Limit of Free Salicylic Acid in Aspirin Tablets Using the Kinetex® 5 µm C18 Under USP Allowable Adjustments

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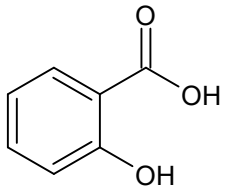


Overview

In this application is the robust separation of Aspirin (Acetylsalicylic Acid) and related impurity Salicylic Acid under the USP conditions. The application demonstrates the potential method improvements that can be achieved per the allowable adjustments outlined in USP General Chapter <621> relative to the original column and conditions referenced in the monograph.

Monograph: Acetylsalicylic Acid
pK_a: 3.5
LogP: 1.2

USP Monograph: Aspirin Tablet, Limit of Free Salicylic Acid	
Standard Stock Solution	0.015 mg/mL of USP Salicylic Acid RS in *Diluent*
Standard Solution	0.015 mg/mL of USP Salicylic Acid RS and 0.5 mg/mL of USP Aspirin RS in *Diluent*
Diluent	Mixture of Acetonitrile and Formic Acid (99:1)
Column	
Size	Method 1: 300 x 3.9 mm, Method 2: 150 x 4.6 mm
Stationary Phase	Method 1: µBondapak® 10 µm C18, Method 2: Kinetex 5 µm C18
Temperature	30 °C
Mobile Phase	2 g/L of Sodium 1-heptanesulfonate in a mixture of Acetonitrile and water (15:85). Adjust with glacial Acetic Acid to a pH of 3.4.
Isocratic	Premixed
Flow Rate	2.0 mL/min
Detector	UV @ 280 nm
Injection Volume	10 µL of System Suitability solution and Standard solution

System Suitability – System Suitability solution

Sample: System Suitability solution:

- Resolution (Rs): NLT 2.0 between Salicylic Acid and Aspirin for System Suitability solution
- Relative Standard Deviation: NMT 4.0 % for Standard solution (5 replicate injections)

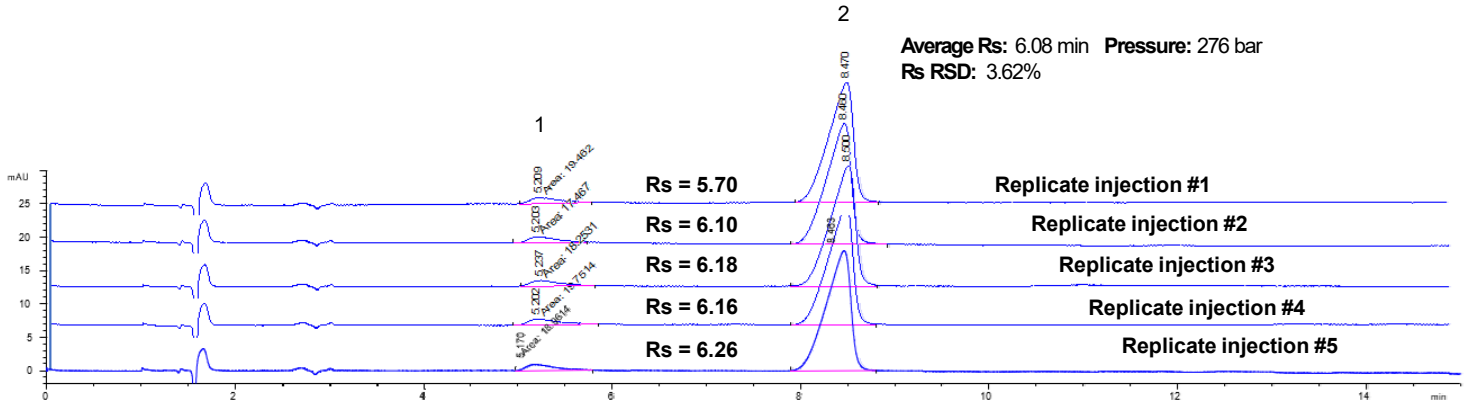
* Retention times are provided for information only and are not mandatory. The relative retention times for Salicylic Acid and Aspirin are about 0.7 and 1.0, respectively.

Method 1

Original Method: System Suitability solution for Aspirin

Column: µBondapak 10 µm C18 Fully Porous
Dimensions: 300 x 3.9 mm
Flow Rate: 2.0 mL/min
Sample: 1. Salicylic Acid
2. Aspirin

Average Rs: 6.08 min **Pressure:** 276 bar
Rs RSD: 3.62%



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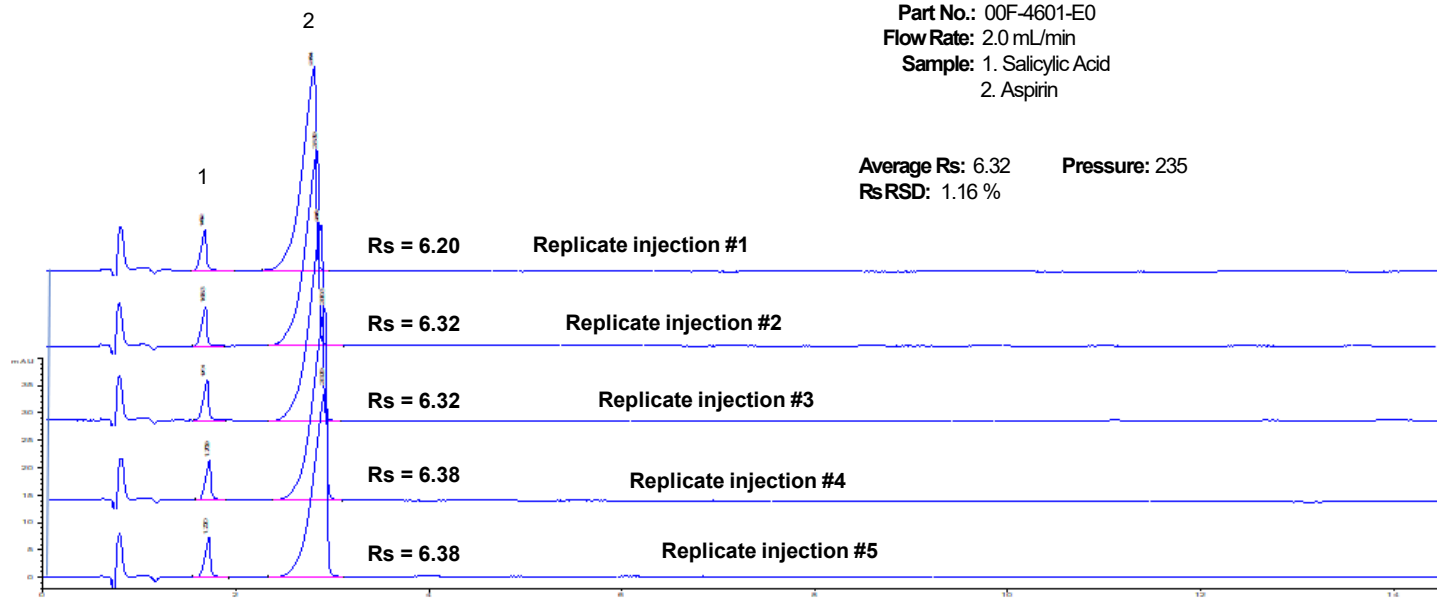
Method 2

Alternative Method: System Suitability solution for Aspirin

Column: Kinetex® 5 µm C18 Core-Shell
Dimensions: 150 x 4.6 mm
Part No.: 00F-4601-E0
Flow Rate: 2.0 mL/min
Sample: 1. Salicylic Acid
2. Aspirin

Average Rs: 6.32 **Pressure:** 235
Rs RSD: 1.16 %



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Adjustments for Meeting System Suitability

Method Parameter	Allowed Adjustments (isocratic elution)	Method 1	Method 2
Mobile Phase pH	± 0.2 units	As specified	As specified
Concentration of Salts in Buffer	± 10 %	As specified	As specified
Composition of the Mobile Phase	± 30 % Relative; cannot exceed ± 10 % Absolute adjustment; cannot be reduced to zero	As specified	As specified
Wavelength of Detector	No deviations permitted	280 nm (as specified)	As specified
Injection Volume	Can be adjusted as much as needed; must be consistent with linearity, precision, and detection requirements	10 µL (as specified)	10 µL (Allowed)
Column Temperature	± 10 °C	30 °C (Allowed)	30 °C (Allowed)
Stationary Phase	No change of the identity of the substituent permitted (e.g. no replacement of C18 by C8)	L1 (as specified)	As specified
Column Length	Column length (L) to particle size diameter (dp) ratio can be adjusted between -25 % and +50 %*	300 mm (as specified)	150 mm (Allowed)
Column Internal Diameter	Can be adjusted so long as linear velocity is maintained	4.0 (as specified)	4.6 mm (Allowed)
Particle Size	Column length (L) to particle size diameter (dp) ratio can be adjusted between -25 % and + 50 %*	10 µm (as specified)	5 µm (Allowed)
Flow Rate	± 50 % (at given ID)	2.0 mL/min (as specified)	2.0 mL/min**

*Alternatively (as for the application of particle size adjustment to superficially porous particles), other L/dp combinations can be used provided that the number of theoretical plates (N) is within -25 % to +50 %.

**To maintain equivalent linear velocity for 4.6 mm ID column, flow rate should be adjusted to 2.64 mL/min; the flow rate of 2.0 mL/min is within the allowed adjustment of ± 50 %.

Allowable Column Adjustments: L/dp Ratio -25 % to 50 %

Column	Length (mm)	ID (mm)	dp (µm)	L/dp	Allowable Range
Original	300	4.0	10	30,000	22,500 – 45,000
Alternative	150	4.6	5	30,000	ALLOWED

Method Summary and Comparison

	Method 1	Method 2
Column	µBondpak® 10 µm C18	Kinetex® 5 µm C18
Aspirin Average Rt (min)	8.5	5.5
Salicylic Acid and Aspirin Average Rs	6.08	10.05
System Suitability solution Rs RSD (n=5)	3.24 %	0.89 %
Backpressure (Bar)	276	235

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