SHIMADZU

A novel automated 2D-LCMS-IT-TOF system compatible with non-volatile salts applied to accelerating impurity ID workflow in chemistry, manufacturing and controls

ASMS 2011 MP119

Ichiro Hirano, Yusuke Inohana, Tairo Ogura, Yoshikatsu Umemura, Hiroyuki Yasuda, Yoshihiro Hayakawa SHIMADZU CORPORATION, Nishinokyo-kuwabaracho, Nakagyo-ku, Kyoto 604-8511, Japan

SHIMADZU

A novel automated 2D-LCMS-IT-TOF system compatible with non-volatile salts applied to accelerating impurity ID workflow in chemistry, manufacturing and controls

Introduction

Chemistry, manufacturing, and controls (CMC) information is required to support the approval of an abbreviated new drug application (ANDA). It allows reviewers to assess critical formulation and manufacturing process variables and identify potential risks involved with the design and manufacturing of the product. Due to the globalization of supply chain and associated regulatory issues, the requirement for impurity profiling and identification has dramatically increased. However, impurity profiling and identification is often based on optimized separations developed with non-volatile-salt and ion-pair reagents. Transferring methods to volatile buffer separations amenable for MS detection is labor-intensive and risks missing impurities. To automate non-volatile based impurity analysis a 2D-LCMS-IT-TOF has been developed and applied to the separation of sulfa drugs using phosphate buffers.

Methods

Co-Sense for LC/MS system in collaboration with Eisai Pharmaceuticals, Japan in 2000. The premise of the system design is to collect components separated by non-volatile-salt and ion-pair reagents as individual fractions, trap/desalt and concentrate and transfer to a 2D volatile buffer based separation for LC/MS analysis. Whilst this design is highly successful and robust there is a need for the trap column conditions to be optimized for new product and by-product chemistries.

In this design, the trap column has been removed from the Co-sense system, and a UV detector has been added to the second-dimension HPLC flow path. The addition of the UV detector to the second dimension HPLC greatly facilitates the detection of impurities. In an actual workflow, both impurity data and corresponding blank data are acquired, and the impurity peaks are identified through comparison of the respective chromatograms.

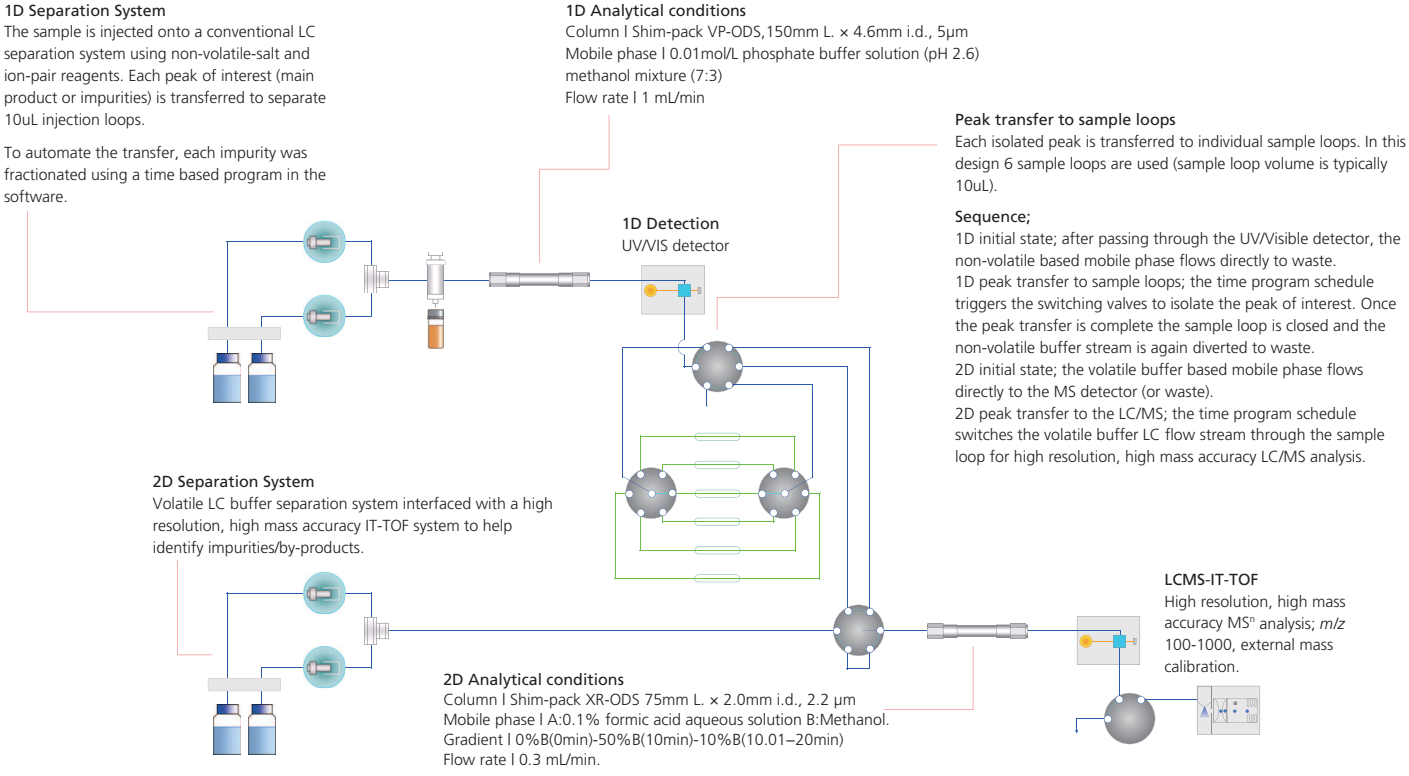


Figure 1.
Components separated by a 1D non-volatile or ion-pair reagent are isolated and transferred to individual sample loops using a series of switching valves controlled by a software application. Isolated peaks in the sample loops are transferred to a volatile buffer system for high mass accuracy LC/MS analysis.

A novel automated 2D-LCMS-IT-TOF system compatible with non-volatile salts applied to accelerating impurity ID workflow in chemistry, manufacturing and controls

Phosphate buffer analysis

A mixture of 5 different sulfa drugs (Sulfadimethoxine, Sulfamerazine, Sulfadimidine, Sulfamonomethoxine and Sulfaquinoxaline) was used as a test model. Sulfadimethoxine was selected as main API compound and prepared at a concentration of 500 ug/mL. The remaining sulfa drugs were prepared at a concentration corresponding to 0.1% of the main API compound Sulfadimethoxine.

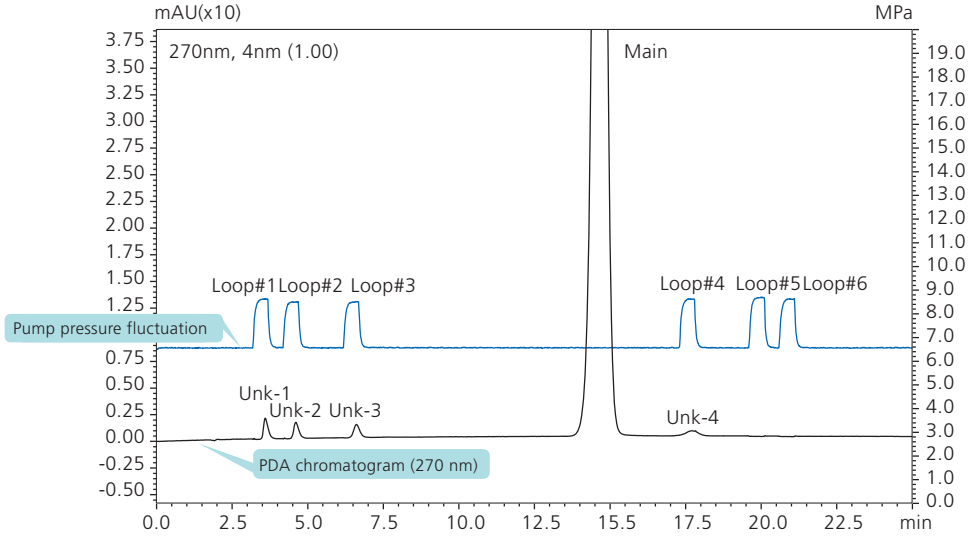
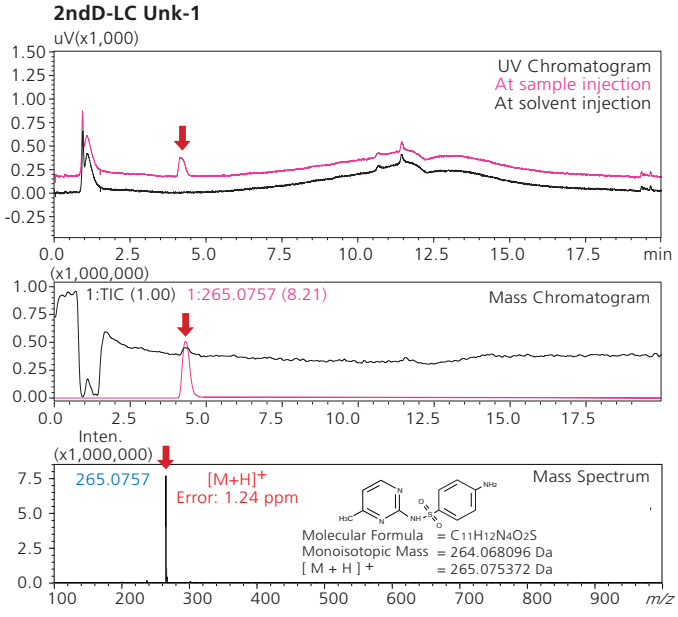
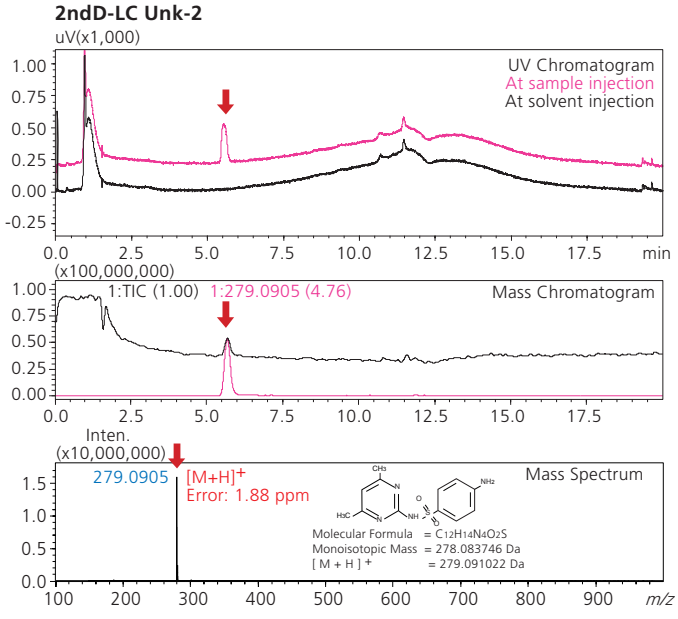


Figure 2.
1D separation was applied with a conventional 0.01mol/L phosphate buffer (pH2.6) / MeOH (7:3) at a flow rate of 1 mL/min. To automate the transfer, each impurity was fractionated using a time based program. Each impurity was subsequently identified using a 2D volatile buffer separation and high mass accuracy MS^n data analysis and formula prediction software (LCMS-IT-TOF, Shimadzu Corporation, Japan).





SHIMADZU

A novel automated 2D-LCMS-IT-TOF system compatible with non-volatile salts applied to accelerating impurity ID workflow in chemistry, manufacturing and controls

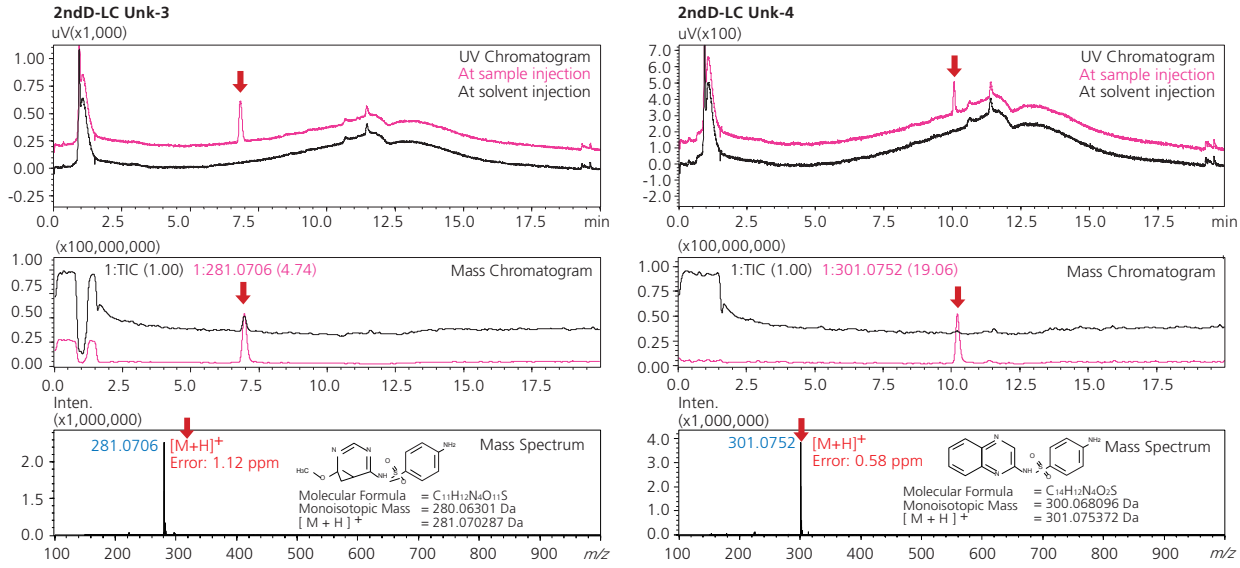
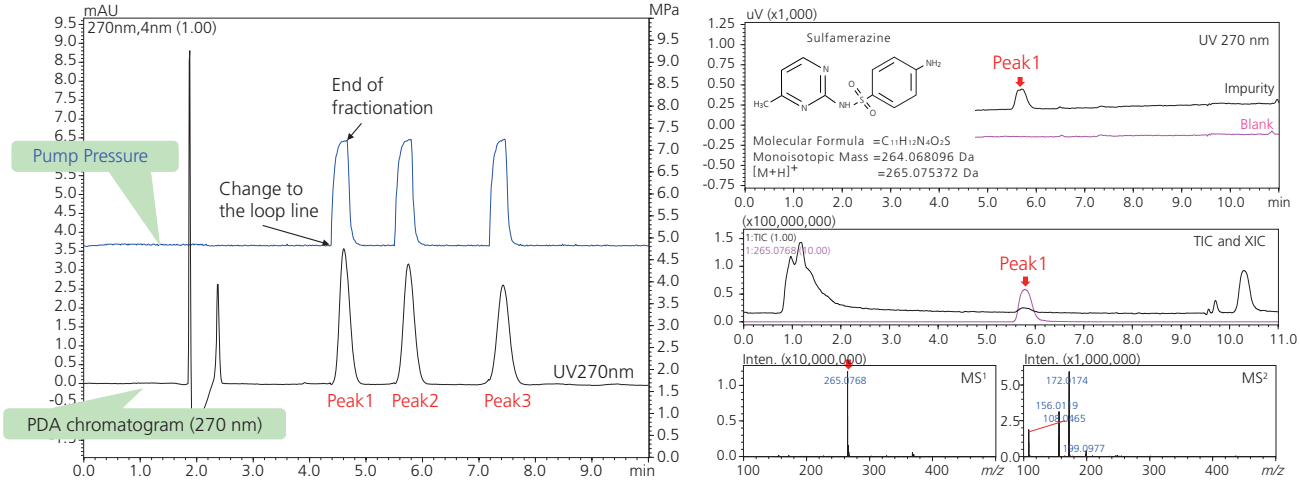


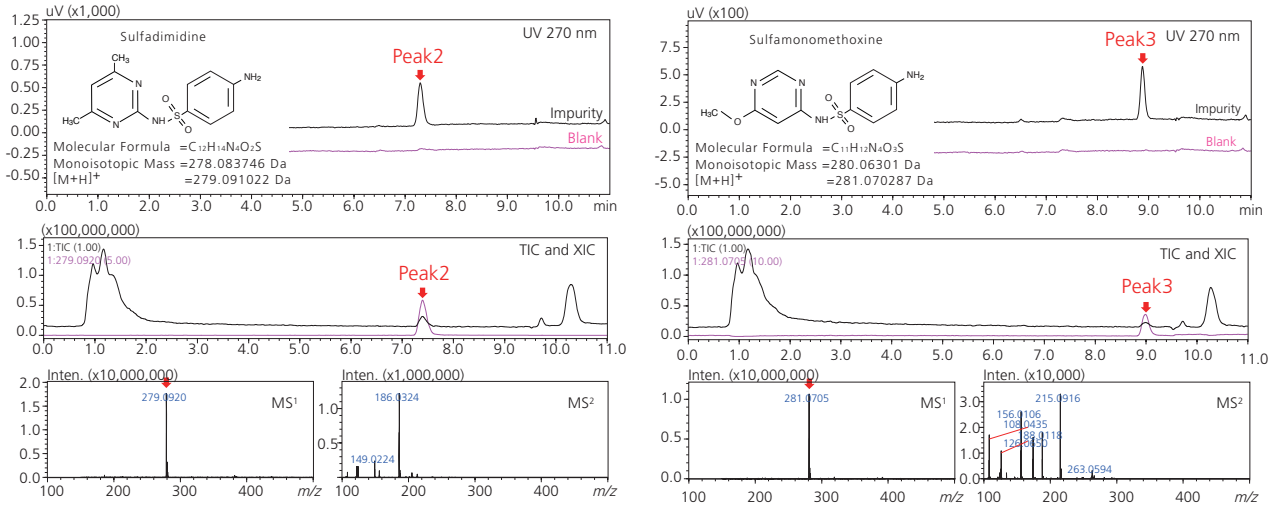
Figure 3.
Components separated in a 1D phosphate buffer mobile phase determined by 2D high mass accuracy LCMS-IT-TOF.

Ion Pair reagent analysis

The ion-pair chromatography (Shim-pack VP-ODS; 20mol/L KH2PO4 / 5mmol/L 1-heptane sulfonic acid sodium salt / ultra pure water (pH3.0) : ACN = 80 : 20) at 1 mL/min flow rate was applied to a 1D separation using three sulfa drugs (Sulfamerazine, Sulfadimidine and Sulfamonomethoxine) which were prepared as the mimic impurities. The concentration of three compounds was 0.1% against main compound (1000 ug/mL). 2D analysis was achieved using a Shim-Pack XR-ODS and a formic acid solution:acetonitrile mobile phase.



A novel automated 2D-LCMS-IT-TOF system compatible with non-volatile salts applied to accelerating impurity ID workflow in chemistry, manufacturing and controls



As opposed to the phosphate buffer results, the ion-pair regent is usually highly retained on the 2D analytical column compared to the target impurities, however, it can be easily elimination using a divert valve. Completely cleaning the 2D column requires a further column washing step (this is simply inserted on the time program). It is also important to note that the loop volume in ion-pair chromatography should be less than 10 uL as the loop volume affects the separation between impurity and ion-pair regent.

Conclusions

2D LC-IT-TOF system accelerates method transfer to high mass accuracy MS analysis and can be a key technology in impurity analysis.

- Supports non-volatile LC separations developed as part of standard test methods.
- Simplifies impurity detection by comparing UV chromatograms.
- Integrated transfer to structure elucidation by accurate mass MS^n measurement and significantly reduced workloads in impurity identification.

Founded in 1875, Shimadzu Corporation, a leader in the development of advanced technologies, has a distinguished history of innovation built on the foundation of contributing to society through science and technology. We maintain a global network of sales, service, technical support and applications centers on six continents, and have established long-term relationships with a host of highly trained distributors located in over 100 countries. For information about Shimadzu, and to contact your local office, please visit our Web site at **www.shimadzu.com**

SHIMADZU

SHIMADZU CORPORATION. International Marketing Division
3. Kanda-Nishikicho 1-chome, Chiyoda-ku, Tokyo 101-8448, Japan
Phone: 81(3)3219-5641 Fax. 81(3)3219-5710
URL http://www.shimadzu.com