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ORIGINAL ARTICLE

Direct detection and identification of active pharmaceutical ingredients in intact tablets by helium plasma ionization (HePI) mass spectrometry

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Abstract A simple modification converts an electrospray ion source to an ambient-pressure helium plasma ionization source without the need of additional expensive hardware. Peaks for active ingredients were observed in the spectra recorded from intact pharmaceutical tablets placed in this source. A flow of heated nitrogen was used to thermally desorb analytes to gas phase. The desorption temperatures were sometimes as low as 50 °C. For example, negative-ion spectra recorded from an aspirin tablet showed peaks at m/z 137 (salicylate anion) and 179 (acetylsalicylate anion) which were absent in the background spectra. The overall ion intensity increased as the desorption gas temperature was elevated. Within the same acquisition experiment, both positive- and negative-ion signals for acetaminophen were recorded from volatiles emanating from Tylenol tablets by switching the polarity of the capillary back and forth. Moreover, different preparations of acetaminophen tablets could be distinguished by their ion-intensity thermograms.

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1. Introduction

Traditional techniques for analysis of pharmaceutical formulations, such as chromatographic and excitation spectroscopic methods, are time-consuming and need specific sample handling procedures. In contrast, mass-spectrometry-based techniques are considered more efficient. With the introduction of the new approach of desorption

electrospray ionization mass spectrometry (DESI-MS) [1], the sampling methods focused on ambient ionization techniques have received considerable attention [2,3]. DESI, which uses a spray of charged solvent droplets from an electrospray ion source, relies upon the formation of secondary ions from analytes present in a sample. By this procedure, active ingredients in drug formulations and intact pharmaceutical tablets have been detected directly [4–8]. However, for more efficient sample desorption the tablets should be broken into pieces [9,10]. Additionally, although rapid switching between positive- and negative-ion generating modes is possible with DESI, the chemistry of the spray solution should be modified for each mode to optimize signal intensity [10]. Furthermore, the use of a solvent spray sometimes interferes with the integrity of the sample. Moreover, DESI is well-known to form cationic metal adducts, in addition to the desired protonated molecules [11].

Another commonly used method for direct determination of pharmaceutical drug formulations is direct-analysis-in-real-time mass spectrometry (DART-MS). DART is able to detect principal compounds directly without the need of solvents or prior sample preparation [12]. For DART ionization, gaseous metastable atoms or molecules produced from a glow discharge, together with neutral molecules, are heated and directed toward a sample held between the ion source outlet and the mass spectrometer interface inlet [12]. It is known that sample orientation and sample proximity to the ion source inlet strongly influence the signal variance; inconsistent sample positioning results in variable heating due to differences in thermal gradients [13]. In contrast to DART, which is a corona-to-glow discharge, the flowing atmospheric-pressure afterglow (FAPA) source described by Shelley et al. employs a corona-to-glow transition discharge. For FAPA, helium or some other discharge gas is passed over a pin cathode [14]. Both methods generate somewhat similar mass spectra. One drawback of helium-mediated ion sources, such as DART and FAPA, is that they require expensive hardware modifications and consume excessive amounts of helium [15].

In order to develop a high-throughput and more economical procedure, particularly for switching between positive- and negative-ion generating modes and for the analysis of intact tablets, we investigated the applicability of the recently described helium-plasma ionization mass spectrometric method [15–17] to the direct analysis of pharmaceutical preparations. Results obtained from several over-the-counter and prescription pharmaceutical tablets and capsules are reported here.

2. Experimental

2.1. Materials

Advil® (Wyeth, Madison NJ; Ibuprofen: 200 mg), Aspirin (Wakefern, Elizabeth NJ; 325 mg), Claritin® (Schering-Plough, Memphis TN; Loratadine: 10 mg), Regular Strength Tylenol® (McNeil, Fort Washington PA; Acetaminophen: 325 mg), Extra Strength Tylenol® (McNeil, Fort Washington PA; Acetaminophen: 500 mg), Children's Tylenol® Meltaways® (McNeil, Fort Washington PA; Acetaminophen: 80 mg), Paracetamol (Bufferin Cold) Daytime formulation (Sino-American Shanghai Squibb Pharmaceuticals Ltd, Shanghai CN; Acetaminophen: 500 mg, Pseudoephedrine HCl: 30 mg, Dextromethorphan HBr: 15 mg), Paracetamol (Bufferin Cold) Nighttime formulation (Sino-

American Shanghai Squibb Pharmaceuticals Ltd, Shanghai CN; Acetaminophen: 500 mg, Pseudoephedrine HCl: 30 mg, Dextromethorphan HBr: 15 mg, Chlorpheniramine Maleate: 2 mg), CVS® Pharmacy Severe Head Congestion Cold Relief Daytime formulation (CVS® Pharmacy, Woonsocket RI; Acetaminophen: 325 mg, Dextromethorphan HBr: 10 mg, Phenylephrine HCl: 5 mg, Guaifenesin: 200 mg), CVS® Pharmacy Multi-Symptom Cold Relief Nighttime (CVS Pharmacy, Woonsocket RI; Acetaminophen: 325 mg, Chlorpheniramine Maleate: 2 mg, Dextromethorphan HBr: 10 mg, Phenylephrine HCl: 5 mg), Dramamine® (Prestige Brands, Tarrytown NY; Dimenhydrinate: 50 mg), and Bonine® (Insight Pharmaceuticals, Trevose PA; Meclozine HCl: 25 mg) were obtained without prescription from a pharmacy. Simvastatin (Merck, Whitehouse Station NJ; 20 mg), Verapamil (Mylan, Canonsburg PA; 120 mg), and Clindamycin HCl (Teva, North Wales PA; 300 mg) were obtained by prescription.

2.2. Instrumentation and procedures

A commercially available Z-electrospray ion source of a Waters Micromass Quattro Ultima mass spectrometer was modified into a helium-plasma ionization source as described previously [14–16]. In brief, a stream (25–30 mL/min) of high-purity helium (99.999%, Airgas, Radnor, PA) was supplied through the sample delivery metal capillary held at a high voltage (typically, −3 kV). The capillary was placed at an angle of 90°, about 10 mm away from the outer cone orifice. Mass spectra were recorded upon exposure of each tablet to the helium plasma generated in this way, at the tip of the metal capillary (Fig. 1). Each tablet was held in a fixed position with a pair of tweezers, and exposed to the helium plasma ionization source. The results were processed using the MassLynx software (version 4.0). The ion source was cleaned by wiping with a methanol-soaked cotton swab before each new sample was introduced. The cone voltage was held between 10 and 20 V. The source temperature was maintained at 100 °C. Nitrogen was used as the desolvation gas (Gas 2, Fig. 1) at a flow rate of about 3.5 L/min. The heater in the desolvation gas line was used to increase the temperature of the nitrogen desolvation gas (in other words, the desolvation gas of the electrospray ionization source was used as the thermal desorption agent). Each tablet was analyzed at seven different desorption temperatures: 50 °C, 100 °C, 150 °C, 200 °C, 250 °C, 300 °C, and 350 °C. Simvastatin and other high-molecular-weight analytes were investigated at higher temperatures such as 400 °C, 450 °C, and 500 °C. Background spectra were acquired at each desolvation-gas temperature and subtracted from the raw spectra. Mass spectra were recorded under both positive- and negative-ion generating modes. For tandem mass spectrometric experiments, the pressure of argon used as the collision gas was adjusted to attenuate the ion beam by 50%.

For thermograms, total ion intensity profiles (m/z 15–500) were recorded under negative-ion generating conditions from volatiles emanating from two types of preparations containing acetaminophen. The two types of preparations used were Regular Strength Tylenol® and CVS® Pharmacy Severe Head Congestion Cold Relief Daytime formulation. Initially, background spectra were recorded at 50 °C for the first 2 min. The tablet was then introduced into the ion source at 50 °C, and the temperature was increased by 50 °C every 2 min to reach a final temperature of 300 °C at 12 min.
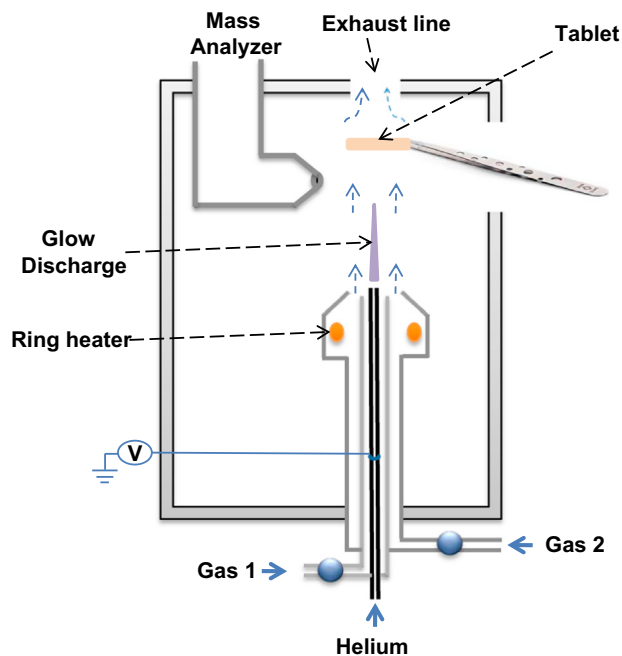
Fig. 1 A schematic diagram that illustrates an electrospray ionization source modified to function as a helium plasma ionization source (HePI) (Gas 1 supply was not used; Gas 2 was nitrogen). The tip of the capillary is about 10 mm from the cone orifice inlet of the mass analyzer.

3. Results and discussion

The formation of a zone of helium plasma at the tip of the capillary was noted when a low flow of helium gas was passed through the tube of the modified electrospray source while a high potential was being applied [15]. In this way, any electrospray ionization source can be converted to a helium-plasma ionization source without the need for any additional hardware. Apparently, the use of helium as the coaxial nebulizing gas has been avoided by the pioneers of the electrospray technique because the facile formation of a low-voltage plasma caused complications with the electrospray ionization process. We also found that the glow discharge obtained by using helium as the coaxial nebulizer gas is erratic. However, we discovered that a more stable plasma can be obtained if helium is passed through the capillary. The spectra recorded from ions generated in this way from similar samples were comparable to those obtained by other ambient pressure ionization mass spectrometric methods such as DART-MS. For DART, the potential is applied to an external needle exposed to a flow of 1.5–3 L of helium per minute. In contrast, our method consumes only about 20–30 mL of helium per minute.

The excited helium atoms in the plasma are in the so-called "metastable" state (2^3S_1) and carry about 19.8 eV of energy. Upon interactions with ambient molecules (or any analyte molecules) with an ionization potential lower than the energy carried by excited helium atoms, a process called Penning ionization takes place. Ionized molecules generated in this way then transfer charge to other analyte molecules by secondary charge-exchange reactions [15].

The amount of volatile molecules emanating from pharmaceutical preparations at ambient, or slightly above ambient, temperatures was expected to be relatively low. However, prominent peaks were observed when mass spectra were recorded after intact pharmaceutical tablets were exposed to a HePI source.

For example, the spectra recorded under negative-ion generating conditions from an intact Aspirin tablet showed sample-specific peaks at m/z 137 and 179. The generation of these ions in the source was evident even at desorption temperatures as low as 50 °C (Fig. 2B). These peaks were absent in the spectra recorded from background ions (Fig. 2A). Other spectra shown in Fig. 2 were recorded from volatiles emanating from an unbroken aspirin tablet at different desorption temperatures (50–350 °C, Fig. 2B–H). The peaks at m/z 60 ($CO_3^{-\bullet}$), 61 (HCO_3^-), 77 ($CO_2 \cdot OOH^-$), and 212 represent background ions generated by the ionization of ambient gases and source impurities [12]. The peaks at m/z 137 (salicylate anion) and 179 (acetylsalicylate anion) appeared only after an aspirin tablet was introduced to the source (Fig. 2B). As the temperature of the thermal desorption gas was increased, a gradual increase of the overall ion intensity was recorded. At higher temperatures, the intensities of sample peaks were so overwhelming that the background peaks were no longer significant (Fig. 2H). Moreover, at about 350 °C, a peak appeared at m/z 275 for the salicylic acid dimer. The identities of m/z 179 and m/z 137 ions were confirmed by tandem mass spectrometric experiments (Supplementary Fig. 1).

Fig. 3 depicts signal intensity profiles recorded after placing an intact Extra Strength Tylenol tablet in the helium plasma ionization source. The desorption gas temperature was held at 300 °C. Initially, signals were recorded under positive-ion generating conditions (Fig. 3A). After 2 min, the capillary voltage was switched to negative polarity, and negative-ion spectra were recorded for 2 min (Fig. 3B). The switching between the positive and negative modes was repeated every 2 min (Fig. 3C and D). In this way, mass spectral peaks for the active ingredient (acetaminophen; nominal mass 151) were observed as a protonated species (m/z 152) or a deprotonated species (m/z 150) in consecutive positive- and negative-ion generating modes within one experiment. The results demonstrated the versatility of the helium plasma
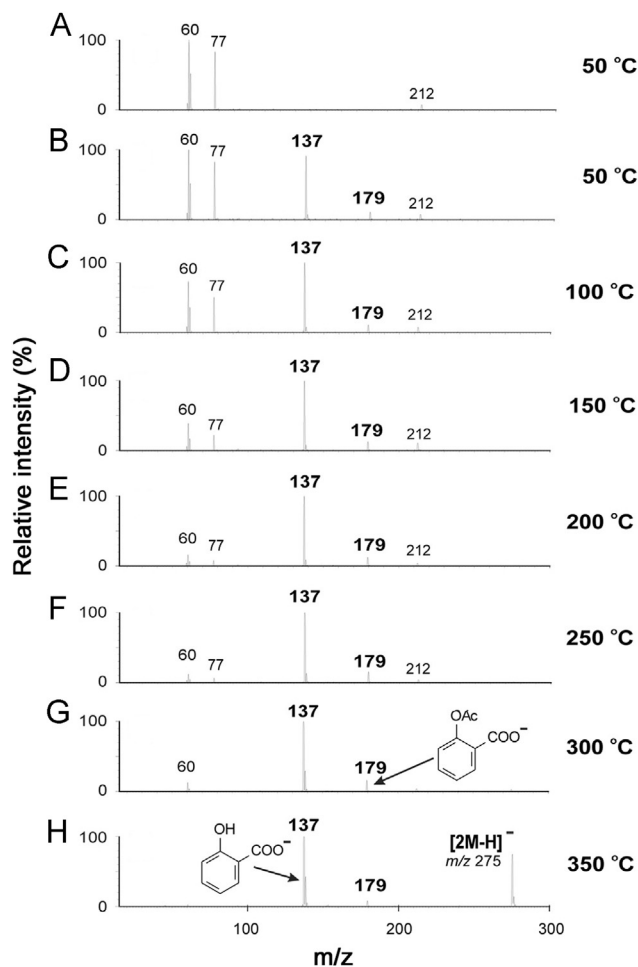
Fig. 2 Mass spectra recorded under negative-ion generating HePI-MS conditions from ambient background volatiles (A), and those emanating from an Aspirin tablet exposed to "desolvation gas" heated to different temperatures (50–350 °C) (B–H). The spectra are shown without any background subtraction. Peaks at m/z 60, 61, 77, and 212 represent background ions present in the source.

ionization procedure for rapid switching between positive- and negative-ion generating modes. Obtaining both positive and negative spectra is vital for complete characterization of ingredients because certain compounds selectively ionize in one mode. For example, peaks for the minor components dextromethorphan [(M+H)$^+$, m/z 272] and chlorophenamine [(M+H)$^+$, m/z 275 and 277] in CVS$^®$ Pharmacy Multi-Symptom Cold Relief caplets are observed only in the positive ion mode (Supplementary Fig. 2A), whereas the phenolic compound phenylephrine [(M−H)$^-$, m/z 166] is detected under the negative mode (Supplementary Fig. 2B).

Although rapid polarity switching is also possible under desorption electrospray ionization (DESI) conditions, for optimal ion generation the chemistry of the spray solvent should be varied between modes [10]. Moreover, ESI-related desorption techniques charge analytes not only by protonation but also by cationization with metal ions, which most analytical chemists consider a nuisance [18]. Chan et al. described a procedure to evade metal adduct formation by using toluene as the spray solvent [19]. On the other hand, the HePI procedure described here is not only suitable for rapid polarity switching within one experiment, but it also avoids complexities due to the formation of metal adducts.

Results similar to those obtained from Extra Strength Tylenol tablets (Fig. 3) were obtained from Paracetamol Daytime tablets (Supplementary Fig. 3). Both Tylenol and Paracetamol contain acetaminophen as the active pharmaceutical ingredient, and its identity was confirmed by tandem mass spectrometry (Supplementary Fig. 4A and B). However, the spectra recorded from Paracetamol showed several additional peaks (Supplementary Figs. 3 and 5). For example, the peak at m/z 166 in the negative-ion spectra, and that at m/z 168 in the positive-ion spectra represented an additional ingredient of nominal mass 167, which was identified as phenylephrine by its product-ion spectrum recorded by tandem mass spectrometry (Supplementary Fig. 4C).

Although profile data obtained from Paracetamol Nighttime tablets (Supplementary Figs. 6 and 7), were very similar to those obtained from Paracetamol Daytime tablets (Supplementary Figs. 3 and 5), it was noted that the intensities of acetaminophen-related peaks (for example m/z 150 and 301 in the negative mode) relative to the background peaks (m/z 60 and 77) increased more rapidly for Paracetamol Daytime tablets (Supplementary Fig. 3) than those for Paracetamol Nighttime tablets (Supplementary Fig. 6) as the temperature of the desorption gas was increased. Many acetaminophen preparations have additional ingredients including pharmacologically inactive excipients (Supplementary Fig. 8). In order to find out the diagnostic value of the mass spectral profiles obtained from total volatiles at different thermal desorption temperatures, spectra were recorded from two different preparations of acetaminophen tablets. At first, background spectra were recorded at 50 °C for 2 min, then a tablet was introduced into the ion source, and after an initial isothermal period of 2 min the desorption temperature was increased every 2 min by 50 °C. Total-ion spectral profiles obtained for the m/z 15–500 range from volatile compounds emanating from intact Regular Strength Tylenol and Paracetamol Daytime tablets are depicted in Fig. 4. Both these tablets are different preparations of acetaminophen. However, the former is an uncoated tablet whereas the latter is coated. A comparison of the intensity curves obtained from three determinations for each tablet showed that the profiles were specific and reproducible for each preparation (Fig. 4). For example, the total-ion signals recorded from the emanating volatiles from the uncoated Regular Strength Tylenol tablets reached the maximum ("saturation" at 1×10^{10} arbitrary units) at 250 °C (upper three profiles; Fig. 4) whereas the coated Paracetamol Daytime tablets required a temperature of 300 °C for saturation (lower three profiles; Fig. 4). Presumably, the differences observed are due to the presence of a thicker outer coating in the coated Paracetamol Daytime tablets.

The applicability of the thermal desorption procedure to characterize volatiles emanating from pharmaceutical preparations was further tested with Advil$^®$, Claritin$^®$, Simvastatin, Dramamine$^®$, Bonine$^®$, Verapamil, and Clindamycin tablets. The spectra acquired under negative-ion generating mode from Advil tablets showed a peak at m/z 205 ion for the deprotonated active ingredient ibuprofen (Supplementary Fig. 9). A product-ion spectrum of m/z 205 confirmed that it is a carboxylic acid (Supplementary Fig. 10). At higher temperatures (>350 °C), three new peaks appeared at m/z 325, 383, and 397 in the spectra recorded from Advil tablets. Collision-induced dissociation of ions of m/z 325 and 383 indicated that these ions are related to ibuprofen (Supplementary Fig. 11).

The active ingredient in Claritin tablets is loratadine. Relatively high desorption gas temperatures were required for the thermal desorption of loratadine from Claritin tablets. The first signals for protonated loratadine appeared only at about 200 °C. At 350 °C,
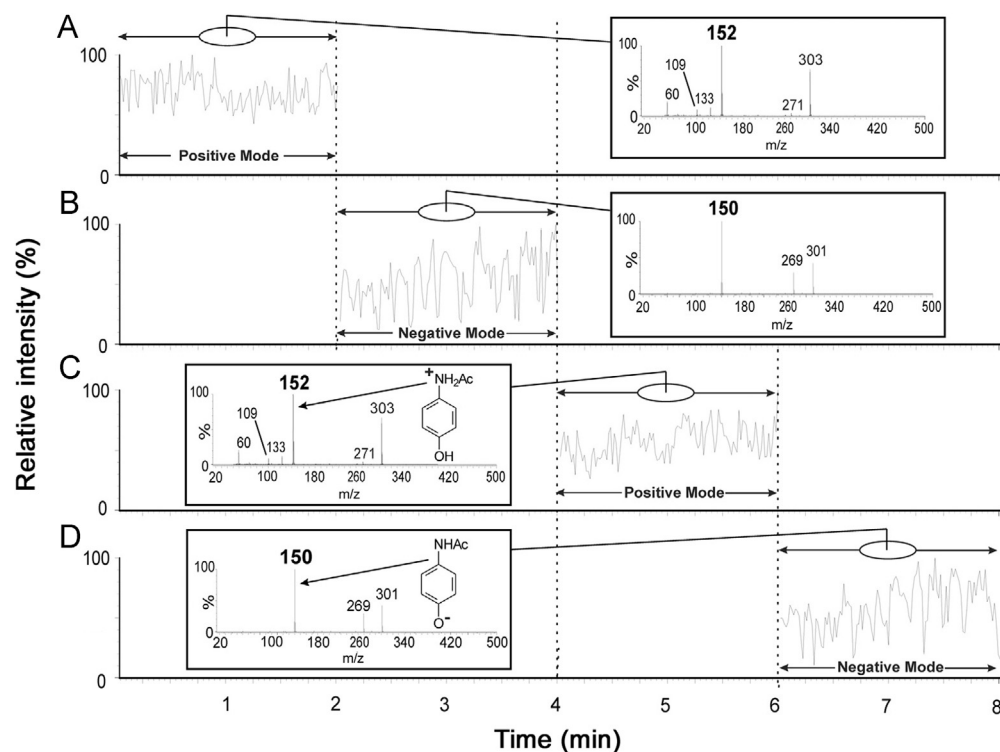
Fig. 3 Total ion intensity profiles (*m/z* 15–500) recorded from volatiles emanating from an Extra Strength Tylenol tablet exposed to "desolvation gas" heated to 300 °C. Spectra were recorded under positive-ion generating conditions for 2 min (A), and then under negative-ion generating mode for the next 2 min (B). This rapid switching procedure was repeated at 2-min intervals (C and D). Spectra shown in insets were obtained by co-adding all spectra for each segment.
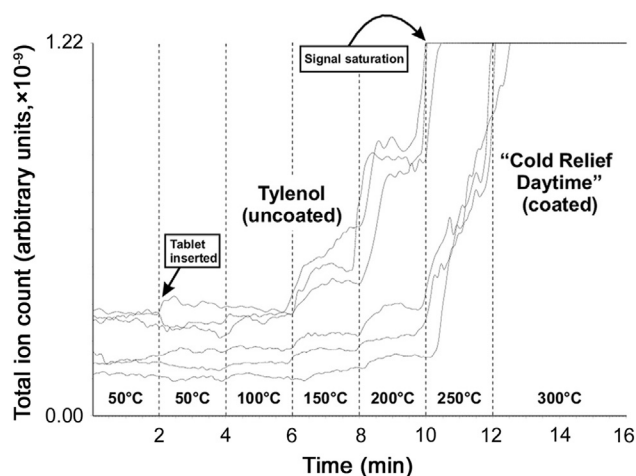
Fig. 4 Total ion intensity profiles (*m/z* 15–500) recorded under negative-ion generating conditions from volatiles emanating from two different preparations of acetaminophen tablets exposed to hot "desolvation gas." The two types of tablets exposed were regular strength (upper traces), and cold-relief daytime (lower traces). Background spectra were recorded at 50 °C for the first 2 min. The tablet was then introduced into the ion source at 50 °C, and the temperature was increased by 50 °C every 2 min to reach a final temperature of 300 °C at 12 min.

a well-defined peak cluster with the characteristic intensity profiles for the different isotopologs of protonated loratadine was visible (Supplementary Fig. 12). The identity of loratadine was confirmed by tandem mass spectrometry (Supplementary Fig. 13). The spectra

recorded from both Dramamine and Meclozine tablets showed intense peaks for the active ingredients (Supplementary Figs. 14 and 15, respectively). To demonstrate the high-throughput applications of the method described, we exposed four different pharmaceutical tablets (simvastatin, verapamil, meclozine, and loratadine), one at a time, within a span of 5 min (Fig. 5). Each tablet was exposed for approximately 30 s. The total ion intensity sharply increased at each tablet insertion and immediately decreased to background level once the tablet was removed from the source. For our experiments, tablets were introduced manually. Automation should decrease the per tablet analysis time to less than 1 min.

By the technique described, peaks were recorded even from active ingredients with molecular weights above 400. For example, the positive-ion spectrum recorded from simvastatin tablets showed a peak at *m/z* 419 for the protonated species (Supplementary Fig. 16). The signals started to appear only at about 350 °C because simvastatin is a relatively large molecule. At the same high temperature, a peak was observed at *m/z* 455 for the active ingredient of Verapamil tablets (Supplementary Fig. 17), and at *m/z* 425 for that of Clindamycin tablets (Supplementary Fig. 18).

4.   Conclusions

We have described a high-throughput procedure for the direct analysis of intact pharmaceutical tablets by an ambient-pressure mass spectrometric technique. Compared to the widely deployed DESI-MS procedures, which often generate sodium and other cationic adducts (and anionic adducts under negative-ion generating conditions), our helium plasma ionization procedure does not generate any metal adducts. For rapid switching between positive- and negative-ion
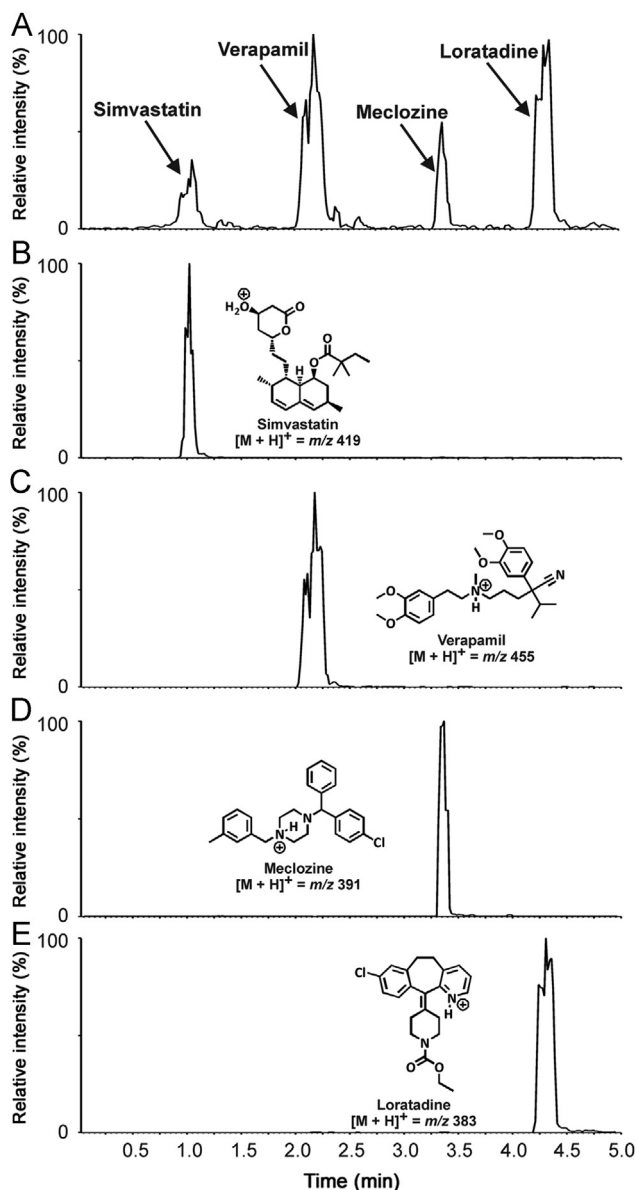
Fig. 5 The total ion intensity profile (m/z 25-500) recorded from volatiles emanating from simvastatin (0.75–1.25 min), verapamil (2.00–2.50 min), meclozine (3.25–3.50 min), and loratadine (4.00–4.50 min) tablets exposed to "desolvation gas" heated to 350 °C under positive-ion generating conditions (A), and the extracted ion intensity profiles for simvastatin ([M+H]$^+$, m/z 419) (B), verapamil ([M+H]$^+$, m/z 455) (C), meclozine ([M+H]$^+$, m/z 391) (D), and loratadine ([M+H]$^+$, m/z 383) (E).

generating modes, DESI-MS is not very practical because the chemistry of the spray solution must be changed and optimized for each mode. In the solventless HePI-MS procedure, the polarity can be switched from one acquisition mode to the other without the need for reoptimization. Moreover, the HePI-MS procedure consumes much less helium than that required for DART or FAPA-MS. The results reported here from several over-the-counter and prescription pharmaceutical preparations demonstrate the potential of the helium plasma ionization procedure for developing high-throughput protocols for drug analysis. Furthermore, peaks for sodium and other metal adducts were not observed in the spectra recorded under the positive-ion-generating

mode. This is a key advantage of HePI over most spray methods because spectral complexity is reduced.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jpha.2013.09.010.

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