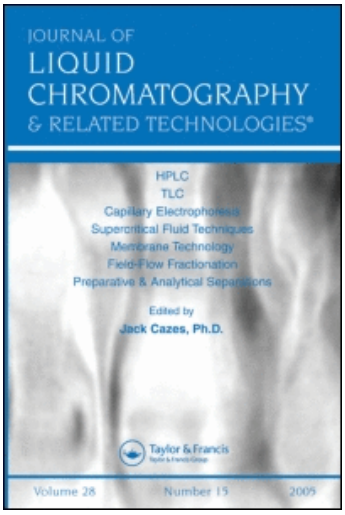


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# THE RETENTION BEHAVIOR OF LORATADINE AND ITS RELATED COMPOUNDS IN ION PAIR REVERSED PHASE HPLC

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# THE RETENTION BEHAVIOR OF LORATADINE AND ITS RELATED COMPOUNDS IN ION PAIR REVERSED PHASE HPLC

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□ *Organic amines are important pharmaceutical molecules and appropriate reversed phase HPLC methods for quality control are desirable for them. The development of IP-RPLC methods is challenging for complex profiles of organic amines. Mobile phase pH and ion pair reagent concentration are two important factors affecting the retention behavior of organic amines in IP-RPLC. Loratadine and its eight related compounds were used as the model compounds for studying their retention behavior and the elution profile using a gradient IP-RPLC condition. The parameters examined included the mobile phase pH and the concentration of an ion pairing reagent, SDS. The chromatographic separation and retention factor (k) of each analyte were monitored at different SDS concentrations (0 to 20 mM) and different pH values (6.2 and 3.0). Due to the basicity of the nine compounds in the study, each compound responded differently to the varying ion pairing reagent (SDS) mobile phase concentrations at different pH values. The ionized analytes had increasing retention factors with increasing SDS concentration, while the non-ionized analytes had nearly constant retention factors as a function of the SDS concentration. For the nine organic amines studied, optimal overall separation and resolution were achieved at 3 mM SDS under pH of 6.2 and at 1 mM under pH 3.0, respectively.*

**Keywords** chromatographic retention behavior, chromatographic retention mechanisms, ion pair chromatography reversed phase HPLC (IP-RPLC), loratadine, sodium dodecyl sulfate (SDS)

## INTRODUCTION

Organic amines are important molecules in the pharmaceutical industry as either active pharmaceutical ingredients (APIs) or critical synthetic intermediates. Appropriate reversed phase HPLC (RP-HPLC or RPLC) methods for quality control are desirable for pharmaceutical compounds.

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However, RPLC would yield limited success for highly complex organic amines (multiple ionic or polar analytes). In these cases, ion pair chromatography (IPC) can be utilized to develop an appropriate quality control method by achieving the required separation of complex mixtures of polar and ionic molecules. The selectivity of IPC is determined by the mobile phase supplemented with a specific ion pair reagent, which is typically a large ionic molecule that has both a hydrophobic region to interact with the stationary phase and a charged region to interact with the analyte. Although the retention mechanism for ion pair chromatography is not fullyunderstood, three major theories have been proposed: (a) ion pair formation; (b) dynamic ion exchange; and (c) ion interaction.[1,2] Despite the different retention mechanisms, IPC and RPLC use similar columns and mobile phases. The major difference is the appearance of an ion pair reagent in the mobile phase for IPC. The retention process of IPC is very different from RPLC, which means that a large change in separation selectivity for ionic samples can be anticipated upon adding appropriate ion pair reagents to the mobile phase used for RPLC.[3] Ion pair reversed phase HPLC (IP-RPLC) has become an important technique with a broad scope of applications.[4–10] Multiple chromatographic retention mechanisms reinforce the chromatographic capability to separate complex analyte mixtures and provide tremendous advantages for IP-RPLC. Common mobile phase ion pair reagents include alkyl sulfate salts, naphthalene-2-sulfonic acid (negative ion pair reagents), and tetrabutyl ammonium halides (positive ion pair reagents). Trifluoroacetic acid (TFA) and heptafluorobutyric acid (HFBA) are also used as mobile phase ion pair reagents, especially in peptide and protein chromatographic analysis.



Because of the multiple retention mechanisms present in IP-RPLC, development of IP-RPLC methods usually involves extensive experimental studies. The pH of the mobile phase aqueous component and the ion pair reagent concentration are two of the most important factors to be investigated and optimized during the development of new IP-RPLC methods.

Due to the nature of IPC, the analytes of interest needs to be ionized to bear the charge opposite to the ion pair ion in order to respond to the ion pair reagent in the mobile phase. Therefore, compounds with different ionization states (e.g., different pKa's) react differently to the mobile phase ion pair reagent in IPC. Ionized compounds with an opposite charge to the ion pair ion will behave as IPC analytes, but neutral compounds or ionized compounds with the same charge as the ion pair ion will behave as RPLC analytes. Thus, taking advantage of the appropriate mobile phase pH and ion pair reagent for the optimal IPC retention mechanism of the ionized compounds and taking advantage of the RPLC retention

mechanism for the neutral compounds can achieve the desired specificity for complex analyte mixtures (e.g., organic amines).

Since the retention mechanism of IPC is influenced mainly by the ion pair reagent, the retention of the analytes of interest will increase as the concentration of reagent is increased. However, electrostatic repulsion of reagent molecules on the stationary phase surface will ultimately limit the degree to which the separation capacity can be increased. The typical working concentration for the ion pair reagents in ion pair chromatography is between 0.5 and 20 mM.[11] The optimized ion pair reagent concentration would minimize or eliminate the interference in the elution of the ionic analytes, which respond to the IPC mechanism, and the neutral analytes, which behaves under the RPLC mechanism.

Understanding of the physiochemical properties of the analytes and their retention behaviors facilitates the appropriate choice of the mobile phase pH and the ion pair reagent concentration. Well designed method development strategy and experiments will ensure efficient and accurate selection of these two factors. Many papers have described method development activities in optimizing the pH and/or ion pair reagent concentration for IP-RPLC. The theoretical model of IPC mechanism was proposed and investigated, where effects of different pH values and ion pair reagent concentrations on the retention of individual compounds were demonstrated, by Bartha and co-workers.[12] These effects on the separation of a single pair of compounds were reported by Larew and co-workers.[13]



This paper describes the study on the impact of the variation in the concentration of the ion pair reagent, sodium dodecyl sulfate (SDS), and the mobile phase pH value on the retention behavior and elution profile of a complex mixture of nine pharmaceutical organic amines. Loratadine (compound **4**), a long acting antihistamine agent[14] and hence, a well known API, and its eight related compounds were used as the model analytes under the IP-RPLC condition. It is demonstrated that, by varying the mobile phase pH and the SDS concentration, different amines show different retention behavior trends. The elution profile of the nine organic amines then changes, and the overall separation of them can be achieved under appropriate combination of the mobile phase pH value and the SDS concentration. The chemical structures of the model organic amines Loratadine and its related compounds are provided in Figure 1. Their key physical properties, which have the greatest impact on their chromatographic separation, are listed in Table 1. The wide range of the approximate pKa's of the analytes made it desirable to utilize IP-RPLC for their separation.

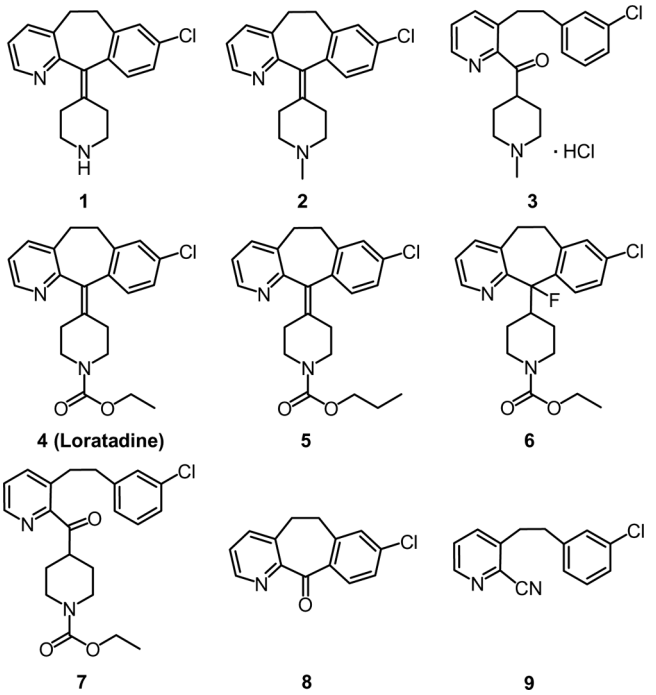


**FIGURE 1** Chemical structures of Loratadine (compound **4**) and its related compounds.



**TABLE 1** Key Physical Properties of Loratadine (compound **4**) and its Related Compounds

| Compound | Empirical Formula | Molecular Weight | UV Absorbance ($\lambda_{max}$, in nm) | Estimated pKa[a] |
|---|---|---|---|---|
| **1** | $C_{19}H_{19}ClN_2$ | 310.82 | 242 | $4.33 \pm 0.2$<br>$10.27 \pm 0.2$ |
| **2** | $C_{20}H_{21}ClN_2$ | 324.85 | 242 | $2.85 \pm 0.2$<br>$8.67 \pm 0.2$ |
| **3** | $C_{20}H_{24}Cl_2N_2O$ | 379.32 | 277 | $1.17 \pm 0.22$<br>$8.68 \pm 0.4$ |
| **4 (Loratadine)** | $C_{22}H_{23}ClN_2O_2$ | 382.88 | 240 | $-1.59 \pm 0.2$<br>$4.81 \pm 0.2$ |
| **5** | $C_{23}H_{25}ClN_2O_2$ | 396.91 | 248 | $-1.6 \pm 0.2$<br>$4.81 \pm 0.2$ |
| **6** | $C_{22}H_{24}ClFN_2O_2$ | 402.89 | 265 | $-2.05 \pm 0.4$<br>$3.88 \pm 0.4$ |
| **7** | $C_{22}H_{25}ClN_2O_3$ | 400.90 | 274 | $-3.13 \pm 0.4$<br>$1.4 \pm 0.22$ |
| **8** | $C_{14}H_{10}ClNO$ | 243.69 | 290 | $0.83 \pm 0.2$ |
| **9** | $C_{14}H_{11}ClN_2$ | 242.70 | 272 | $-0.15 \pm 0.1$ |

[a]The approximate pKa's were estimated from the respective chemical structure of each compound by the software ACD/Lab [15, http://www.camsoft.co.kr/chemnews/art/70.htm].

## EXPERIMENTAL

### Reagents

Loratadine and its related compounds (compounds **1–9**; refer to Table 1 and Figure 1) were provided by Global Quality Services – Analytical Sciences group in Schering-Plough (Union, NJ).

HPLC grade acetonitrile and electrophoresis SDS were obtained from Fisher Scientific (Hampton, NH, USA). ACS reagent grade sodium citrate dehydrate was purchased from Sigma-Aldrich (St. Louis, MO, USA). Reagent ACS grade sulfuric acid was bought from Acros (Fair Lawn, NJ, USA). Water was obtained from an in-house Milli-Q system (Millipore, Billerica, MA, USA).

### Apparatus

A Waters (Milford, MA, USA) Alliance HPLC system, equipped with a 2695 separation module, a 2996 photodiode array detector, and a 2487 dual wavelength UV detector was used. Data acquisition, analysis, and reporting were performed by Millennium[32] chromatography software (Waters). The HPLC column was an YMC-Pack Pro C18 column (15 cm × 4.6 mm I.D., 3 μm particle size, 120 Å pore size) purchased from Waters.



### Chromatographic Conditions

The experiments were carried out on an ACE 3 C18 column [(150 × 4.6 mm, 3 μm, Advanced Chromatographic Technologies (UK)] operated at 35°C. The column effluent was monitored at 270 nm.

The mobile phase A was the aqueous solution containing 10 mM of sodium citrate and SDS at varying concentrations with pH adjusted to 6.2 or 3.0 by 25% sulfuric acid. The mobile phase B was acetonitrile. The mobile phase was delivered to the analytical column using a linear gradient program, starting at a composition of 60% A and 40% B, changing to 100% B after 20 min. The flow rate was 1.5 mL/min. An equilibration time of 10 min was required between runs. Injected sample volume was 10 μL.

### Preparation of Standard Solutions

Stock solutions of individual compounds were prepared by dissolving appropriate amounts (e.g., 2 mg) of each compound in 10 mL of water-acetonitrile (1:1 v/v). The mixture solution was prepared by mixing approximately 1 mL of each of the individual stock solutions and diluting to 10 mL with water-acetonitrile (1:1 v/v).

### Calculations

The retention factor (k; or capacity factor, k′) is defined and calculated as

$$k = (t_R - t_0)/t_0$$

where $t_R$ is the peak retention time (in minutes) and $t_0$ is the column dead time (in minutes). In this study, $t_0$ (=1.0 min) is determined from the retention time of the solvent front.

The resolution factor (Rs) calculations were performed by the Waters data acquisition system Millennium.[32]

## RESULTS AND DISCUSSION

### HPLC Chromatographic Conditions and Experiment Design



The HPLC chromatographic conditions were determined by a series of method development activities in order to ensure proper retention for all nine compounds.[16] The model compounds **1** to **9** are basic organic amine analytes. The use of reversed phase HPLC columns with end capping and/or polar embedded functional group would minimize the silanol active sites and, therefore, minimize peak tailing of the analytes. Also, for these basic compounds, stronger retention characteristics are generally observed for $C_{18}$ or $C_8$ based HPLC columns than for phenyl or cyano based HPLC columns. Column screening was performed on over thirty different commercially available $C_{18}$, $C_8$, and $C_4$ columns from well established, highly reputable HPLC column manufacturers [e.g., YMC (YMC, Japan); ACE (Advanced Chromatographic Technologies, UK); Waters (Waters, USA)]. The YMC-Pack Pro C18 4.6 × 150 mm (3 μm particle size, 120 Å pore size) column was identified as the appropriate HPLC column for this study. The general approach of chromatographic methods development used by our laboratory has been reported[17] and the details of the method development activities were described elsewhere.[16]

To investigate the effect on chromatographic separation of the Loratadine and its related compounds using ion pair reagent, two aqueous solution pH values were utilized, pH 6.2 and pH 3.0. Since all the analytes are amines (refer to Figure 1), acidic mobile phases (pH < 7) would be preferred for reasonable retention times and good peak shapes. Selection of these two pH values ensures that certain compounds will respond differently to the ion pair reagent at different pH values. At each pH value, a series of aqueous solutions with six different concentrations of SDS, ranging from 0 to 20 mM, were used as mobile phase A. Mobile phase B remained

constant as 100% acetonitrile. The other chromatographic conditions were held constant during this study.

## Effect of Changes in SDS Concentration and Mobile Phase pH Value

The retention factors (k's) of the model compound analytes were calculated at each SDS concentration and were plotted against corresponding SDS concentration as shown in Figure 2 (at pH 6.2) and Figure 3 (at pH 3.0).

As shown in Figure 2 and Figure 3, at each pH value, the nine compounds can be categorized into two groups (as Group I and Group II) based on the changing retention factor (k) as a function of the SDS concentration in the aqueous mobile phase A. Group I compounds exhibited slightly decreasing retention factors (k) when the SDS concentration increased from 0 mM to 20 mM. This group (Group I) includes compounds **4–9** at pH 6.2 or compounds **7–9** at pH 3.0. Group II compounds exhibited increasing retention factors (k) when the SDS concentration increased from 0 mM to 20 mM. This group (Group II) includes compounds **1–3** at pH 6.2 or compounds **1–6** at pH 3.0. The different responses of the two groups of compounds to the SDS concentration



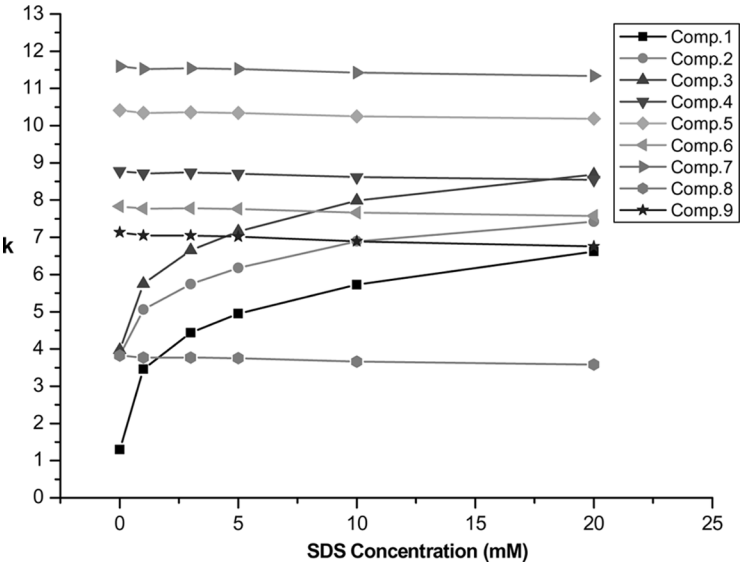


**FIGURE 2** The dependency of the retention factor (k) of the nine model compounds on the SDS concentration in the aqueous mobile phase A at pH 6.2.

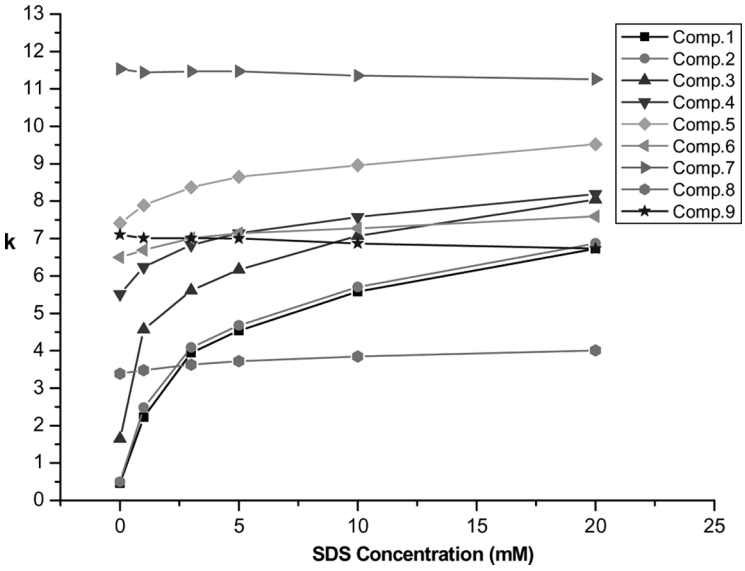


**FIGURE 3** The dependency of the retention factor (k) of the nine model compounds on the SDS concentration in the aqueous mobile phase A at pH 3.0.



change are due to the retention mechanism of ion pair chromatography (IPC). In order to respond to the negative charged dodecyl sulfate ions, an analyte needs to be positively charged. Although all of the model compounds are amines, their conjugated acids (e.g., the protonated amines) have different pKa's (refer to Table 1) and, therefore, different basicity. As a result, the analytes will exhibit different ionization states depending on the pH value of the mobile phase. With the employed mobile phase combinations, compounds in Group II (compounds **1–3** at pH 6.2 or compounds **1–6** at pH 3.0) are mainly protonated and behave as positively charged ionic molecules, but those in Group I (compounds **4–9** at pH 6.2 or compounds **7–9** at pH 3.0) are mainly neutral molecules. Thus, Group II compounds responded to the ion pair reagent concentration change continuously, but Group I compounds were not impacted to any meaningful extent when SDS concentration changed from 1 mM to 20 mM.

When more SDS was added in the aqueous mobile phase A, more SDS was available for the column stationary phase, which in turn had a higher uptake of the amount of SDS on the column stationary phase surface. As a result, Group II compounds, as ionized species, were more retained on the column and exhibited increased retention factor (k) values with increasing SDS concentration. The retention factor (k) change for each Group II compound was drastic from 0 mM to 10 mM SDS. Beyond the

10 mM SDS concentration, the retention factor (k) change leveled off, which means the uptake amount of SDS on the stationary phase reached its saturation level and was no longer impacting the analyte retention.

Group I compounds, as neutral molecules, were not involved in the ion pair retention process. Therefore, when SDS concentration changed from 0 mM to 20 mM, the analyte retention factor (k) would not be affected by ion pair chromatography. However, due to the blockage of the stationary phase surface by the ion pair reagent, decreasing chromatographic retention of Group I compounds was observed with increasing SDS concentration.

The difference in the basicity of the nine compounds can be demonstrated by their chemical structures, as shown in Figure 1. All nine compounds have basic nitrogen (N) and their basicity is determined by their predominant nitrogen (N) site. There are two types of nitrogen (N) in the nine compounds: pyridine N, and piperidine N. Pyridine has a pKa of 5.23 and piperidine has a pKa of 11.24, but substituted pyridine or piperidine can have dramatically different pKa values from that of an unsubstituted pyridine or an unsubstituted piperidine. When a compound has both types of nitrogen atoms, the higher pKa (more basic) of them will be the predominant and working pKa which determines the basicity of the compound. In summary, the pKa, and therefore the basicity, order of the nine compounds should be: **1** > (**2**, **3**) > pH 6.2 > (**4**, **5**) > **6** > pH 3.0 > (**7**, **8**) > **9** (also refer to Table 1). This basicity order agrees with the aforementioned categorization of Group I and Group II based on the IPC response at both pH 6.2 and pH 3.0.



From both Figures 2 and 3, it can be seen that ion pair reagent does not change the selectivity among compounds **1**, **2**, and **3**, which responded to IPC at both pH values. In other words, peak spacing among these analyte peaks remain almost the same across the ion pair concentration range studied. This is further demonstrated by their similar retention factor (k) versus SDS concentration curves (Figures 2 and 3). However, at pH 3.0, not all compounds that responded to IPC have consistent peak spacing as a function of SDS concentration. Compounds **4** and **5** have similar peak spacing between each other across the SDS concentrations. Compounds **1**, **2**, and **3** also have similar peak spacing among each other across the SDS concentrations but they have slightly different trends than compounds **4** and **5**. Compound **6** is unique because it responded to IPC to a lesser extent as compared to compounds **1–5**. Therefore the peak spacing of compound **6** relative to compounds **1–5** changed as a function of SDS concentration. Most probably this is due to the fact that pH 3.0 is close to the working pKa's of compounds **6** (pKa 3.88), **4**, and **5** (pKa 4.81). Compounds **4–6** existed in comparable amounts of neutral or ionic (protonated) molecules. Therefore, both RPLC and IPC mechanisms took

effect on them. RPLC mechanism changed the selectivity of the compounds. Compound **6** has the pKa closest to pH 3.0 and was affected the least by IPC.

As a result of the different responses of the nine model compounds to the ion pair reagent, the overall elution profile and separation differed as a function of SDS concentration. Any closeness of retention factors (k) in Figure 2 or Figure 3 means poor separation (partial coelution or coelution) of the corresponding compounds. Under pH 6.2, all compounds were completely resolved at SDS concentration of 3 mM. The closest or critical chromatographic pair was compounds **3** and **9**, whose resolution factor (Rs) was 2.8 under these conditions [pH 6.2 and 3 mM SDS; Figure 4(a)]. Under pH 3.0, all nine compounds were completely resolved at SDS concentration of 1 mM. The closest or critical chromatographic pair was compounds **1** and **2**, whose resolution factor (Rs) was 1.9 under these conditions [pH 3.0 and 1 mM SDS; Figure 4(b)].

It is noteworthy that compounds **1**, **2**, and **3** had poor peak shapes at pH 6.2 [Figure 4(a)] exhibiting tailing factors of 1.4, 2.7, and 1.4, respectively. However, the peak shape of compounds **1**, **2**, and **3** improved at pH 3.0 [Figure 4(b)] exhibiting tailing factors of 1.2, 1.2, and 1.0, respectively. For basic analytes such as amines, low pH mobile phases (e.g., close to or below 3) typically produce better peak shape than high pH mobile phase (e.g., close to or above 7) by providing more complete ionization of the analytes. Therefore, the condition for Figure 4(b), that is, using 1 mM SDS at pH 3.0 will be more favorable from the application perspective.



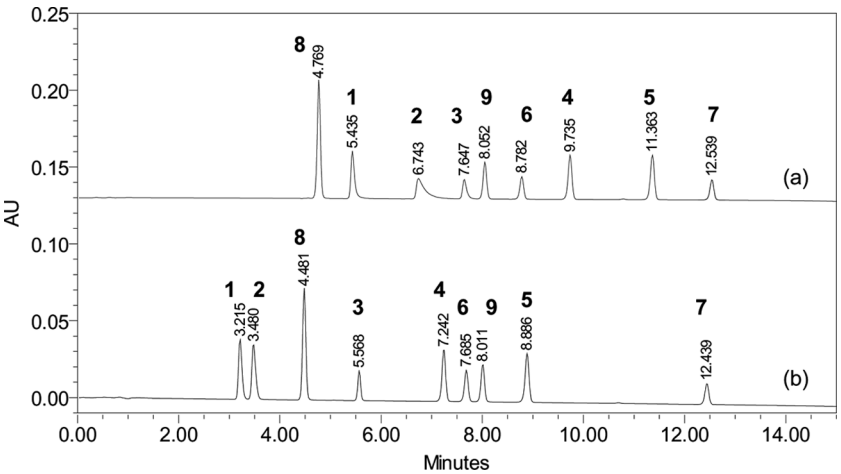


**FIGURE 4** Separation of the nine model compounds (a) utilizing an aqueous mobile phase A of pH 6.2 and 3 mM SDS concentration and (b) utilizing an aqueous mobile phase A of pH 3.0 and 1 mM SDS concentration.

## CONCLUSIONS

In IP-RPLC, ionized analytes will behave via the IPC retention mechanism while neutral analytes will maintain RPLC retention mechanism behavior. When basic analytes have different pKa's, appropriately selected mobile phase pH value can make some ionized analytes dependent on the IPC retention mechanism while keeping some neutral analytes dependent on the RPLC retention mechanism. Furthermore, compounds that have pKa's close to the employed aqueous mobile phase pH would be dependent to both IPC and RPLC retention mechanisms. When method development experiments on the change of mobile phase pH value and the change of ion pair reagent concentration under IP-RPLC condition were properly designed, the optimal combination of these two factors can be efficiently and effectively determined for the optimal overall chromatographic selectivity of complex analyte mixtures. The chromatographic condition for separating Loratadine and its eight related compounds was successfully identified based on the above IP-RPLC strategy.



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