Analytical Systems

Discrete Automated Chemistry System with Tableted Reagents
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An instrument/reagent system with tableted reagents has been developed for performing ultraviolet/visible photometric assays. Preformed disposable plastic cuvettes pass through a stationary track every 5 s, providing a maximum throughput of 688 tests/h. The photometric system consists of a single light source with a separate set of light guides for each of eight photometer stations; bichromatic readings are possible at any of seven wavelengths between 340 and 630 nm. Tablets for 30 different analytes have been developed, each of which contains all necessary components for a single determination. Tablets are dispensed from disposable dispensers into cuvettes under the direction of the system's microprocessor and are completely dissolved within 45 s by ultrasonic agitation. Sample volumes range from 2 to 20 μL. Test requests are selected on a cathode-ray tube display, and sample-container bar-code labels are automatically printed. Sample entry is totally random. The system is designed to provide reagent quality control and also serum and reagent blank corrections for each test. Examples of equilibrium, zero-order, and first-order kinetic assays are presented.

Additional Keyphrases: kinetic assays · use of multiple photometers · bichromatic analysis

Research activities in our laboratories have been focused on the development of tableted reagents containing all the necessary components for clinical analysis by spectrophotometric measurement. In conjunction with this, we have been designing an analytical instrument based on a microprocessor-controlled, multiphotometer optical tracking arrangement. The Paramax® Analytical System is intended to provide: increased analytical reliability by eliminating most of the liquid-handling assemblies through the use of tableted reagents, increased on-analyzer reagent stability, high test throughput without sacrificing optimal reaction timing, discrete testing capability, and positive sample identification.

Here, we demonstrate the versatility of the tableted reagent/multiphotometer optical-tracking approach by reporting quantitative information on six analytes. In addition, the problems associated with this novel system and their solution will be discussed. The data presented are the results of research and development work in progress and should not be construed as claims for commercial products.

Materials and Methods

Instrumentation

The analyzer makes use of a continuous belt of flexible plastic cuvettes carried through the analyzer's water bath on the main drive track. Figure 1 is a schematic diagram of the major components of the analyzer. The cuvettes are loaded onto the analyzer from a continuous spool containing 2100 cuvettes. These index through the analyzer at a rate of one every 5 s. During their passage through the analyzer, the cuvettes are cut into sections as required, tableted, and 200 μL of water is added to each. Dissolution is completed by a 45-s passage in front of an ultrasonic device. Reagent integrity is examined at the photometer station located immediately ahead of the sampling position. The addition of sample starts each reaction, which can be monitored from 40 s to 10 min after reaction initiation at seven additional photometer stations located along the cuvette track. After passing through the 10-min photometer station, the cuvettes are heat-sealed and ejected into a disposal bin.

Cuvette loading. Cuvettes are loaded onto the main drive track by a clutch-driven loading belt. Between the loading belt and the main track is a scissors-type cuvette cutter. The engagement of the loading clutch and the activation of the scissors mechanism are under microprocessor control so that the cuvette belt is loaded at the beginning of a run and cut when no new samples are pending. This eliminates wasted cuvettes. A cuvette sensor mechanism located at the beginning of the main track ensures proper loading and signals an analyzer shut-down if there is improper engagement of the cuvette belt with the track.

Tablet-dispenser carousel. The reagent carousel has positions for 32 disposable plastic tablet dispensers, each of which contains a maximum of 300 tablets. The dispenser's mechanism arm, activated by the analyzer, allows the ejection of a single tablet. The tablet-dispenser carousel includes an optical code reader to identify the reagent contained in each dispenser. This feature allows the loading of dispensers randomly (i.e., without a programmed sequence) into the carousel. Each reagent is correlated with a specific carousel position in the system's memory; when a reagent is requested, the carousel rotates to the appropriate position for dispensing that reagent into the cuvette. When a new dispenser is inserted into the carousel, the system's tablet inventory is updated; as the tablets are used, the count of tablets in the dispenser is maintained and can be retrieved upon command. A warning is printed when a dispenser's tablet content is getting low. The system can accommodate more than one dispenser of the same chemistry; in such cases, it will deplete one dispenser before

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dispensing from the next. To ensure maximum reagent life for reagents on the instrument, the temperature and relative humidity of the carousel are controlled at approximately 10 °C and less than 10% relative humidity. This environmental control ensures on-instrument life of at least three months for the vast majority of reagents.

**Tablet dissolution.** Immediately after a tablet is dispensed into a cuvette, 200 μL of water is added and the tablet is completely dissolved during its 45-s passage in front of an ultrasonic device. The typical dissolution time for the majority of reagent tablets ranges from 5 to 20 s. During this time, the reagent temperature reaches approximately 45 °C, but no detrimental effect of sonication on reagents has been detected.

**Liquid reagent/diluent dispenser systems.** The analyzer features two fixed-volume dispenser systems for liquid reagents. The first, a 200-μL dispenser located just before the ultrasonic device, is used for the tablet diluent and liquid reagents. The second, a 25-μL dispenser located at 4 min 20 s after reaction initiation, is used for reactions requiring addition of a second reagent. Each position uses a software-controlled, sliding boom-arm mechanism to position the appropriate reagent probe over the cuvette.

**Sample dispenser system.** The sample dispenser system uses computer-controlled stepping motors to drive both the sampling syringe and the washout syringe. Every 5 s, as cuvettes pass the sampling station, the sampling probe enters the sample container, withdraws the required volume of sample, moves to the cuvette, and dispenses the sample with an appropriate volume of water to wash out the probe. The sample volumes available are 2, 3, 5, 10, 15, and 20 μL, and washout volume is adjusted to yield a final reaction volume of 300 μL. Immediately after the sample addition station and the 4 min 20 s reagent addition station are the mixing devices, in which high-frequency ultrasonic energy ensures that the contents of the cuvettes are completely mixed.

"Dilute mode." If a procedure's range of linearity is exceeded by a high concentration of analyte, the system's printout will call attention to this result and denote the sample's location in the unloading carousel. The sample may be retrieved and that test repeated on a diluted sample—in the "dilute mode." No actual sample dilution is required; the analyzer merely withdraws one-fourth of the original sample volume, repeats the test, and calculates the new result. For example, if the original sample volume was 5 μL, the sample volume in the dilute mode is 1.25 μL and the water washout volume is increased by 3.75 μL.

**Sample handling.** The system is capable of handling standard 16 × 100 mm evacuated collection tubes directly or can make use of special micro or semimicro sample containers accommodating volumes of 30 to 400 μL and 100 to 1000 μL, respectively. The analyzer's data system automatically prints a bar code to be applied to the sample container at the time test requests are entered for the sample. This allows random entry of the sample container into the loading carousel. The loading and unloading carousels consist of two removable interchangeable halves that may be removed from the analyzer for sample loading. On the analyzer, they are located under plastic dust covers, which minimizes evaporation. As the analyzer operates, sample containers are automatically moved to the central transfer carousel. At five positions before the sampling station, the sample container's bar code is read, which initiates tablet dispensing.
for the requested tests. Simultaneously, the sample container is raised until the meniscus is detected by an infrared reflecting sensor. Raising the meniscus to a constant height results in a consistent depth of sampling for all sample containers, preventing excessive wetting of the exterior of the probe and minimizing carryover. As the sample and washout are dispensed into the cuvette, the liquid rises to the point where any remaining liquid on the probe is stripped off by the surface tension of the reagent. The sample container remains in position until all tests requested for that sample have been initiated. Each sampling from a given sample container lowers the meniscus; to compensate, the probe is automatically lowered by an amount proportional to the volume removed, maintaining the depth of penetration at a constant 1 mm. The system software automatically changes the rate of lowering, depending on the type of sample container present. When sampling is completed, the transfer carousel rotates, moving the next container into the sampling station.

"Stat" analysis. Random entry of sample containers facilitates "stat" analysis. "Stat" samples may be inserted at any of six positions on the transfer carousel before the bar-code reading station. This may be done while the system is idle or during analysis, at which time "stat" samples will be given priority and analyzed before other samples on the loading carousel.

Optical system. Figure 2 is a schematic diagram of the optical system of the analyzer. So that a single light source can serve eight photometer stations, light guides carry the incident radiant energy to each of the eight photometer stations, and carry the transmitted energy to the photomultiplier tubes (PMTs). The light guides, liquid-filled tubes with quartz end-pieces, efficiently conduct radiant energy by virtue of the difference in refractive index between the liquid core and the tubing. The liquid light guides transmit about 10-fold more 340-nm light than do quartz fiber bundles. At each photometer station, rounded tips attached to the end of each light guide compress the flexible cuvettes to a constant path length of 0.5 cm.

The single tungsten–halogen light source is located in a parabolic reflector, which reflects light through eight radially arranged condensing lenses, through a spinning filter wheel, and into eight radially arranged incident-light guides. Light transmitted through the cuvette is carried by the receiving light guides to the PMT housing. The PMT ends of the receiving light guides are arranged in a similar radial array so that light from each passes through a second spinning filter wheel and into eight radially arranged PMTs. The two filter wheels are located on the same rotating shaft and are thus synchronized. Both filter wheels contain seven narrow-bandpass interference filters with wavelengths of 340, 405, 450, 525, 550, 575, and 630 nm. The shaft spins at approximately 1800 rpm. During a cuvette's 5-s residence at any photometer station, it will receive approximately 100 pulses of each of the seven wavelengths. The particular wavelength pair used to calculate results is chosen by the analyzer's microprocessor to correspond with the test being run. An analog-to-digital converter transforms output voltages from the PMTs into bichromatic absorbance differences.

Data Handling

All raw data from the analyzer are in the form of uncorrected bichromatic absorbance differences. In addition to the concentration and spectrum of the chromophore being measured, this absorbance difference also depends on the relative balance of the two interference filters for the wavelength pair being used, the wavelength dependence of the light guides' transmission properties, and the spectral response characteristics of the PMTs. This value is "zeroed" by the subtraction of averaged readings taken on the water bath (without cuvettes) at periodic intervals. This corrected value (Ad) is used in all subsequent calculations.

Serum blanking. The first cuvette for each specimen is reserved for a serum blank measurement. Five microliters of the specimen is diluted to 300 μL with water, and is examined with a different wavelength pair at each of the seven photometer stations. Estimates are made of the degree of hemolysis, sample turbidity, and icterus, in addition to readings at wavelengths of the equilibrium tests. This allows for correction of serum absorbances in equilibrium measurements where the reagent matrix does not shift these absorbances.

Reagent blanking. The photometer station located just before the sample-addition station measures the reagent absorbance, which is used in the calculation of equilibrium results. Reagent blanking on every cuvette corrects for variability in the absorbance at equilibrium due to tablet and cuvette variability; it also provides a check on reagent integrity.

Calibrated results. All methods except the measurement of serum enzymes are calibrated by assaying two concentrations of a calibrator, each in triplicate. These results generate values for slope and intercept, which are used to calculate results after the appropriate changes in Ad have been determined for the unknown sample. Calibrator set-values for creatinine and uric acid were assigned by reference to National Bureau of Standards (NBS) Standard Reference Materials.

Enzyme chemistries. Enzyme activity from "pseudo zero-order" reactions are calculated by reference to the bichromatic absorptivity of the various chromophores measured. These values, Ad per unit of concentration of product or substrate, are determined and specified for each analyzer. After rates based on readings from adjacent or alternate photometers (Figure 3) are calculated, a comparison algorithm is used by which closely agreeing, consecutive rates are selected for calculation of the final answer. The system's computer also examines the absolute Ad to ensure that a sample with exceptionally high activity has not produced such rapid substrate exhaustion that an erroneously low rate is accepted for the calculation of results.

Reagents

Formulations for 32 different analytes have been developed.

Equilibrium
Albumin
Alcohol
Ammonia
Direct bilirubin
Neonatal bilirubin
that 

Triglycerides Reaction kinetic, 

Creatinine 

Urea 

Aspartate Creatine 

Alkaline Acid 

Uric Salicylate 

Cerebrospinal Phosphorus Glucose Cholesterol Calcium 

Magnesium 

Bilirubin, 

TABLET 

Reagent. 

405/405 nm bichromatic wavelengths, and 40 s to 10-min reaction-monitoring period. Reaction concentrations per liter: 12.5 mmol of m-hydroxybenzoic acid, 1.5 mmol of 4-aminoantipyrine, 700 U of uricase, and 20 000 U of peroxidase. 

Bulking agents, lubricants, and anti-adherents are included in the above formulations to help maintain desirable tableting characteristics.

**Results**

**Analyzer Characteristics**

The noise characteristics of each photometer channel at 340/405 nm are shown in Figure 4 for a preliminary "breadboard" version of the analyzer. The data were generated by running the analyzer without cuvettes for the equivalent of 150 indices of the drive track, or 12.5 min. By omitting the cuvettes, only the noise of the analyzer system itself was measured. The standard deviations for the channels range from 0.10 to 0.18 mA.

Typical photometric linearity is shown in Figure 5 for serial dilutions of NADH (0.1 mol/L glycine, pH 10.0) monitored at 340/405 nm. That wavelength pair was chosen because the radiant energy output from the tungsten-halogen lamp is lowest in the near ultraviolet. All photometers demonstrate essentially identical linearity to approximately 1.5 $A_d$. Between 1.7 and 2.2 $A_d$, slight deviations from linearity not apparent from the Figure are present, the extent of which varies among the eight photometers. These deviations from linearity are of the order of 0.005 to 0.010 $A_d$. Such deviations are not readily detectable in the standard curves of the calibrated methods because of the large magnitude of change required to yield $A_d$ values in the

methyl)methylamine salt, 130 mmol of sodium carbonate, and 1 mmol of magnesium acetate.

**Amylase.** The formulation is based on the method of Driscoll et al. (2). Reaction characteristics: 15-μL sample volume, 405/405 nm bichromatic wavelengths, and 5.5 to 10 min reaction-monitoring period. Reaction concentrations per liter: 2 g of $p$-nitrophenyl-$d$-maltoside, 6 g of α-cyclodextrin, 25 mmol of sodium chloride, and 350 000 U of maltase.

**Creatine kinase.** The formulation is based on the Rosalki (3) modification of the Oliver procedure. Reaction characteristics: 10-μL sample volume, 340/405 nm bichromatic wavelengths, and 2 to 10 min reaction-monitoring period. Reaction concentrations per liter: 25 mmol of glucose, 2 mmol of tetrasodium EDTA, 20 mmol of magnesium acetate, 10 mmol of AMP, 4.4 mmol of trilithium ADP, 25 mmol of N-acetyl-l-cysteine, 16.5 μmol of trilithium diadenosine pentaphosphate, 2.3 mmol of disodium NADP⁺, 4333 U of glucose-6-phosphate dehydrogenase, 4333 U of hexokinase, and 35 mmol of creatine phosphate.

**Creatinine.** A modified (4) kinetic Jaffe procedure is used. Reaction characteristics: 20-μL sample volume, 525/630 nm bichromatic wavelengths, and 40 s to 3.5 min reaction-monitoring period. Reaction concentrations per liter: 250 mmol of lithium hydroxide, 24 mmol of picric acid, and 35 mmol of sodium dodecyl sulfate.

**Lactate dehydrogenase.** The lactate-to-pyruvate pathway is used in a modification of the procedure of Amador et al. (5). Reaction characteristics: 5-μL sample volume, 340/405 nm bichromatic wavelengths, and 40-s to 10-min reaction-monitoring period. Reaction concentrations per liter: 10 mmol of NAD⁺, 189 mmol of Tris, and 109 mmol of d,t-lithium lactate.

**Uric acid.** The formulation is a modification (6) of the enzymatic procedure of Trivedi et al. (7). Reaction characteristics: 10-μL reaction volume, 525/630 nm bichromatic wavelengths, and 5.5 min reaction-monitoring period. Reaction concentrations per liter: 12.5 mmol of m-hydroxybenzoic acid, 1.5 mmol of 4-aminoantipyrine, 700 U of uricase, and 20 000 U of peroxidase.

**Here we present six of the more thoroughly developed formulations, as representative of equilibrium, zero-order kinetic, and first-order kinetic assays.**

**Alkaline phosphatase.** This procedure is modified from that of Bowers and McComb (1). Reaction characteristics: 10-μL sample volume, 405/405 nm bichromatic wavelengths, and 40 s to 10 min reaction-monitoring period. Reaction concentrations of dissolved tablet formulation, per liter: 15 mmol of $p$-nitrophenyl phosphate [di-tris(hydroxy-

**Zero-order kinetic**

Acid phosphatase 

Alkaline phosphatase 

Amylase 

Creatine kinase (total) 

Creatine kinase MB  

Aspartate aminotransferase (GOT) 

Alanine aminotransferase (GPT) 

γ-Glutamyltransferase 

Lactate dehydrogenase 

Lipase 

**First-order kinetic**

Urea (BUN) 

Creatinine

* Liquid reagent. * Table + liquid reagent.

The right-angle brackets indicate the intervals used to calculate rates. The four calculated rates are compared, and closely agreeing consecutive rates are averaged for calculation of the final answer.
The analyzer's ability to follow a kinetic reaction accurately by using seven channels is demonstrated in Figure 3 for high and low activity samples of creatine kinase. Figure 3 also shows the $A_d$ differences examined by the comparison algorithm for CK to determine lag or substrate exhaustion.

Temperature control in a cuvette is shown in Figure 6. A thermocouple probe (Model BAT-8; Bailey Instruments, Saddle Brook, NJ 07662) was inserted into a cuvette as it moved through the analyzer's main track. The temperature was monitored and recorded as a tablet was dispensed, dissolved, and the sample and washout were added. Beginning with the 40-s photometer station, the temperature within the cuvette is maintained at $37 \pm 0.1 \, ^{\circ}C$.

Sample dispenser linearity, determined by replicate dispensing of protein-based solutions containing NADH, is shown in Figure 7.

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**Fig. 4.** Noise characteristics of the eight photometers over a period of 12.5 min

**Fig. 5.** Linearity of one photometer at 340/405 nm

The 100% represents an NADH concentration of 0.77 mmol/L. The numbers in parentheses are the CVs of 25 replicate dispensings of the indicated sample volume

**System Performance**

**Precision.** Within-run and between-run precision were determined by pooling reconstituted commercial serum-based controls, freezing aliquots at $-70 \, ^{\circ}C$, and assaying in the analyzer. The imprecision contributed by within-run and between-run factors were separated by using an analysis of variance (Table 1).

**Method linearity.** Reagent linearity was determined for five of the six reagents by assaying standards prepared by lyophilizing solutions containing known amounts of the...
particular analyte in a matrix of 50 g of bovine serum albumin and 9 g of NaCl per liter. Five replicates of each concentration were assayed. The linearity of the creatine kinase reagent was determined by analyzing five replicates of various sample sizes. Typical linearity data for the creatine kinase assay are plotted in Figure 8; Table 2 summarizes the results for the six methods tested.

![Fig. 8. Linearity plot for the creatine kinase reagent](image)

### Table 1. Within-Run and Between-Run Precision for Creatine Kinase, Alkaline Phosphatase, Amylase, Uric Acid, Lactate Dehydrogenase, and Creatinine

<table>
<thead>
<tr>
<th></th>
<th>Within-run (n = 40)</th>
<th>Between-run (n = 10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{x} )</td>
<td>SD</td>
</tr>
<tr>
<td>Creatine kinase, U/L</td>
<td>133</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>498</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>785</td>
<td>12.2</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>49.5</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>288</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>461</td>
<td>7.0</td>
</tr>
<tr>
<td>Amylase, U/L</td>
<td>58.9</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>486</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>807</td>
<td>10.0</td>
</tr>
<tr>
<td>Uric acid, mg/L</td>
<td>37.2</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>74.2</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>143</td>
<td>2.4</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/L</td>
<td>249*</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>501*</td>
<td>8.1</td>
</tr>
<tr>
<td>Creatinine, mg/L</td>
<td>11.7( ^{a} )</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>60.9( ^{a} )</td>
<td>1.14</td>
</tr>
</tbody>
</table>

- \( ^{a} \) n = 88. \( ^{b} \) n = 90.

**Method correlation.** As a general estimate of reliability of this instrumentation, we performed correlation studies between these six representative methods and the DuPont aca. For more definitive assessment, comparison with available reference methods will be done. Frozen normal and abnormal serum specimens were thawed and analyzed by the DuPont aca and the Paramax System. Each specimen was assayed by both analyzers within the same hour. Figure 9 shows the correlation results for creatinine. Table 3 lists the correlation statistics for all six analytes.

### Table 3. Analytical Recovery of Creatinine and Uric Acid

<table>
<thead>
<tr>
<th>Added</th>
<th>Recovered</th>
<th>Recovery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>8.0</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>14.0</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>102.2</td>
</tr>
<tr>
<td></td>
<td>200.0</td>
<td>196.0</td>
</tr>
<tr>
<td>Uric acid</td>
<td>50.0</td>
<td>51.3</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>98.7</td>
</tr>
<tr>
<td></td>
<td>250.0</td>
<td>249.7</td>
</tr>
</tbody>
</table>

**Accuracy.** To determine the accuracy of the calibrated methods, we performed analytical recovery studies by dissolving weighed NBS Standard Reference Materials directly into human serum-based material; five replicates at each concentration, including the serum matrix, were analyzed and the mean values were used to calculate percentage recovery after correction for the matrix. Results for creatinine and uric acid are presented in Table 3.

![Fig. 9. Correlation between the Paramax System and the DuPont aca for determination of creatinine](image)

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Table 4. Correlation Studies between the Paramax System and the DuPont aca for the Six Methods Evaluated

<table>
<thead>
<tr>
<th>Method</th>
<th>n</th>
<th>Slope</th>
<th>Intercept</th>
<th>Correlation coefficient</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>50</td>
<td>0.974</td>
<td>5.4 U/L</td>
<td>0.997</td>
<td>5.5 U/L</td>
</tr>
<tr>
<td>Amylase</td>
<td>37</td>
<td>1.342</td>
<td>−6.1 U/L</td>
<td>0.998</td>
<td>5.2 U/L</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>45</td>
<td>1.003</td>
<td>2.7 U/L</td>
<td>0.995</td>
<td>26.4 U/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>53</td>
<td>0.972</td>
<td>0.17 mg/L</td>
<td>0.999</td>
<td>0.8 mg/L</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>45</td>
<td>0.919</td>
<td>1.27 U/L</td>
<td>0.985</td>
<td>13.2 U/L</td>
</tr>
<tr>
<td>Uric acid</td>
<td>50</td>
<td>1.03</td>
<td>−4.28 mg/L</td>
<td>0.995</td>
<td>3.5 mg/L</td>
</tr>
</tbody>
</table>

Discussion

The single track configuration results in a constant cuvette throughput of 720/h, but the actual throughput of test results and patients' samples varies. If only one test per sample is requested, the throughput is 360 results and 36 samples per hour, a serum blank being measured for each sample. If a series of 19-test profiles is requested, the throughput is 680 results and 36 samples per hour. Identification of samples by affixing unique bar codes, printed by the analyzer upon test selection, enables error-free sample handling and random entry into the loading carousel, and facilitates "stat" analysis.

The use of eight photometer stations allows wide latitude in reaction timing. Rates can be measured for as long as 9 min 20 s for low enzyme activity. Where the instrument's noise is the predominant source of error, longer reading intervals result in greater absolute changes in absorbance, thereby improving precision. When enzyme activity is high and substrate is depleted, a shorter measurement period can be used, effectively extending the system's dynamic range. End-point times for the various equilibrium methods are from 40 s to 10 min. For example, interference of the slow reaction of gamma-globulin with bromcresol green dye (8) in the albumin method is minimized by reading at 40 s. A reaction requiring a longer incubation to reach equilibrium (e.g., determination of cholesterol) can be read at the 10-min photometer station.

The ability of the analyzer to measure the initial absorbance of each dissolved tablet virtually eliminates tablet absorbance variability as a source of error in equilibrium assay results. In addition, a warning is printed if the $A_d$ of the reagent blank is outside a specified range; this ensures that each tablet is properly dissolved and has absorbance properties consistent with those expected. Reading a sample blank for each sample also contributes to the analytical accuracy by noting any result for which the estimated amount of turbidity, hemolysis, or icterus may be sufficient to cause a significant interference. In addition, the actual absorbance of the sample may be used in the correction of equilibrium $A_d$ values. This correction cannot be used for some methods, e.g., those in which the reagent matrix either clears sample turbidity or produces a significant shift in the spectrum of hemoglobin or bilirubin.

By supplying reagents in tablet form, we avoid the complexity of multiple pumps and tubing required for liquid reagents and the inherent instability of liquids; on-analyzer reagent storage is at least three months.

In summary, we have described an instrument/reagent system for the spectrophotometric determination of biochemical analytes. Specific examples were chosen as representative of equilibrium, zero-order kinetic, and first-order kinetic assays.

References