PHARMACEUTICAL Application Briefs

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AUTOMATED DISSOLUTION TESTING WITH ION CHROMATOGRAPHIC ANALYSIS OF POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS

Introduction

Dissolution testing of solid dosage forms of drugs- tablets, capsules or caplets- is required by the US Food and Drug Administration as specified in the US Pharmacopeia (USP) and other pharmacopeias (British, European, etc.).

Many dissolution methods permit drug concentrations to be measured by direct UV absorbance. However, on-line UV detection will not work for non-UV active substances including inorganic ions such as potassium. Flexibility in system configuration is a major criterion for today's dissolution testing systems.

Total system automation simplifies dissolution testing and offers four distinct advantages: 1) Precise timing of sample removal from six vessels simultaneously; 2) Concurrent analysis of samples and standards by the HPLC during the dissolution study; 3) Elimination of the lag time between manual sample collection and analysis; and 4) Easy sample data reduction calculations and graphic presentation.

For extended release tablet regulations, sample collection may extend over a 12 or 24 hour period requiring numerous analyses. The manual withdrawal of samples and calculations required to produce dissolution profiles are time consuming and can lead to variability or errors.

Complete automation of the dissolution testing for inorganic ions is now possible as exemplified with Waters automated dissolution testing of potassium chloride. Samples are transferred directly from the dissolution bath to the Waters HPLC system followed by analysis using ion chromatography and conductivity detection and data reduction.

Instrumentation and Methods

Instrumentation - A Hanson SR2 dissolution bath with Validata and Hanson transfer module (Hanson Research Corp., Chatsworth, CA) was linked to a Waters Automated Dissolution System consisting of a 600E Powerline™ solvent delivery system, a Waters 712D autosampler and a Waters 431 conductivity detector. In addition to the HPLC injection mechanism, the 712D contains a multiple port injector to directly introduce dissolution samples into six sample vials simultaneously, eliminating the need to manually transfer samples. Data was collected and processed on a Waters 860 Networking Computer System.

The 600E controller coordinates dissolution start, sampling times, and analysis sequence. The 600E controller also controls the HPLC analysis conditions including: flow rate, column temperature, injection volume, sample processing sequence, and detector settings (Figure 1). With the Waters Automated Dissolution System, the HPLC analyses occurs concurrently with the dissolution testing maximizing laboratory throughput.

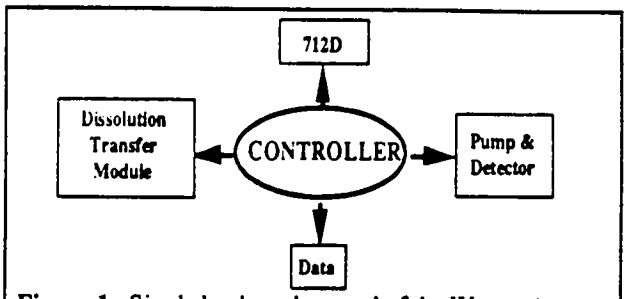

Figure 1: Single keyboard control of the Waters Automated Dissolution System is centralized in the 600E controller.

Dissolution sampling times receive the highest priority, and the system automatically ensures samples will be collected on time over the 20 hour testing interval. This eliminates the need to stagger dissolution starting times to ensure proper sampling sequences.

Analysis and Data Reduction Method - Potassium was analyzed using Method C-202 of the Waters Innovative Methods for Ion Analysis. Only 10 µl sample volumes were required for each analysis.

Dissolution data reduction requires three steps: 1) Analyze the standard results with System Suitability software to ensure the suitability of the HPLC system; 2) Quantitate potassium for each dissolution sample and calculate the mEq/ml in the dissolution medium; and 3) Calculate the relevant statistics with the post-run dissolution software and plot the dissolution profiles.

Results

Method validation and system suitability - The HPLC method for potassium was validated to comply with GLP requirements. Linearity of the assay was determined over the potassium concentration range of 50 to 600 ppm, 1.3 to 15.3 mEq/L. The correlation coefficient was 0 998.

The system suitability software automatically calculated the mean, standard deviation and %RSD for peak area, retention time and tailing factor. Six standard injections were tested at the beginning of the dissolution test and six standards were spaced throughout the 20-hour dissolution test (Table 1). System suitability trend data can also be graphically represented to easily review system's performance throughout the test.

Dissolution test results - No sample preparation is required for the analysis of the potassium ion by ion exchange chromatography (Waters Method C-202). Figure 2a is an example of a 12.8 mEq standard chromatogram of potassium. Under these analytical conditions, the potassium peak is well resolved from any tablet excipients (Figure 2b). or other inorganic ions including lithium and sodium (Figure 2c).

With the Waters dissolution software, the calculated concentrations for each sample, at each time point, is automatically calculated as a percent release of the drug's label claim (10 mEq). The required statistics, maximum and minimum values, mean, standard deviation and %RSD, are also calculated; and then presented in both a tabular (Table 2) and graphic form (Figure 3).

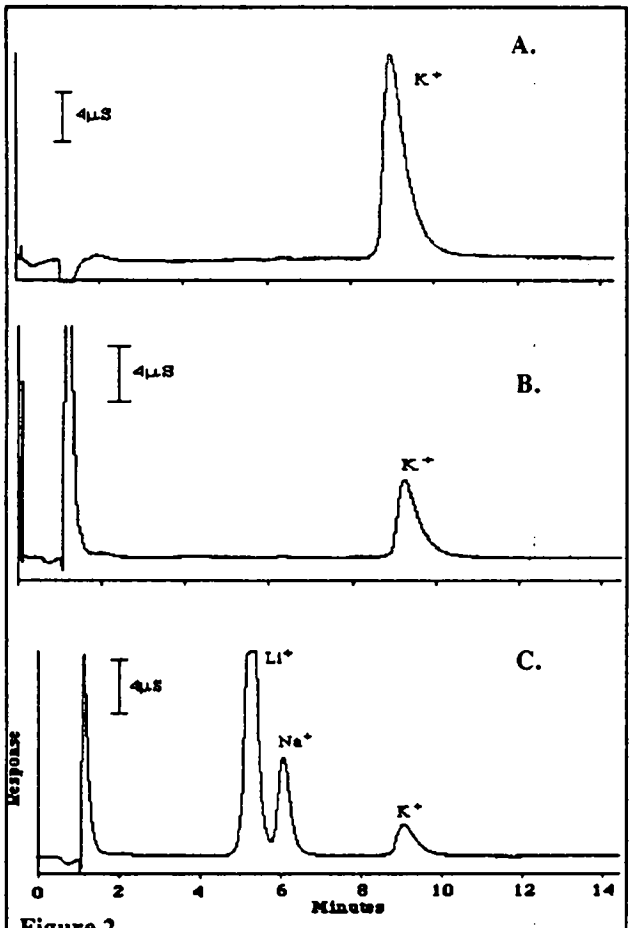

Figure 2

a: Chromatogram of KCl Standard, 12.8 mEq/L (500 ppm) b: There are no interferences from the tablet matrix of the KCl tablet after 2 hours dissolution. c: Chromatogram of lithium, sodium, and potassium standards shows that other inorganic ions do not interfere with quantitating potassium.

Table 1: System Suitability Results for the Six Potassium Standards before the Dissolution Test

Name	Statistic	Ret. Time	Area	Height	Tailing
KCl Standard	Mean	8.98	674510	17388	2.15
for system	Std. Dev.	0.01	9708	284	0.02
suitability	% RSD	0.14	1.39	1.64	1.06

Table 2: Dissolution Test Results - Summary Statistics

Time	Max	Min	Mean	SDev	%RSD
30	11.6	8.2	10.1	1.3	13.1
60	20.5	16.8	18.8	1.5	8.3
120	37.3	32.2	35.2	1.8	5.2
240	64.0	58.1	62.4	2.2	3.6
480	95.8	90.1	92.6	1.9	2.1
840	100.8	93.0	96.7	2.8	2.9
1200	101.1	93.7	97.8	3.3	3.4

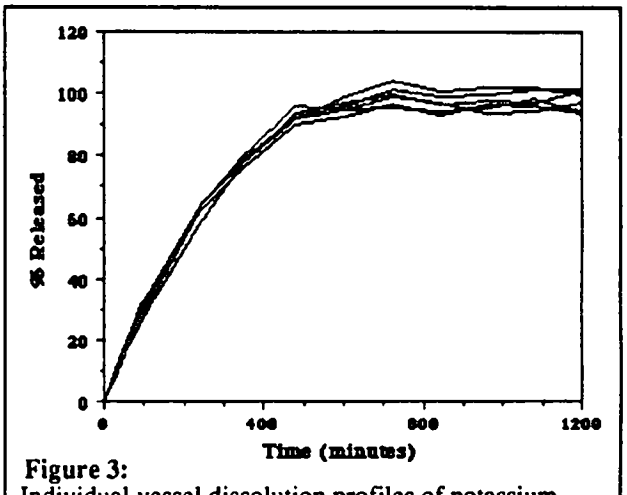

Figure 3:
Individual vessel dissolution profiles of potassium released over 20 hours.

Conclusions

Dissolution testing on potassium chloride tablets or other inorganic ions is easily automated with Waters Automated Dissolution System configured as an ion chromatograph with a conductivity detector. With Waters data station, it is possible to collect and analyze the data for the percent of potassium released at each time point during the dissolution test.

Automating this test minimized labor, increased laboratory productivity, and reduced data transcription errors.

The Waters Automated Dissolution System offers the analyst flexibility to use UV absorbance, refractive index (RI) or conductivity detection mode, permitting the optimization of the dissolution testing.