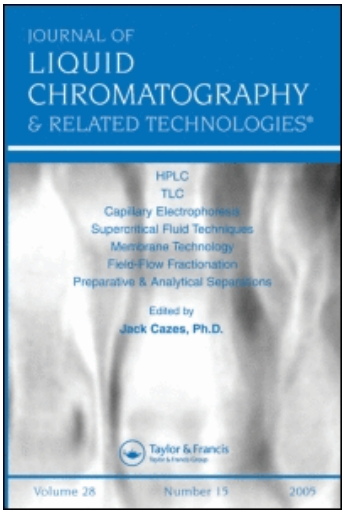

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The Use of the Laboratory Robot for Sample Preparation

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THE USE OF THE LABORATORY ROBOT FOR SAMPLE PREPARATION

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ABSTRACT

This paper reviews the basics of laboratory robotics for sample preparation by describing its status, implementation, applications and benefits. the integration of sample preparation with on-line chromatograph analysis for total automation is illustrated with a tablet assay application.

I. INTRODUCTION

A. Scope

This paper has two major objectives:

1. To review the basics of automated sample preparation via robotics.

2. To illustrate the integration of sample preparation with on-line (liquid chromatographic) LC analysis.

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The first objective is addressed in sections II and III by describing the status, implementation, applications and benefits of laboratory robotics. The focus is on sample preparation for liquid chromatographic analysis.

The second objective is addressed in section IV by a detailed documentation on integrating sample preparation with on-line LC analysis using a newly developed robotic language. It serves to supplement and illustrate the basic principles described in the previous sections.

While the description and discussion of sections II and III are generic, those in section IV are specific and limited to the robotics system and language used in this study.

B. Sample Preparation - the Weak Link in Laboratory Automation

Today, most analytical laboratories are facing a severe challenge of ever increasing workload. to gain higher productivity without increasing the technical staff, many laboratories are turning to automation (1,2). Autosamplers, computerized data handling and laboratory information management systems (LIMS) have contributed to significant productivity gains in recent years.

Although the analysis and data manipulation steps are highly automated, sample preparation remained largely a manual procedure. Due to its complex and varied nature, it often is a rate-limiting step of the entire analytical sequence, and poses severe problems to automation. While dedicated autoanalyzers can respond to a few high-volume assays (e.g., testing for blood chemistries), their

inflexibility precludes general laboratory use. Not until the advent of laboratory robotics in the early 80's, was there a general solution to the cost-effective automation of sample preparation (3-5).

II. THE BASIC OF LABORATORY ROBOTICS

A. Basic Components

A typical laboratory robotic system consists of a robot, a microcomputer and its peripherals, several work modules and a device interface. The functions of each basic component are listed in Table I.

TABLE I

BASIC COMPONENTS OF A LABORATORY ROBOTICS SYSTEM

Component	Function
Microcomputer	Coordinates all activities of the robot and modules
Robot	Transports samples to modules and instruments
Work Modules	Perform various sample preparation operations
Device Interface	Controls non-intelligent modules and devices

For on-line chromatographic analysis, a chromatograph and its associated data handling device are included.

Figure 1 shows a schematic diagram of a robotic system configured for content uniformity assay of prednisone tablets (details in section IV). The diagram serves to illustrate the operation of each system component.

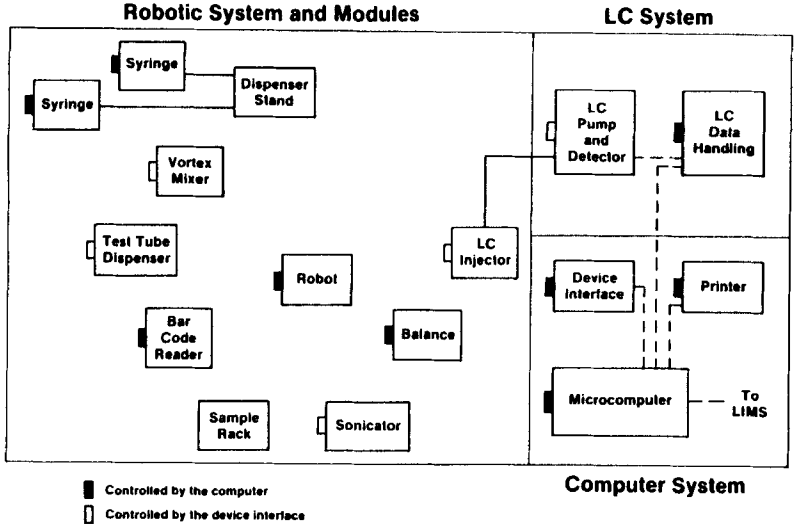

Figure 1. A Schematic Diagram of a Robotic System for Tablet Assays.

Surprisingly, the heart of the system is not the robot, but rather the microcomputer, which directs the robot and the modules, and coordinates all their activities. The robot is really an extension of the computer which allows it to perform physical work. The robot's major task is to transport the sample from one module to the next.

microprocessor-controlled devices such as the balance, the bar code reader, and the syringe station. They receive their commands directly from the computer via RS-232 serial interfaces. Other modules are non-intelligent devices, such as the vortex mixer, the sonicator, and the LC injector. They are controlled indirectly by the computer, through an electronics 'box' called the device interface (or power and event control module), which provides contact closures and ON/OFF AC controls.

In addition, the microcomputer can communicate with the chromatograph for instrument control, the data handling device for data transfer and report generation, and the LIMS (Laboratory Information Management System) for data archival.

B. Important Characteristics of a Laboratory Robot

Table II summarizes important characteristics of a laboratory robot (6). Most laboratory robots are small robot arms mounted on the bench-top or hood ceilings, and can be cylindrical, joint-articulated, cartesian or gantry type. Electrical motors, either DC servo or stepper, are used to drive the robot arm, although some motions (e.g., gripper) can be pneumatically driven.

Limit switches in combination with optical encoders, or potentiometer wires are used for position detection in a closed loop feedback mode (1). A position accuracy better than 1 mm is generally required to handle tasks such as syringe injection into an LC injector. The ability to change fingers or hands on-the-fly is required for handling various tools and containers in myriad sample preparation situations.

TABLE II

SOME IMPORTANT CHARACTERISTICS OF A LABORATORY ROBOT

Attribute	Typical Type or Range
Type	Small Industrial type, Bench-top or ceiling mounted, Joint-articulated or cylinderical 4 to 7 degrees of freedom, 1-2 kg payload
Power	Electric Motors (DC Servo or stepper) (Gears, chains, timing belts or cables)
Position Detection and Accuracy	Potentiometer wires, or limit switches and optical encoders, Closed-loop feedback, < +/- 1 mm repeatability
Grippers	Interchangeable fingers or hands, Programmable gripper position and Grip pressure

C. Modules

Table III lists robotics modules for common laboratory operations. Many modules (e.g., bar code reader, electronic balance, vortex mixer, syringe station, block heater, etc.) are common laboratory devices used without modifications. Others require redesign to render them "robotically friendly" (e.g., centrifuges and shakers that terminate in a fixed position). Still others have no manual predecessors (e.g., capping stations, single-shot LC injector, etc.).

TABLE III

MODULES FOR COMMON LABORATORY OPERATIONS

Operation	Module
Sample Identification	Bar code reader
Capping or Crimping	Capper or crimper
Weighing	Electronic balance
Mixing	Vortex or shaker
Liquid Handling	Syringe station, pumps
Solid Handling	Autogrinder, powder handling
Heating	Heaters, microwave oven, evaporator
Separation	Filtration station, solid-phase extraction, centrifuge
Chromatography	HPLC injector station, GC single-shot injector
Verification	Optical, acoustic, tactile and contact sensors

The development of robotics modules plays an important role in extending the capability of the laboratory robot in difficult sample preparation operations.

D. HPLC Injector Station

Robotics can be used to prepare samples for either off-line or on-line HPLC analysis. In off-line analysis, the robot fills autosampler vials with the prepared samples, crimp-caps the vials and places them into an autosampler tray. The operator then takes the tray to an autosampler for LC analysis. In this manner, a dedicated LC is not required.

In on-line LC analysis, the robot prepares the samples serially and injects them directly into the HPLC injector station located in the robotic envelope.

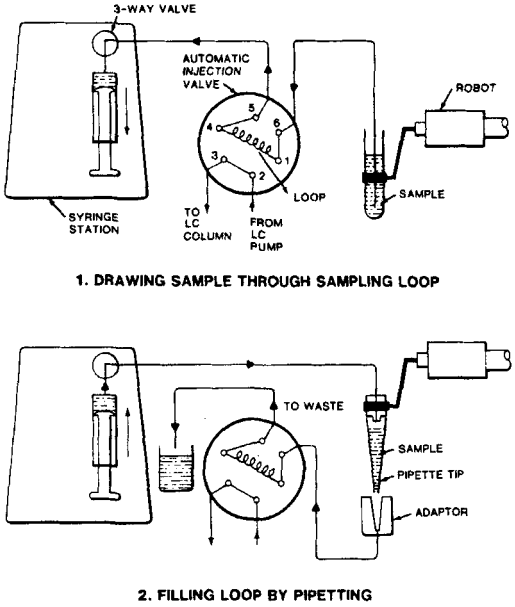

Figure 2. Two Approaches for HPLC Injection by Robotics.

Data from the LC handling device can be transferred back to the robot controller (computer) for further processing and evaluation. This mode is a prerequisite for total automation and high sample throughputs. However, a dedicated HPLC system is required. Figure 2 illustrates two common approaches to HPLC injection via robotics.

E. Software Characteristics

A robot can be controlled by common programming languages such as BASIC, FORTRAN or PASCAL (1). However, for maximum flexibility, many system vendors design their own robot languages. Examples are ARL (A Robot Language) from IBM, PERL (Perkin-Elmer Robot Language) and EasyLab from Zymark.

TABLE IV

USEFUL SOFTWARE FEATURES FOR LABORATORY ROBOTICS
- Controls robot and modules
- Executes user's programs
- User friendliness: (Menu driven, English-like syntax, interpretive, etc.)
- Provides a standard programming environment: (Performs mathematical and logical functions; handles alphanumeric and array variables, etc.)
- Allows communication with instruments, data handling devices and other computers

Table IV summarizes some desirable characteristics for laboratory robotics software. Some robotic software (e.g., PERL, EasyLab, etc.) are structured after BASIC for its simplicity and user-friendliness.

Besides the capability to control all robotic and module functions, the software should allow standard mathematical functions (e.g., multiplication, exponentiation, etc.) and easy communication with other instruments and computers. These aspects are becoming increasingly important for advanced applications and total automation.

III. IMPLEMENTATION PROCEDURES, APPLICATIONS AND BENEFITS

A. Getting Started in Laboratory Robotics

Table V lists key steps used by many laboratories to implement robotics (7,8). The recipe for success appears to be careful planning and the assignment of an in-house specialist dedicated to the robotization project. Laboratories with well defined automation problems and a realistic understanding of the capabilities and limitations of robotics appear to realize the automation benefits sooner. In many aspects, the implementation of robotics is similar to that of a LIMS. Procedures for preparing financial justifications are published elsewhere (7).

B. Automating Sample Preparation: Programming the Robot

After the appropriate robotics system is purchased and installed, the laboratory is faced with the actual development of the automation procedure. In many cases, the robot is programmed to emulate the

manual procedure. Although actual programming procedures vary from system to system, enough similarities exist to permit a description of a generic procedure here.

TABLE V

GETTING STARTED IN LABORATORY: A RECIPE FOR SUCCESS

1. Identify Applications to be Automated

   - List step-by-step procedure
   - List exact modules and instrument models
   - Determine extent of automation

2. Select Candidate Robot or System Vendor

   - Review specifications
   - Specify special hardware and software
   - Define level of vendor support, acceptance criteria, and time frame
   - Prepare financial justification and budget

3. Pre-installation Planning

   - Assign in-house robotic champion
   - Determine bench-top layout and physical location
   - Pre-installation training

4. Installation and Method Development

   - Installation
   - Integration with analytical instruments
   - Method development
   - Validation and documentation

First, the appropriate modules are set up in the robot work envelope and each communication pathway is defined in a computer file (system configuration file). This process is often termed system configuration.

Next, the operator moves the robot sequentially to all the pertinent positions using a teaching pendant. Each position is named by the operator and stored in a directory file. Similarly, commands to syringe station, device interface, and other modules are named. These operations of naming the positions or commands are often referred to as "teaching".

Then, a subroutine is created for each unit operation such as, getting the sample, weighing and dilution, etc., by stringing together a sequence of commands and position names.

Finally, a program for the entire sample preparation procedure is built from the subroutines. This program is then edited, debugged, and validated by comparison of the generated data with that for the manual procedure.

Experience from many users shows that the first robotics application can take months to automate. However, subsequent applications take progressively less time and effort. Once again, initial planning often determines the payback period (7).

C. Applications in Chromatography Laboratories

Table VI lists common robotic applications for chromatographic samples. The number of documented applications is growing rapidly and spans in many areas (e.g., pharmaceutical (9-13), food (14-16),

clinical (17-18), polymer characterization (19), environmental (20-21) and analytical derivatization (22)). Of particular interest is the use of the robot to control liquid chromatographs (23-25) and to optimize organic reactions (26,27).

TABLE VI

SOME COMMON ROBOTIC APPLICATIONS IN CHROMATOGRAPHY LABS

- Content uniformity assays of pharmaceutical products	(LC)
- Drugs in physiological fluids	(LC)
- Nutritional labelling in foods	(LC,GC)
- Analytical derivatizations	(LC,GC)
- PCB's in transformer fluids	(GC)
- Residual solvents in polymers	(GC)
- Pesticides in waste waters	(GC)
- Toxic waste analysis	(GC/MS)

D. Benefits of Laboratory Robotics

Table VII summarizes the benefits of laboratory robotics. Driven by these benefits and the excellent successes of many laboratories,robots are rapidly becoming a familiar tool in many modern laboratories. As technology advances, robotics will no doubt be more powerful and cost-effective in the very near future (28).

IV. AUTOMATED TABLET ASSAY: PREDNISONE CONTENT UNIFORMITY

A. General Description

Content uniformity assays are common quality control tests performed by the pharmaceutical industry to check the amounts of active drug ingredients in the finished dosage forms (e.g., tables).

TABLE VII

BENEFITS OF LABORATORY ROBOTICS

1. Increases Productivity

   - Flexible and reprogrammable automation
   - Extended and unattended operation
   - Faster sample turnaround
   - Cost effective means for total automation

2. Improves Data Quality

   - Reduces human errors
   - Better precision
   - Reliable documentation

3. Lowers Analyst's Exposure to Hazardous Material

   - Carcinogens, radioactive material, corrosive chemicals, infectious samples

4. Reduces Sample Contaminations

   - Sterile testing
   - Clean room operations

These tests are performed to satisfy regulatory agency compliance (e.g., FDA) and to ensure that the manufacturing process is under control. These assay procedures are documented in the United States Pharmacopeia (29) and are followed judiciously by the industry.

Liquid chromatography is a common analysis method for content uniformity assays. Other are UV spectroscopy, GC, titration, TLC and microbial assay. Typically, assays on 10 individual tablets are performed. The assay results are compared with published specifications (typically +/-10 to 15% of the label claim) to determine the PASS/FAIL status of the manufactured batch.

Although the simple tablet is the most common, other types of oral dosage forms are available. These include coated tablets, capsules, controlled released capsules, osmotic dosage forms, elixirs, suspensions, emulsions and syrups. Other non-oral dosage forms such as injectable, intravenous solution, topical ointment, gel, suppository and aerosol, are also commonly encountered in assay situations. Prednisone is a common steriod drug used in the treatment of asthma and respiratory allergies.

In this robotics application, we demonstrated automation of the entire analytical sequence from sample identification, preparation and analysis, to report generation. The unit operations automated include:

1. Identifying the sample
2. Weighing the tablet
3. Adding diluent and internal standard
4. Tablet disruption by vortex action
5. Tablet extraction by sonication

6. Sample dilution (1:10)
7. On-line LC injection
8. LC analysis and data transfer
9. Data tabulation
10. Generation of the final report

Up to 40 tablets (4 batches) can be processed unattendedly with precision levels of 1-2% (RSD). A detailed description of the automated procedure is documented in section IV-C.

B. Experimental

1. Robotic System

The robotic system used was the Perkin-Elmer MasterLab system for automated sample preparation. The robot was a joint-articulated robot arm with 5 degrees of freedom and closed-loop control. The robotic controller was an IBM personal computer (PC) with 640 kilobytes RAM, dual floppy disk drives, and ten RS-232 communication ports for instrument communication and module control. An Epson FX-85 was used as the system printer.

2. Modules and Accessories

Two Model 9040 MasterLab syringe stations were used for all liquid handling. A device interface station was used to control non-intelligent devices such as the HPLC injector, sonicator and vortex mixer.

The HPLC injector station was a pneumatically actuated Rheodyne Model 7000 valve with a top-mounted teflon syringe adaptor. The remote syringe accessory consisted of a Delrin arm mounted on the side of the robot hand, an 8' x 1/16" o.d. teflon tube (connected

to a syringe station), a Hamilton Luer-Lok adapter (Hamilton #32836), and a 22- gauge blunt-tip needle. This accessory was useful for performing liquid aliquoting and direct injection into the LC.

Other modules included a Mettler PE-160 Electronic balance, a sonicator (Mettler), a test tube dispenser and a vortex mixer.

3. Software

The application programs and communication subroutines used were written in PERL. PERL is a high-level, BASIC-like language which allows robot and instrument control. The structure of PERL is described elsewhere (5.30). Actual PERL programs for this application are also documented (30).

4. LC System

The LC system consisted of a Series 410 pump, a LC-90 variable wavelength detector,and an LCI-100 integrator with an RS-232 communication accessory (all from Perkin-Elmer).

The column used was either a Perkin-Elmer Pecosphere-5C C18 (150 mm x 4.6 mm i.d.) or a Pecosphere-3X3C C18 column (33 mm x 4.6 mm i.d.). To prolong column lifetime, the analytical column was protected by a C18 pellicular guard column (32 mm x 2.1 mm i.d.) and an 8-μm C18 scavenger column (33 mm x 4.6 mm i.d.) (31).

5. Reagents

The mobile phase was methanol:water (60:40). The extraction solvent and diluent was methanol:water (1:2). The internal standard solution was

acetanilide (Sigma Chem.) prepared in the diluent at a level 550 µg/mL.

C. Automation Procedure

The USP manual procedure for testing content unformity of prednisone tablets (29) was emulated and followed as closely as possible in our development of the automated procedure. However, some modifications were necessary to adapt manual procedures into robotic procedures. (For instances, instead of using a volumetric flask for the dilution step, an automated syringe method was developed).

1. Identifying the Sample

Samples are identified by entering sample i.d. or log numbers at the PC console (up to 4 batches of 10 tablets each). Alternately, a bar-code reader can be incorporated in the system for automated transfer of sample i.d. to the PC.

2. Weighing the Tablet

The robot places an empty test tube (150 x 16 mm) in the balance tube adaptor and a tared weight is transferred to the PC. the robot then fetches sample tube (75 x 12 mm) containing a prednisone tablet pours it into the empty tube. The tablet weight is transferred to the PC and is displayed, together with lot i.d. and tablet number by the PC monitor. The same data are printed in the LCI-100 heading before the chromatogram.

3. Adding Diluent and Internal Standard

The robot brings the test tube containing the tablet to stationary dispensing probe #1 and

dispenses 10.0 mL of diluent. It then brings the tube under dispensing probe #2 and dispenses 2.5 mL of the internal standard solution.

4. Tablet Disruption by Vortexing

The robot takes the sample tube to the vortex mixer and initiates mixing for at least 1 min. During the mixing, the robot weighs the next sample. This kind of process overlapping, while requiring more complex programming, creates more efficient sample processing.

5. Tablet Extraction by Sonication

The robot places the sample tube in the sonicator and initiates sonication for 1 min. The sample is then vortexed for 20 sec. to ensure homogeneity.

6. Sample Dilution (1:10)

The robot places the sample under dispensing probe #1, and withdraws 1.5 mL of the sample into the lines of the dispenser #1. The robot disposes of the remainder of the sample and places a new empty test tube under dispensing probe #1 to receive the 1.5 mL of sample plus 13.5 mL of fresh diluent. The robot mixes the diluted sample in a vortex mixer for 230 sec. and places it in a tube adaptor for LC injection.

7. LC On-Line Injection Using the Remote Syringe Accessory

The robot withdraws an 0.1 mL air gap and 0.5 mL of the diluted sample into its remote syringe and injects 0.4 mL of the sample into the syringe port of

the HPLC injector station. The injector valve is then turned from LOAD to INJECT while the LCI-100 integrator is triggered simultaneously by a contact closure. The actual injection volume is 10 µL. After 4 seconds the injector valve is turned back to the LOAD position and the injection loop (10-µL) is then washed with 1.0 mL of the diluent.

8. LC Analysis and Data Transfer

During LC analysis, the robot proceeds to process the next tablet sample. At the end of the analysis (during the vortex disruption of the next tablet), the PC requests transfer of the prednisone data from the LCI-100 integrator. The data are displayed on the video monitor screen. Bidirectional communication between the lCI-100 and the PC is accomplished under PERL (30).

9. Data Tabulation at the end of 10 Assays

At the end of 10 assays, the PC calculates the average and the relative standard deviation of the tablet weights and the prednisone data and displays them on the screen. A hard copy of the screen is printed by involving a 'screen-dump' onto the Epson printer. Alternately, the same information can be printed by the LCI-100 integrator.

10. Report Generation

After 10 tablets are assayed, a formatted report containing pertinent data such as sample i.d., average prednisone assayed values, precision data and the PASS/FAIL status of the batch is displayed and printed. The total assay time for 10 samples is about 60 minutes.

D. Results and Discussion

1. System Configuration

Figure 1 shows the schematic diagram of the bench lay-out and Figure 3 is a photograph of the actual robotic system used in this application.

Figure 3. A Picture of the Automated Content Uniformity Assay for Prednisone Tablets.

2. LC Conditions

The LC conditions and a sample chromatogram are shown in Figure 4. The USP mobile phase conditions were modified to eliminate the use of THF which caused baseline instabilities.

For faster analysis a shorter 3-μm C18 column (33 mm x 4.6 mm i.d.) (31) yielded adequate separation in less than 2 minutes using MeOH:H_2O (1:1) as the mobile phase.

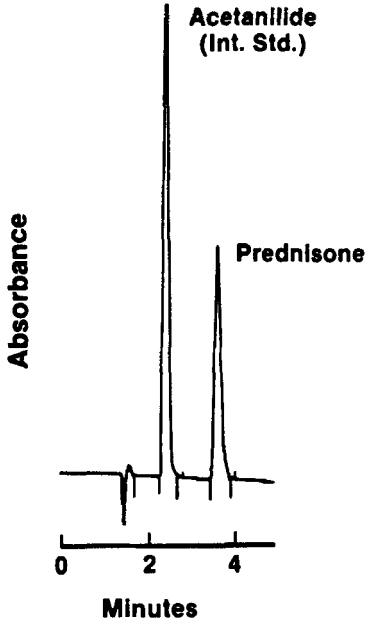

Figure 4. Liquid Chromatogram of the Prednisone Assay. LC Conditions: Pecosphere-5C C18 column, MeOH/H2O (60:40), 1.0 mL/min, UV detection at 254 nm.

3. PERL Screen Display and Report Format

A typical PERL generated screen displayed at the PC monitor during the uniformity assay is shown in Table VIII. The display includes table #, sample id, tablet wt, prednisone data, an average and precision

(both weights and prednisone data). The system is capable of precision levels of 1% RSD using the internal standard method.

Table IX shows a final report for a 10 tablet assay. It contains pertinent sample data and assay.

TABLE VIII

PERL SCREEN DISPLAY DURING ANALYSIS
PREDNISONE CONTENT UNIFORMITY ASSAY

Tablet No.	Sample I.D.	Tablet Wt. (mg)	Prednisone (mg)
1	Lot 101	89	2.48
2	Lot 101	90	2.49
3	Lot 101	90	2.49
4	Lot 101	91	2.45
5	Lot 101	89	2.43
6	Lot 101	91	2.45
7	Lot 101	90	2.51
8	Lot 101	91	2.43
9	Lot 101	91	2.48
10	Lot 101	90	2.47
Average (RSD)	Lot 101	90.2 (0.87%)	2.46 (1.09%)

It contains pertinent sample data and assay results.

A final status of "PASS" is assigned only if:

1. The precision level is less than 6% RSD.

2. Each assayed prednisone value is within the USP specification of +/- 10% of the label claim, or between 2.25 mg and 2.75 mg of prednisone.

Otherwise, a "FAIL" status of the entire batch is assigned and the tablet numbers which failed are listed.

TABLE IX

FINAL FORMATTED REPORT
PREDNISONE CONTENT UNIFORMITY ASSAY

Sample I.D.	Deltasone 2.5	mg
Lot Number	Lot 101	
Label Claim	2.50	
USP Specifications	2.25 - 2.75	mg
Assay Date	1-28-86	
Assay Result	2.468	
Assay Precision	1.09%	(RSD)
Assay Status	*******PASS*******	

4. Precision

To test the precision of the system performing the entire analytical sequence, four batches of prednisone tables were assayed using a calibrated external standard method. The external standard method was used since it is a better indication of volume and analysis accuracies. Precision levels of 1.80, 1.51, 1.89, and 1.65 respectively were obtained. These data show that precision levels of bout 1.5 to 2% RSD are obtainable under fairly typical conditions.

Since the precision level of LC analysis alone (injection, chromatography and data handling) has been determined to be 0.7% RSD (30), the robotic sample preparation variation can be calculated to be about 1% RSD.

5. Advantages of the Automated Tablet Assay System

The advantages of the automated tablet assay system are listed in Table X. The main benefits are increased precision, faster sample turnaround time, enhanced productivity and lower cost per sample.

TABLE X

FEATURES AND BENEFITS OF THE AUTOMATED TABLET ASSAY

Features	Benefits
Automated sample preparation and analysis	Improves precision 1% RSD (Int. Std) 1.5 to 2% RSD (Ext. Std)
Unattended analysis of 40 tablets	Reduces sample turnaround
Identify samples and generate final report	Reduces transcription errors
Total automation	Increases productivity Lowers cost per analysis

6. Total Automation Capability

This prednisone tablet application is an excellent example of total automation in which the entire analytical sequence from sampling to report

generation is automated. Total automation is the goal for many laboratories with heavy sample loads. A sophisticated robotic system such as this is one of the most cost effective and flexible means towards total automation.

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