95-0695

Uniformity Testing with Integrated HPLC, Results Management, and Control

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Abstract

Tablet processing: content uniformity testing and composite assay of tablets, capsules, patches, and other solid dosages, typically consumes 50% of the time and effort of an analytical testing lab. Labor is spent in dispersing the tablet matrix, accurately weighing and diluting materials for subsequent HPLC analysis. Sample prep coupled with the need for a complete audit trail for GMP/GLP compliance make content uniformity testing a cumbersome step in production. The Waters Tablet Processing System (WTPS) automates the time-consuming steps. WTPS prepares samples, performs HPLC analysis, and publishes test reports with validated instrumentation, hardware and software assuring GLP/GMP compliance by linking sample prep and analytical testing data in a relational database. Advanced detection options, such as photodiode array detection provide qualitative compound identification, peak purity, and assist methods development.

Introduction

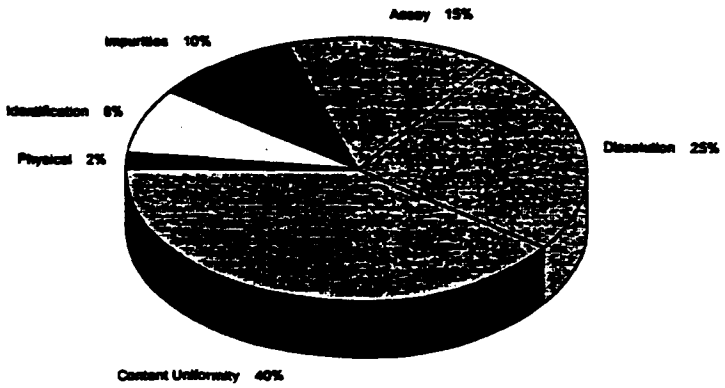
- Content uniformity and composite assay testing are labor intensive analytical tests required for release of solid dosage forms by the pharmaceutical industry. The repetitive nature of this testing along with the requirement for accuracy, precision, and complete documentation make automation essential.

- Frequently laboratory records are required for review during on-site regulatory inspections or in the course of laboratory investigations. The use of a relational database, where all sample prep and analytical results are stored, can permit tracking and trending of product quality. A full data reduction and report publishing function remove the need for third-party applications that may require data transfer on floppy disks.

- The use of a fully automated analysis platform for routine tablet processing can relieve the need for comprehensive training of laboratory personnel. This can be of benefit to those facilities with temporary or contract employees.

Analytical Testing

Time & Effort

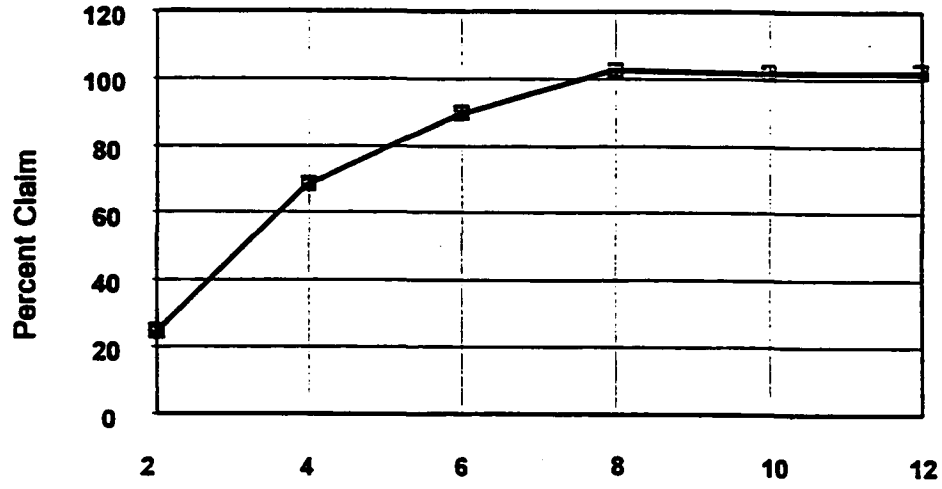


Sample Prep Method: Tab_Uniformity

	Event	Directive	Parameters
1	TRANSFER	CONTAINER	{STUBE150,SRACK30,BAL,LFA}
2	BFPMP	INITIAL	{H2O/MEOH,100,F}
3	TRANSFER	CONTAINER	{STUBE150,BAL,EXTRACTOR}
4	EXTRACT	SAMPLE	{0,8,8,8,0}
5	TRANSFER	CONTAINER	{STUBE150,EXTRACTOR,CANNULAS,W}
6	TRANSFER	CONTAINER	{DTUBE150,DRACK30,BAL,LFB}
7	BFPMP	TRANSFER	{ALIQUOT,5}
8	BFPMP	FINAL	{MOBILE_PHASE,95,F}
9	TRANSFER	CONTAINER	{STUBE150,CANNULAS,SRACK30,UFA,W}
10	TRANSFER	CONTAINER	{DTUBE150,BAL,CANNULAS}
11	MIX	SAMPLE	{0,8,8,8,0}
12	FLLC	SAMPLE	{DTube}
13	TRANSFER	CONTAINER	{DTUBE150,CANNULAS,DRACK30,UFB,W}

e.g.: step 2 directs the balance feedback pump (BFPMP) to dispense the initial solvent for extraction (100mL of a water/methanol mix)

Extraction Profile, Acetaminophen



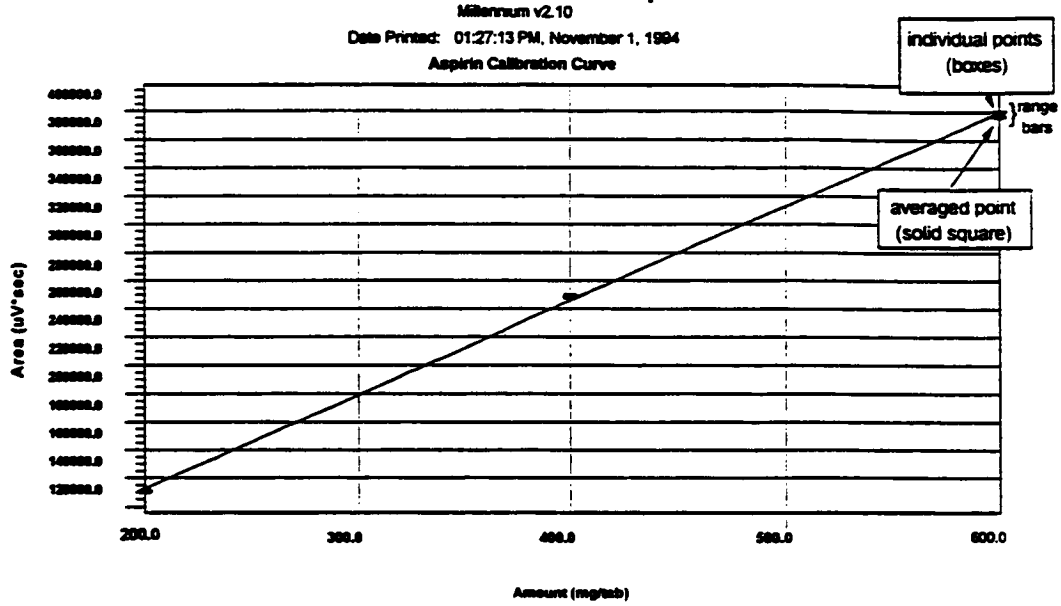
optimize efficiency and validate equivalency to the manual extraction technique

Full Calibration Report

Millennium v2.10

Date Printed: 01:27:13 PM, November 1, 1994

Aspirin Calibration Curve



Interpret calibration graphically...

Aspirin Calibration Information

Processing Method	Prealiquh_TriActive	System	960System
Channel	SATIN	Date	01-NOV-94
Type	LC	Name	Asp
Retention Time	5.540 min	Order	1
A	-1529.800000	B	3343813.750000

Was any data removed from the curve fit?

Residuals about the regression

Aspirin Point Table

#	Level	Amount	Response	Calc. Amount	% Deviation	Manual	Ignore?
1	Low	200.00	130953.398438	198.10	0.958	No	No
2	Low	200.00	131005.000000	198.18	0.919	No	No
3	Med	400.00	268420.812500	403.65	-0.906	No	No
4	Med	400.00	268504.000000	403.78	-0.936	No	No
5	High	600.00	397059.000000	596.01	0.670	No	No
6	High	600.00	399909.593750	600.27	-0.045	No	No

Aspirin Average Table

Was data altered?

average within a level

#	Level	Average Amount	Average Response	Calc. Amount	% Deviation	Standard Deviation	Repetitions
1	Low	200.00	130979.199219	198.14	0.938	36.487815	2
2	Med	400.00	268462.406250	403.72	-0.921	58.822445	2
3	High	600.00	398484.296875	598.14	0.358	2015.674171	2

...or in tabular form

Print Edit

Equilibrate	Equil_for_Tabs	5.00				
Inject Standards	RunTabs	15.00	AssayTabs	2	20
Inject Samples	RunTabs	15.00	AssayTabs	1	20
Inject Samples	RunTabs	15.00	AssayTabs	1	20
Inject Samples	RunTabs	15.00	AssayTabs	1	20
Calibrate	ProcessTabs				
Quantitate	ProcessTabs				
Report	SummaryReport				
Condition Column	Change_to_Caps	17.00			
Inject Standards	RunCaps	22.00	AssayCaps	2	20
Inject Samples	RunCaps	22.00	AssayCaps	1	20
Inject Samples	RunCaps	22.00	AssayCaps	1	20
Inject Samples	RunCaps	22.00	AssayCaps	1	20
Calibrate	ProcessCaps				
Quantitate	ProcessCaps				
Report	SummaryReport				

Set LC method , run time, and prep method for one product...

then change over, unattended, to run another product...

Increase productivity by analyzing more than one sample type in a single run.

Millennium Summary Report

Waters Tablet Processing System
Result Summary Table for Generic Acetaminophen

Page: 1 of 1

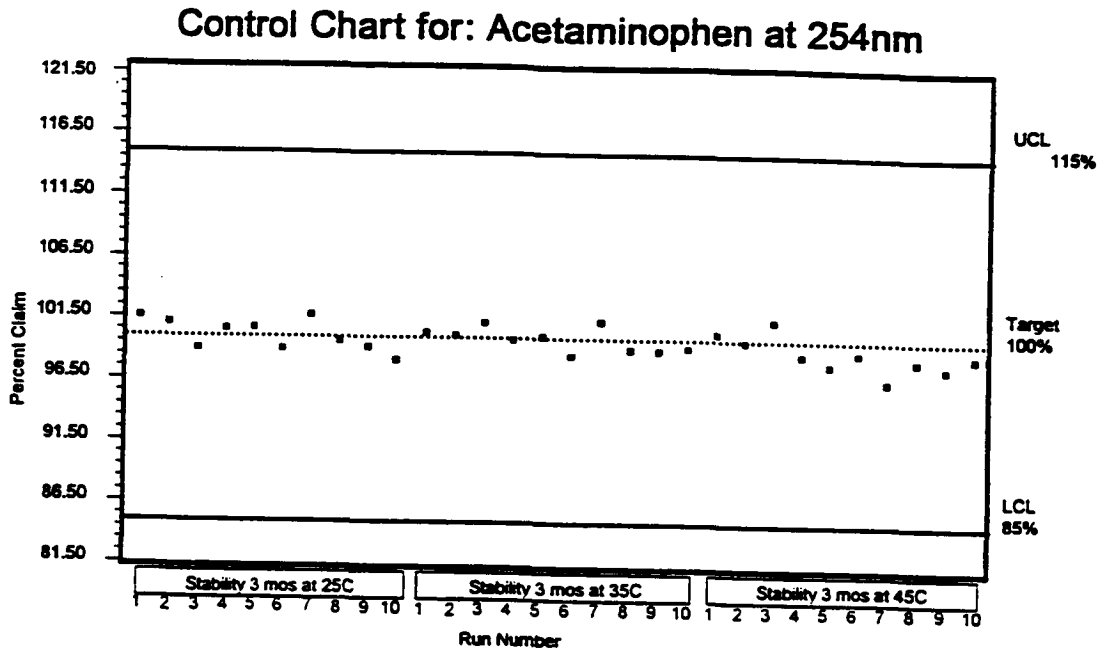
LotCode: 3H06A
Project Name: AmtsTabs
Printed: October 31, 1994
Username: Rick E.

#	SampleName	Vial	Inj	Name	RT (min)	Area (uV*sec)	Amt (mg/tab)	Percent_Claim
1	3mo_45C_01	24	1	Acetaminophen	2.403	4637910	313.059	96.326
2	3mo_45C_02	25	1	Acetaminophen	2.403	4669552	315.069	96.944
3	3mo_45C_03	26	1	Acetaminophen	2.403	4590467	309.547	95.245
4	3mo_45C_04	27	1	Acetaminophen	2.403	4728782	318.491	97.997
5	3mo_45C_05	28	1	Acetaminophen	2.403	4749926	321.005	98.771
6	3mo_45C_06	29	1	Acetaminophen	2.407	4699522	317.916	97.820
7	3mo_45C_07	30	1	Acetaminophen	2.407	4815339	325.231	100.071
8	3mo_45C_08	31	1	Acetaminophen	2.407	4745110	319.783	98.395
9	3mo_45C_09	32	1	Acetaminophen	2.407	4777477	321.577	98.947
10	3mo_45C_10	33	1	Acetaminophen	2.407	4700567	318.621	98.037

-- Peak Results Summary --

Batch statistics for both HPLC performance and product claim...

RT Min:	2.403
RT Max:	2.407
RT Average:	2.405 +/- 0.0021
RT %RSD:	0.088
Area Min:	4590467
Area Max:	4815339
Area Average:	4711465 +/- 66772.8
Area %RSD:	1.417
Amt (mg/tab) Min:	309.547
Amt (mg/tab) Max:	325.231
Amt (mg/tab) Average:	318.030 +/- 4.5015
Amt (mg/tab) %RSD:	1.415
Percent_Claim Min:	95.245
Percent_Claim Max:	100.071
Percent_Claim Average:	97.855 +/- 1.3852
Percent_Claim %RSD:	1.416

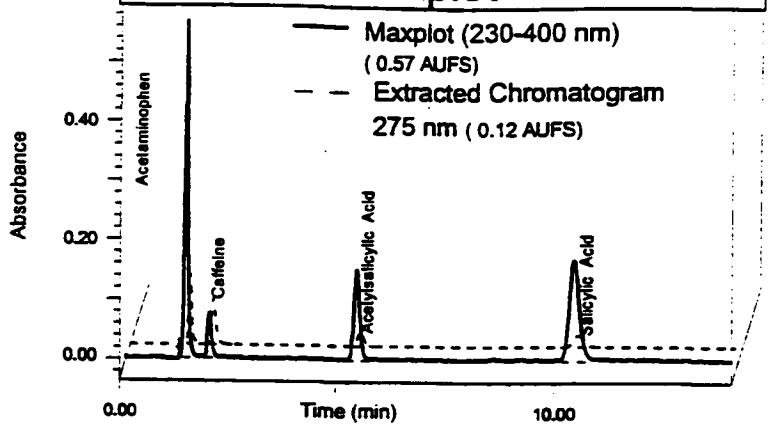


Plot product trends vs time or storage condition

Use of Photodiode Array Detection

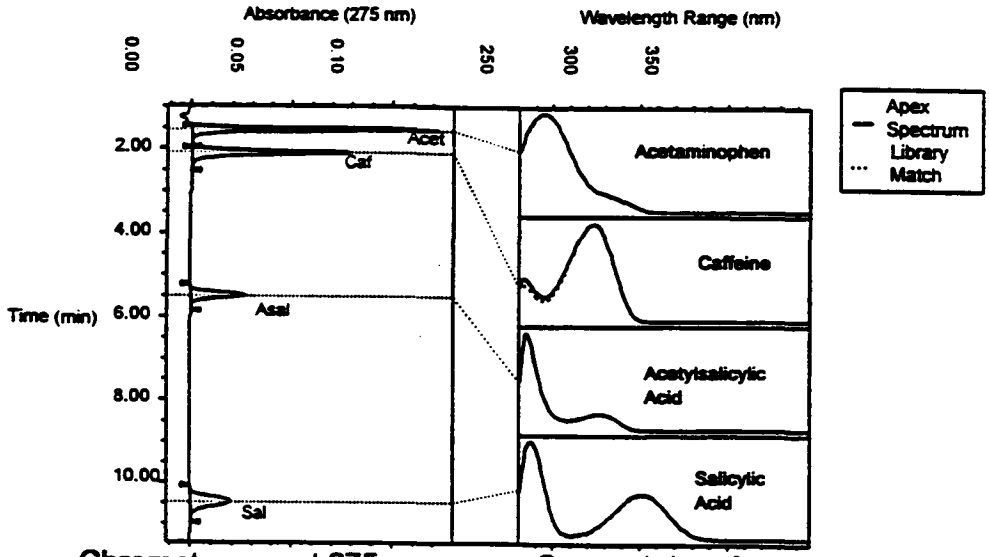
Peak Purity Analysis
and
Spectral Matching

Increased Signal-to-Noise Ratio with Maxplot



Not all active ingredients have the same maximum absorbency. When examining a single wavelength chromatogram, active ingredients may appear as small components of the mixture. A maxplot chromatogram plots each compound at its maximum absorbance wavelength. With this we can better quantify all the active ingredients and detect unknown peaks that may be impurities. To demonstrate this, we have displayed a chromatogram extracted at 275 nm (dashed line). To this we have added a maxplot in the 230 nm to 400 nm range (solid line). One peak, caffeine, has equivalent absorbency in the maxplot and at 275 nm; however, the other three components have increased absorbency in the maxplot.

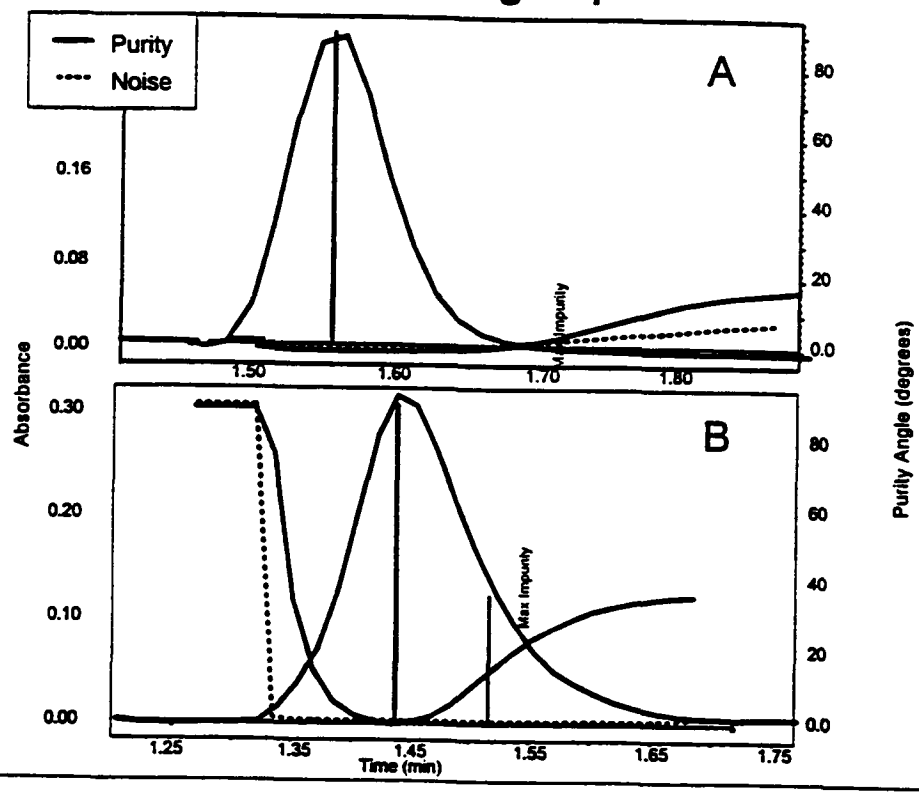
Spectrum Index Plot for Triactive Drug with Aspirin Degradation Product: Standards



Chromatogram at 275 nm Spectral data from 230-400nm

Spectrum Index Plot correlates the single wavelength data of a chromatogram at 275 nm with full spectral data from each standard component (—) along with the Library Match Spectrum for each component (·····).

Symmetrical Chromatographic Peaks may have Co-Eluting Impurities



A. Isocratic elution of Acetaminophen on L1 (methanol:water:acetic acid, 72:25:3). In this mobile phase, acetaminophen is well resolved from caffeine (see Maxplot). Additional assurance of product purity can be derived from spectral data. Software-driven spectral contrast algorithms compare spectra within the peak to determine sites of spectral inhomogeneity where impurities may reside. These data can be reported in a Purity Plot (above) or tabulated as a Purity Angle (below). As shown above (A), for the acetaminophen peak, the purity trace does not exceed the noise trace throughout the boundary of the peak, an indication of peak purity. This plot combined with tabulated data reporting Purity Angle with the absence of Purity Flag indicate that Peak Purity is within established confidence limits.

Purity Pass	Purity Angle	Purity Flag	RT for Max Impurity
1	0.544		1.700

B. Isocratic elution of Acetaminophen, co-elution with Caffeine, on L1. By increasing the concentration of methanol, acetaminophen now co-elutes with caffeine. This is not apparent from the symmetrical peak shape (B). However, by comparing the spectra within the peak, we can see that significant spectral inhomogeneity exists where the purity trace exceeds the noise trace. This is further supported by the high Purity Angle and Purity Flag reported in the table below.

Purity Pass	Purity Angle	Purity Flag	RT for Max Impurity
1	9.861	*	1.518

Conclusion

- Fully automated system for the analysis of solid dosage forms
- Single keyboard control and documentation of the entire process
- Easy to use Windows user interface
- Relational database for product tracking and trending
- Spectral Data from Photodiode Array Detection can be used for purity assessment, library matching, and trace analysis