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The effect of drift gas on the separation of active pharmaceutical ingredients and impurities by ion mobility–mass spectrometry

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ABSTRACT

The effect of drift gas and binary gas mixtures on the separation of active pharmaceutical ingredients and related compounds has been investigated for the first time using tri-wave ion mobility–mass spectrometry. The drift times for $[M+H]^+$ ions were measured in argon, carbon dioxide, nitrogen, helium and binary mixtures of these gases as a function of pressure and drift gas composition. At the same drift cell pressure the drift times of the protonated ions decreased in order; carbon dioxide > argon > nitrogen > helium. The drift times of compounds in the different drift gases were dependent on the polarizability of the drift gas, the size of the drift gas and the reduced mass of the analyte ion/drift gas pair. Resolution of the active pharmaceutical ingredients Lamotrigine and Rosiglitazone increased with drift cell pressure for argon and nitrogen, but showed no significant increase in carbon dioxide. Enhanced selectivity is demonstrated for the separation of pharmaceutical components using binary drift gas mixtures in tri-wave IM–MS.

1. Introduction

Ion mobility (IM) spectrometry has been used primarily to identify low molecular weight volatile analytes, most commonly using ^{63}Ni atmospheric pressure chemical ionisation. This has led to the widespread use of IM in military/security applications, because of the suitability of the technique for the detection of vapours associated with chemical warfare agents and explosives. The development of electrospray ionisation (ESI) for ion mobility–mass spectrometry (IM–MS) [1–5] has extended the range of IM to the analysis of high molecular weight and polar compounds.

IM spectrometry separates ions on the basis of their differing mobilities in a drift gas, typically nitrogen, air or helium, under the influence of a weak electric field gradient, where ion mobility (K), is defined as

$$K = \frac{v}{E} \equiv \frac{L^2}{Vt_d} \quad (1)$$

v is the average velocity of an ion moving through the drift cell, E is the electric field gradient applied along the drift cell, L is the length of the drift cell, V is the total voltage drop applied along the drift cell, and t_d is the drift time of the ion (i.e., the time taken for an ion to drift the length of the cell). The factors determining ion mobility under low field conditions ($<2 \times 10^{-17}$ V cm^{-2}) are defined by the simplified Mason–Schamp equation [6]:

$$K = \frac{3ze}{16N}\left(\frac{2\pi}{\mu k_b T}\right)^{1/2}\left(\frac{1}{\Omega_D}\right) \quad (2)$$

where ze is the charge of an ion, N is the number gas density of the drift gas, k_b is Boltzmann's constant, μ is the reduced mass of the drift gas-ion pair, T is the temperature of the drift cell, and Ω_D is the collision cross-section of the drift gas/analyte ion pair.

IM is a low-resolution technique compared to mass spectrometry, with resolutions typically in the range 10–40 (FWHH). Combined with orthogonal m/z separation by mass spectrometry, hybrid IM–MS has been shown to enhance separations in a range of analytical applications compared to mass spectrometry alone. However, in some cases such as complex mixture analysis, improved selectivity and resolution is required. Three methods are commonly used to increase the selectivity of drift tube IM separations: (1) the use of higher electric fields and pressures, combined with longer drift tubes, has been used to achieve resolutions up to ≈200 [7–12], (2) the use of shift reagents [13–17], defined as chemicals which complex or react selectively with an analyte to form a gas-phase ion of decreased mobility and increased drift time, or (3) changes to the drift gas composition or temperature [18–24].

The use of IM drift gases other than nitrogen, air or helium has been investigated for a range of analytes [11,12,20–32]. Generally, ion mobility is lowest in large polar gases, such as carbon dioxide and SF_6, and highest in small non-polar gases, such as helium. The

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more massive gases also tend to cause fragmentation and result in poor sensitivity due to the longer ion residence times in the drift tube. The mobility of ions in carbon dioxide and other polarizable gases depends strongly on the temperature of the IM drift cell, because clustering occurs at lower temperatures reducing ion mobility [27,30]. Asbury and Hill reported that the drift sequence for fluoroaniline and aminobenzonitrile was reversed by using carbon dioxide as the drift gas, in comparison to the order observed in nitrogen, argon, and helium [12] and also studied the effect of drift gas on the separation of amines and glycine containing peptides in various drift gases (nitrogen, argon, helium, and carbon dioxide) using ambient pressure IM–MS [25]. They concluded that the reduced mass of the ion-neutral pair and collision cross-section are both important parameters influencing the mobility of an ion and demonstrated a linear correlation between ionic radii and the drift gas polarizability [25]. Matz et al. analysed four classes of compound (cocaine/metabolites, amphetamines, benzodiazepines, and peptides) in four drift gases (argon, carbon dioxide, helium, and nitrogen) using an atmospheric pressure high resolution IM–MS [31]. For all the compounds studied, the highest mobilities were observed in helium and the lowest in carbon dioxide. The highest selectivity between cocaine and its metabolite compounds was achieved in helium. Two classes of amphetamine were studied (simple and methylene dioxy) and helium provided the best selectivity between the three compounds in each class. However, carbon dioxide provided the best selectivity between the two classes. It was possible to obtain baseline separation of all of the benzodiazepines using the appropriate choice of drift gas (argon, nitrogen, and helium), demonstrating that the drift gas can be changed to enhance ion mobility separations. The location of charge on a series of peptide ions was established by comparing the intrinsic (zero polarizability) radii, obtained from IM–MS measurements of peptide ions in helium, nitrogen, argon, and carbon dioxide, with the radii generated from molecular models [32].

The use of drift gases other than air and nitrogen was described theoretically in the 1970s and it was suggested that the use of drift gas mixtures would be advantageous [6]. The effect of drift gas mixtures on ion mobility has been studied using atomic ions [19,33–35], but there have been few reports of the use of binary drift gas mixtures in the analysis of molecular species to enhance ion mobility separations. The mobilities of SF_6 clusters in mixtures of SF_6 and methane have been reported using atmospheric pressure IM [19] and a 10% methane in argon drift gas mixture has been used to study the mobilities of low molecular weight aromatic compounds at atmospheric pressure using IM–MS [29].

In this paper, we describe a tri-wave IM–MS investigation of the effect of drift gas composition and pressure on the separation of active pharmaceutical ingredients (APIs) and related analytes, and the first use of binary gas mixtures in IM spectrometry. Four drift gases, helium, argon, nitrogen, carbon dioxide, and binary mixtures of these four were used to study the effect of drift gas composition on drift time and resolution.

2. Experimental

2.1. Materials

Rosiglitazone, Paroxetine, desfluro-Paroxetine, Lamotrigine, Lamivudine and Lamivudine impurity were supplied by GSK. Standard samples were prepared in 49.5/49.5/1 (v/v/v) acetonitrile/water/formic acid and then serially diluted in the same solvent to give a final concentration of 200 ng mL^{-1}. Nitrogen and helium gases were obtained from a communal on-site supply. Argon (≥99.998%) and carbon dioxide (≥99.8%) were obtained from Sigma (St. Louis, MO, USA).

2.2. Ion mobility–mass spectrometry data acquisition

Direct infusion IM–MS experiments were performed on a Synapt High Definition spectrometer (Waters Corporation, Manchester, UK) [36,37]. The ion mobility region contains three (trap, IM, and transfer) travelling wave stacked ion guides (TWIGS). The travelling wave velocity was set to 300 ms^{-1} with a pulse height of 12 V in all acquisitions. Ions were injected into the IM TWIG from the trap TWIG for 200 μs in every ion mobility separation. Each ion mobility spectrum consists of 200 sequential ToF mass spectra (acquisition time typically less than 15 ms). IM–MS data were obtained by combining all the ion mobility spectra acquired in a 90 s infusion (approximately 10,000 spectra).

2.3. Ionisation conditions

The IM–MS instrument was operated in positive electrospray ionisation (+ve ESI) mode, with the electrospray probe held at 3.0 kV and the cone voltage set to 30 V. The nitrogen desolvation and cone gas flow rates were set to 500 and 50 L h^{-1}, respectively. The source and desolvation temperatures were set to 100 and 150 °C, respectively.

2.4. Drift gas experiments

Helium, nitrogen, argon, and carbon dioxide were introduced directly into the IM TWIG and the pressure was altered using the Synapt's 0–200 mL min^{-1} (calibrated to nitrogen) mass flow controller (Bronkhorst, Sawston, UK). The IM TWIG cell pressure was monitored using the Synapt pirani gauge (BOC-Edwards model APG-L calibrated for nitrogen), located in the housing surrounding the IM TWIG cell. Calibration data obtained from the manufacturer was used to convert the pirani output voltage to corrected pressure for argon, helium, and carbon dioxide.

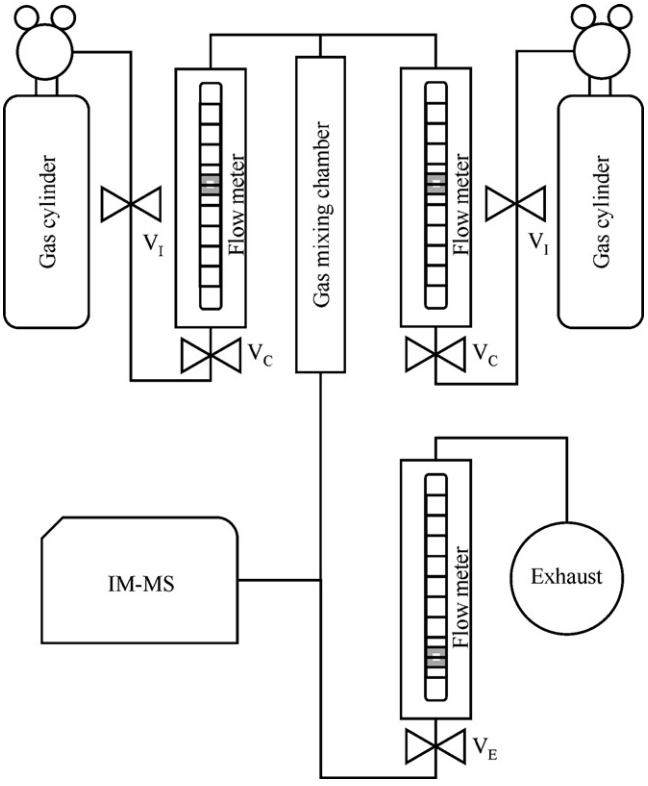

Fig. 1. Schematic diagram of the gas mixing manifold used to introduce binary drift gas mixtures into the IM TWIG of the IM–MS spectrometer.

2.5. Binary drift gas mixtures

A gas mixing manifold, shown schematically in Fig. 1 was fabricated to allow binary gas mixtures to be introduced into the IM TWIG region. The drift gas composition was controlled by needle valves (V_C; Fig. 1) on each of the gas lines and the flow rates were measured using 60–600 mL min^{-1} flow meters (Platon, Basingstoke, UK). Isolation valves (V_I) allowed the control valves (V_C) to be isolated from the gas supplies. A mixing chamber (8 in. × 1/2 in. diameter stainless steel tube) was used to ensure thorough mixing of the gases. A portion of the resulting gas flow was sampled into the spectrometer using the Synapt mass flow controller, with the remainder being vented through the exhaust line. The flow of exhaust gas was measured using a 0.1–1.2 L h^{-1} flow meter (Platon, Basingstoke, UK). Closure of the exhaust control valve (V_E) and isolation valves (V_I) allowed the entire gas mixing manifold to be isolated. The reported composition of the drift gas refers to the composition at the inlet to the IM TWIG.

3. Results and discussion

3.1. Effect of drift gas and pressure on ion mobility

IM–MS spectra for the API test mixture obtained using nitrogen drift gas (0.69 mbar) and by combining all 200 ion mobility bins are displayed in Fig. 2. The selected ion mobility responses for the [M+H]$^+$ ions of Lamivudine (*m*/*z* 230), Lamotrigine (*m*/*z* 256), Rosiglitazone (*m*/*z* 358), desfluro-Paroxetine (*m*/*z* 312), Paroxetine (*m*/*z* 330) and Lamotrigine impurity (*m*/*z* 382) are presented in Fig. 2b. In all of the gas mixture experiments using nitrogen, argon, helium and carbon dioxide, the

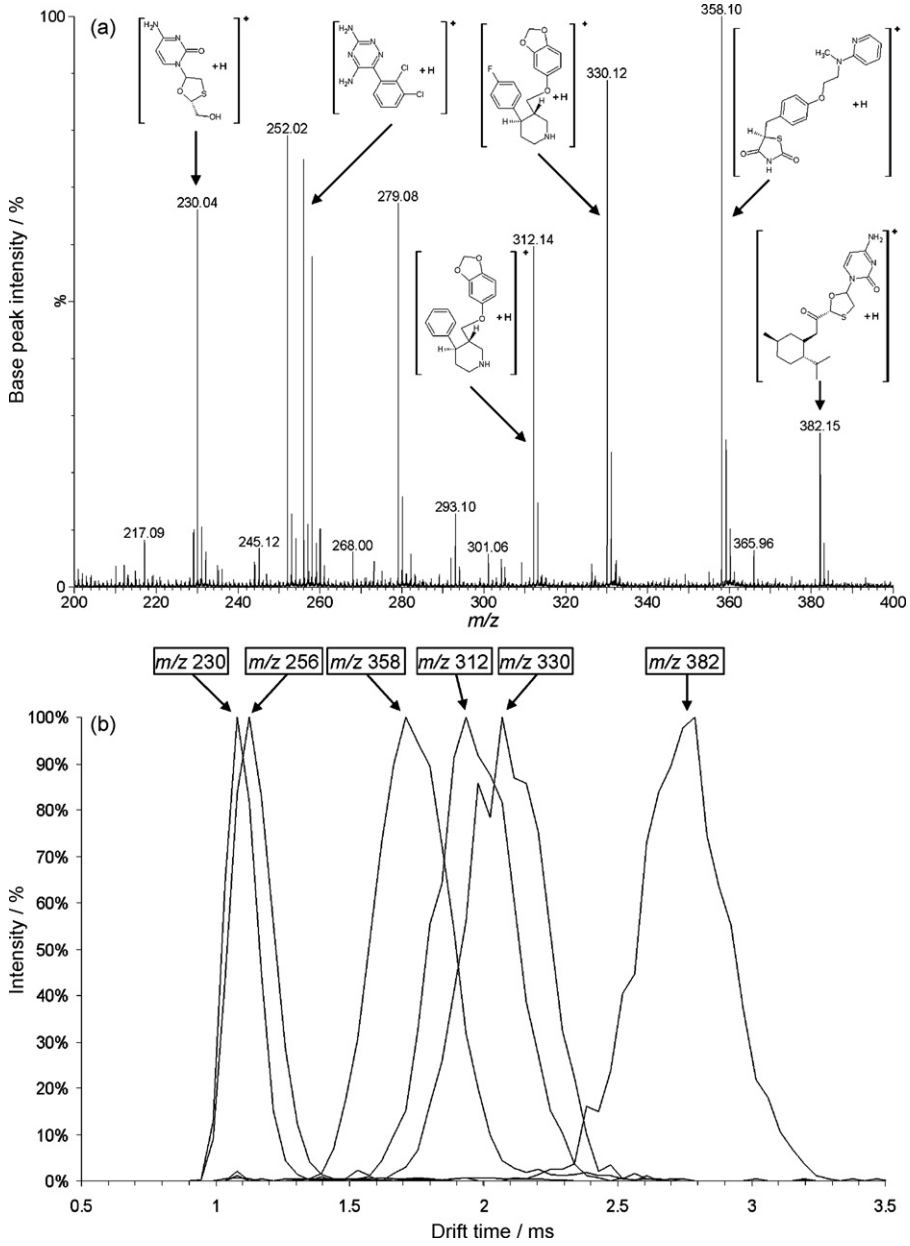

Fig. 2. IM–MS spectra obtained from an electrosprayed infusion of the API test mixture at a concentration of 200 ng mL^{-1} in 49.5/49.5/1 (v/v/v) acetonitrile/water/formic acid, acquired using nitrogen (0.69 mbar) drift gas showing (a) the mass spectrum obtained by combining all 200 bins, acquired during acquisitions of the ion mobility separation. (b) The selected ion mobility responses for the [M+H]$^+$ ions of Lamivudine (*m*/*z* 230), Lamotrigine (*m*/*z* 256), Rosiglitazone (*m*/*z* 358), desfluro-Paroxetine (*m*/*z* 312), Paroxetine (*m*/*z* 330), Lamotrigine impurity (*m*/*z* 382).

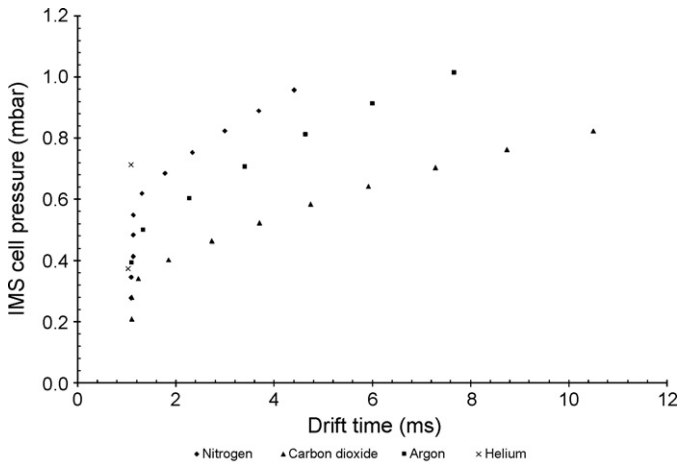

Fig. 3. Effect of drift gas and pressure on the drift time of the Rosiglitazone $[M+H]^+$ ion in helium, nitrogen, argon and carbon dioxide at pressures in the range 0.2–1.0 mbar.

drift times of the $[M+H]^+$ ions decreased in the order; Lamivudine impurity > Paroxetine > desfluro-Paroxetine > Rosiglitazone > Lamotrigine > Lamivudine. Generally drift times increase with increased m/z for ions of the same charge state, but the Rosiglitazone $[M+H]^+$ ion does not fit this trend. The drift time for Rosiglitazone (t_d = 1.71 ms; m/z 358) is lower than Paroxetine (t_d = 2.07 ms; m/z 330) and desfluoro-Paroxetine (t_d = 1.94 ms; m/z 312) despite having a higher mass, because collision cross-section rather than the reduced mass of the ion-neutral pair is the key factor governing the ion mobility (Eq. (2)). The lower than expected drift time can be explained by the flexible backbone linking the two aromatic rings, which allows the Rosiglitazone ion to adopt a more compact structure with a smaller collision cross-section than the Paroxetines and the Lamotrigine impurity. The ability to detect subtle changes in molecular structure is apparent from the partial separation of the structurally related Paroxetine and desfluoro-Paroxetine, which differ only in the para-substituted fluorine. However, full resolution of the Paroxetine analogues in nitrogen would require a resolving power (FWHH) of ≈65. The drift times for the Rosiglitazone $[M+H]^+$ ion in helium, nitrogen, argon and carbon dioxide are presented in Fig. 3, as a function of drift gas and pressure. The drift time and the peak width of the Rosiglitazone ion was observed to increase with increasing pressure in nitrogen, argon and carbon dioxide, as expected from relationship the between the number density of the drift gas, N, and K (Eq. (2)). However, the drift time in helium did not change significantly with pressure because the travelling wave height was optimised for transmission of ions through the heavier drift gases. The intensity of the $[M+H]^+$ ion decreased with increased pressure in all the gases. Similar drift time-pressure plots where obtained for all of the $[M+H]^+$ ions generated from the test mix (data not shown). Drift times for all $[M+H]^+$ ions in the test mix increased in the order; $He < N_2 < Ar < CO_2$ at a given pressure. This novel observation for a tri-wave IM analysis agrees with previous reports of IM separations in conventional drift cells with these gases [25,26].

Drift gas parameters which affect the mobility of an ion are the polarizability of the drift gas, the reduced mass of the drift gas/analyte ion pair, the drift gas pressure and temperature, and the effective radius of the drift gas. The effective radius of the drift gas atoms or molecules reported in Table 1 was calculated using a simple hard sphere collision model [26] and is related to the measured collision cross-section by

$$\Omega_m = \pi(r_{ion} + r_{gas})^2 \quad (3)$$

where Ω_m is the collision cross-section measured using IM, r_{ion} is the radius of the analyte ion and r_{gas} is the radius of the drift gas. The polarizability and effective molecular radius of nitrogen are both slightly higher than argon (Table 1), but the drift time of the Rosiglitazone $[M+H]^+$ ion is significantly longer in argon than in nitrogen at the pressures above 0.5 mbar. This may be explained by the higher reduced mass of the Rosiglitazone $[M+H]^+$ in argon (35.95) compared to that in nitrogen (25.97) (Table 1), which lead to decreased ion mobilities and longer drift times in argon (Eq. (2)).

The longest drift times, for all $[M+H]^+$ ions were observed in carbon dioxide, due in part to the greater reduced mass of the analyte ion in carbon dioxide compared to argon or nitrogen (Table 1). However, carbon dioxide also has a significantly larger effective molecular radius (2.02 Å) and polarizability volume (2.91×10^{23} cm^3) than either argon or nitrogen, increasing the number of collisions between the analyte ion and the neutral gas molecules, which reduces ion mobility. The increased drift times observed in carbon dioxide may therefore be explained by a combination of the larger size of the drift gas, increased polarizability volume and greater reduced mass compared to nitrogen and argon at the same pressure. However, like nitrogen and helium the use of carbon dioxide had no effect on the selectivity of the analysis.

3.2. Effect of drift gas and pressure on resolution

The selected ion mobility responses for the Lamotrigine and Rosiglitazone $[M+H]^+$ ions in argon, nitrogen and carbon dioxide at pressures in the range 0.6–0.8 mbar are presented in Fig. 4. The resolution (R_s) between the compounds was calculated using Eq. (4) [38]. R_s values greater than or equal to 1.5 indicate full baseline separation:

$$R_s = \frac{2\Delta t_d}{w_{b1} + w_{b2}} \quad (4)$$

where Δt_d is the difference in drift times and w_{b1} and w_{b2} are the base peak widths of the ions.

The best separation between the Lamotrigine and Rosiglitazone ions (R_s = 1.76–1.92) was achieved using argon as the drift gas at all pressures. Complete resolution of the Rosiglitazone and Lamotrigine was only achieved in nitrogen at the highest pressure used in these studies (0.82 mbar). The two analytes were only partially resolved in carbon dioxide and increasing pressure did not result in the increased resolution observed for nitrogen or argon. In all

Table 1
Polarizability volume, effective radius and reduced mass for the drift gases utilised in this study.

Drift gas	Molecular weight (amu)	Polarizability volume ($\times 10^{23}$ cm^3) [40]	Effective radius (Å) [26]	Calculated reduced mass (μ) of gas/Rosiglitazone $[M+H]^+$ ion pair
Helium	4.0026 (^{4}He)	0.21	1.03	3.96
Nitrogen	28.0061 ($^{14}N_2$)	1.74	1.73	25.97
Argon	39.9624 (^{40}Ar)	1.64	1.67	35.95
Carbon dioxide	43.9898 ($^{12}C^{16}O_2$)	2.91	2.02	39.18

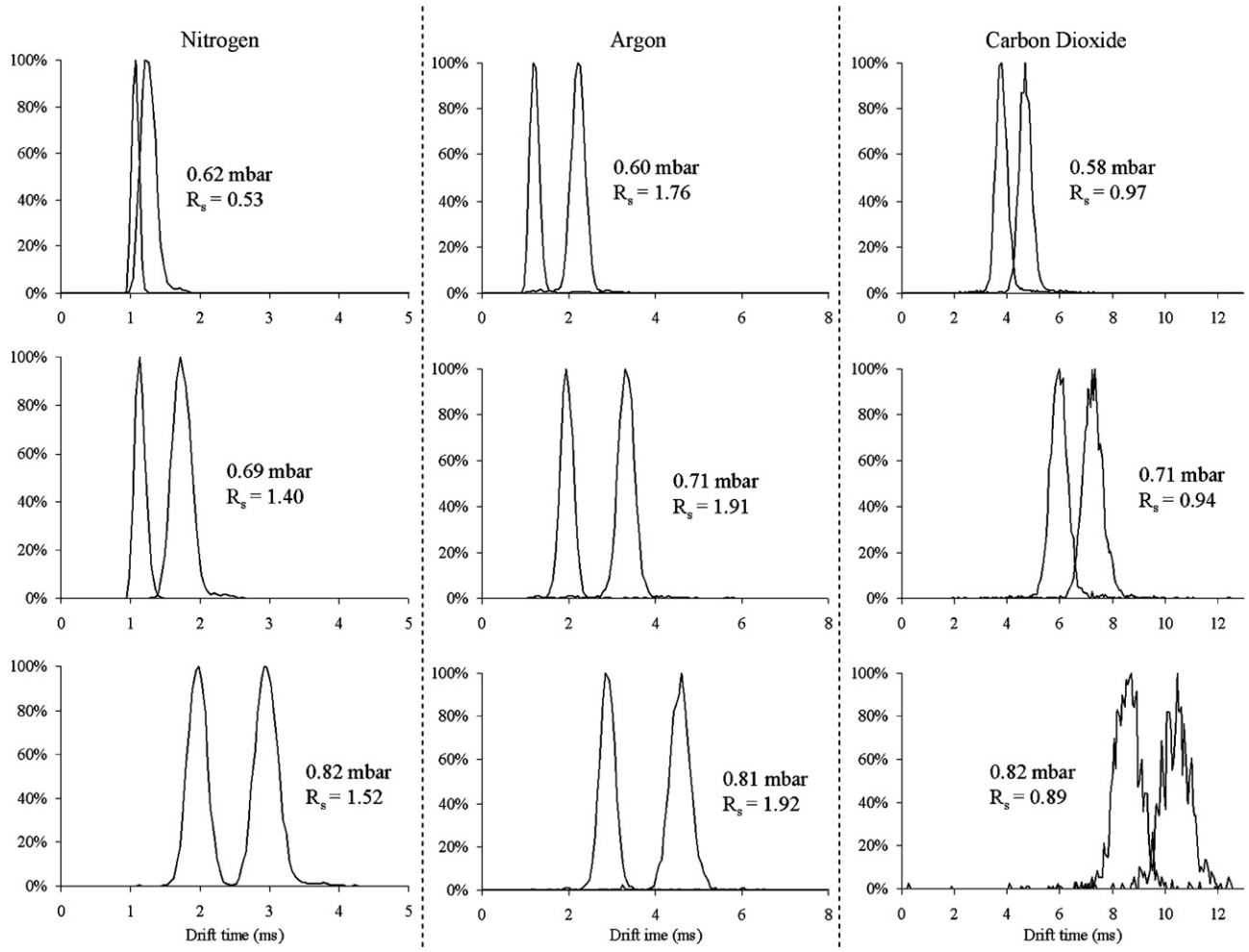

Fig. 4. IM–MS separation of Lamotrigine and Rosiglitazone $[M+H]^+$ ions in pure drift gases (nitrogen, argon and carbon dioxide) at pressures in the range 0.60–0.82 mbar (superimposed selected ion mobility responses for *m/z* 256 and *m/z* 358).

cases, an increase in pressure resulted in broader $[M+H]^+$ peak widths, which is most apparent in carbon dioxide (Fig. 4). In order to examine how drift gas composition affected ion mobility separation for the other components of the six component API test mix, R_S was calculated for each pair of analyte ions. The resolution of all of the test mix $[M+H]^+$ ion pairs followed the same trend observed for Lamotrigine/Rosiglitazone, with resolution increasing with increased pressure in all three gases and higher pressures resulting in reduced sensitivity. Separations in nitrogen resulted in the highest signal-to-noise ratio with carbon dioxide showing the lowest signal-to-noise ratio.

Partial fragmentation of Lamivudine impurity, Lamivudine, desfluoro-Paroxetine and Paroxetine was observed in argon, nitrogen, and carbon dioxide drift gases. In the case of Lamotrigine and Rosiglitazone no fragmentation was observed. The intensities of the $[M+H]^+$ and fragment ions for Paroxetine and desfluoro-Paroxetine, and the degree of fragmentation $(I_{F^+}/(I_{F^+} + I_{[M+H]^+}) \times 100)$ as a function of drift gas and pressure are presented in Table 2. The degree of fragmentation observed for Paroxetine and desfluoro-Paroxetine was lower in nitrogen than in argon and was relatively unaffected by pressure, although a small increase was observed for desfluoro-Paroxetine in argon. However, there was significantly greater fragmentation in carbon dioxide as the pressure was increased from 0.6 to 0.8 mbar: rising from 3.2 to 14.9% for Paroxetine and from 5.3 to 24.2% for desfluro-Paroxetine. The fall in signal intensity observed at elevated pressures in carbon dioxide is there-

Table 2
Ion intensities for $[M+H]^+$ and fragment F^+ ions, for APIs and related compounds as a function of drift gas and pressure.

Drift gas	Pressure (mbar)	Paroxetine			Desfluro-Paroxetine		
		$I_{[M+H]^+}$ (*m/z* 330)	I_{F^+} (*m/z* 192)	$(I_{F^+}/(I_{F^+} + I_{[M+H]^+})) \times 100$	$I_{[M+H]^+}$ (*m/z* 312)	I_{F^+} (*m/z* 174)	$(I_{F^+}/(I_{F^+} + I_{[M+H]^+})) \times 100$
Nitrogen	0.6	1510	38	2.5%	1030	84	7.5%
	0.7	1550	42	2.6%	1040	73	6.6%
	0.8	1240	21	1.7%	725	40	5.2%
Argon	0.6	894	82	8.4%	739	74	9.1%
	0.7	673	52	7.2%	613	53	8.0%
	0.8	476	48	9.2%	356	57	13.8%
Carbon dioxide	0.6	958	32	3.2%	659	37	5.3%
	0.7	376	25	6.2%	246	25	9.2%
	0.8	57	10	14.9%	47	15	24.2%

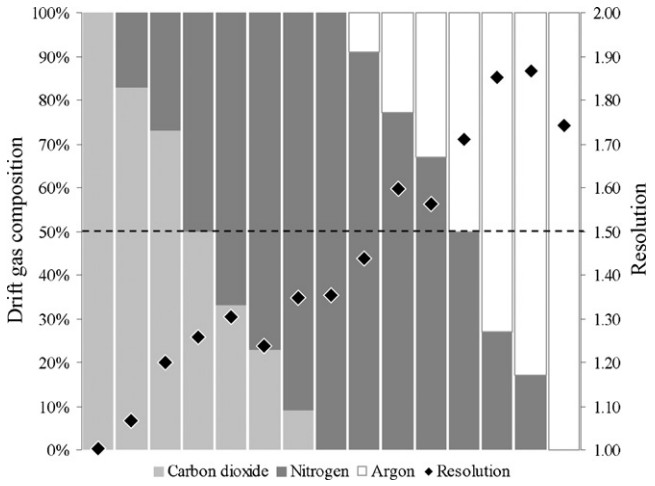

Fig. 5. Effect of drift gas composition on the ion mobility resolution of Rosiglitazone and Lamotrigine $[M+H]^+$ ions in binary drift gas mixtures. The composition of the binary drift gas mixtures are represented by shaded bars indicating the percentage of each gas in the mixture (left hand axis). Resolving powers greater than 1.5 indicate full separation of components and this threshold is indicated by the dashed line at a resolution of 1.5. The resolution of Lamotrigine and Rosiglitazone is indicated by ♦ (right hand axis).

fore due to fragmentation of the $[M+H]^+$ ion and ion scattering in the IM TWIG.

3.3. Binary drift gas mixtures

The resolution of the Lamotrigine and Rosiglitazone $[M+H]^+$ ions as a function of drift gas composition for binary mixtures of carbon dioxide/nitrogen and nitrogen/argon is shown in Fig. 5. These data were recorded with the IM flow controller set to pass 40 mL min^{-1} (calibrated to nitrogen) of the binary gas mixture prepared using the drift gas mixture manifold into the IM TWIG. The composition of the binary drift gas mixtures are represented by shaded bars indicating the percentage of each gas in the mixture (left hand axis). Resolving powers greater than 1.5 indicate full separation of components and this threshold is indicated in Fig. 5 by the dashed line. The resolution of Lamotrigine and Rosiglitazone indicated by ♦ (right hand axis) was lowest in pure carbon dioxide, but increased steadily as the drift gas composition changed from pure carbon dioxide to mixtures with nitrogen. The intensities of the $[M+H]^+$ ions also improved with increasing nitrogen content. However, even in pure nitrogen the Lamotrigine and Rosiglitazone are not fully resolved (R_s = 1.35).

Complete separation of the APIs was achieved using mixtures of nitrogen and argon. The resolution of the two peaks increased with the proportion of argon in the nitrogen/argon binary gas mixtures until better than full resolution (R_s > 1.5) was achieved with 23% argon in nitrogen. The highest resolution (R_s = 1.87) was obtained using a drift gas mixture containing 83% argon. However, increasing the argon content of the mixture decreased the intensity of the Rosiglitazone and Lamotrigine $[M+H]^+$ ions by 95 and 90%, respectively, going from pure nitrogen to pure argon, so a compromise must be made between enhanced resolution and adequate signal intensity. However, the S/N ratio was still greater than 10:1 in pure argon for the Rosiglitazone and Lamotrigine $[M+H]^+$ ion peaks.

4. Conclusions

The drift times of APIs and related $[M+H]^+$ ions vary with drift gas composition in carbon dioxide, argon, nitrogen and helium, increasing in the order; He < N_2 < Ar < CO_2. Drift times of the $[M+H]^+$ ions are significantly longer in argon than nitrogen, even though nitrogen has a slightly higher polarizability volume and effective molecular radius, because of the higher reduced mass in argon. The intensity of the $[M+H]^+$ ions decreased and the IM peak width increased at elevated drift gas pressure. At a given pressure the signal intensity is greatest in helium and decreases in the order nitrogen > argon > carbon dioxide. The decreasing signal intensity can be explained by the ion residence time within the drift tube [39], ion scattering in the IM TWIG and increased fragmentation in carbon dioxide.

The separation of the Lamotrigine and Rosiglitazone $[M+H]^+$ ions was increased by using binary drift gas mixtures. Resolution increased with nitrogen content in carbon dioxide/nitrogen mixtures and was further improved by increasing the argon content in argon/nitrogen mixtures, but with the loss of signal intensity as the proportion of argon increased. This work shows that tuneable selectivity enhancements in the analysis of mixtures of pharmaceutical related compounds are possible with binary drift gas mixtures using tri-wave IM–MS.

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