

Shim-pack Arata LC column

CoreFocus

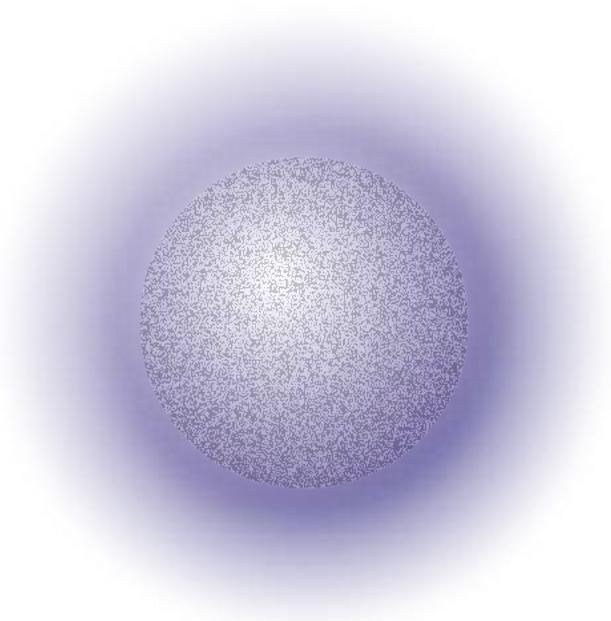


Unprecedented Resolution and Peak Shape of Basic Compounds

Even for LC columns that claim to be designed for basic compounds, adequate resolution often can not be obtained due to problems such as leading of highly polar basic compounds, peak shape deterioration of acidic compounds, or long equilibration time required for low ionic strength acidic mobile phase.

All of these issues have been solved with Shim-pack Arata that was specifically designed to give unmatched peak shape for basic compounds.

Shim-pack Arata™ Enabling technology



Developer Comments

The separation of analytes of interest is a major concern for LC users. Choosing the best column for this always requires a lot of experience. One of the reasons for the challenge is that the nonspecific interaction between silanol (residual unreacted hydroxyl groups on the surface of silica gel) and the analytes complicates the separation behavior.

We have developed the Shim-pack Arata series as the next-generation reversed-phase column with a new concept to suppressing interactions of analytes with the silanol. We hope Shim-pack Arata columns will make a significant contribution to many LC and LC/MS(/MS) users.

~ Shim-pack Arata Developer Team ~

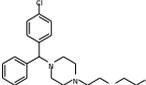
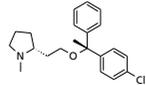
Unmatched Peak Shape

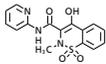
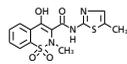
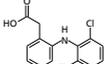
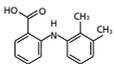
Unmatched peak shape of basic compounds can be achieved while maintaining good peak shape for acidic compounds using Shim-pack Arata LC columns.

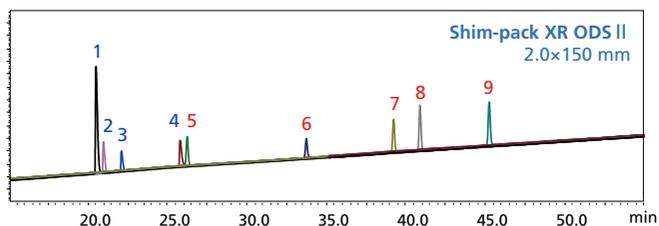
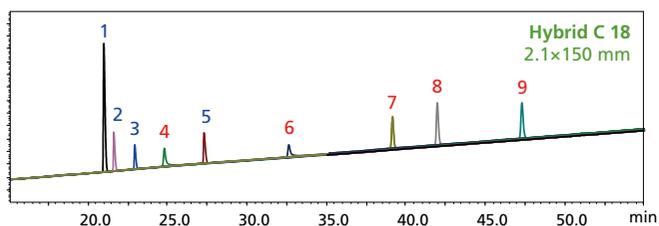
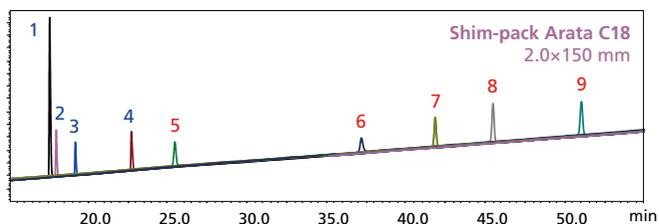
Analysis of Mixtures of Basic and Acidic Drugs (Particle size: 2.2 -2.5 μm)

Under low ionic acidic mobile phase (0.1% formic acid mobile phase) condition, where the peak shape of basic compounds tends to deteriorate, Shim-pack Arata C18 column achieved outstanding peak shape for all four basic and five acidic drugs.

Analytes

| No. | Basic Drugs | | | |
|--------------------|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Compound Name | Cyproheptadine | Hydroxyzine | Mequitazine | Clemastine |
| Structural Formula |  |  |  |  |

| No. | Acidic Drugs | | | | |
|--------------------|---|---|---|---|---|
| | 5 | 6 | 7 | 8 | 9 |
| Compound Name | Piroxicam | Meloxicam | Flurbiprofen | Diclofenac | Mefenamic acid |
| Structural Formula |  |  |  |  |  |



Analytical Conditions

LC system : Nexera™ X2_SPD20A (semi-micro cell)

LC column :

Shim-pack Arata C18 (2.0x150 mm, 2.2 μm)

Hybrid C18 (2.1x150 mm, 2.5 μm)

Shim-pack™ XR ODS II (2.0 x 150mm, 2.2 μm)

Mobile phase A : 0.1% HCOOH in H₂O

Mobile Phase B : 0.1% HCOOH in CH₃CN

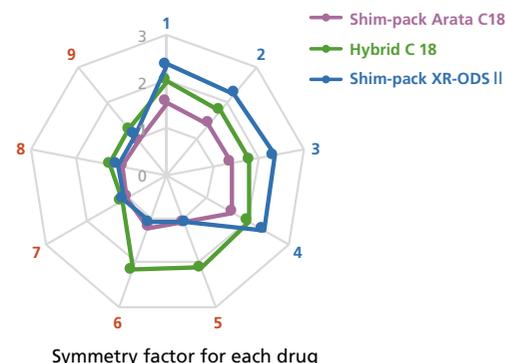
Gradient : 10%B (0 min) →70%B (50-60 min)→10%B (60.01-70 min.)

Flow rate : 0.2 mL/min

Detection : 226 nm

Column temp. : 40 °C

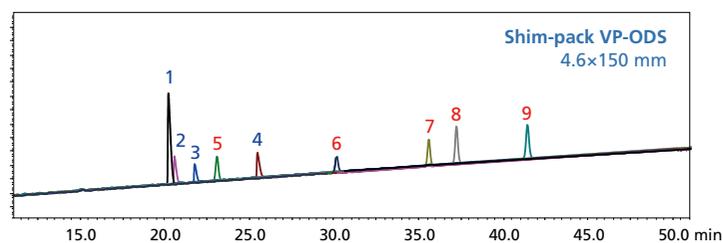
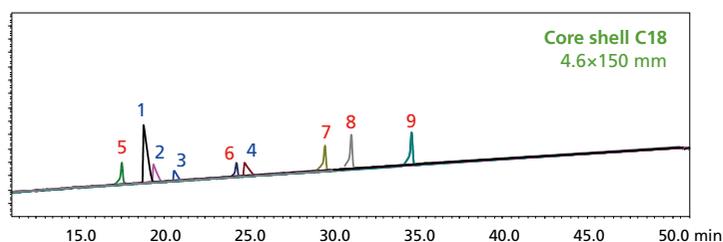
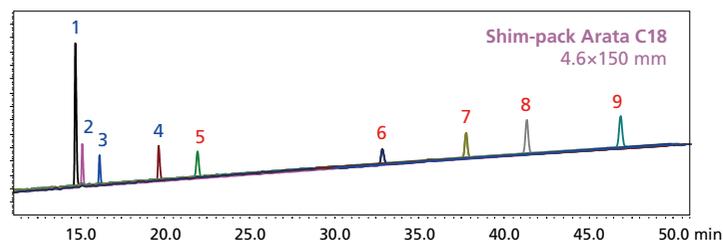
Injection volume : 1 μL



A mixture of 4 basic drugs and 5 acidic drugs was analyzed using a Shim-pack Arata C18 column (2.2 μm), a Hybrid C18 column (designed for improving peak shape of basic compounds: 5 μm), and a typical ODS column (Shim-pack XR-ODSII column: 2.2 μm). This mixture was analyzed under the low ionic strength acidic mobile phase (0.1% formic acid mobile phase) condition, in which the peak shape of basic compounds tends to deteriorate so that the peak shapes (symmetry factors) of each drug were compared. The peak symmetry of basic drugs (1-4) was improved using the hybrid C 18 column, which is specifically claimed to be good for the peak shape of basic compounds under low ionic acidic mobile phase conditions, compared to the typical ODS column. While, the peak symmetry of acidic drugs (5-9) on the hybrid C18 column was deteriorated showing tailing. On the other hand, the Shim-pack Arata C18 column not only showed the best peak symmetry for the basic drugs, but also showed similar or better peak symmetry for acidic drugs compared to the general ODS.

Analysis of a mixture of basic and acidic drugs (particle size: 5 μm)

Under 0.1% formic acid mobile phase condition, Shim-pack Arata C18 column achieved outstanding peak shapes for all 4 basic and 5 acidic drugs.



Analysis conditions

LC system : NexeraX2_SPD20A (Semi-micro Cell)

LC column :

Shim-pack Arata C18 (4.6x150 mm, 5 μm)

Core shell C18 (4.6x150 mm, 5 μm)

Shim-pack VP-ODS (4.6 x 150 mm, 5 μm)

Mobile phase A : 0.1% HCOOH in H₂O

Mobile Phase B : 0.1% HCOOH in CH₃CN

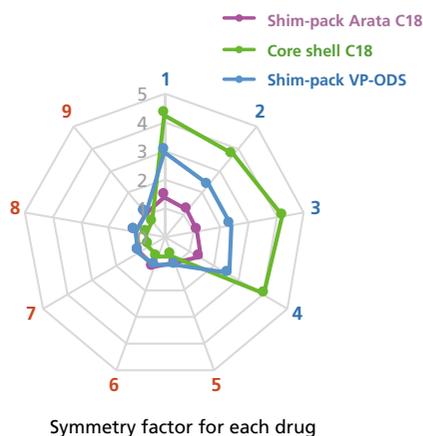
Gradient : 10%B(0 min) →70%B(50-60 min)→10%B(60.01-70 min)

Flow rate : 1.0 mL/min

Detection : 226 nm

Column Temp. : 40 °C

Injection volume : 5 μL



1. Cyproheptidine 2. Hydroxyzine 3. Mequitazine 4. Clemastine (basic drug)
 5. Proxicam 6. Meloxicam 7. Flurbiprofen 8. Diclofenac 9. Mefenamic acid (acidic drug)

Under 0.1% formic acid mobile phase conditions, the peak shapes (symmetry factors) of a mixture of 4 basic drugs and 5 acidic drugs were compared using a Shim-pack Arata C18 column (5 μm), a Core shell C18 column (5 μm) and a typical ODS column (Shim-pack VP ODS: 5 μm).

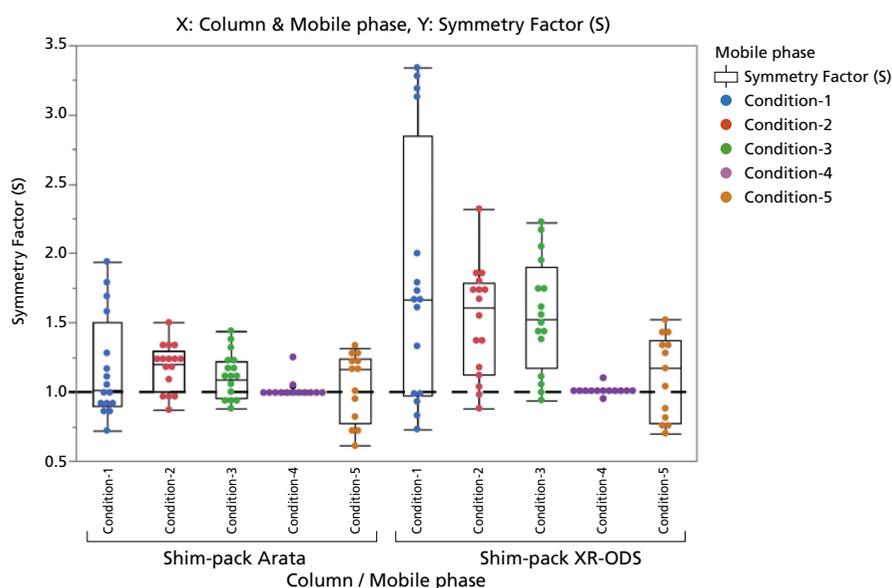
With the Core shell C18 column, deterioration of peak symmetry for four basic drugs (1 -4) was observed which seemed to be due to overload. Additionally, deterioration of peak shape for the acidic drugs (5 -9) due to leading was observed. The Shim-pack Arata C18 column showed the best peak symmetry for the basic drugs and showed good peak symmetry for the acidic drugs.

User Review

► Tsukasa Sasaki, Ph.D., Daiichi Sankyo Co., Ltd.

Researcher, Analytical Science Research Group IV, Analytical & Quality Evaluation Research Laboratories, Pharmaceutical Technology Unit

The Shim-pack Arata column provides symmetrical peaks for basic compounds and stronger retention for acidic compounds under acidic mobile phase conditions (phosphate buffer and formic acid), which follows its development concept. Indeed, the peak shapes of basic compounds with Shim-pack Arata was superior to Shimadzu standard ODS columns, especially under the acidic conditions. On the other hand, when analyzing acidic compounds under neutral mobile phase conditions, the Shim-pack Arata column also provided superior peak shape against Shimadzu standard ODS columns. These results gave me the impression that this column is promising for the simultaneous analysis of acidic and basic compounds under weakly acidic to weakly basic mobile phase conditions. Such a unique characteristic of the Arata column offers an advantage by eliminating ion-pairing additives when considering LC/MS applications.



| | Analyte | Mobile phase | |
|-------------|-------------|------------------------------------|-----------------|
| | | Aqueous | Organic |
| Condition-1 | H1 blockers | 10 mmol/L phosphate buffer, pH 2.5 | MeCN/MeOH=30/70 |
| Condition-2 | H1 blockers | 10 mmol/L phosphate buffer, pH 5.4 | MeCN/MeOH=35/65 |
| Condition-3 | H1 blockers | 0.1% formic acid | MeCN/MeOH=30/70 |
| Condition-4 | NSAIDs | 10 mmol/L phosphate buffer, pH 3.4 | MeCN/MeOH=85/15 |
| Condition-5 | NSAIDs | 10 mmol/L phosphate buffer, pH 7.0 | MeCN/MeOH=30/70 |

| Histamine H1-receptor blockers (H1Bs): |
|--|
| Brompheniramine |
| Chlorpheniramine |
| Diphenhydramine |
| Diphenhydramine |
| Clemastine |
| Triprolidine |
| Mequitazine |
| Cyproheptadine |
| Hydroxyzine |
| Loratadine |
| Amoxapine |
| Desloratadine |
| Olopatadine |

| Non-steroidal anti-inflammatory drugs (NSAIDs): |
|---|
| Ibuprofen |
| Loxoprofen |
| Naproxen |
| Fenoprofen |
| Flurbiprofen |
| Pranoprofen |
| Indoprofen |
| Mefenamic Acid |
| Diclofenac |
| Indomethacin |
| Sulindac |
| Meloxicam |
| Piroxicam |

*This is a personal opinion and does not guarantee the performance or quality of the product.

Rapid Equilibration and Stable Retention Times

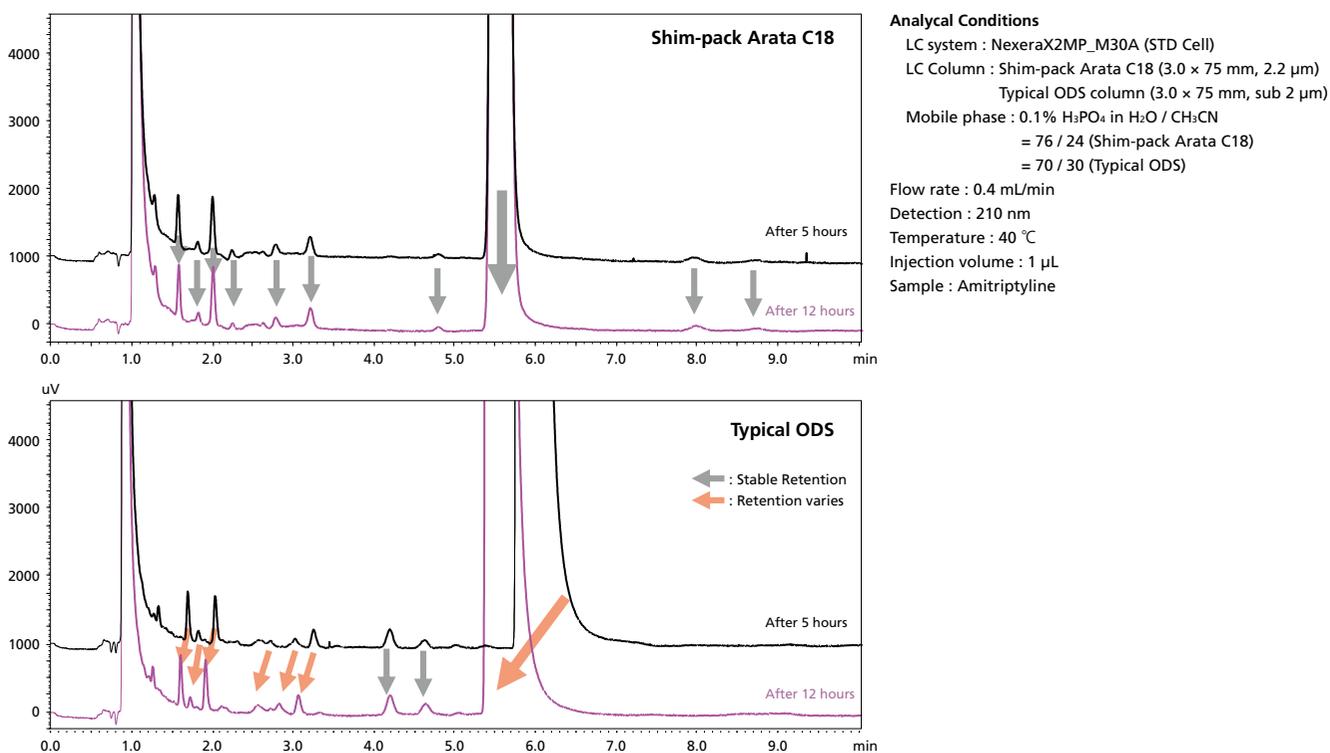
When analyzing basic compounds on a typical ODS column with low ionic acidic mobile phase (0.1% formic acid, phosphoric acid, and others), not only poor peak shape but also long equilibration time required to obtain stable data is a common problem faced by customers. Shim-pack Arata C18 column can be rapidly equilibrated in low ionic strength acidic mobile phase conditions yielding excellent peak shape and stable retention times, which allows reliable qualitative and quantitative analysis.

Drug Purity Test

~ Retention Behavior of Basic Drug and its Impurities under 0.1% Phosphoric Acid Mobile Phase Condition ~

Impurity control in drug substances and drug products is strictly regulated in the quality control process of pharmaceutical manufacturing. Impurities in the drug substances and drug products, which are final products, are controlled through impurity control in the raw materials and in each manufacturing process. As the concept of "Quality by design in manufacturing processes" is basically required, it is particularly important to improve the qualitative efficiency of impurity management in the CMC departments of pharmaceutical companies. In particular, ensuring the reliability (ruggedness) of the methods used for impurity control is a key factor affecting the quality control of pharmaceutical products.

Shim-Pack Arata C18 columns provides a method that yields stable separation performance through rapid equilibration under 0.1% phosphoric acid mobile phase condition and secures high reliability (ruggedness) not only for basic drugs but also for trace amounts of related impurities.

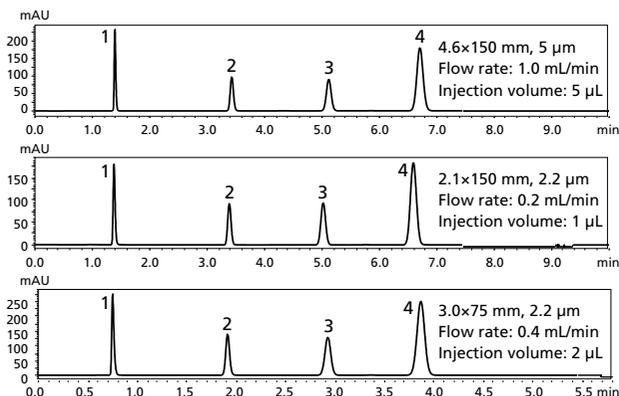


Both columns were equilibrated with mobile phase containing 0.1% phosphoric acid and the retention behavior of Amitriptyline and its impurities were compared after 5 hours and 12 hours of equilibration. Retention time change of Amitriptyline and many related impurities depend on the equilibration time with the typical ODS column. This results in a concern about what effect the change in the retention time has on the resolution and selectivity. On the other hand, no change was observed in the retention time of Amitriptyline and its impurities regardless of the equilibration time with the Shim-Pack Arata C18 column. This difference in retention time change is suggested to be due to the difference in column equilibration time required under 0.1% phosphate mobile phase condition.

Seamless Method Transfer Across Different Particle Sizes and Column Dimensions

Seamless method transfer with consistent results across different particle sizes and columns dimensions with Shim-pack Arata LC columns allows easy method transfer between HPLC and UHPLC.

Method Transfer of Reversed-phase Test Mix



Analytical Conditions

LC column : Shim-pack Arata C18
 Mobile phase : H₂O / CH₃CN = 40 / 60
 Detection : 254 nm
 Column temp. : 40°C
 Analytes : 1. Uracil, 2. Methyl benzoate, 3. Toluene, 4. Naphthalene

| | 4.6x150 mm, 5 µm | 2.0x150 mm, 2.2 µm | 3.0x75 mm, 2.2 µm | CV(%) |
|------------------|------------------|--------------------|-------------------|-------|
| k (Naphthalene) | 3.82 | 3.81 | 3.77* | 0.6 |
| α _{2,3} | 1.83 | 1.82 | 1.87 | 1.17 |
| α _{3,4} | 1.43 | 1.43 | 1.43 | 0.0 |

*Value corrected by cross section ratio

Seamless method transfer could be achieved across different particle sizes and column dimensions while maintaining selectivity.

Method Transfer of Basic and Acidic Drug Mixtures

Even for gradient analysis of ionic compounds under low ionic acidic mobile phase conditions where robust data acquisition is difficult, the Shim-pack Arata C 18 column provides seamless analytical transfer.

Analytical conditions

LC Column : ① Shim-pack Arata C18 (4.6 × 150 mm, 5 µm)
 ② Shim-pack Arata C18 (3.0 × 75 mm, 2.2 µm)

Detection : 226 nm
 Column Temp. : 40°C

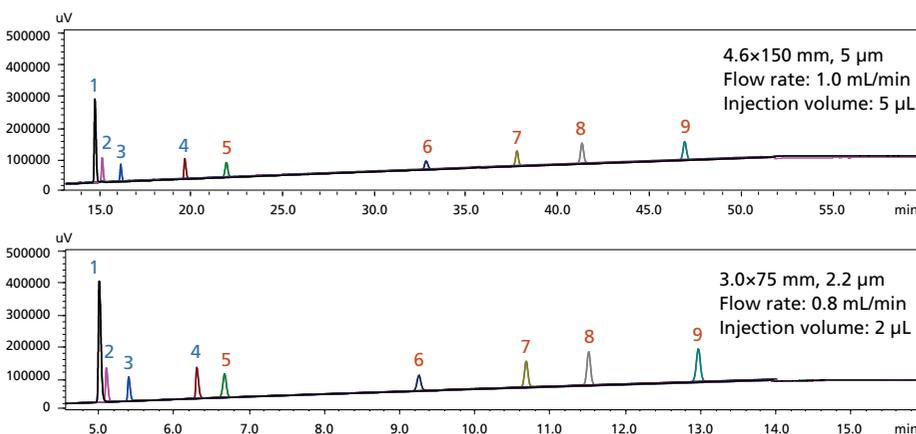
Mobile Phase A : 0.1% HCOOH in H₂O

Mobile Phase B : 0.1% HCOOH in CH₃CN

Gradient :

① 10%B (0 min)→70%B (50-60 min)→10%B (60.01-70 min)

② 10%B (0 min)→70%B (12.5-15 min)→10%B (15.01 – 17.5 min)



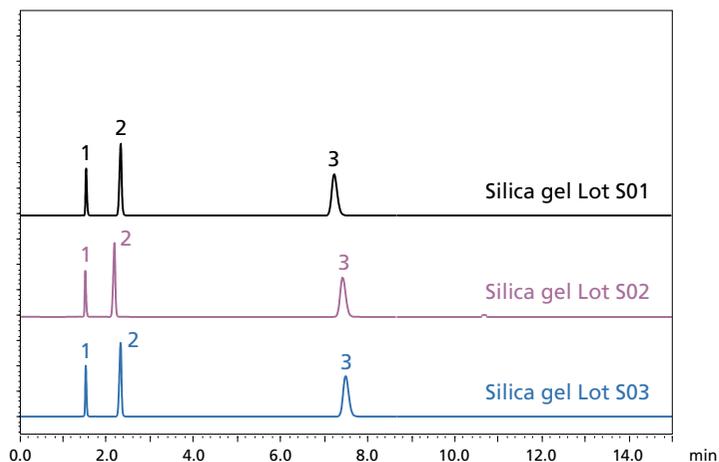
1. Cyproheptidine 2. Hydroxyzine 3. Mequitazine 4. Clemastine (Basic Drugs)
 5. Proxicam 6. Meloxicam 7. Flurbiprofen 8. Diclofenac 9. Mefenamic acid (Acidic Drugs)

| | α _{1,2} | α _{2,3} | α _{3,4} | α _{4,5} | α _{5,6} | α _{6,7} | α _{7,8} | α _{8,9} |
|--------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| 5 µm | 1.03 | 1.08 | 1.24 | 1.13 | 1.54 | 1.16 | 1.10 | 1.14 |
| 2.2 µm | 1.02 | 1.06 | 1.18 | 1.06 | 1.41 | 1.16 | 1.08 | 1.13 |

Both basic and acidic drugs can be seamlessly transferred while maintaining selectivity across different particle sizes and column dimensions with Shim-pack Arata C18 columns. By transferring from Shim-pack Arata C18, 4.6 × 150 mm, 5 µm to Shim-pack Arata, 3.0 × 75 mm, 2.2 µm the analysis time and solvent consumption can be reduced to 1/4 and 1/5, respectively.

Excellent lot-to-lot reproducibility

Lot-to-lot reproducibility of columns is important for long-term reliability and robustness of an analytical method. Each lot of Shim-pack Arata C18 material is QC tested with basic and acidic compounds. This test is conducted under the strict condition using 0.1% formic acid mobile phase to ensure consistent column performance.



Analytical conditions

LC column : Shim-pack Arata C18 (4.6×150 mm, 5 μm)
 Mobile phase : 0.1% HCOOH in H₂O / CH₃CN = 70 / 30
 Flow rate : 1.0 mL/min
 Detection : 254 nm
 Column Temp. : 40 °C
 Injection volume : 5 μL

*Gel Lot QC test analytical condition.

1. Uracil
2. Amitriptyline
3. Benzoic acid

Three different Shim-pack Arata C18 material derived from three different lots of silica demonstrates the excellent reproducibility.

Shim-pack Arata Chemistry

| Shim-pack Arata | C18 |
|----------------------------------|--------------|
| Particle size | 2.2 μm, 5 μm |
| Pore size | 12 nm |
| Surface Area (m ² /g) | 340 |
| Carbon content (%) | 17 |
| End-cap | proprietary |
| pH range of use | 2 -7.5 |
| 100% aqueous condition | Yes |
| USP classification | L1 |

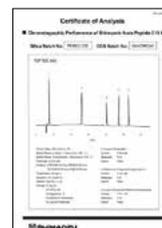


Excellent Separation Performance of Peptides

Typically, in order to obtain good peak shape of peptides under reversed phase chromatography, TFA containing mobile phases are frequently used which the ion pairing effect is relatively strong. However, TFA could cause ion suppression in LC/MS(/MS) analysis. Excellent peak shape and separation performance for peptides could be achieved on the Shim-pack Arata LC column even under formic acid (weak ion pairing acid) containing mobile phase conditions, which are suitable for LC/MS(/MS) without the use of typical ion pairing agents.

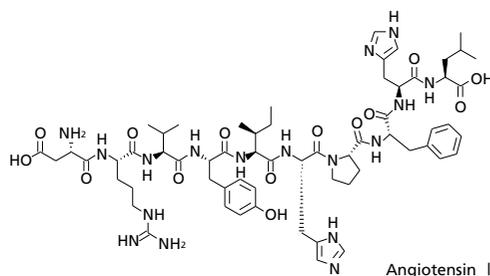
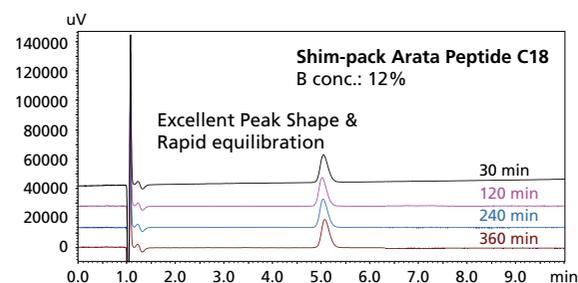
Increased Assurance of Peptide Analysis ~ Shim-pack Arata Peptide C 18 column ~

In order to ensure lot-to-lot reproducibility in peptide analysis, each lot of Shim-pack Arata Peptide C18 material is tested using a mixture of peptide standards in addition to the standard Shim-pack Arata C18 lot QC test. This test is carried out under severe condition using 0.1% formic acid mobile phase to help ensure consistent column performance for requirements of customers under regulated requirements.

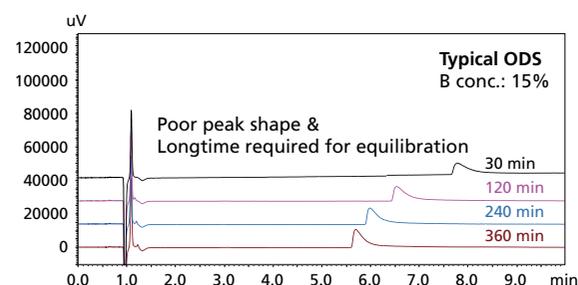


Excellent peak shape and rapid column equilibration of peptides

When analyzing peptides on a typical ODS column with 0.1% formic acid mobile phase, not only poor peak shape but also long equilibration time required to obtain stable retention times and area is a common problem. Shim-pack Arata Peptide C18 columns can be rapidly equilibrated even in 0.1% formic acid containing mobile phase, achieving excellent peak shape, stable retention and area of peptides at the same time.



| Compounds | Equilibration time (min) | 30 | 60 | 120 | 180 | 240 | 360 | CV |
|---------------|--------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|-----|
| Angiotensin I | Retention time (min) | 5.05 | 5.03 | 5.03 | 5.03 | 5.04 | 5.06 | 0.3 |
| | Symmetry factor | 1.26 | 1.24 | 1.25 | 1.25 | 1.24 | 1.25 | 0.4 |
| | Area | 2.17×10 ⁵ | 2.13×10 ⁵ | 2.26×10 ⁵ | 2.25×10 ⁵ | 2.23×10 ⁵ | 2.24×10 ⁵ | 1.9 |



Analytical Conditions

LC system : NexeraX2 MP_SPD20A (Semi-micro Cell)
 LC column :
 Shim-pack Arata Peptide C18 (3.0 × 75 mm, 2.2 μm)
 Typical ODS (3.0 × 75 mm, Sub 2 μm)
 Mobile Phase A : 0.1% HCOOH in H₂O
 Mobile Phase B : 0.1% HCOOH in CH₃CN
 Flow rate : 0.4 mL/min

Detection : 214 nm
 Column temp. : 40 °C
 Injection volume : 1 μL
 Sample : Angiotensin I
 Vial : Torast-H Bio Vial

*Peptide is usually analyzed using gradient conditions. Isocratic condition was used for this application in order to show the difference of LC columns more clearly. Acetonitrile concentration was adjusted in order that the retention time of peptide on each column become similar.

| Compounds | Equilibration time (min) | 30 | 60 | 120 | 180 | 240 | 360 | CV |
|---------------|--------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|------|
| Angiotensin I | Retention time (min) | 7.78 | 7.15 | 6.53 | 6.20 | 5.98 | 5.82 | 11.0 |
| | Symmetry factor | 4.89 | 4.38 | 4.85 | 4.87 | 4.93 | 4.92 | 3.9 |
| | Area | 1.65×10 ⁵ | 1.58×10 ⁵ | 1.76×10 ⁵ | 1.78×10 ⁵ | 1.83×10 ⁵ | 1.84×10 ⁵ | 5.3 |

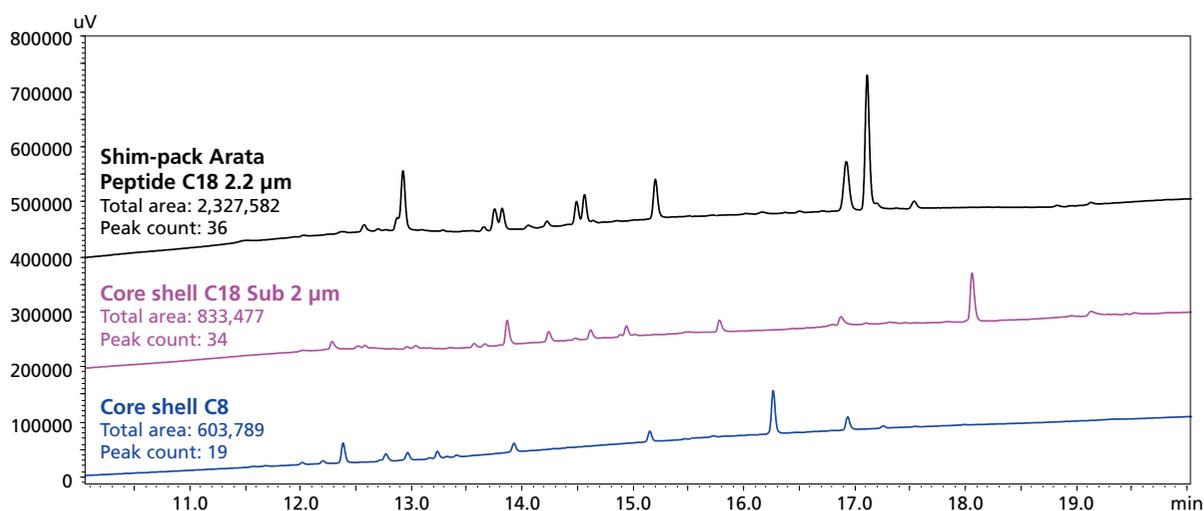
Both columns were new columns (shipping solvent: acetonitrile) and equilibrated with mobile phase without any conditioning. Angiotensin I was analyzed after a certain period of equilibration and retention time, symmetry factor and area of Angiotensin I were compared. The typical ODS showed poor peak symmetry and unstable retention time even after 360 minutes of equilibration. In contrast, Shim-pack Arata peptide C18 already showed stable retention after 30 minutes of equilibration and excellent peak shape was obtained.

High Peptide Recovery enabled by Shim-pack Arata technology

Since the adsorption of peptides to particles is minimized, high recovery of peptides is ensured and excellent peptide analysis can be provided by Shim-pack Arata Peptide C18 column.

Analysis of Tryptic Digest of Myoglobin

Peptides are known to show non-specific adsorption to particles of LC columns. A Shim-pack Arata Peptide C18 column showed high recovery of peptides.



Analytical Conditions

| | |
|---|-----------------------------------|
| LC System : NexeraX2MP_M30A (STD Cell) | Flow rate : 0.2 mL/min |
| LC Column : Shim-pack Arata Peptide C18 (2.0 × 150 mm, 2.2 µm) | Detection : 214 nm |
| Core shell Peptide C18 (2.1 × 150 mm, sub 2 µm) | Column Temp. : 40 °C |
| Core shell C8 (2.1 × 150 mm, sub 4 µm) | Injection volume : 5 µL |
| Mobile Phase A : 0.1% HCOOH in H ₂ O | Sample : Myoglobin tryptic digest |
| Mobile Phase B : 0.1% HCOOH in CH ₃ CN | Vial : TORAST-H Bio Vial |
| Gradient : 2%B (0-5 min) → 45%B (20 min) → 100%B (20.01 – 25 min) | |
| → 2%B (25.01 – 30 min) | |

Tryptic digest of myoglobin was analyzed using Shim-pack Arata Peptide C18 (2.2 µm), Core shell C18 (sub 2 µm) and a Core shell C8 (sub 4 µm). Compared to the other two columns, Shim-pack Arata Peptide C18 showed significantly larger peak area, which suggests that higher recovery could be obtained with Shim-pack Arata Peptide C18 column.

► **Yoshiki Asakawa, Sunplanet Co., Ltd.**
Manager, DMPK & Bioanalysis Unit, Tsukuba R & D supporting division

Liquid chromatography/mass spectrometry (LC/MS) method is becoming an important approach for therapeutic antibody assays as an alternative to the ligand binding assay (LBA) method. Selective reaction monitoring (SRM)-MS of tryptic signature peptides performed on triple-quadrupole (QqQ) mass spectrometer is widely applied to bioanalytical quantification of therapeutic antibodies. Insufficient LC separation of target signature peptides and a large amount of contaminating peptides derived from the biological matrix in trypsin digestion results in decrease in selectivity and sensitivity (due to ion suppression). Therefore, sample purification in pretreatment and high reproducibility in LC separation are the keys to achieving highly sensitive and accurate quantitative determination of peptides. For LC/MS quantitation of peptides, small organic acid concentration in the mobile phase affects the detection sensitivity, which is contrary to that of small molecule analytes. Therefore, it is necessary to use a mobile phase with lower organic acid concentration such as 0.01 – 0.05% (v/v) acid (for small molecule quantitation, 0.1% formic acid containing mobile phase is generally used). Consequently, it is desirable to use a column with high separation under such mobile phase conditions.

The performance of Shim-pack Arata C18 was evaluated for bioanalytical quantitation of therapeutic antibodies using LC/MS analysis. Good peak shape of the target peptide was obtained from the 1st injection with the mobile phase containing 0.02% (v/v) formic acid, and good peak shape was maintained with stable retention through successive injections. In order to obtain good peak shape with a typical ODS column, long term conditioning (masking) by continuously injecting tryptic digested sample (biological blank sample) is often performed to suppress nonspecific adsorption of peptides onto the silica particles. In contrast, Shim-pack Arata C18 showed good peak shape and highly reproducible separation of peptides without conditioning due to the minimized adsorption of peptides onto the silica particles.

These results suggest that Shim-pack Arata C18 provides unprecedented separation not only for small molecule basic compounds analysis but also for peptides analysis.

Advantages of using Shim-pack Arata C18 column for the measurement of the antibody drug concentration in blood by LC/MS method are as follows.

- Good peak shape of peptide in mobile phase with lower concentration of organic acid (Less than 0.1% [v/v] formic acid)
- Improved accuracy for the quantitative analysis of peptides
- Improved separation by decreasing nonspecific interaction of peptides with silica particles
- Improved recoveries of peptides and stability of the column due to the minimized adsorption of peptides onto the silica particles
- Reduced column conditioning

*This is a personal opinion and does not guarantee the performance or quality of the product.

Order Information

Shim-pack Arata C18 2.2 μ m

| Length(mm) | ID(mm) | 2.0 | 3.0 |
|------------|--------|--------------|--------------|
| | 50 | | 227-32801-01 |
| 75 | | 227-32801-02 | 227-32802-02 |
| 100 | | 227-32801-03 | 227-32802-03 |
| 150 | | 227-32801-04 | 227-32802-04 |

Shim-pack Arata C18 5 μ m

| Length(mm) | ID(mm) | 2.0 | 3.0 | 4.6 |
|------------|--------|--------------|--------------|--------------|
| | 50 | | 227-32803-01 | 227-32804-01 |
| 75 | | 227-32803-02 | 227-32804-02 | 227-32805-02 |
| 100 | | 227-32803-03 | 227-32804-03 | 227-32805-03 |
| 150 | | 227-32803-04 | 227-32804-04 | 227-32805-04 |
| 250 | | | | 227-32805-05 |

Shim-pack Arata Peptide C18 2.2 μ m

| Length(mm) | ID(mm) | 2.0 |
|------------|--------|--------------|
| | 50 | |
| 100 | | 227-32806-02 |
| 150 | | 227-32806-03 |

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