned with the ARS. The day 0 tablets were used as the test spectral set, and the samples from each subsequent day were used as the calibration sets from which the distances to the day 0 spectra were calculated. Figure 8 plots the tablet distances vs. the time exposed to moisture for each of the carbamazepine tablets. The data appeared heteroscedastic, and, in fact, the day 0 tablets had the greatest dis-

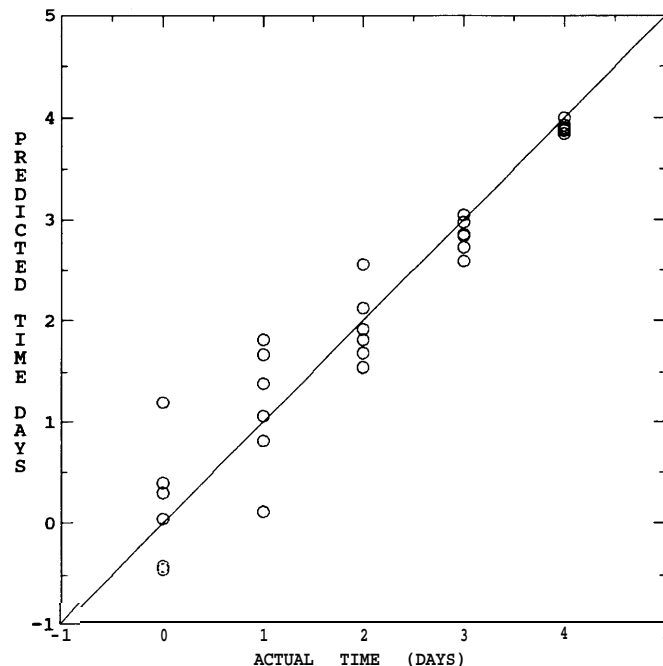


FIG. 9. A plot of actual vs. predicted time spent in hydrator for carbamazepine tablets. The groups become smaller as the tablets reach their maximum hydration, and the spectra begin to appear more similar.

persion (volume) in hyperspace because the tablets were exposed to varying amounts of moisture throughout production, shipping, and handling by the pharmacist. As time passed with the tablets in the hydrator, the tablets absorbed much more water, overwhelming the initial differences in moisture content and making the spectra of the tablets appear more uniform. A parallel experiment was conducted with the use of tablets stored in a desiccator for 0-4 days. As time passed, the spectra of the desiccated tablets moved in a direction in hyperspace opposite to those of the hydrated tablets, and also began to appear increasingly similar.

Principal component regression (PCR) was performed on the logarithm of the spectra in Fig. 8 with the use of time in the hydrator as the dependent variable. PCR yielded a good correlation ($r^2 = 0.914$) with a t-statistic for the third principal component of 15.359. PCR of the logarithm of the dry tablet spectra vs. time in the desiccator also yielded a good correlation with a t-statistic of 12.0 for the third principal component. The opposite sign on the correlation indicates that the tablets in the desiccator changed in a direction opposite to the tablets in the hydrator. The tablets exposed to moisture in the hydrator slowly absorbed water and became more similar, shown in Fig. 9 by the progressively smaller group sizes in the actual-vs.-predicted time in hydrator plot. The tablets in the desiccator dried steadily with time, also becoming more similar, as demonstrated in Fig. 10.

Figure 11 shows the results of PCR on the carbamazepine tablet spectra with the use of the average daily percent dissolved after 1 h for the hydrator tablets as the dependent variable and the logarithm of the average daily acoustic-resonance spectra as the independent variable. PCR yielded a correlation coefficient of 0.985, which allowed a prediction of percentage dissolved at 1 h with a standard error of 4.6%.

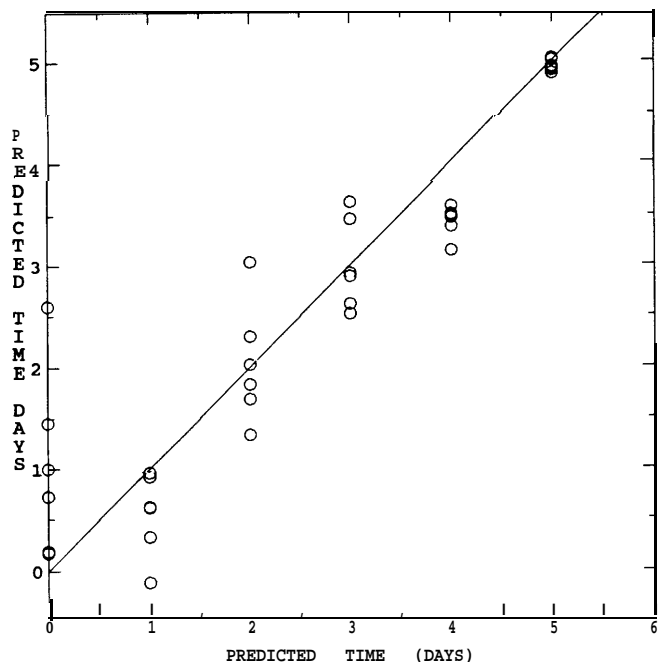


Fig. 10. A plot of actual vs. predicted time spent in desiccator for carbamazepine tablets. These groups also become smaller as the tablets dry, and the spectra begin to appear more similar.

CONCLUSION

The acoustic-resonance spectrometer is able to predict the percentage of carbamazepine dissolved at 1 h to within $\pm 4.6\%$. This error is comparable to that achieved by normal destructive dissolution testing and very similar to the error achieved by nondestructive near-IR dissolution testing.⁹ ARS also has the advantage of being non-destructive. The ARS costs less than a typical near-IR spectrometer, which has a price of \$20,000 to \$70,000. The ARS used in this research cost less than \$4000, including the cost of the personal computer and A/D. Application of ARS could reduce the cost of dissolution testing for pharmaceutical companies and potentially enable defect-free production by the analysis of every tablet on the line. Complete quality assurance in this way can prevent medical complications and deaths due to misidentification, mislabeling, and improper dissolution of tablets.

ARS offers low hardware cost because the analytical power of the instrument lies in the computerized analysis of the data. The universal numeric optimization technique takes further advantage of computer analysis, and allows the instrument to be optimized for a task even though the details of the physics of the instrument remain to be determined. Research is currently underway to optimize ARS for liquids and to define further the mechanism of resonances and interferences.

Advances in computer technology are enabling a new approach to chemical analysis. With the computer, many simultaneous interactions between matter and energy can be identified, quantified, reproduced, and used effectively, even though these interactions are not necessarily specific in the chemical sense. Therefore, an instrument that measures enough of these interactions in parallel with sufficiently high signal-to-noise ratio collects enough infor-

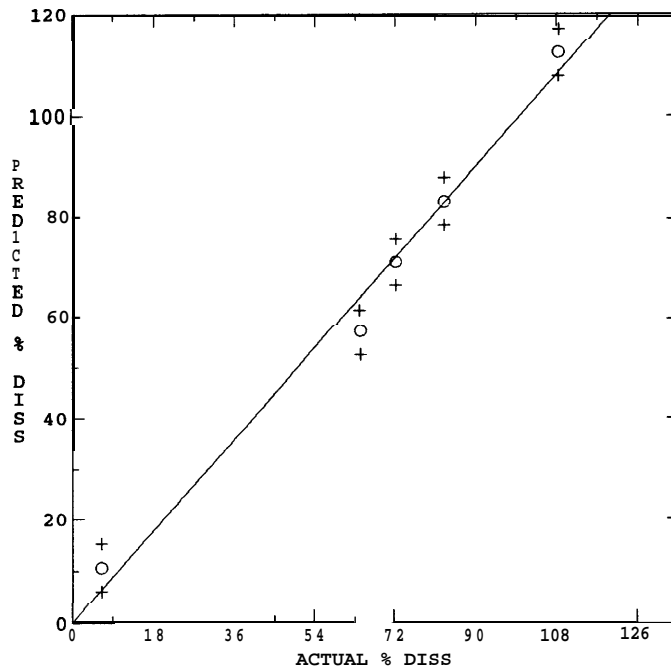


Fig. 11. A plot of actual vs. predicted percent dissolution at one hour for carbamazepine tablets from the hydrator. The circles represent the mean percent dissolution, and the pluses represent the error bars on the mean.

mation to become specific in the chemical sense. Simple sensing devices such as the ARS, constructed with high S/N with the use of the principle of sound wave propagation, can provide enormous amounts of information about the interactions between matter and energy. The analytical burden is thus shifted from chemical and physical separations to the computer, which can sort through an enormous amount of data with ease. As conventional analytical instruments become increasingly expensive and complex, computer hardware and software become cheaper and faster and easier to use. The new paradigm for analytical instrumentation, with simple sensors and parallel computers, is now seen in a mirror darkly, known in part. Soon it shall be understood fully, as the older patterns are also understood.

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