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Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection☆

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ABSTRACT

A high-pressure liquid chromatography-diode array detection and multi-mode ionization tandem mass spectrometry (HPLC-DAD–MMI-MS/MS) method was used to identify amino-tadalafil and rimonabant in electronic cigarette (e-cigarette) cartridges. Amino-tadalafil is a drug analogue of the commercially approved Cialis™ (i.e. tadalafil). Rimonabant is a drug that was, at one time, approved for weight loss in Europe (although approval has been retracted), but not in the United States. In addition, poor quality control over the e-cigarette products analyzed here is shown by the presence of nicotine in products labeled as containing no nicotine or by the presence of significant amounts of rimonabant oxidative degradant in e-cigarette products containing rimonabant. Identification was accomplished by comparing the retention time of relevant peaks in the sample with those of standard compounds, in addition to comparison of the UV spectra, mass spectra and/or product ion mass spectra.

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1. Introduction

Adulteration of products such as dietary and herbal supplements with drugs is a practice which can lead to potentially serious health consequences. Numerous reports exist in the literature of various matrices (e.g. herbal supplements, dietary supplements, pills, etc.) being adulterated with various drug compounds [1–6]. Safety issues are complex and include possible toxicity of natural constituents, presence of contaminants or adulterants, and potential interactions between natural constituents, adulterant compounds and any prescription drugs a user may be taking. For example, tadalafil which is used for treatment of erectile dysfunction (ED), has been found as an adulterant in a variety of products [2,5]. It is known that this drug can drastically lower blood pressure when taken in conjunction with certain nitrate containing drugs creating the possibility of a serious life-threatening event [7].

Electronic cigarettes are new devices being marketed as a way to enjoy the benefits of smoking without the serious health hazards associated with it. E-cigarette devices are designed to be refilled by purchasing either replacement liquids which are then used to refill existing delivery cartridges or new cartridges containing the desired flavor blend. Two basic designs of e-cigarettes currently exist, and their design differs in how the flavor solution is contained and heated. Both designs are based on the same principle: inhalation on the mouth piece activates a heater element. The heater element then aerosolizes the flavor solution which can consist of various combinations of propylene glycol, nicotine, tobacco extracts, flavorants and/or adulterants.

A thorough review of the legal status of e-cigarettes is beyond the scope of this publication, however, regulations concerning the distribution and/or sales of e-cigarettes are quite variable depending on the region. For example, e-cigarettes cannot be sold in Australia, Brazil, Canada, Panama, Singapore or Switzerland, but their sale is authorized in Britain, China, Denmark, Italy, the Netherlands and New Zealand. However, in Denmark and New Zealand, electronic cigarettes are considered medical devices and their sale is contingent on approval of the government or prescription by a medical authority [8,9]. Within the United States, the sale of e-cigarette products is legal, however, the importation of e-cigarette products is currently prohibited.

☆ The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

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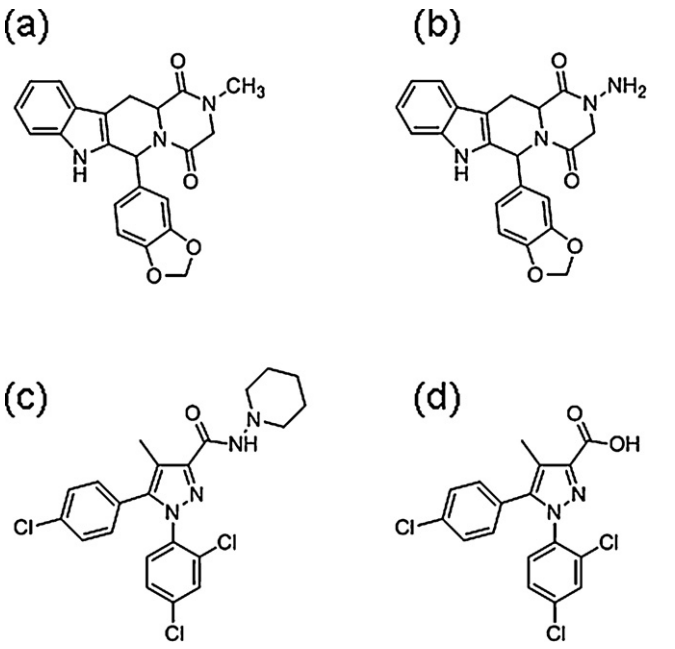

Fig. 1. Structures of (a) tadalafil ($[M+H]^+ = 390$) and (b) amino-tadalafil ($[M+H]^+ = 391$). Structure of (c) rimonabant ($[M+H]^+ = 463$) and (d) rimonabant impurity ($[M+H]^+ = 381$) formed under oxidative conditions.

Further, the classification of e-cigarettes either as a tobacco product or as a drug delivery device is currently being contested [10].

Amino-tadalafil is a structural analogue of tadalafil, (6R,12aR)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [10,20:1,6] pyrido[3,4-b]indole-1,4-dione, the active pharmaceutical ingredient in Cialis™, a prescription drug approved in the US for treatment of ED. The structures of tadalafil and amino-tadalafil are shown in Fig. 1(a) and (b), respectively. It has been reported that ED drugs such as tadalafil, have been added to other, unapproved, matrices ostensibly to treat ED [2]. Similarly, there have also been reports of herbal or dietary supplements being adulterated with designer ED analogues such as amino-tadalafil [5].

Rimonabant, 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-1H-pyrazole-3-carboxamide (trade name Zimulti™), was approved for the treatment of obesity in Europe, however its marketing authorization was withdrawn by the European Medicines Agency in 2009. Approval by the US FDA has been withheld due to unresolved issues between rimonabant therapy and increased frequencies of psychiatric adverse events, including suicide and an ill-defined constellation of neurological symptoms and seizures [11]. The structures of rimonabant and its oxidative impurity are shown in Fig. 1(c) and (d) respectively.

The purpose of this communication is to show the presence of an unapproved active pharmaceutical ingredient (API), rimonabant, and an ED drug analogue, amino-tadalafil in e-cigarette products. We will show that the contents of e-cigarette cartridges or refill solutions are poorly controlled as evidenced by the presence of compounds where they should not be (e.g. nicotine present in products advertised as containing no nicotine) or by the undisclosed degradation of advertised ingredients. Finally, we will show that e-cigarette products can now be included in the array of products which can be adulterated with active pharmaceutical ingredients or their analogues.

Table 1
Summary results of E-Cialis products.

Product	Label Nicotine content	Tadalafil Present?	Amino-tadalafil Present?	Rimonabant Present?	Rimonabant oxidation product Present?	Nicotine Present?
E-Cialis Cartridge	E-High	No	Yes			Yes
E-Cialis Cartridge	None	No	Yes			Yes
E-Cialis Cartridge	High	No	Yes			Yes
E-Cialis Refill Liquid	11 mg	No	Yes			Yes
E-Cialis Refill Liquid	0 mg	No	Yes			Yes
E-Rimonabant Cartridge	None			Yes	Yes	Yes
E-Rimonabant Cartridge	None			Yes	Yes	Yes
E-Rimonabant Cartridge	E-High			Yes	Yes	Yes
E-Rimonabant Refill Liquid	11 mg			Yes	Yes	Yes
E-Rimonabant Refill Liquid	0 mg			Yes	Yes	Yes

Note: E-High ("E" as in extra), High and None refer to nicotine levels.

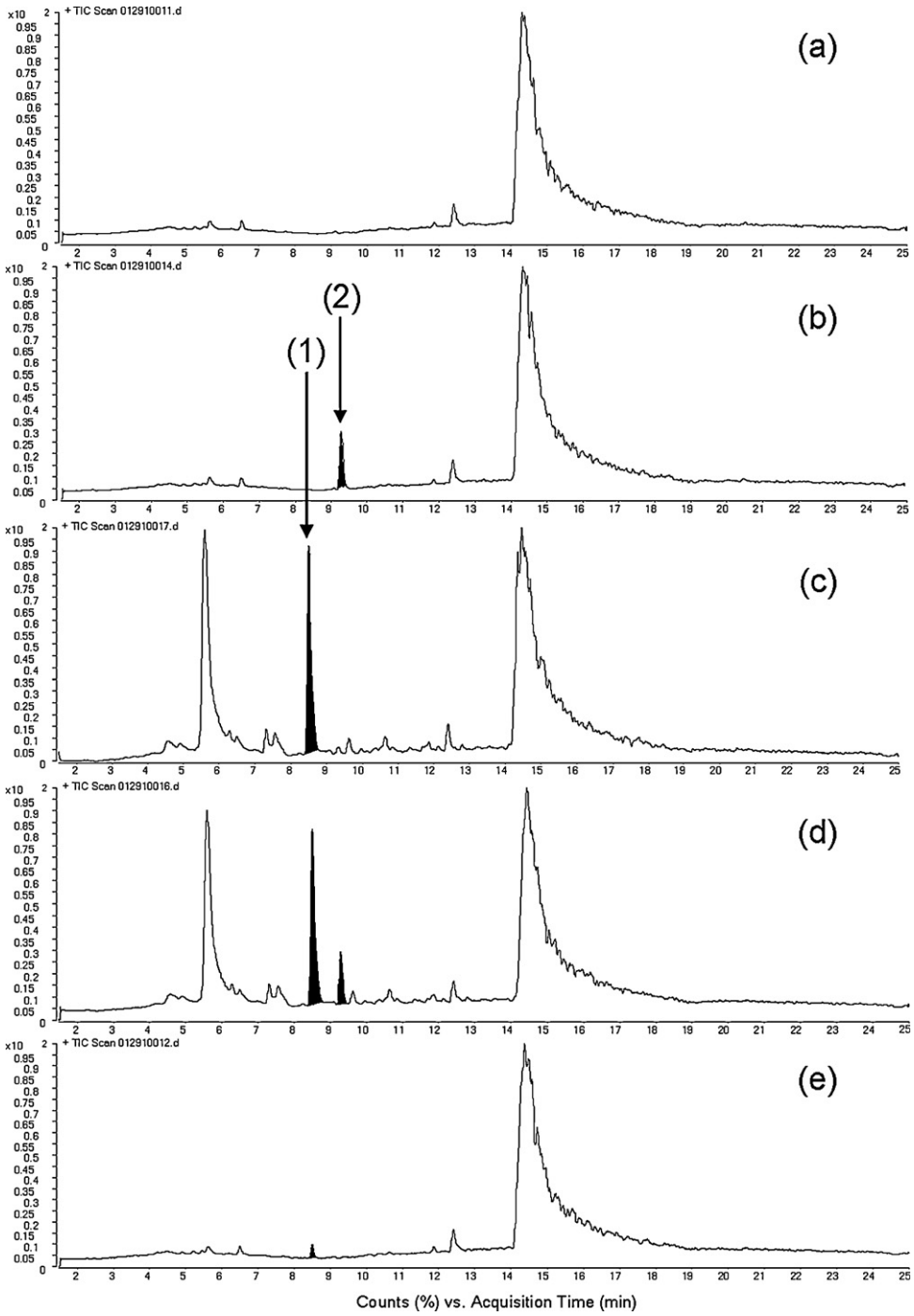

Fig. 2. TICs of (a) blank, (b) tadalafil standard solution, (c) e-cigarette sample solution labeled as containing Cialis, (d) e-cigarette solution spiked with tadalafil, (e) 10 μg/mL amino-tadalafil. (1) Amino-tadalafil, retention time at about 8.5 min, (2) Tadalafil, retention time at about 9.3 min.

2. Materials and methods

2.1. Chemicals and reagents

Rimonabant HCl (99%) was purchased from AK Scientific (Mountain View, Ca, USA). Tadalafil (99.7%, commercial name Cialis™) was supplied by Eli Lilly. Amino-tadalafil was purchased from Toronto Research Chemicals (North York, Ontario, Canada). Acetonitrile (Optima LC/MS grade) and water (Optima LC/MS grade) were purchased from Fisher Scientific (Pittsburgh, PA, USA). Ammonium acetate was purchased from Sigma Chemicals (St. Louis, MO, USA). A HALO C18 (2.1 mm × 100 mm, 2.7 μm) column was purchased from Phenomenex (Torrance, Ca, USA). E-cigarette samples were purchased by the FDA via the internet.

2.2. Equipment

An Agilent 1200 HPLC system consisting of an autosampler (G1367C), binary gradient pump (G1312B), column heater (G1316B), diode array detector (G1315C), eluent degasser (G1379B) and triple quadrapole mass spectrometer (G6410B) was used for analysis. The mass spectrometer was equipped with a multi-mode

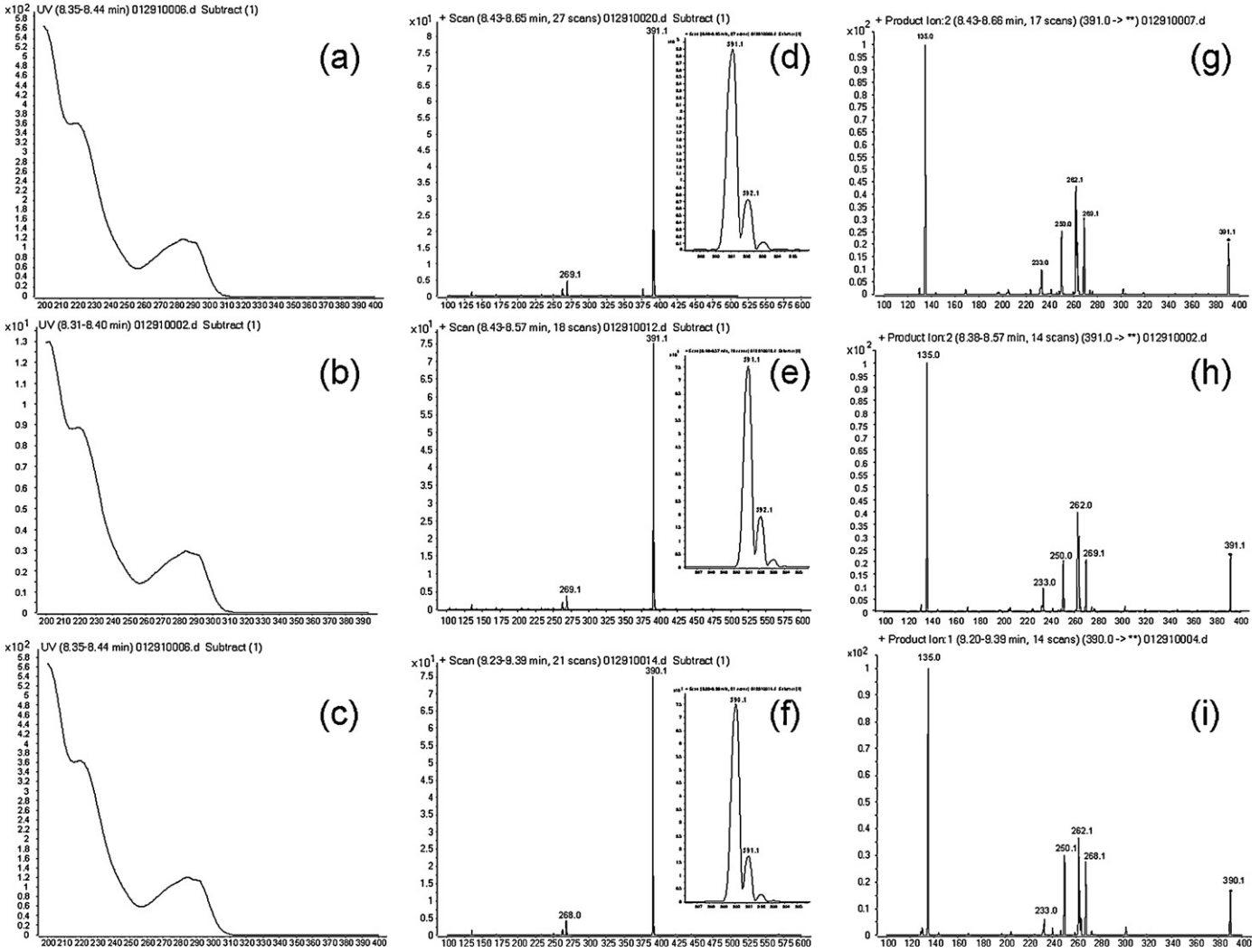

Fig. 3. Representative spectra of amino-tadalafil. UV spectra of (a) peak eluting at about 8.5 min in e-cigarette sample solution in Fig. 2, (b) 10 μg/mL amino-tadalafil standard solution, and (c) 10 μg/mL tadalafil standard solution. Mass spectra of (d) peak eluting at about 8.5 min in e-cigarette sample solution in Fig. 2, (e) 10 μg/mL amino-tadalafil standard solution, and (f) 10 μg/mL tadalafil standard solution. Isotopic peak distribution for full scan mass spectra are shown in the insets. Product ion mass spectra of (g) peak eluting at about 8.5 min in e-cigarette sample solution in Fig. 2, (h) 10 μg/mL amino-tadalafil standard solution, and (i) 10 μg/mL tadalafil standard solution.

ionization (i.e. ESI and APCI simultaneously) source (G1978B) and operated in the positive ion mode.

2.3. Standard solution preparation

Stock standard compounds were used as received and prepared at a concentration of approximately 1 mg/mL in acetonitrile. Working standard solutions were prepared by serial dilution of the stock standard solution in either 1:1 (v:v) methanol:acetonitrile or 3% H_2O_2 in 1:1 (v:v) acetonitrile:water (for oxidative degradation).

2.4. Sample extract preparation

Sample preparation varied depending on whether a replacement cartridge or refill solution was being analyzed. If a cartridge was being analyzed the following method was employed. Both white plastic cartridge end covers were removed from the black cartridge body. A white (retaining) plug was removed from one end revealing the cartridge contents. The heater element wire was cut and a rolled up mat impregnated with e-cigarette solution was removed from the black plug body using a pair of tweezers. All components were placed in a 25 mL Erlenmeyer flask, 10 mL of acetonitrile was added to each flask and the mixture was shaken for 30 min on a flat bed shaker. One 100 μL aliquot was taken from each sample solution, transferred to (separate) HPLC sample vials and then 900 μL of acetonitrile was added.

If cartridge refill liquid was being analyzed then an alternative preparation method was used. The e-cigarette liquid was a suspension of solid particulates in a viscous liquid (usually propylene glycol). The solution was homogenized by gently inverting the vial until the particulates were evenly distributed. 1 mL of the liquid was added to a 100 mL volumetric flask using a 1 mL volumetric pipette. 50 mL of acetonitrile was added, then 50 mL of HPLC grade methanol was added and the flask was swirled until all solid particulates dissolved yielding a pale yellow solution. The methanol:acetonitrile solution was able to dissolve all particles and the viscous liquid.

2.5. Oxidative degradation of rimonabant

A rimonabant degradation solution was made by dilution of an aliquot of the stock solution to 10 μg/mL in 3% H_2O_2 in 1:1 acetonitrile:water. This solution was injected immediately after preparation. Concurrently an aliquot of the degradation solution

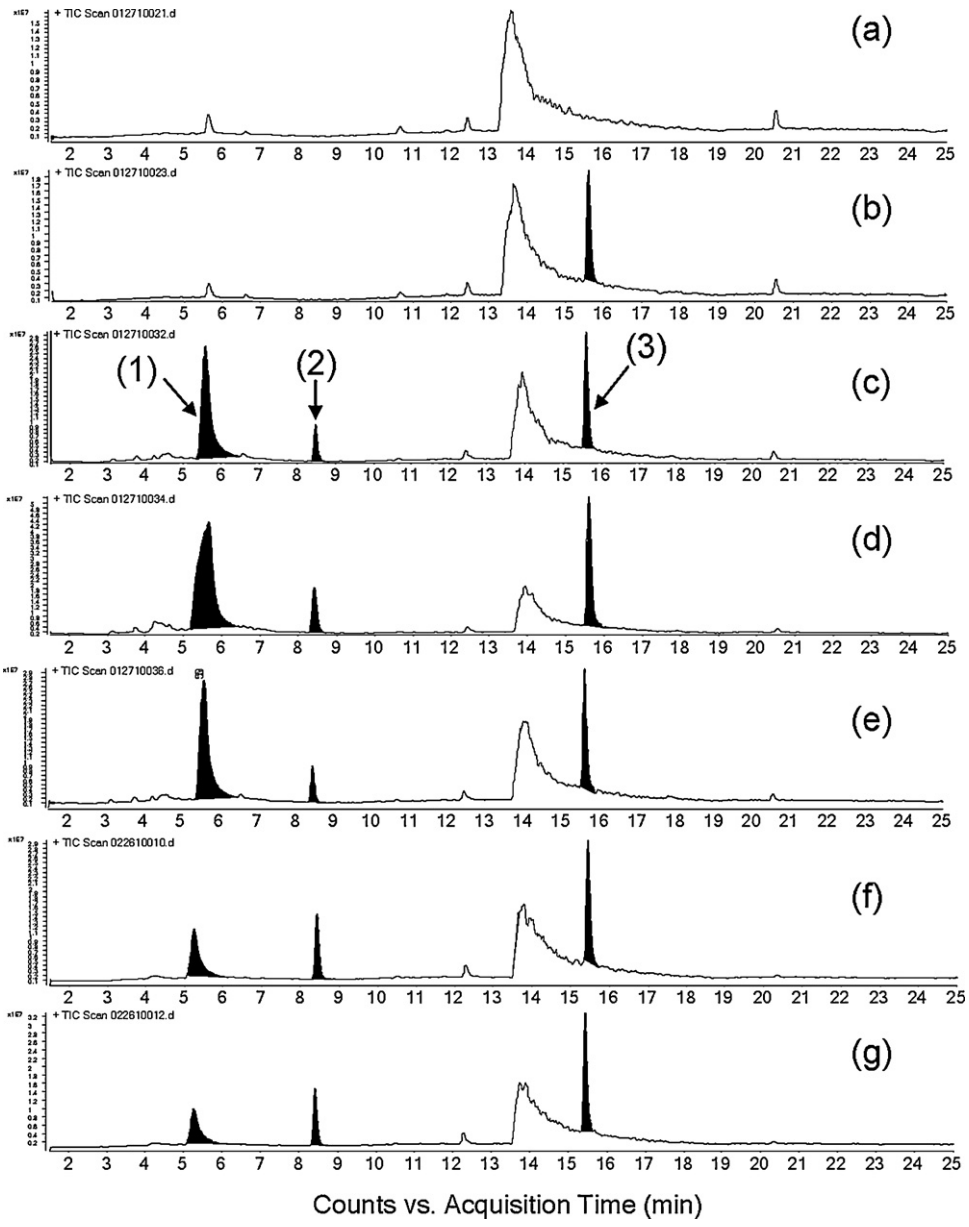

Fig. 4. TICs of (a) blank solvent, (b) 10 μg/mL rimonabant, (c)–(e) extracts from cartridges labeled as containing rimonabant, (f)–(g) e-cigarette refill liquid sample extracts. (1) Nicotine (~5.4 min), (2) rimonabant oxidative degradation impurity (~8.5 min), and (3) rimonabant (~15.5 min).

was transferred to a capped glass vial and placed in a heating block at 45 °C for 24 h, and an aliquot of the heated solution was also analyzed using the HPLC method described below.

2.6. Liquid chromatography

A gradient method was used to evaluate e-cigarette sample solutions. A Phenomenex HALO C18 (2.1 mm × 100 mm, 2.7 μm) column was employed for the separation. The autosampler was programmed with an injection volume of 2 μL and a 20 s external needle wash using 1:4 (v:v) water:isopropanol. The autosampler tray temperature was set to 8 °C. The flow rate was 300 μL/min. The column temperature was 50 °C. The diode array detector was programmed to scan from 200 to 400 nm, and chromatograms were monitored at 230 nm. A binary gradient method was used: eluent A was 1 mM ammonium acetate in water and eluent B was acetonitrile. The gradient began at 5% B, then ramped to 95% B over 18 min (linear ramp), held at 95% B for 5 min, then the column was re-equilibrated at 5% B for 10 min prior to the next injection. The same HPLC operational parameters were used for both mass spectrometric methods.

2.7. Mass spectrometric operational parameters

Two mass spectrometric methods were employed: full scan mode and product ion mode. Both mass spectrometer methods consisted of two segments: the first segment diverted the HPLC eluent flow to waste for 1.5 min to prevent undesired early eluting compounds from contaminating the source. The second segment was programmed for the desired acquisition mode. The multimode ionization source parameters used were the same for both methods and were: positive ion mode, gas temperature: 300 °C; vaporizer temperature: 250 °C; gas flow: 5 L/min; nebulizer pressure: 60 psi; capillary voltage: 2000 V; charging voltage: 2000 V; corona current: 1 μA. Full scan mode settings were m/z range 100–600, scan rate 500, and fragmentor voltage = 125 V. In product ion mode, ions of

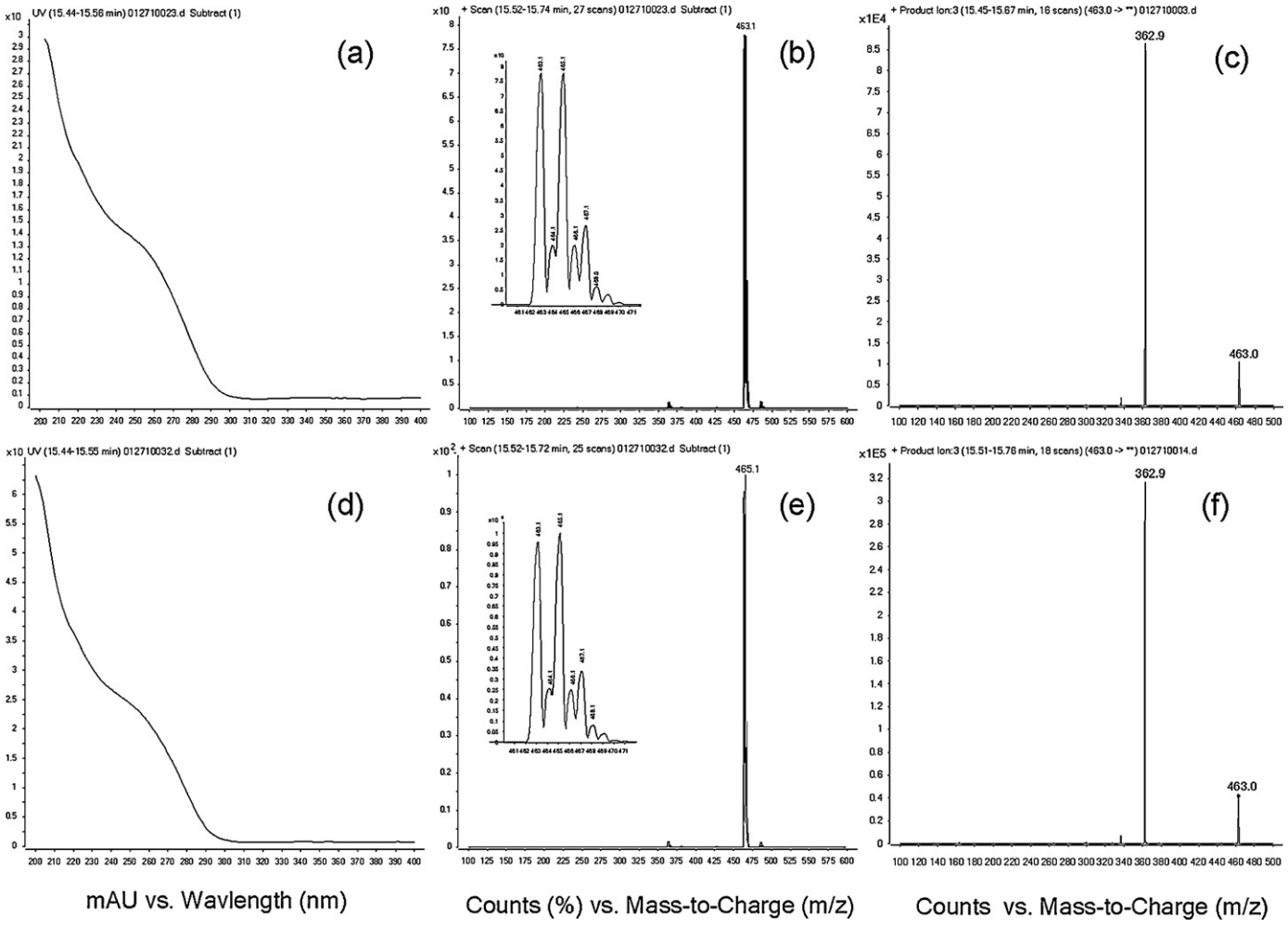

Fig. 5. Representative spectra of rimonabant. UV spectra of (a) 10 μg/mL rimonabant standard and (d) Peak eluting at approximately 15.5 min in Fig. 4(c). Mass spectra of (b) 10 μg/mL rimonabant standard and (e) peak eluting at approximately 15.5 min in Fig. 4. Isotopic peak distribution shown in the insets. Product ion mass spectra of (c) 10 μg/mL rimonabant standard and (f) peak eluting at approximately 15.5 min in Fig. 4.

m/*z* 390 (tadalafil), 391 (amino-tadalafil) or 463 (rimonabant) were isolated in quadrapole 1 (Q1), fragmented in Q2 using collision energies of 15 V (tadalafil and amino-tadalafil) and 25 V (rimonabant) and the resultant product ion spectra collected in Q3 using a scan range of 100–500 *m*/*z* for rimonabant and 100–400 *m*/*z* for tadalafil and amino-tadalafil.

3. Results and discussion

A gradient eluent program was used to screen the various e-cigarette products. Standard solutions of tadalafil, amino-tadalafil and rimonabant were prepared at approximately 10 μg/mL and analyzed to determine their retention times, UV spectra, mass spectra and product ion mass spectra. The initial selection of standard compounds was dictated by the label information provided on the e-cigarette product package.

Sample extracts were analyzed using both diode array and mass detection with the mass spectrometer operating in full scan mode over an *m*/*z* range of 100–600. If the retention times of the peaks in the UV and total ion chromatograms of the sample matched those of the standard compounds, then the UV and mass spectra of the sample peaks were extracted. If the UV and mass spectra of the sample peaks matched one of the standards, then the product ion mass spectra of the sample peaks were acquired in separate analyses. If the retention time, UV spectrum, mass spectrum and product ion mass spectrum of a peak from the analysis of the sample matched that of the relevant standard, then positive identification was confirmed.

If a significantly intense peak was observed but did not match the retention times of the rimonabant or tadalafil standards, then the process of identification was initiated. First, the literature was searched for promising pseudo-molecular ions or MS–MS transitions. If the literature yielded an article reporting the same UV spectra, mass spectra or MS–MS spectra and a standard of the suspected moiety could be purchased, then the standard was analyzed and the data compared to that of the unknown compound. If a retention time, UV spectral, MS and/or product ion MS–MS spectral match were obtained, no additional identification work was performed, and an identity was assigned. If no hits were obtained from a literature search, then the formal process of collecting the peak eluent, evaporating it and characterizing it by NMR, IR, etc. would begin. This last step proved unnecessary for this work.

3.1. Identification of amino-tadalafil in e-cigarette products

E-cigarette products labeled as containing E-Cialis™ were analyzed and one example is shown in Figs. 2 and 3.

Fig. 2 shows the total ion chromatograms (TIC) obtained from the analysis of one e-cigarette sample solution, an amino-tadalafil standard and a tadalafil standard solution. As shown in Fig. 2, the peak at about 8.5 min in the chromatogram from the analysis of the e-cigarette solution labeled as containing Cialis™ (Fig. 2(c)) is not

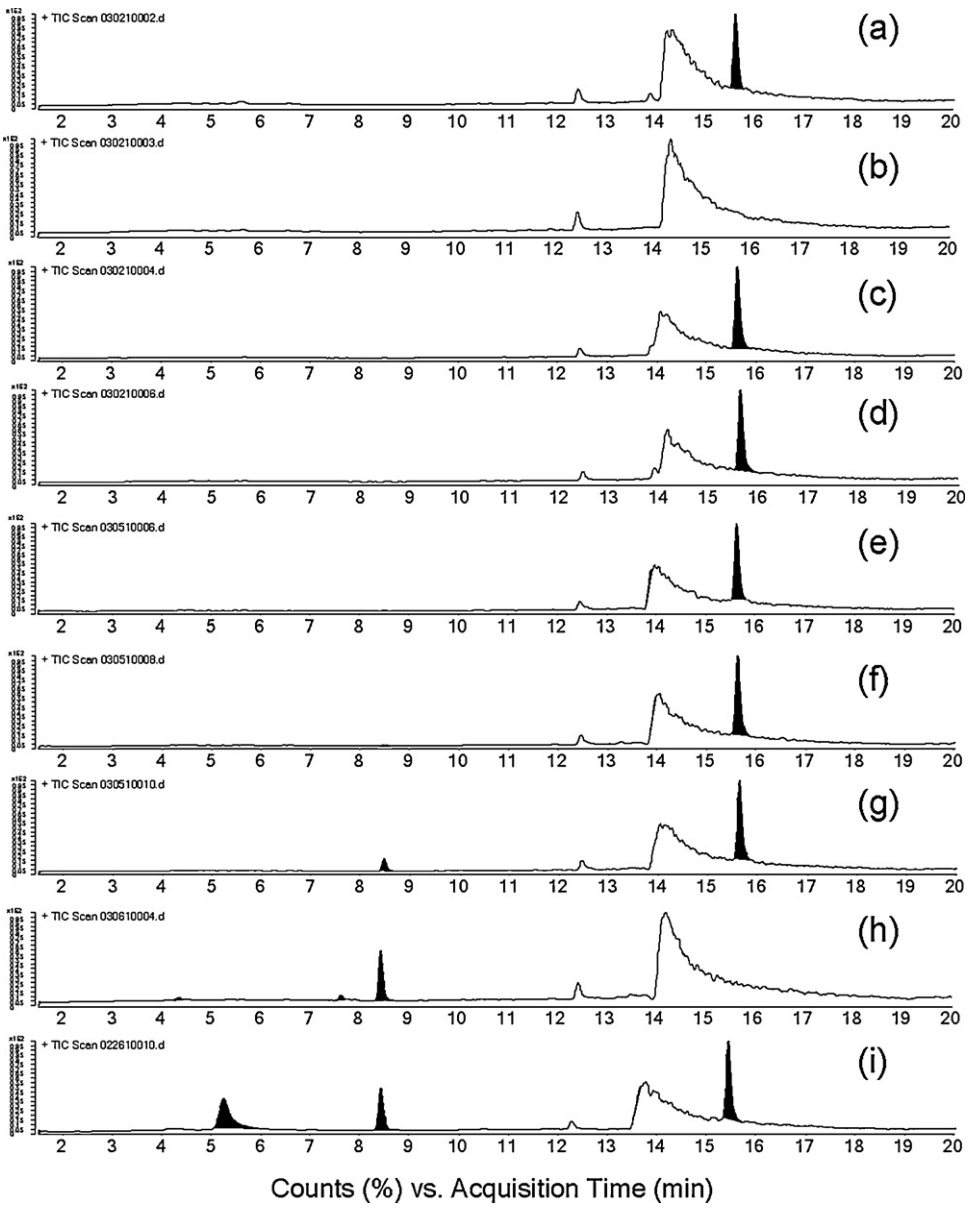

Fig. 6. Full scan TIC chromatograms of rimonabant degradation. (a) 20 μg/mL rimonabant standard solution; (b) blank; (c) 20 μg/mL rimonabant standard in 100 mM HCl; (d) 20 μg/mL rimonabant standard in 100 mM NaOH; (e) 20 μg/mL rimonabant standard in 100 mM HCl after 48 h at 45 °C; (f) 20 μg/mL rimonabant standard in 100 mM NaOH after 48 h at 45 °C; (g) 20 μg/mL rimonabant standard in 3% H_2O_2 in water:acetonitrile (1:1, v/v); (h) 20 μg/mL rimonabant standard in 3% H_2O_2 in water:acetonitrile (1:1, v/v) after 24 h at 45 °C; (i) e-cigarette refill liquid sample solution. A new column was used for 12(a)–12(h), the slight shift in retention time in 12(i) is attributable to use of an older column of the same type.

tadalafil. Tadalafil had a retention time of about 9.3 min (Fig. 2(b)) with this method. Therefore the UV spectrum, full scan mass spectrum and product ion mass spectrum were extracted from peak eluting at 8.5 min in the sample chromatograms.

Comparison of the UV spectra showed that the spectrum of the unknown compound (Fig. 3(a)) and tadalafil (Fig. 3(c)) were nearly identical, suggesting the unknown compound was structurally similar to tadalafil. However, the extracted full scan mass spectrum and product ion mass spectrum observed for the unknown compound ($[M+H]^+$, m/z 391), were different than those for tadalafil ($[M+H]^+$, m/z 390) shown in Fig. 3(f) and (i). So the label claim that the e-cigarette solution contains Cialis™ was not true.

A review of the literature revealed that amino-tadalafil (m/z 391) has been used as an adulterant in other matrices such as herbal products [2,5]. The Nitrogen Rule states that organic compounds containing exclusively carbon, hydrogen, oxygen, nitrogen, sulfur, and halogen atoms either have (1) an odd nominal mass that indicates an odd number of nitrogen atoms are present or (2) an even nominal mass that indicates either no or an even number of nitrogen atoms are present in the molecular ion [12]. The unknown compound yielded a nominal mass of 390 (i.e. $391-1=[M+H]^+-H^+=390$) and therefore should contain either no or an even number of nitrogen atoms, and amino-tadalafil satisfies this requirement. Other pieces of information from the literature such as the work by Zou et al. [5] provided both UV and product ion mass spectra for amino-tadalafil which were very similar to those observed here. Analysis of an amino-tadalafil standard solution confirmed the identity of the unknown compound. The retention time (Fig. 2(c) and (e)), UV spectrum (Fig. 3(a) and (b)), full scan mass spectrum (Fig. 3(d) and (e)) and product ion mass spectrum (Fig. 3(g) and (h)) of the unknown matched those of amino-tadalafil.

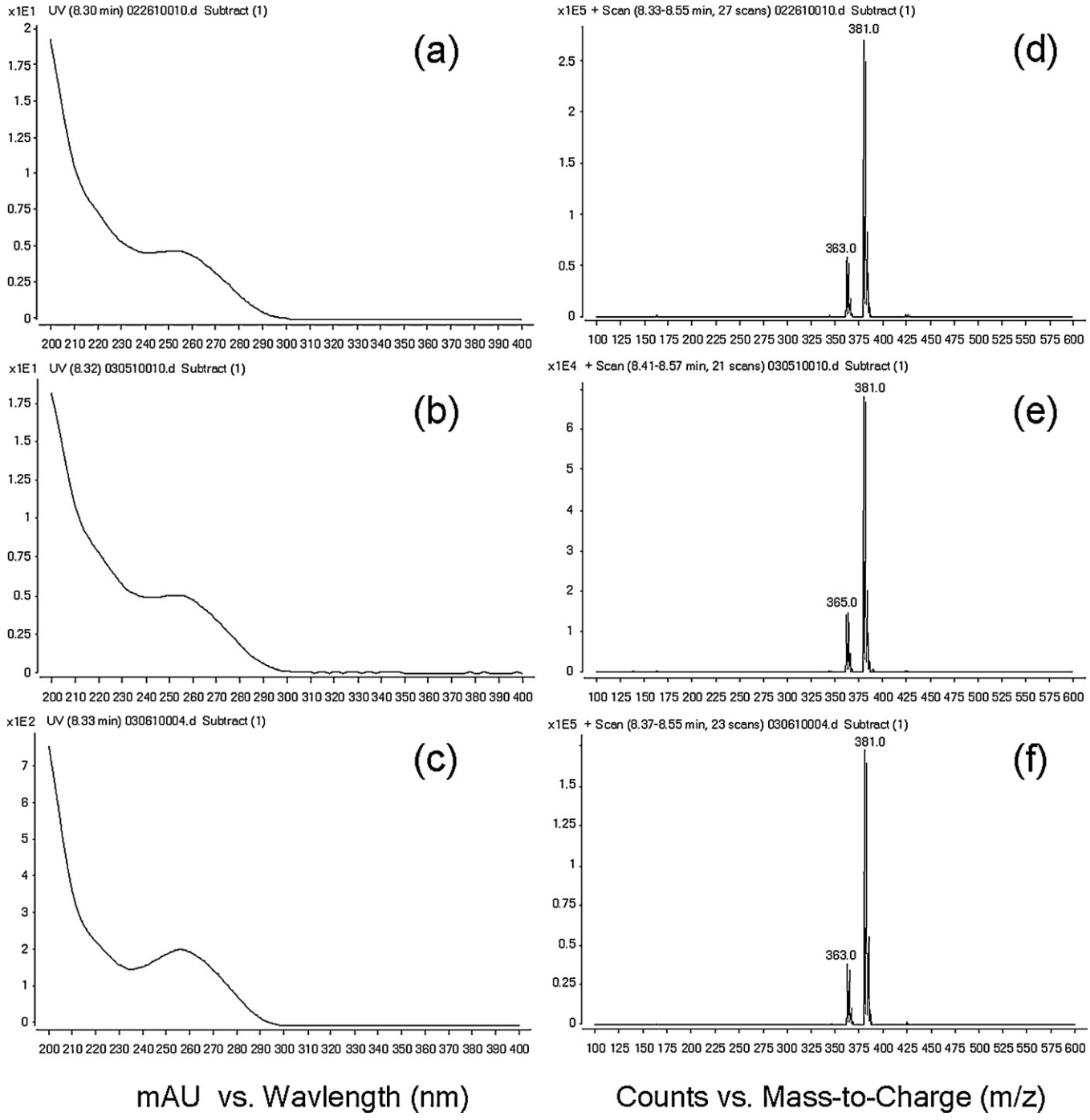

Fig. 7. Representative spectra of rimonabant degradant. UV spectra of rimonabant degradation peak eluting at approximately 8.4 min from (a) 20 μg/mL rimonabant standard in 3% H_2O_2 in water:acetonitrile (1:1, v/v); (b) 20 μg/mL rimonabant standard in 3% H_2O_2 in water:acetonitrile (1:1, v/v) after 24 h at 45 °C and (c) e-cigarette refill liquid sample solution in Fig. 6(i). Full scan mass spectra of rimonabant degradation peak eluting at 8.4 min from (d) 20 μg/mL rimonabant standard in 3% H_2O_2 in water:acetonitrile (1:1, v/v); (e) 20 μg/mL rimonabant standard in 3% H_2O_2 in water:acetonitrile (1:1, v/v) after 24 h at 45 °C and (f) e-cigarette refill liquid sample solution in Fig. 6(i).

In summary, none of the e-cigarette products labeled as containing E-cialis contained tadalafil, instead all of the products tested contained amino-tadalafil as shown in Table 1.

3.2. Identification of rimonabant and rimonabant degradation product in e-cigarette products

Fig. 4 shows the TICs obtained from the analysis of several rimonabant fortified e-cigarette sample extract solutions and a rimonabant standard solution. Peak 2 is due to a rimonabant impurity formed most easily under oxidative conditions. Peak 3 corresponds to rimonabant. As shown in Fig. 4, a comparison of the retention time of the peak of interest eluting at about 15.5 min in the e-cigarette solutions labeled as containing rimonabant (Fig. 4(c)–(g)) elutes at the same time as the rimonabant standard solution (Fig. 4(b)). Since a retention time match was obtained for the rimonabant standard and a peak in several samples, the UV, full scan mass spectra, and product ion mass spectra were extracted from for the peak of interest at 15.5 min.

One example is shown in Fig. 5. Examination of the UV absorbance spectrum of the unknown compound in Fig. 5(a) eluting at approximately 15.5 min matches that of the rimona-

bant standard in Fig. 5(d). The extracted full scan mass spectrum of the rimonabant standard, Fig. 5(b), matched the mass spectrum obtained for the peak eluting at approximately 15.5 min in the sample, Fig. 5(e). Further, the isotopic distribution of the peaks also matched as shown in the insets of Fig. 5(b) and (e). Lastly, the product ion mass spectrum of the rimonabant standard showed the loss of mass 101, Fig. 5(c), which was the same loss observed for the unknown compound in the sample as shown in Fig. 5(f). In summary, the retention times, UV spectra, mass spectra, isotopic distribution, and product ion mass spectra of the peak eluting at approximately 15.5 min in the sample peak and rimonabant standard matched, therefore the e-cigarette samples labeled as containing rimonabant did contain rimonabant.

Examination of the full scan TICs in Fig. 4(c)–(g) also reveal other fairly intense peaks of interest eluting at approximately 5.3 and 8.5 min. The extracted mass spectrum of the peak eluting at 5.3 min yielded an m/z of 163, which is that of nicotine. As stated above, it is not the focus of this paper to quantify nicotine, but what is of interest is that chromatograms 4(c) (replacement cartridge) and 4(g) (refill solution) obtained from e-cigarette products labeled as containing no nicotine, do apparently contain nicotine. Like the amino-tadalafil adulterated products described above, these products would expose the unwitting user to the risk of nicotine addiction.

It has been reported that rimonabant will degrade under oxidative conditions to 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylic acid, PubChem CID 1519421; Fig. 2(b) [13]. Fig. 6 supports this finding and shows a rimonabant standard solution prepared under various challenge conditions and an e-cigarette sample solution. Fig. 6(c)–(f) show that rimonabant is stable in solution to alkaline (0.1 M NaOH), acidic (0.1 M HCl) and mild heat (45 °C) challenges. However, the chromatogram in Fig. 6(g) and (h) show the rapid formation of a compound eluting at approximately 8.5 min when rimonabant was dissolved in a solution of 3% hydrogen peroxide in water:acetonitrile (1:1, v/v). As shown in Fig. 6(i), a degradation peak in an e-cigarette sample extract also elutes at 8.5 min.

UV spectra and full scan mass spectra were extracted from the degradation peak eluting at approximately 8.5 min in Fig. 6 are shown in Fig. 7. Both the UV spectra and full scan mass spectra for the oxidative degradation impurity of the rimonabant standard, Fig. 6(g) and (h), are identical to those of unknown compound in the sample as shown in Fig. 6(i). Where this impurity is actually formed in the product (e.g. from poor storage practices, from purchase of low purity lots of rimonabant, from poorly controlled production practices, in solution, etc.) is not known, however, it is present in all tested e-cigarette products labeled as containing rimonabant.

In summary, the e-cigarette products claiming to contain e-rimonabant do contain rimonabant. In addition, all of these products contained a rimonabant degradation product which forms best under oxidative stress. A summary of the results from the analysis of five e-cigarette products are shown in Table 1.

3.3. Nicotine

Analysis of e-rimonabant products produced chromatograms which contain a peak eluting at about 5.4 min such as that shown in Fig. 6(i). Extraction of the mass spectrum from this peak revealed an intense ion at m/z 163 and this peak was determined to be nicotine (MW = 162). It should be noted that this particular sample extract was from an e-rimonabant cigarette cartridge which was labeled as containing no nicotine. Similarly, a peak eluting at approximately 5.4 min yielding a pseudo-molecular ion of m/z 163 was observed in all e-cigarette products labeled as containing E-Cialis (data not shown). As the identification and quantification of nicotine in e-cigarette products is the subject of a separate manuscript and as the current HPLC method was inadequate for resolution of certain nicotine impurities, no further analytical work on nicotine was pursued with this method. However, for the products analyzed in this work, the obvious implication is that the unwary e-cigarette user could be exposed to the risk of nicotine addiction by purchasing a product which while advertised as containing no nicotine, does contain nicotine. The presence of nicotine in the various e-cigarette products analyzed here is summarized in Table 1.

4. Conclusion

Two forms of e-cigarette products (refill solution and replacement cartridges) advertised as containing either E-Cialis or E-rimonabant were analyzed. E-cigarette products advertised as containing E-Cialis did not contain tadalafil (i.e. Cialis™), rather they contained amino-tadalafil. E-cigarette products advertised as containing rimonabant, did contain rimonabant and a significant amount of an oxidative impurity of rimonabant. Finally, of the samples analyzed, E-cigarette products advertised as containing no nicotine, did contain nicotine thus exposing the unwitting user to the risk of nicotine addiction.

References

[1] M.J. Bogusz, H. Hassan, E. Al-Enazi, Z. Ibrahim, M. Al-Tufail, J. Pharm. Biomed. Anal. 41 (2006) 554.
[2] S.R. Gratz, C.L. Flurer, K.A. Wolnik, J. Pharm. Biomed. Anal. 36 (2004) 525.
[3] J.C. Reepmeyer, J.T. Woodruff, J. Pharm. Biomed. Anal. 44 (2007) 887.
[4] J.C. Reepmeyer, J.T. Woodruff, d'Avignon D.A., J. Pharm. Biomed. Anal. 43 (2007) 1615.
[5] P. Zou, P. Hou, M.-Y. Low, H.-L. Koh, Food Addit. Contam. A: Chem. Anal. Control Expo. Risk Assess. 23 (2006) 446.
[6] P. Zou, S.S.-Y. Oh, P. Hou, M.-Y. Low, Koh. H.-L., J. Chromatogr. A 1104 (2006) 113.
[7] Eli Lilly, Cialis (Tadalafil) Full Prescribing Information, 2010, http://pi.lilly.com/us/cialis-pi.pdf.
[8] Wikipedia, August 2010, http://en.wikipedia.org/wiki/Electronic cigarette.
[9] J. Etter, Electronic cigarettes: a survey of users, BMC Public Health 10 (2010) 231, http://www.biomedcentral.com/1471-2458/10/231.
[10] News staff, AAFP News Now, March 2, 2010, http://www.aafp.org/online/en/home/publications/news/news-now/health-of-the-public/20100302e-cig-fda.html.
[11] FDA, FDA Briefing Document NDA 21-888, 2007, http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4306b1-fda-backgrounder.pdf.
[12] R.M. Silverstein, G.C. Bassler, T.C. Morrill, Spectroscopic Identification of Organic Compounds, John Wiley & Sons, New York, 1981.
[13] T.S. Raju, M. Ravikumar, K.V. Kumar, K.S.V. Raghavachary, M.S. Varma, C.S.N.M. Rao, P.Y. Swamy, Chromatographia 67 (2009) 97.