PHARMACEUTICAL NOTES

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New PowerLine Based Automated System For Dissolution Control: Waters 610/600E PowerLine System for Dissolution Testing

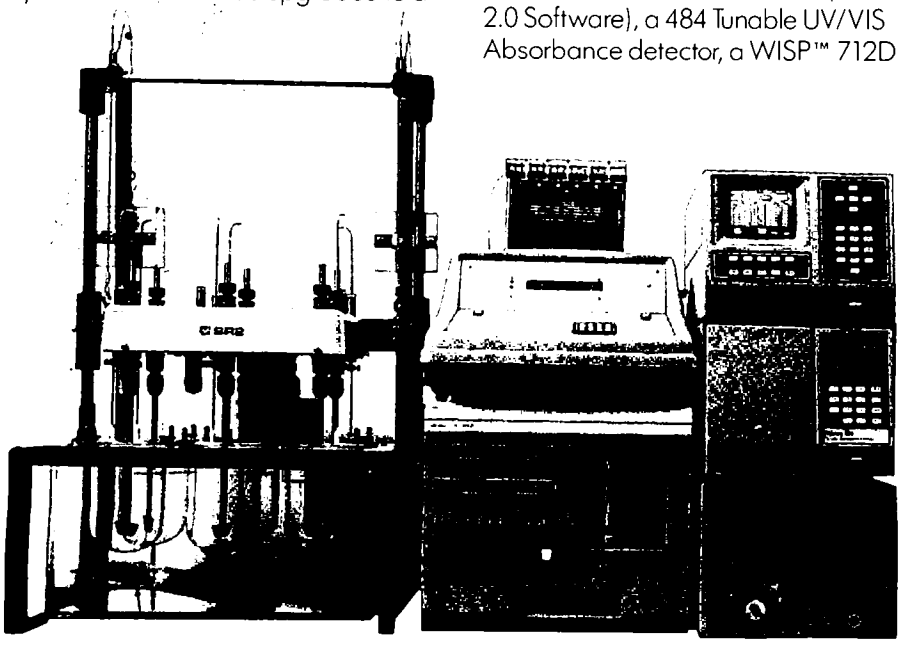
IN THIS ISSUE

Introduction

In 1987 Waters first introduced an automated dissolution/HPLC (High Performance Liquid Chromatograph) interface based on the 840 Data and Chromatography Control Station. This system improves the efficiency of the dissolution lab by transferring samples directly from the dissolution test station to the HPLC, analyzing those samples and documenting the results.

In March of this year, at the 40th Annual Pittsburgh Conference and Exposition, Waters announced the incorporation of dissolution acquisition software in the PowerLine™ 610 isocratic and the 600E gradient solvent delivery and system control modules. The 610 isocratic PowerLine system module can be upgraded to a four solvent gradient system (functionally equivalent to the 600E) with the addition of a gradient valve station. These PowerLine modules are a new way to integrate the latest technologies of today's HPLC system components into a combined centralized controller, providing complete system communication and system parameter documentation. This new approach from Waters provides power beyond that of stand-alone HPLC components. Additionally, PowerLine HPLC systems can be configured with either an integrator, or a chromatography workstation using Waters Maxima™ or Expert Ease™ software.

The PowerLine Automated Dissolution/HPLC system consists of a 600E or 610 PowerLine module (Rev. 2.0 Software), a 484 Tunable UV/VIS Absorbance detector, a WISP™ 712D sample processor, and a Hanson Transfer Controller (TC)* which transfers dissolution samples from the dissolution test apparatus directly into the active 712D sample processor.



Waters PowerLine Dissolution System including Waters 600E Gradient PowerLine Module, Waters 484 detector, the WISP 712D, and the Hanson Transfer Controller. (Hanson SR-2 Dissolution Bath courtesy of Hanson Research Corporation.)

How the PowerLine System for Dissolution Testing Works

The following operational description is applicable to either the 610 or the 600E PowerLine solvent delivery and system control modules.

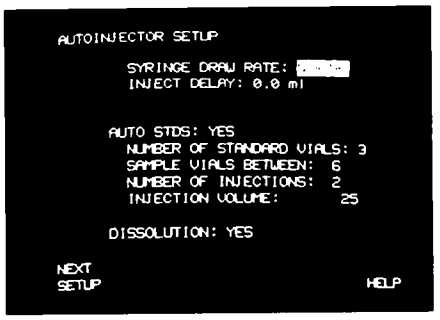
Dissolution control is accessed from the Autoinjector Setup screen of the 600E controller. When enabled, the 600E coordinates the transfer of dissolution samples into the active 712D autosampler carousel while performing chromatography on previously collected dissolution samples or calibration standards.

*Hanson Research Corporation
9810 Variel Avenue
Chatsworth, CA 91311

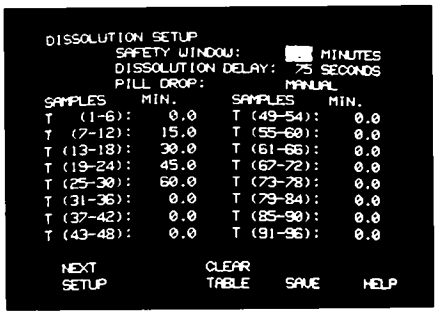
The Hanson Transfer Controller (TC), activated by the 600E, removes samples from the dissolution bath at times specified in the Dissolution Table editor. Autoprobes, equipped with 5–10 micron filters, are lowered simultaneously into each of the dissolution vessels at the specified sampling time. Excess filtered sample is withdrawn into six volumetric cylinders under vacuum. Each of the six cylinders have a liquid leveling rod to determine the sample volume that will be dispensed into the 712D autosampler carousel. Using positive pressure, the TC delivers the excess sample back into the dissolution vessels, simultaneously backflushing the autoprobe filters. The remaining measured and filtered sample is then dispensed into empty, capped one ml vials inside the active 712D sample processor.

Dissolution sampling times are entered in the Dissolution Table editor of the 600E Controller according to the protocol specified by the dissolution test. The injection sequence consisting of samples and standards, and chromatography run times are entered in the Program Methods editor.

The 600E dissolution software determines whether an HPLC injection can be made without interfering with the acquisition of dissolution samples. If it can, the HPLC injection is completed and the 712D sample carousel is rotated to the correct position to collect the dissolution samples. On the other hand, if the system determines that it cannot make the next scheduled injection before the next set of dissolution samples are acquired, it interrupts the injection sequence to rotate the 712D carousel to the correct dissolution sample acquisition position. Once dissolution samples are acquired, the carousel is rotated back to the position it was in before the sample transfer took place and the injection sequence continues. In all cases, the 600E software prioritizes dissolution sample acquisition over that of a sample or standard injection.



Waters 600E PowerLine Module Autoinjector Setup Screen Editor allows you to activate dissolution software. In the pharmaceutical industry, it is common to periodically run calibration standards after a predetermined number of samples have been analyzed. A convenient feature of the 600E PowerLine control module is the Auto Standards routine, which allows the user to program standard vial injections between a set number of sample vials.



Waters 600E Dissolution Table screen editor allows entry of sampling times. The automated dissolution system uses the 96 vial carousel in the 712D autosampler to accommodate the many samples taken during a dissolution test. The Dissolution Table editor provides the user with documentation of sample times and vial location of dissolution samples. Typically, the first six positions of the carousel are reserved for multilevel calibration standards.

There are cases where it is possible that the samples scheduled to be injected into the HPLC have not yet been acquired. This may happen in a situation where the dissolution sampling intervals are hours apart and the chromatography is programmed at minutes per injection. In this case, the dissolution software recognizes that the samples scheduled for analysis have not been acquired and will delay injections from these vials until they have been filled with dissolution samples.

Through intelligent software routines and advanced sample handling techniques, the Waters Automated Dissolution/HPLC system provides greater confidence in sampling and analytical results. Should verification of specific sample data be necessary, identified samples can be re-injected, since all dissolution samples are retained until the analyst approves all the data.

Combined Dissolution Testing and Content Uniformity for Quality Control

In addition to dissolution analyses, content uniformity determinations are also routinely performed in the pharmaceutical laboratory. Content uniformity determinations are usually performed separately by HPLC techniques, while dissolution results are more often based on spectrophotometric techniques. Waters Automated Dissolution System lets the pharmaceutical chemist combine dissolution testing and content uniformity determinations using a single automated method.

In combining these two tests, three criteria must be met. First, two dissolution baths must be used. Most dissolution tests require that only six samples be analyzed; however content uniformity determinations are usually performed on a minimum of ten samples, necessitating the use of a second dissolution bath (six additional samples).

Second, content uniformity determinations must be performed when the active ingredient(s) are 100% dissolved.

Third, the same HPLC method must be capable of analyzing dissolution samples as well as performing content uniformity determinations. If all three of these criteria are met, content uniformity determinations can be made utilizing either the same samples analyzed for the dissolution test (if actives are known to be completely dissolved), or samples withdrawn from the dissolution test vessels at a later time point (if the last dissolution sampling time is known to occur before the actives are 100% dissolved).

To demonstrate the feasibility of combining these two test procedures, identical HPLC methods (See Figure 1) were used for both the dissolution test samples and content uniformity determinations for the antihypertensive product Timolide®. Timolide contains hydrochlorothiazide and timolol maleate at 25 mg and 10 mg per tablet respectively.

The Waters Automated Dissolution System was used to control the sampling of 12 dissolution test vessels, transfer the samples to the active 712D autosampler, and analyze the dissolution sample and standard solutions. In this case, the Timolide actives were completely dissolved at the final dissolution test time point. Content uniformity determinations were based on the HPLC results obtained from 10 of the 12 dissolution samples. Additional content uniformity samples prepared offline by accepted United States Pharmacopeia (USP) methodology, were manually loaded into the WISP carousel for comparison with the dissolution samples (see Table 1).

Conclusion

The Waters PowerLine System for Dissolution testing brings a new dimension to dissolution analyses. Its ease of use, versatility, precision and reliability surpass all other dissolution sample assay techniques. It is the only online dissolution HPLC system that performs a complete drug product release study. Now for the first time researchers can execute extended dissolution profiles, content uniformity studies and composite drug assays on a single automated system providing them with the specificity and sensitivity demanded by today's drug formulations.

The data in Table 1 indicates that the automated method (different sample preparation method, but same chromatographic method of analysis), gives a similar mean and variance indicating that this method does not significantly affect the outcome of the content uniformity test. From the analysis of the means and variances by T-tests and F-tests respectively, we conclude that the manual method of sample preparation for content uniformity could be substituted with the automated dissolution method without significant bias to the results.

Figure 1: Waters 860 Networking Workstation Chromatography Sample Report of Timolide Separation

```
Header:
Acquisition method      COMBINED3       Processing method      COMBINED3
Units                                   System number          1
Channel                 1               Vial                   30
Injection               1               Total injections       1
Run time                9.00 min        Sample rate            1.00 per sec
Injection volume        50 uL           Mode                   Analysis
Acquisition version     840/6.21        Processing version     V1.2

Description:
M484 @295 NM

First Plot:
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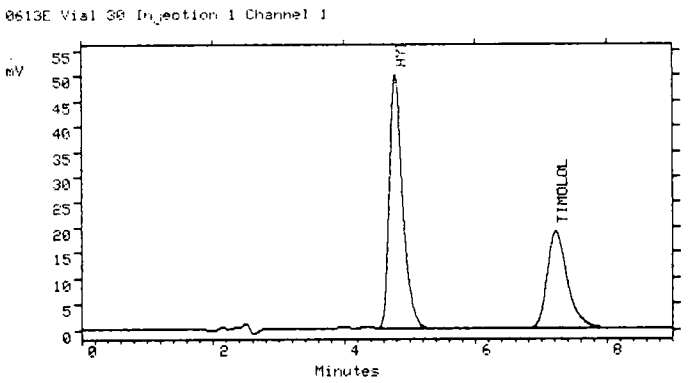



```
Conditions:
Run time                9.00 min        Sample rate            1.00 per sec
Injection volume        50 uL           Sample amount
Internal standard amt                   Scale factor
Mode                    Analysis
Keyboards of Remote Devices Locked

Peak Detect Threshold     25            Peak Width               20 sec
Integration Delay       3.00 min        Area Reject            25000

Single Point Calibration                Quantitation by Area
Retention Time Offset   0.00 sec        Force Through Zero is Disabled
Relative Peak Window      10%           Absolute Peak Window     OFF

LC Results:
```

Peak Name	Ret Time	Area	Height	Int	Amount	Intercept
HYDROCHLORTH.	4.78	693929	49907	BB	0.028	0.000e+00
TIMOLOL	7.22	394845	18768	BB	0.011	0.000e+00

Peak Name	Slope	Response
HYDROCHLORTH.	2.516e+07	6.93929e+05
TIMOLOL	3.647e+07	3.94845e+05

HPLC separation of Timolide active ingredients, hydrochlorothiazide and timolol maleate on a Waters μBondapak C_{18} column. The mobile phase consisted of water, acetonitrile, methanol and pH 3.0 phosphate buffer (38:8:2:2). The separation was monitored at 295 nm as specified in USP XXI.

Table 1: Comparison of Manually Prepared Content Uniformity Sample Data to the Combined 10 Vessel Dissolution Data

	Hydrochlorothiazide				Timolol Maleate			
	Manual		Auto		Manual		Auto	
Tablet	mg/ml	Tablet	mg/ml	Tablet	mg/ml	Tablet	mg/ml
1	25.05	11	24.53	1	9.88	11	9.93
2	25.38	12	24.58	2	10.01	12	9.92
3	25.10	13	24.62	3	9.80	13	9.78
4	24.93	14	25.23	4	9.81	14	9.99
5	25.03	15	24.78	5	9.97	15	10.00
6	24.83	16	25.34	6	9.74	16	10.20
7	25.23	17	24.61	7	9.98	17	9.63
8	25.05	18	25.50	8	9.85	18	9.79
9	25.18	19	25.21	9	9.89	19	10.06
10	25.88	20	25.25	10	10.30	20	9.93
AVG	25.17		24.96		9.92		9.92
SDV	0.28		0.35		0.15		0.15
RSD	1.11		1.42		1.51		1.52

Dissolution Testing Requiring High Sensitivity Analysis

The trend in the pharmaceutical industry is toward more complex formulations, lower dosages, and more sophisticated drug delivery systems such as controlled release products. As a result, pharmaceutical researchers are moving away from the traditional analytical spectrophotometric techniques and are turning to HPLC for dissolution analyses and quality control. The excellent specificity of HPLC makes it a more sensitive and reliable analytical tool than spectrophotometry. In addition, the USP accepts HPLC as a method of analysis for dissolution samples.

Dissolution Testing of Oral Contraceptives

Sensitive and reproducible HPLC separations of 23 different commercial oral contraceptive tablets, containing norethindrone and ethinyl estradiol at very low levels, have been described by Papas, et al.[1] Their method involved dispersing the tablet in 10 ml of a mixture of methanol and water (80%/20%). This corresponded to working concentrations of 100 µg/ml and 5 µg/ml for a tablet containing 1 mg norethindrone and 0.05 mg ethinyl estradiol respectively.

Dissolution testing of oral contraceptives was modified by the USP[2] in 1988 to reflect the use of HPLC as a method of analyzing dissolution samples. Using this method the tablets are dissolved in 600 ml of dissolution media and the samples analyzed by HPLC. The formulation described above would provide working concentrations of 1.7 µg/ml for norethindrone and 0.08 µg/ml for ethinyl estradiol. This represents a 60-fold dilution over the methodology originally described by Papas.

Figure 2: Waters 860 Expert Ease System Suitability Report

System Suitability Report from line 1 of multi-method SYSS

Acquisition method	SYSSUIT	Processing method	SYSS
Units		System number	1
Channel	1	Vial	1
Injection	2	Total injections	9
Run time	15.00 min	Sample rate	1.00 per sec
Injection volume	100 uL	Mode	Calibration
Acquisition version	840/6.21	Processing Version	V1.2

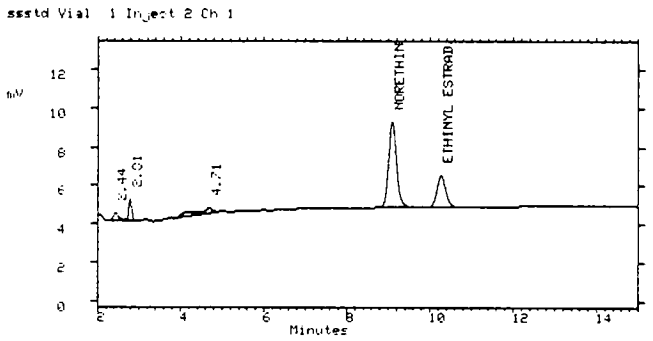


Table of System Suitability Results

Sample Name ssstd Vial 1 Inj 2 Chan 1
Baseline RMS noise 8.161671 (uV) drift -0.035435 (uV / sec)

Name	Ret Time	Area	Height	Plates	Resolution	Tailing Factor
UNKNOWN	2.44	4013	385	798	-	1.272
UNKNOWN	2.81	5235	1073	3972	-	0.725
UNKNOWN	4.71	7805	254	643	-	0.582
NORETHINDRONE	9.11	56495	4420	9575	2.779	1.069
ETHINYL ESTRAD.	10.28	23481	1645	10551	21.282	1.078

Name	Ret Time (minutes)	Width: baseline (data points)	5-sigma (seconds)	half height (seconds)
UNKNOWN	2.44	24	25.924	9.808
UNKNOWN	2.81	15	13.378	5.244
UNKNOWN	4.71	57	55.716	45.028
NORETHINDRONE	9.11	40	27.929	12.005
ETHINYL ESTRAD.	10.28	37	30.030	13.301

System Suitability Report of Oral Contraceptive Standard Injection. The system suitability report for a single vial injection prints the chromatogram and reports the USP parameters such as resolution, plate counts, and tailing factors for all peaks identified in the calibration table. In addition, a summary report is also printed for multiple injections of standard vials, reporting means, standard deviations, and relative standard deviations of area, height, retention time, tailing factor, resolution and plate count.

To demonstrate the sensitivity of Waters 484 Tunable Absorbance Detector, Waters Pharmaceutical laboratory performed the dissolution test outlined in the USP for norethindrone and ethinyl estradiol tablets.

In this experiment, the unique capabilities of the PowerLine Dissolution/HPLC interface were coupled with those of the 484 absorbance detector. The optics of the 484 detector are controlled by the PowerLine 600E system control module by means of an IEEE-488 communications bus. Wavelengths and sensitivity settings are programmable, offering the chromatographer the ability to optimize the detector output.

A standard solution was prepared representing the concentration of a typical oral contraceptive dissolution sample. The HPLC analysis required detection of these compounds at concentrations below 1.7 µg/ml and 0.08 µg/mL for norethindrone and ethinyl estradiol respectively.

[1] Papas, Andrew N., Marchese, Salvatore M., and Delaney, Michael F., *Rapid Determination of Norethindrone and Ethinyl Estradiol in Oral Contraceptive Tablets by Reversed-phase Liquid Chromatography*, LC, Vol 3 No. 4, (April, 1985)

[2] *Norethindrone and Ethinyl Estradiol Tablets*, USP XXI, Seventh Supplement, 2813 (1988)

The USP protocol suggests 100 µl injection sizes which is equivalent to 170 ng of norethindrone and 8 ng of ethinyl estradiol injected onto the HPLC column. Given the poor spectral characteristics of these two compounds, analytical requirements dictate an HPLC method that can provide a stable UV detector response, at high sensitivity, when operating at 200 nm.

Dissolution data was reprocessed on the Waters 860 networking computer system. Accurate and reproducible integration was obtained on peaks representing as little as a two millivolt response.

Figure 2 shows a system suitability report generated by the Waters 860 Networking Computer System, illustrating a typical separation of a synthetically prepared oral contraceptive dissolution sample using a Waters 484 absorbance detector. Five replicate injections of a standard solution resulted in RSD's of 2.5% for both actives, below the 3.0% specification set in the USP monograph.

In addition, the system suitability report shows the theoretical plates for ethinyl estradiol at 10,551 (USP states 7,000 minimum) and the resolution between the two actives at 2.8 (USP states 1.5 minimum). The tailing factor for both actives was well below the maximum of 2.0 described in the USP monograph.

Conclusion

Analysis of dissolution samples by chromatographic techniques can put a burden on the HPLC system. Dilute solutions of active ingredients must be capable of being reproducibly analyzed. The Waters Automated Dissolution System is capable of providing the user with convenient methods setup, variable sample injection volumes and detector options to meet the demands for high sensitivity analyses.

The Waters 845 Chromatography Workstation

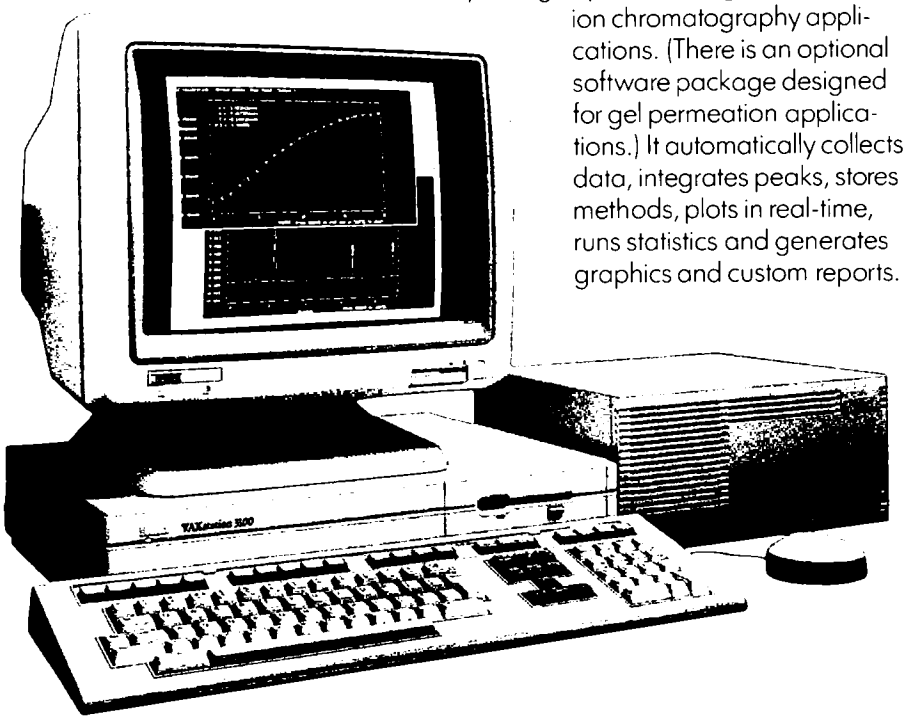
The Ideal Chromatography Workstation for the Pharmaceutical Laboratory.

The Waters 845 Chromatography Workstation is one of the most powerful laboratory data handling and control systems available today. It is a quantitative tool that enables the pharmaceutical chemist to measure area and/or peak height and to accurately calculate the true amount of material present in samples.

The Waters 845 combines the power of the Digital VAXstation 2000 or the VAXstation 3100 Desktop Computer with the latest enhancements of Waters Expert Ease Software. The 845's window environment enhances the system's multitasking capabilities.

Waters Expert Ease Software

Waters Expert Ease software is a direct access, menu driven software package optimized for gas, liquid, and ion chromatography applications. (There is an optional software package designed for gel permeation applications.) It automatically collects data, integrates peaks, stores methods, plots in real-time, runs statistics and generates graphics and custom reports.



Waters 845 Chromatography Workstation featuring the VAXstation 3100 personal computer from Digital Equipment Corporation.

The Waters Expert Ease software offers internal or external, single or multi-point calibrations up to 99 levels. It allows linear, quadratic, cubic, point-to-point and segmented curve fits. Calibration curves and regression statistics can be printed or plotted for presentation or documentation purposes.

The 845 offers default integration parameters to meet the needs of most pharmaceutical applications and integration timed events are provided for complex chromatographic separations.

Waters Easy-View software allows simple mouse driven manual integration and chromatogram zooming to see and accurately integrate even the smallest peaks.

Waters Custom Report Manager allows the user to tailor chromatographic report formats, report sequences and the report print location.

Waters Expert Ease Custom Convert capability allows transfer of valuable chromatographic results into RS-1, Lotus 1-2-3®, 20/20™ or ASCII

formats for further statistical analysis. Complete methods documentation is available for GMP/GLP purposes.

Waters LAC/E Technology

Waters Laboratory Acquisition and Communications Environment (LAC/E™) module provides advanced system control and data acquisition capabilities to increase your laboratory's productivity.

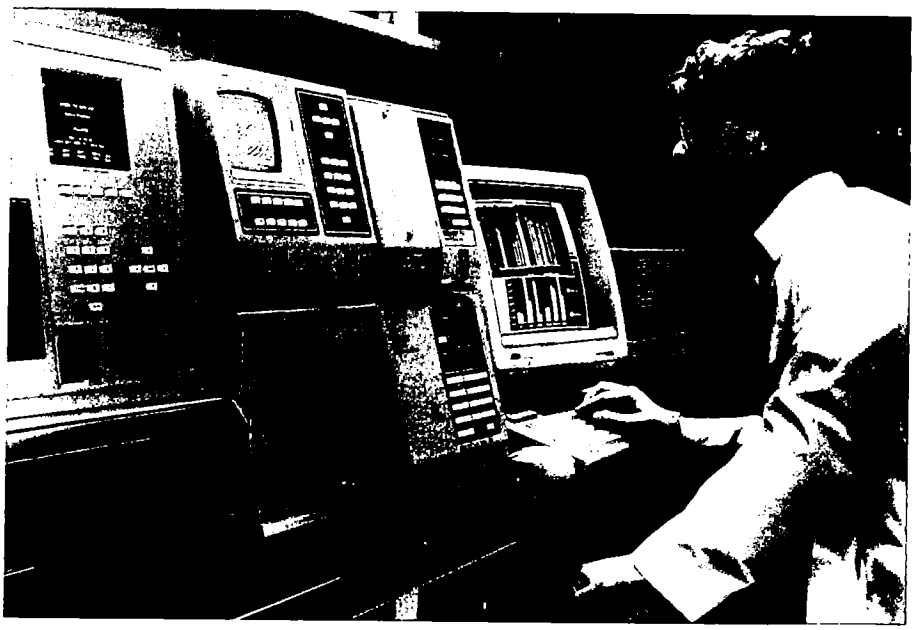
The LAC/E module controls all Waters pumping modules including isocratic, single-pump gradient and multi-pump gradients. It also controls Waters family of WISP sample processors as well as Waters detectors (410 Differential Refractometer, 484 and 490 Absorbance Detectors). LAC/E serial board options offer the ability to connect up to eight additional printers offering a more organized reporting structure for a multiple HPLC/GC laboratory.

Waters SAT/IN™ module provides two channels of high resolution A/D with separate time bases to meet the needs of capillary GC, as well as LC, IC and GPC data collection.

Introducing Waters Expert Ease System Suitability Software Option

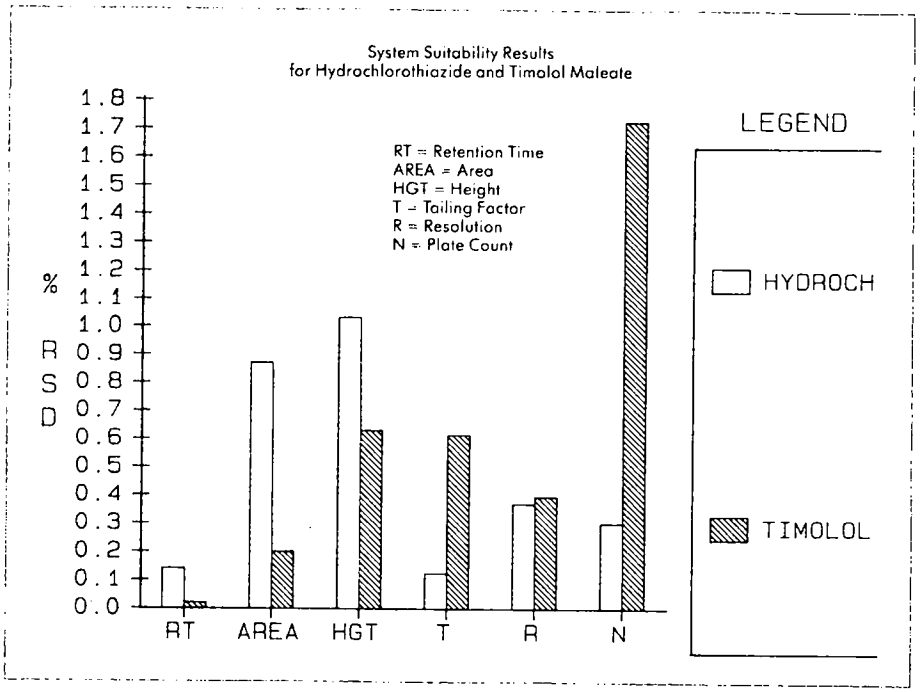
Waters Expert Ease System Suitability software option provides the pharmaceutical chemist with critical HPLC separation data needed to validate chromatographic system performance. The software calculates plate count, resolution, and tailing factors, determines percent relative standard deviation for retention time, area, height, plate count, resolution and tailing factors for single vials or entire multi-methods.

Waters Custom Convert manager transfers summary reports into third party software formats (RS-1, Lotus 1-2-3, 20/20 and ASCII) for further statistical analysis and graphic presentations as shown in Figure 3.



Through advanced communication protocols, the Waters 845 Chromatography software provides unlimited methods development options and sophisticated multiple detector control.

Figure 3: Enhanced Graphic Display of System Suitability Results



Analytical results can be converted to a third party software format for enhanced visual displays. In this example, system suitability results from the analysis of a calibration standard containing hydrochlorothiazide and timolol maleate were converted to a format compatible with Access Technology's 20/20 software, and then graphed to demonstrate advanced reporting capabilities of the 845 system.

Waters Extends its Family of Sample Processors

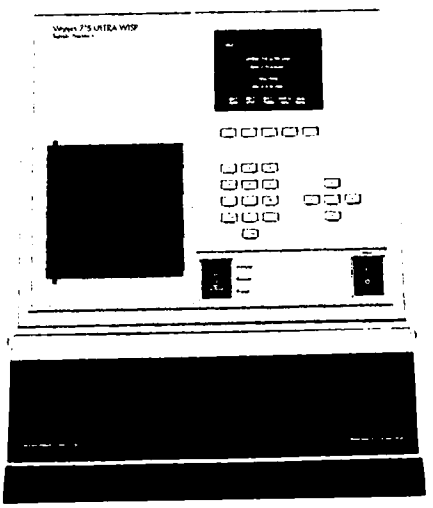
Waters 715 and 1700 WISP Sample Processors for Advanced Sample Handling

Waters has introduced two new products to extend its line of auto injectors, the 715 Ultra WISP and the 1700 WISP Sample Processors. The 715 offers full, flexible programmability with easy-to-use menus and CRT display and an all-electric valve design. It is ideal for applications involving reagent additions and derivatization. It is compatible with automated workstations such as the Millilab™ 1A Sample Preparation Workstation.

The WISP 715 is compatible with Waters PowerLine HPLC system for single keyboard control and documentation of all operating system parameters. In addition, it features an exclusive fluid path design that ensures accuracy and reproducibility for all injector volumes while eliminating cross-contamination and carry-over.

A choice of sample injection volumes, from 1 microliter to 2000 microliters and carousels with either 48 four-milliliter or 96 one-milliliter vials, are available.

The Waters 1700 WISP Sample Processor provides automated sample preparation with Waters Millilab Workstation, plus direct sample injection for on-line HPLC analysis. This innovative system performs filtration, solid phase extraction, liquid-liquid extraction, mixing, addition of internal standards, heating, cooling, evaporation, trace enrichment, plus many other repetitive sample cleanup routines completed unattended.



The CRT in the 715 WISP verifies system status and conveniently programs priority samples as needed without interfering with the run in progress. In addition, system messages and system diagnostic routines make troubleshooting and maintenance easy.

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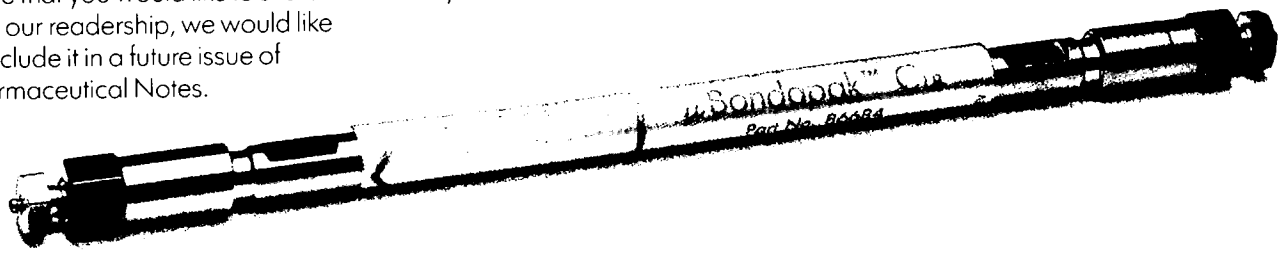

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