
Design and Implementation of a Forced Degradation/Chemical Stress Study Using New LC Column Technology

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Presentation Outline

- Forced Degradation Study Experimental Design Considerations
 - General and Specific Conditions
- Stability Indicating Method
 - Criteria and Development
- Case Study
 - Optimizing Conditions
 - Column Comparisons



Forced Degradation (Chemical Stress) Studies

- Why Do a Forced Degradation Study?
 - Understand the reactive chemistry of the drug substance
 - Help anticipate future stability issues of both drug substance and drug product
 - Provides useful information for formulation and stability
 - May be required for regulatory submissions
- Forced degradation or stress testing is undertaken to demonstrate specificity when developing stability indicating methods
 - Generates a sample for method development, stability support
 - Performed prior to implementation of stability studies

Forced Degradation Experimental Design Considerations

- Drug Substance Vs. Drug Product
 - Chemistry Vs. Packaging

- Single Point in Time Vs. Continuous Monitoring

- Chromatographic Compatibility
 - Solvent
 - Concentration

Example Conditions for Forced Degradation

<u>STUDY</u>	<u>CONDITIONS</u>
Acidic pH	0.1N HCl
Neutral pH	pH 7.0 Phosphate Buffer
Basic pH	0.1N NaOH
Oxidation	O ₂ Atmosphere, or H ₂ O ₂
Photolysis (UV)	1000 Watt h/M2
Photolysis (Fluorescence)	6x10 ⁶ lux h

Goal: Degrade API 5-10%; Stability Indicating Method (SIM)

What is a Stability Indicating Method?

- A Stability Indicating Method (SIM) Is:
 - A **validated** method that can accurately and precisely quantitate the decrease of the API content due to degradation
 - Is specific for the drug substance
 - Shows a decrease in assay value (correlated to drug substance loss) due to degradation
 - Has no interference from excipients, impurities or degradation products
 - Detects and quantitates impurities and degradation products

Why Are Stability Indicating Methods Needed?

- It's good science
- Predominantly to support long term stability testing
 - How the quality of the drug substance or product changes over time in response to environmental factors
 - Temperature
 - Humidity
 - Light
 - Establishes storage and packaging conditions
- It's the law
 - CFR Title 21, Section 211

When to Use Stability Indicating Methods

- When Are SIMs Needed?
 - Stability Studies
 - API release
 - Drug product release
 - Toxicology dosing solutions
 - Excipient compatibility and pre-formulation
 - Packaging studies
 - Line extensions

- When Are SIMs **Not** Needed?
 - In process controls
 - Secondary assay for API
 - Titration
 - Inorganics

Implementing a Stability Indicating Method



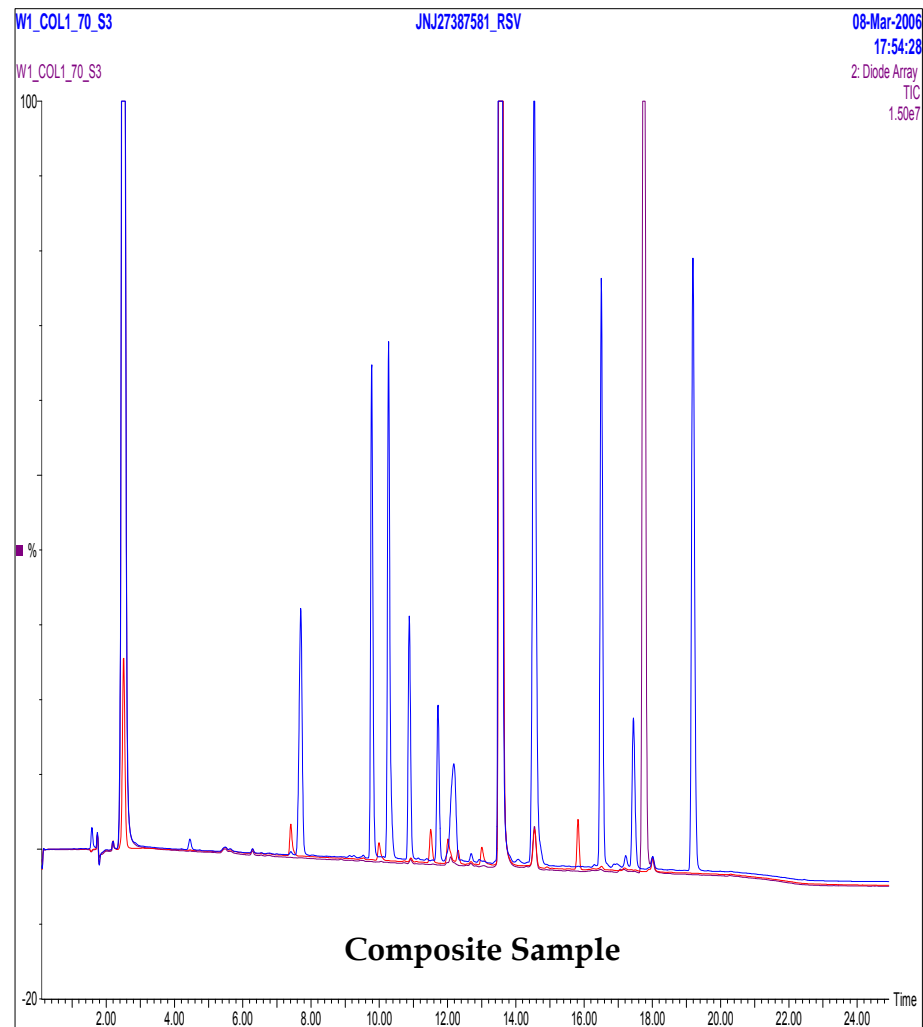
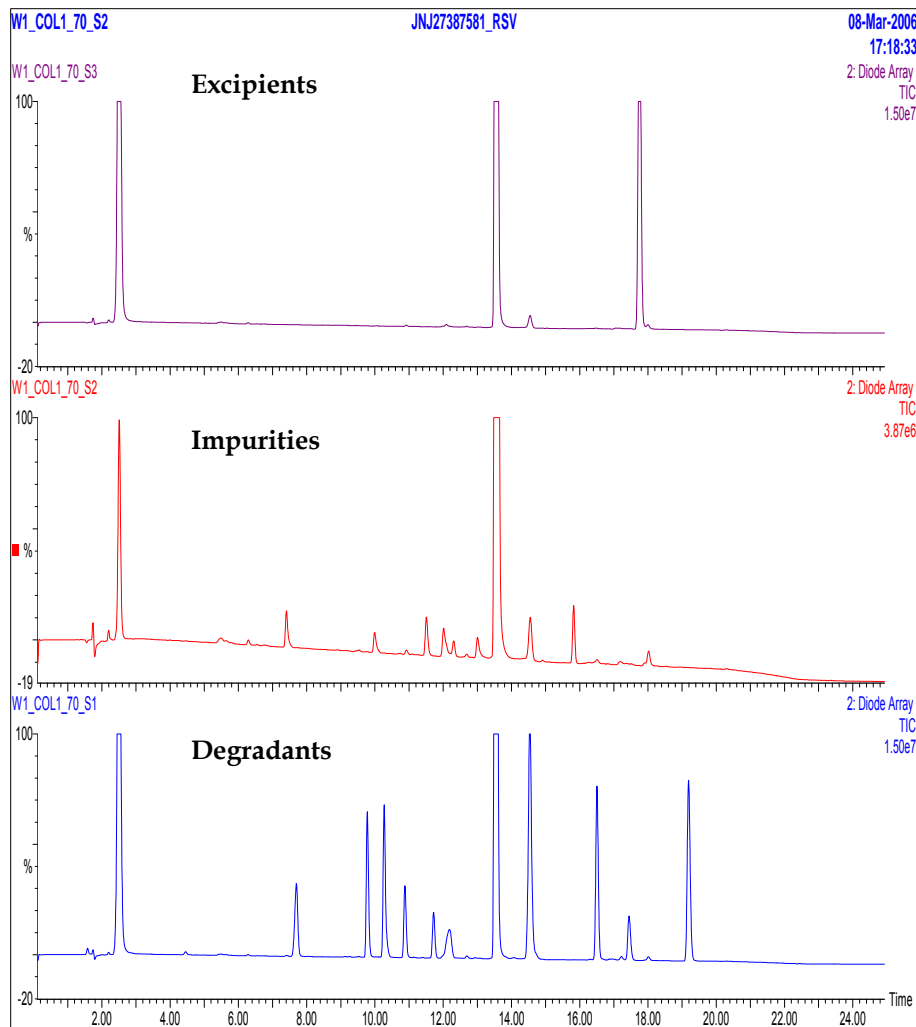
Stability Indicating Methods

Method Development Issues and Challenges

- Same as Method Development in General
 - Additional requirements
 - Resolution
 - UV Sensitivity
 - LOQ
 - Chromatographic speed
 - “Capture” intermediates
 - Column temperature control is critical

SIM Method Development Challenge

Courtesy of
Rudy Sneyers
J&J Belgium



Stability Indicating Method Development

- Manipulate Chromatographic Selectivity
 - Column
 - Mobile phase composition/type
 - pH
 - Temperature
- Specificity
 - PDA or MS

Goal: Baseline Resolution, No Co-elutions

Forced Degradation Case Study

- Simvastatin Drug Substance
- Adapting Typical Forced Degradation Conditions
- Is Method Stability Indicating?
 - New Column Technology
 - Buffer Change for MS Compatibility

Actual Initial Forced Degradation Conditions

Procedure ID	Drug Substance	Reagent #1	Condition	Reagent #2	Diluent	Final Conc.
Drug Substance Control	0.5 mL of 5 mg/mL API Stock Solution	N/A	Immediately diluted to the final concentration	N/A	4.5 mL of Diluent per HPLC Method	0.5 mg/mL
Acidic Solution	0.5 mL of 5 mg/mL API Stock Solution	Add 1.0 mL 0.1N HCl	24 hrs. room temperature	Add 1.0 mL 0.1N NaOH	2.5 mL of Diluent per HPLC Method	0.5 mg/mL
Basic Solution	0.5 mL of 5 mg/mL API Stock Solution	Add 1.0 mL 0.1N NaOH	24 hrs. room temperature	Add 1.0 mL 0.1N HCl	2.5 mL of Diluent per HPLC Method	0.5 mg/mL
Acid/Base Control	NA	Add 1.0 mL 0.1N HCl	NA	Add 1.0 mL 0.1N NaOH	3.0 mL of Diluent per HPLC Method	0.5 mg/mL
Oxidative Solution	0.5 mL of 5 mg/mL API Stock Solution	Add 1.0 mL 3% H ₂ O ₂	24 hrs. room temperature	N/A	3.5 mL of Diluent per HPLC Method	0.5 mg/mL
Oxidative Control	N/A	Add 1.0 mL of 3% H ₂ O ₂	N/A	N/A	4 mL of Diluent per HPLC Method	0.5 mg/mL
Heat	0.5 mL of 5 mg/mL API Stock Solution	N/A	24 hrs at 60°C	N/A	4.5 mL of Diluent per HPLC Method	0.5 mg/mL
Light #1	1.0 mL of 5 mg/mL API Stock Solution	NA	1X ICH Q1B	N/A	9 mL of Diluent per HPLC Method	0.5 mg/mL
Light #2	1.0 mL of 5 mg/mL API Stock Solution	NA	3X ICH Q1B	N/A	9 mL of Diluent per HPLC Method	0.5 mg/mL

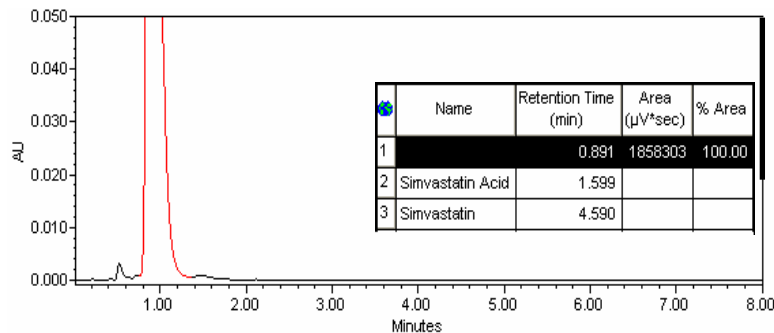
USP HPLC Method Conditions

Waters Alliance HPLC System with a 2996 PDA and a 2487 Variable λ Detector monitoring 238 nm

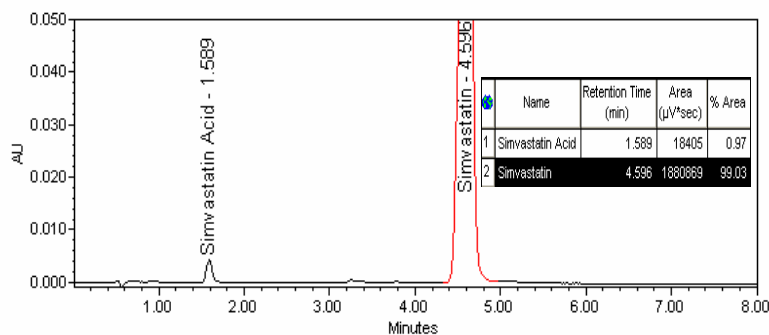
- Column: Waters Xbridge C18, 5 μ m, 4.6 x 250 mm
- 45 °C
- MPA: 15 mM Phosphate pH 4.5
- MPB: ACN
- Flow: 1.5 mL/min
- 40 μ L injection volume



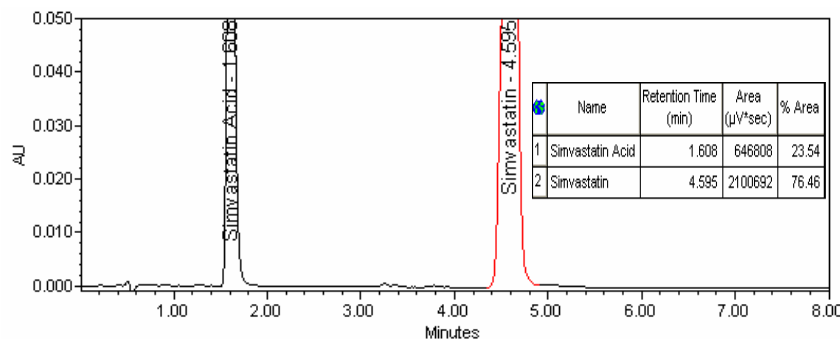
Adapting Typical Forced Degradation Conditions



0.1 N NaOH



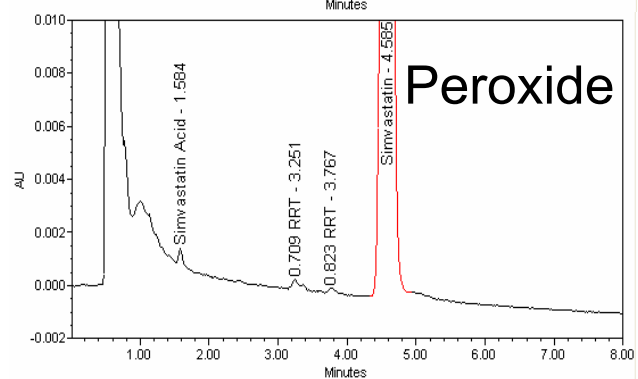
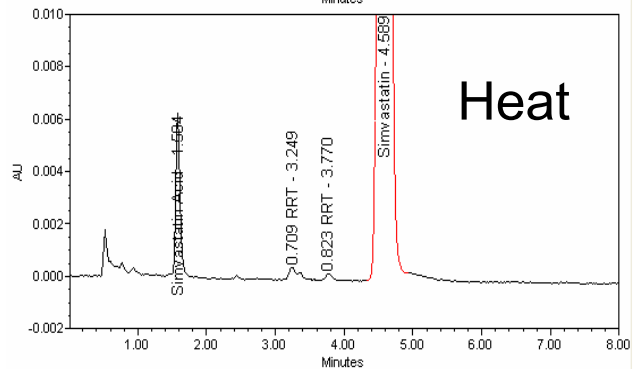
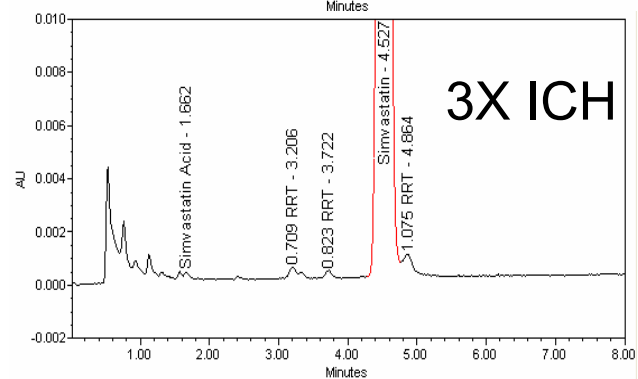
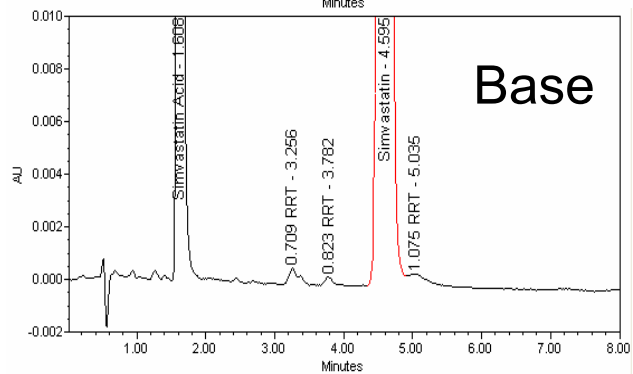
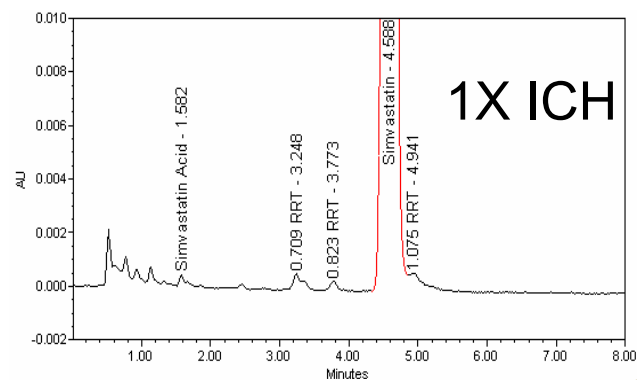
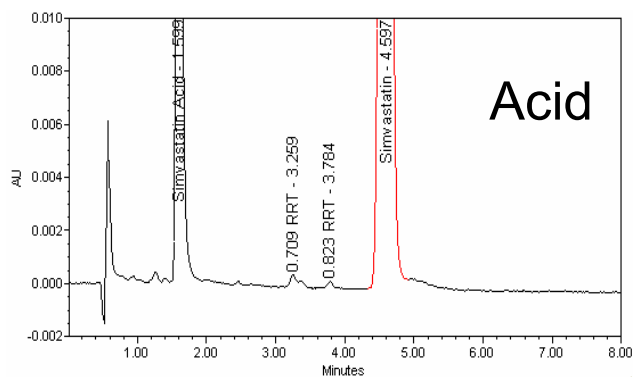
0.015 N NaOH



0.030 N NaOH

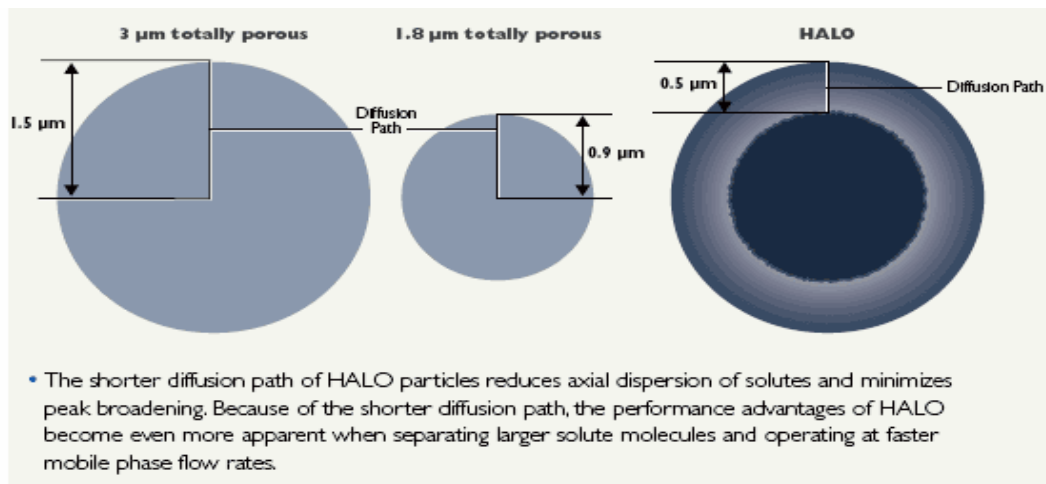
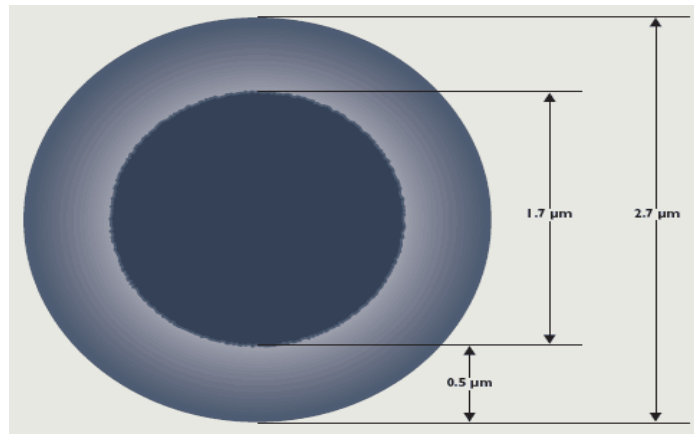
Goal: 5-10%
Degradation

Example Forced Degradation Chromatograms



New Column Technology

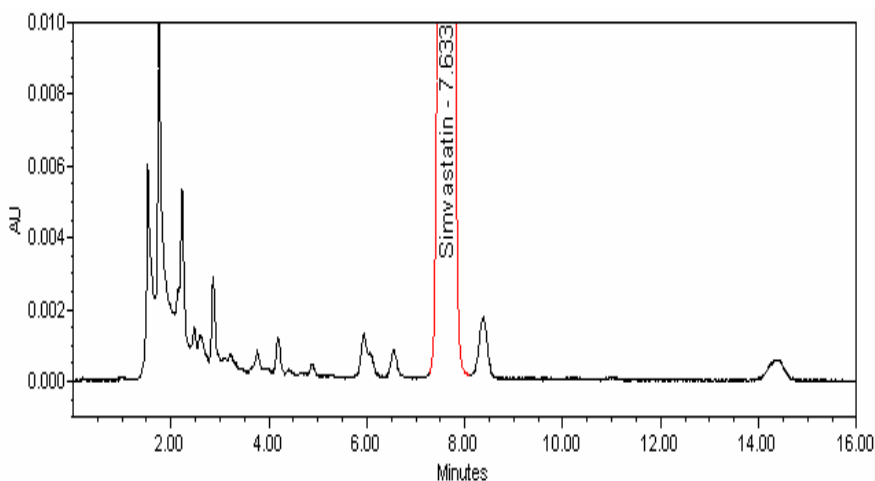
Halo[®] Fused-Core[®] Particles



Figures courtesy of Mac-Mod Analytical Inc.

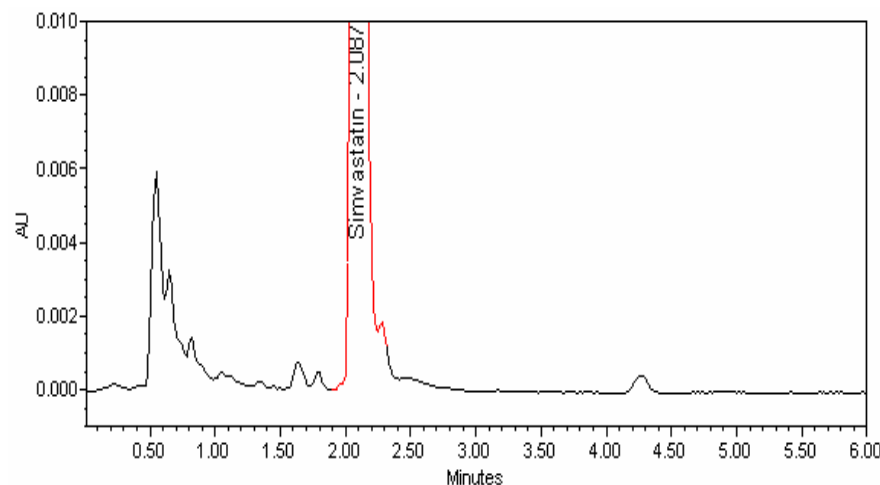
Column Comparison

USP Column



35/65 Phosphate/ACN

Halo Column



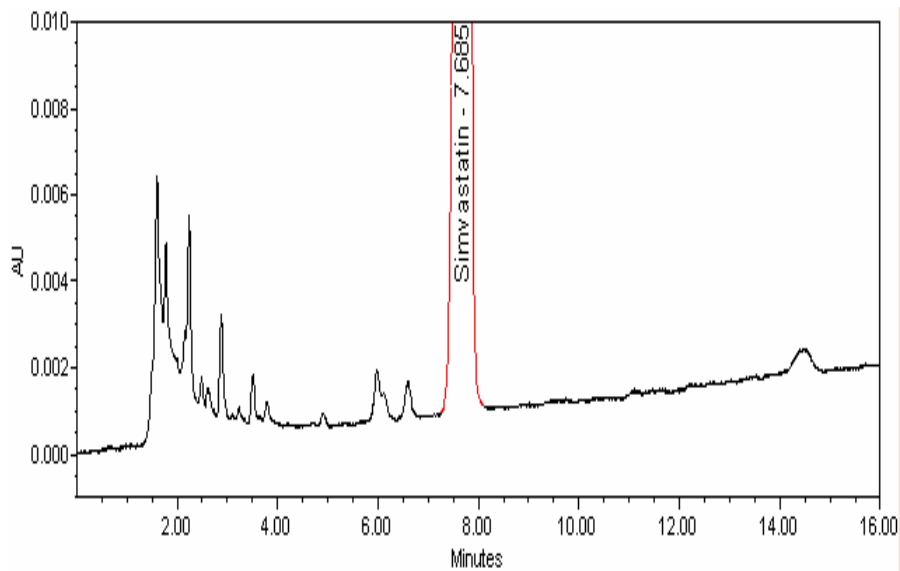
35/65 Phosphate/ACN

Injection Volume scaled from 40 (USP) to 5 μ L (Halo)

Halo column: 3.0 x 75 mm, 0.6 mL/min.

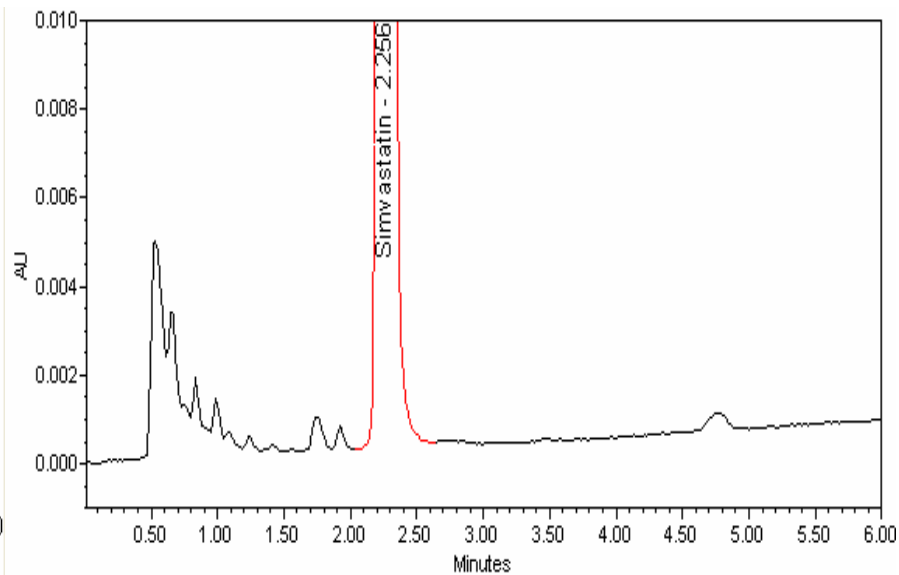
MS Compatible Buffer Stability Indicating?

USP Column



35/65 Acetate/ACN

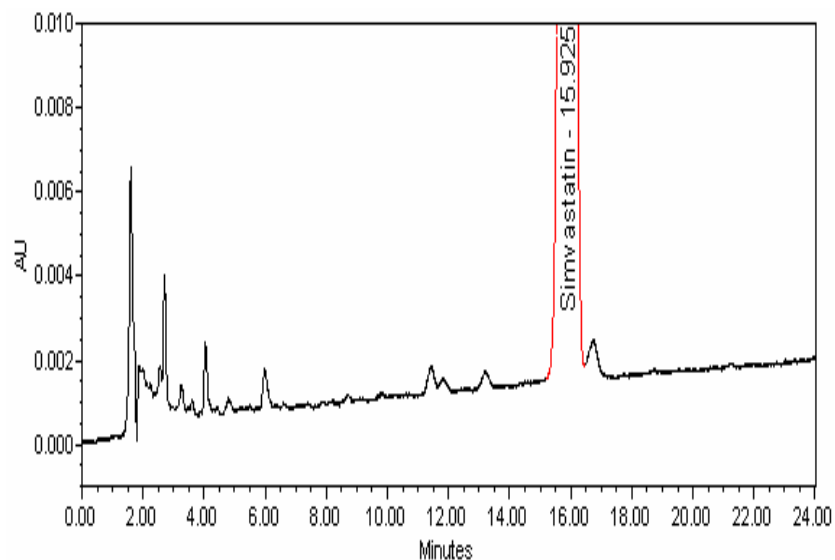
Halo Column



35/65 Acetate/ACN

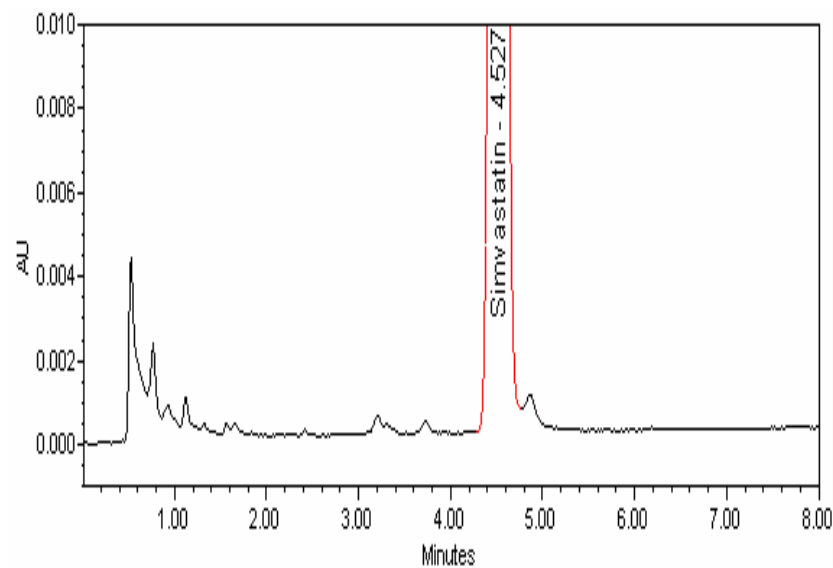
MS Compatible Buffer-Decrease Organic

USP Column



45/55 Acetate/ACN

Halo Column



45/55 Acetate/ACN

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And:

