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Detection and Quantification of Thirty-Two Synthetic PDE-5 Inhibitors and Analogues Adulterated in Health Supplements Using LC/MS/MS

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High Sensitive Detection and Quantification of Thirty-Two Synthetic PDE-5 Inhibitors and Analogues Adulterated in Health Supplements Using LC/MS/MS

Introduction

In recent years, synthetic phosphodiesterase type 5 enzyme (PDE-5) inhibitors like sildenafl (active component of VIAGRA) were found as adulterant in some health supplements described as plant or herbal products [1]. Only seven synthetic PDE-5 inhibitors, namely, sildenafl, tadalafl, vardenafl, avanafl, udenafl, mirodenafl and lodenafl carbonate are approved offcially to be used for the treatment of erectile dysfunction (ED) in men. The adulteration is illegal and may be also dangerous for consumers, because not only the above PDE-5 inhibitors, many newly appeared analogues that are synthesized with minor modifcation of the parent structures are also found used as adulterants. Analytical techniques like HPLC and LC/MS/MS have been applied for screening and quantitation of PDE-5 inhibitors and their analogues [1-3]. We describe here a high sensitivity LC/MS/MS method for detection and quantifcation of thirtytwo synthetic PDE-5 inhibitors and analogues spiked in health products.

Experimental

Thirty-two PDE-5 inhibitors and analogues were obtained from TLC PharmaChem (Canada), which include fve approved ones (sildenafl, tadalafl, vardenafl, avanafl and udenafl) and twenty-seven analogues. These compounds were dissolved in MeOH at 100ppm or 10ppm as stocks which were used to prepare mixed standards calibrant series of ten levels (0.1, 0.5, 1, 2, 5, 10, 50, 100, 200 and 500 ppb) and spiked samples. Five health supplement products in capsules purchased locally were used as model samples for evaluation of method performance. These samples are named as M, C, PP, TA and RK for convenience. The sample was extracted with MeOH at a ratio of 0.2 gram of the powders in 2mL of pure MeOH. The mixture was sonicated for 20 minutes, followed by fltration with 0.2µm PTFE flter before analysis. An LCMS-8040 triple quadrupole mass spectrometer coupled with a Nexera UHPLC was used in this study. A Shim-pack XR-ODS-III UHPLC column (150x2mm, 2.2µm) was adopted and a gradient elution program was used for separation of the thirty-two compounds. The detailed conditions are compiled into Table 1.

Table 1: Analytical conditions of thirty-two PDE-5 inhibitors and analogues on LCMS-8040

Column	Shim-pack XR-ODS-III (150 x 2mm, 2.2µm)
Flow Rate	0.3 mL/min
Mobile Phase	A: H_2O with 0.1% formic acid
	B: CAN with 0.1% formic acid
Elution Mode	Gradient elution, B%: 10% (0.01 min) → 45% (12min) → 80% (15 to 17min)
Oven Temp.	45 ºC
Injection Vol.	2.0 µL
Interface	ESI
MS mode	Positive, MRM
Block Temp.	400 ºC
DL Temp.	250 ºC
CID Gas	Ar (230kPa)
Nebulizing Gas Flow	N_2, 3 L/min
Drying Gas Flow	N_2, 15 L/min

Results and Discussion

Establishment of MRM method for detection and quantitation of thirty-two PDE-5 inhibitors and analogues

The MRM optimization of the thirty-two PDE-5 inhibitors and analogues was carried out using an auto-optimization program of the LabSolutions. Most of the compounds produces three signifcant MRM transitions except two analogues which produced two MRMs. The MRM transition with highest intensity was selected as quantifer ion and the others were used as confirmation ions (Table 2). An UHPLC column (2um particle size) was adopted with a gradient elution program to achieve high peak resolution and high sensitivity. Figure 1 shows the MRM chromatograms of thirty-two PED-5 inhibitors and analogues of mixed standard samples (50 ppb, 2 uL injection). Since this method is for targeted screening and quantitation, a wider time window of (+/-) 2.5min for each targeted MRM peak was set to be able to tolerance the peak shift that may occur in screening of actual samples. A calibrant series of ten levels from 0.1, 0.5, 1, 2, 5, 10, 20, 50, 100, 200 and 500 ppb was prepared for establishment of calibration curves, LOD and LOQ values of the thirty-two compounds studied. The lowest detectable levels (S/N >/= 3 or count >/= 250) of every compounds in the low level mixed standards are used as the LODs. The levels with S/N >/=10 or count >/=800 are used as LOQs of the compounds. Calibration curves were established for a range from LOQ up to 500ppb. A few selected calibration curves are shown in Figure 2, which include the fve approved PDE-5 inhibitors and acetilsildenafl, an analogue of sildenafl. The complete information of the MRM quantitation method of the thirty-two PDE-5 inhibitors and analogues is compiled into Table 3. In brief, the results show that linear calibration curves with R^2 > 0.999 from LOQs up to 500ppb were obtained for all the compounds. The LODs and LOQs of the thirty-two compounds in neat solutions of mixed standards were determined at 0.05~2ppb and 0.2~6.7ppb, respectively. Repeatability of peak areas were evaluated with 10ppb and 100ppb mixed standard samples. The results of %RSD (n=6) are at 1.3~8.8% for 10ppb and 0.4~7.8% for 100ppb, respectively.

Table 2: Names and information of thirty-two compounds and MRM transitions on LCMS-8040

No.	Name	Formula	CAS	Quantifier ion				Conformation ion			
				MRM	Q1 (V)	CE (V)	Q3 (V)	MRM	Q1 (V)	CE (V)	Q3 (V)
1	YOHIMBINE	$C_{21}H_{26}N_2O_3$	146-48-5	354.9>144.1	-30	-32	-28	354.9>212.1	-30	-23	-16
2	ACETYLVARDENAFIL	$C_{25}H_{34}N_6O_3$	1261351-28-3	467.3>151.1	-22	-47	-30	467.3>341.2	-22	-34	-24
3	CARBODENAFIL	$C_{24}H_{32}N_6O_3$	944241-52-5	452.9>339.2	-30	-23	-25	452.9>311.2	-30	-34	-23
4	N-DESMETHYL ACETILDENAFIL	$C_{23}H_{30}N_6O_3$	N.A	439.2>99.1	-30	-31	-20	439.2>70.1	-30	-47	-28
5	N-DESETHYL VARDENAFIL	$C_{21}H_{28}N_6O_4S$	448184-46-1	461.2>151.1	-13	-46	-29	461.2>312.2	-13	-37	-23
6	HYDROXYHOMOSILDENAFIL	$C_{23}H_{32}N_6O_5S$	139755-85-4	504.9>151.1	-34	-47	-29	504.9>312.1	-34	-41	-23
7	VARDENAFIL (Levitra, Bayer)	$C_{23}H_{32}N_6O_4S$	224785-90-4	488.9>72.1	-30	-49	-29	488.9>113.1	-30	-31	-23
8	HYDROXYACETILDENAFIL	$C_{25}H_{34}N_6O_4$	147676-56-0	483.3>127.1	-23	-31	-14	483.3>143.2	-23	-35	-29
9	NORACETILDENAFIL	$C_{24}H_{32}N_6O_3$	949091-38-7	452.9>97.1	-13	-33	-20	452.9>70.1	-13	-45	-29
10	ACETILDENAFIL	$C_{25}H_{34}N_6O_3$	831217-01-7	466.9>111.1	-30	-32	-23	466.9>127.1	-30	-32	-26
11	PIPERIACETILDENAFIL	$C_{24}H_{31}N_5O_3$	147676-50-4	437.9>98.1	-30	-35	-20	437.9>297.1	-30	-37	-22
12	AVANAFIL (Stendra, Vivus)	$C_{23}H_{26}ClN_7O_3$	330784-47-9	483.9>155	-30	-43	-30	483.9>375.1	-30	-27	-28
13	HYDROXYVARDENAFIL	$C_{23}H_{32}N_6O_5S$	224785-98-2	504.9>99.1	-34	-38	-21	504.9>112.1	-34	-31	-23
14	SILDENAFIL (Viagra, Pfzer)	$C_{22}H_{30}N_6O_4S$	171599-83-0	475.2>58.1	-22	-45	-24	475.2>100.1	-22	-30	-20
15	HOMOSILDENAFIL	$C_{23}H_{32}N_6O_4S$	642928-07-2	488.9>72.2	-30	-47	-29	488.9>99.1	-30	-36	-20

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No.	Name	Formula	CAS	Quantifier ion				Conformation ion			
				MRM	Q1 (V)	CE (V)	Q3 (V)	MRM	Q1 (V)	CE (V)	Q3 (V)
16	DIMETHYLSILDENAFIL	$C_{23}H_{32}N_6O_4S$	1416130-63-6	488.9>99.1	-30	-38	-20	488.9>113.1	-30	-32	-23
17	UDENAFIL (Zydena, Dong-A)	$C_{25}H_{36}N_6O_4S$	268203-93-6	516.9>283.1	-40	-46	-30	516.9>112.2	-40	-35	-23
18	HYDROXYTHIOHOMOSILDENAFIL	$C_{23}H_{32}N_6O_4S_2$	479073-82-0	520.9>99.1	-36	-45	-20	520.9>299.1	-36	-42	-21
19	THIOSILDENAFIL	$C_{22}H_{30}N_6O_3S_2$	479073-79-5	490.9>58.1	-23	-48	-24	490.9>100.1	-23	-32	-20
20	THIOHOMOSILDENAFIL	$C_{23}H_{32}N_6O_3S_2$	479073-80-8	504.9>72.1	-40	-50	-29	504.9>113.1	-40	-32	-23
21	BENZYLSILDENAFIL	$C_{28}H_{34}N_6O_4S$	N.A	550.9>91.1	-40	-41	-19	550.9>134.1	-40	-43	-26
22	THIODIMETHYLSILDENAFIL	$C_{23}H_{32}N_6O_3S_2$	856190-47-1	504.9>99.1	-40	-39	-20	504.9>113.1	-40	-32	-23
23	AMINOTADALAFIL	$C_{21}H_{18}N_4O_4$	385769-84-6	391.2>269.1	-27	-14	-20	391.2>135.0	-11	-20	-26
24	NORTADALAFIL	$C_{21}H_{17}N_3O_4$	171596-36-4	376.1>254.1	-17	-13	-29	376.1>169.1	-17	-38	-20
25	VARDENAFIL INTERMEDIATE*	$C_{17}H_{20}N_4O_2$	N.A	312.8>151.1	-30	-30	-30	312.8>110.1	-30	-47	-22
26	TADALAFIL (Cialis, Elli Eilly)	$C_{22}H_{19}N_3O_4$	171596-29-5	390.1>135.1	-18	-20	-15	390.1>268.1	-18	-14	-20
27	CHLOROPRETADALAFIL	$C_{22}H_{19}ClN_2O_5$	171489-59-1	426.4>135.1	-28	-20	-27	426.4>237.4	-20	-20	-28
28	PSEUDOVARDENAFIL	$C_{22}H_{29}N_5O_4S$	224788-34-5	460.2>151.1	-30	-55	-30	460.2>312.2	-30	-37	-23
29	GENDENAFIL	$C_{19}H_{22}N_4O_3$	147676-66-2	354.9>285.1	-30	-31	-21	354.9>327.1	-30	-25	-24
30	N-BUTYL TADALAFIL	$C_{25}H_{25}N_3O_4$	171596-31-9	432.2>135.1	-20	-24	-26	432.2>310.2	-20	-15	-23
31	NORNEOSILDENAFIL	$C_{22}H_{29}N_5O_4S$	371959-09-0	460.2>283.1	-17	-36	-21	460.2>299.2	-17	-37	-22
32	N-OCTYL NORTADALAFIL	$C_{29}H_{33}N_3O_4$	1173706-35-8	488.9>135.1	-14	-35	-27	488.9>366.2	-14	-16	-15

* TLC ID#: V057

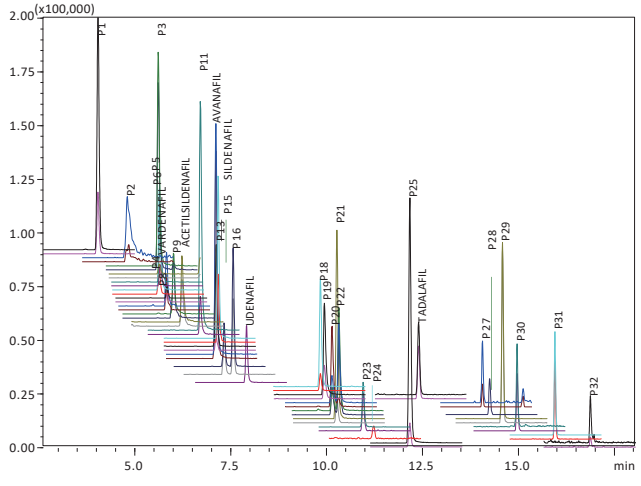

Figure 1: MRM chromatograms of 50ppb mixed standards of 32 PDE-5 inhibitors and analogues (2uL). Each compound was detected and confrmed with a pair of MRMs.

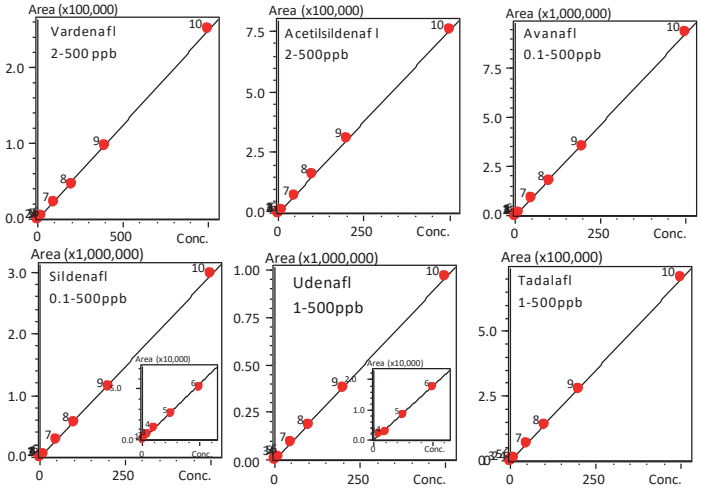

Figure 2: Calibration curves of fve approved PDE-5 inhibitors and acetildenafl (sildenafl analogue).

Matrix effect and reliability of targeted screening method for detection of adulteration

Aimed at detection of adulteration of the thirty-two PED-5 inhibitors and analogues, the LC/MS/MS method established was tested with spiked samples to evaluate the detection reliability and quantitation accuracy. It is well known that health products from herbal plants and other materials are not only very complex, but also greatly different from each other in constituents and compositions. There is not a single sample that could be used as representative to study matrix effect and peak interference. In this study, we selected randomly fve health supplement products from local market and carried out evaluation of matrix effect, peak interferences and their effects to screening reliability. The MeOH extracts of the fve health supplement samples M, C, PP, TA and RK were analysed using the above method and the results confrmed that these samples were free of the thirty-two PDE-5 inhibitors and analogues studied. The matrix effect of every compound in a spiked sample is determined by the ratio of its peak areas in the matrix solution and in neat diluent. The results of matrix effects of the thirty-two compounds in fve different matrixes are summarized in Table 4. The results show that the matrix effects of most compounds are within a range of 70% to 150%. For example, the matrix effects of sildenafl ranges from 90.9% to 149.1% in four samples except one at 162.9% (Sample RK), and acetildenafl from 99.8 to 124.7% except one at 56% (sample C). Several compounds such as thiodimethylsildenafl, thiohomosildenafl and thiosildenafl exhibit strong matrix effect in most samples. The opposite situation of ion suppression, namely ion enhancement were observed with several compounds in different samples (green color in Table 4). It is necessary to clarify whether the strong ion suppression and ion enhancement phenomena observed are due to peak interference of other species.

This could be confrmed by the peak intensity ratios of quantifer ion and confrmation ion (main ion and reference ion). As shown in Figure 3, two compounds, vardendafl which exhibits the strongest ion enhancement (ME: 131.9~221.4%, except sample C) and thiodimethylsildenafl which exhibits the strongest ion suppression (ME:13.8~51.8%), are investigated through comparing their intensity ratios of the quantifer ion and the confrmation ion in different matrixes with that in neat diluent. The results indicate that the matrix effect values are not related to the ion suppression or ion enhancement. Therefore, peak interference due to other chemical species could be excluded. The matrix effect seems to be more related to the compound property and less to the samples under the ESI conditions. However, the same compounds and matrixes were also studied on LCMS-IT-TOF under similar conditions with a different ESI interface [4]. The matrix effect behaviour observed are different, which indicates that instrument performance and LC separation conditions may play important roles too. Based on these studies, reliable detection limits for screening of the thirtytwo PDE-5 inhibitors and analogues by the MRM method are estimated at 0.1~4ppb in extract solutions if a matrix effect factor of 50% is applied as a more secure consideration, and 1~40 ng/g in powders (dilution factor of 10). In the same way, the lowest quantitation levels are estimated at 0.4~13.4ppb in extract solutions and 4~134ng/g in powders. However, this estimation on LODs and LOQs are based assumption of 100% extraction recovery. It is worth to note that the high sensitivity of the MRM method established was achieved with 2uL injection. A smaller injection vol of dirty samples is preferred to reduce MS system contamination.

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Table 3: Calibration and performance of MRM method for 32 PDE-5 inhibitors and analogues on LCMS-8040

P. No.	Compound Name	RT (min)	MRM	Range (ppb)	R^2	LOD (ppb)	LOQ (ppb)	RSD (%), n=6	
								10ppb	100b
1	YOHIMBINE	4.06	354.9>144.1	0.5-500	0.9999	0.1	0.5	1.3	0.4
2	ACETYLVARDENAFIL	4.75	467.3>151.1	5-500	0.9958	2.0	6.7	8.7	7.0
3	CARBODENAFIL	5.63	452.9>339.2	1-500	0.9999	0.3	1.0	3.3	2.2
4	N-DESMETHYL ACETILDENAFIL	5.64	439.2>99.1	2-500	0.9978	1.0	3.5	8.3	3.0
5	N-DESETHYL VARDENAFIL	5.65	461.2>151.1	1-500	0.9994	0.5	1.6	3.2	1.9
6	HYDROXYHOMOSILDENAFIL	5.67	504.9>151.1	0.5-500	0.9997	0.1	0.5	4.4	2.5
7	VARDENAFIL (Levitra, Bayer)	5.83	488.9>72.1	5-500	0.9995	2.0	6.7	7.4	6.5
8	HYDROXYACETILDENAFIL	5.85	483.3>127.1	2-500	0.9994	0.5	1.6	8.9	7.8
9	NORACETILDENAFIL	6.01	452.9>97.1	2-500	0.9997	1.0	3.5	4.3	3.4
10	ACETILDENAFIL	6.23	466.9>111.1	2-500	0.9998	1.0	3.5	7.6	6.0
11	PIPERIACETILDENAFIL	6.72	437.9>98.1	1-500	0.9996	0.3	1.0	4.0	2.1
12	AVANAFIL (Stendra, Vivus)	7.13	483.9>155	0.5-500	0.9994	0.1	0.5	3.1	1.4
13	HYDROXYVARDENAFIL	7.13	504.9>99.1	1-500	0.9999	0.5	1.6	5.3	2.7
14	SILDENAFIL (Viagra, Pfzer)	7.19	475.2>58.1	1-500	0.9997	0.3	1.0	3.1	1.1
15	HOMOSILDENAFIL	7.34	488.9>72.2	1-500	0.9996	0.3	1.0	3.2	1.7
16	DIMETHYLSILDENAFIL	7.58	488.9>99.1	1-500	0.9997	0.3	1.0	1.7	1.6
17	UDENAFIL (Zydena, Dong-A)	7.93	516.9>283.1	1-500	0.9999	0.5	1.6	4.5	2.3
18	HYDROXYTHIOHOMOSILDENAFIL	9.85	520.9>99.1	1-500	0.9999	0.3	1.0	4.4	2.9
19	THIOSILDENAFIL	9.95	490.9>58.1	0.5-500	0.9993	0.2	0.7	6.1	2.6
20	THIOHOMOSILDENAFIL	10.15	504.9>72.1	1-500	0.9995	0.3	1.0	4.6	4.2
21	BENZYLSILDENAFIL	10.28	550.9>91.1	0.5-500	0.9999	0.2	0.7	5.1	1.7
22	THIODIMETHYLSILDENAFIL	10.34	504.9>99.1	1-500	0.9995	0.5	1.6	4.7	3.3
23	AMINOTADALAFIL	10.97	391.2>269.1	1-500	0.9998	0.5	1.6	4.0	3.3
24	NORTADALAFIL	11.24	376.1>254.1	2-500	0.9999	1.0	3.5	7.8	5.1
25	VARDENAFIL INTERMEDIATE*	12.19	312.8>151.1	0.1-500	0.9999	0.05	0.2	1.6	1.4
26	TADALAFIL (Cialis, Elli Eilly)	12.42	390.1>135.1	1-500	0.9999	0.5	1.6	4.9	1.3
27	CHLOROPRETADALAFIL	14.08	426.4>135.1	2-500	0.9994	1.0	3.5	8.8	6.9
28	PSEUDOVARDENAFIL	14.27	460.2>151.1	0.1-500	0.9996	0.05	0.2	1.7	1.6
29	GENDENAFIL	14.60	354.9>285.1	0.5-500	0.9991	0.1	0.5	2.4	1.6
30	N-BUTYL TADALAFIL	14.98	432.2>135.1	2-500	0.9998	1.0	3.5	8.8	2.2
31	NORNEOSILDENAFIL	15.97	460.2>283.1	1-500	0.9988	0.3	1.0	4.9	4.0
32	N-OCTYL NORTADALAFIL	16.89	488.9>135.1	2-500	0.998	1.0	3.5	5.9	2.4

* TLC ID#: V057

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Table 4: Matrix effects of PDE-5 inhibitors and analogues (100ppb) spiked in MeOH extracts of fve health products

P. No.	Name	RT (min)	m/z	Matrix Effect (%)				
				Sample M	Sample C	Sample PP	Sample TA	Sample RK
1	YOHIMBINE	3.88	354.9>144.1	112.4	95.8	141.7	132.9	129.8
2	ACETYLVARDENAFIL	4.71	467.3>151.1	74.8	44.5	79.1	119.1	78.7
3	CARBODENAFIL	5.44	452.9>339.2	110.6	76.8	137.1	114.5	128.2
4	N-DESMETHYL ACETILDENAFIL	5.50	439.2>99.1	134.8	99.8	167.4	135.2	184.0
5	N-DESETHYL VARDENAFIL	5.55	461.2>151.1	92.2	92.8	138.8	110.6	118.4
6	HYDROXYHOMOSILDENAFIL	5.58	504.9>151.1	132.5	151.7	198.0	147.6	218.3
7	VARDENAFIL (Levitra, Bayer)	5.71	488.9>72.1	131.9	52.3	180.7	160.4	221.4
8	HYDROXYACETILDENAFIL	5.74	483.3>127.1	181.8	29.3	143.1	174.6	193.9
9	NORACETILDENAFIL	5.86	452.9>97.1	106.5	41.1	98.2	117.5	112.8
10	ACETILDENAFIL	6.09	466.9>111.1	113.8	56.0	114.6	124.7	99.8
11	PIPERIACETILDENAFIL	6.53	437.9>98.1	103.1	12.7	79.9	116.8	64.7
13	AVANAFIL (Stendra, Vivus)	6.95	483.9>155	146.5	115.9	165.5	160.5	173.5
12	HYDROXYVARDENAFIL	6.96	504.9>99.1	137.9	110.9	144.6	144.7	223.4
14	SILDENAFIL (Viagra, Pfzer)	7.01	475.2>58.1	126.1	90.9	143.4	149.1	162.9
15	HOMOSILDENAFIL	7.18	488.9>72.2	129.3	80.0	129.0	128.6	141.6
16	DIMETHYLSILDENAFIL	7.43	488.9>99.1	98.0	32.1	115.8	112.3	124.7
17	UDENAFIL (Zydena, Dong-A)	7.78	516.9>283.1	133.9	109.7	146.0	148.5	200.9
18	HYDROXYTHIOHOMOSILDENAFIL	9.72	520.9>99.1	30.7	67.6	108.2	52.6	92.9
19	THIOSILDENAFIL	9.82	490.9>58.1	20.2	50.5	99.5	39.6	82.6
20	THIOHOMOSILDENAFIL	10.02	504.9>72.1	20.4	59.4	114.5	39.5	87.5
22	BENZYLSILDENAFIL	10.20	550.9>91.1	139.6	131.3	135.6	136.4	200.0
21	THIODIMETHYLSILDENAFIL	10.35	504.9>99.1	29.1	13.8	84.7	48.3	51.8
23	AMINOTADALAFIL	11.02	391.2>269.1	91.6	65.1	106.7	102.0	81.1
24	NORTADALAFIL	11.29	376.1>254.1	89.0	76.4	108.6	106.7	90.0
25	VARDENAFIL INTERMEDIATE*	12.38	312.8>151.1	99.6	108.1	114.8	113.7	102.3
26	TADALAFIL (Cialis, Elli Eilly)	12.47	390.1>135.1	99.1	88.9	113.2	117.2	101.4
27	CHLOROPRETADALAFIL	14.16	426.4>135.1	88.6	81.9	75.8	101.5	83.1
28	PSEUDOVARDENAFIL	14.34	460.2>151.1	102.6	74.4	109.2	140.6	70.4
29	GENDENAFIL	14.63	354.9>285.1	91.1	96.0	64.4	181.1	86.8
30	N-BUTYL TADALAFIL	15.01	432.2>135.1	96.4	80.1	96.1	122.1	67.3
31	NORNEOSILDENAFIL	15.99	460.2>283.1	67.3	69.3	136.1	72.6	56.4
32	N-OCTYL NORTADALAFIL	16.91	488.9>135.1	103.0	86.5	100.3	106.6	105.9

High Sensitive Detection and Quantification of Thirty-Two Synthetic PDE-5 Inhibitors and Analogues Adulterated in Health Supplements Using LC/MS/MS

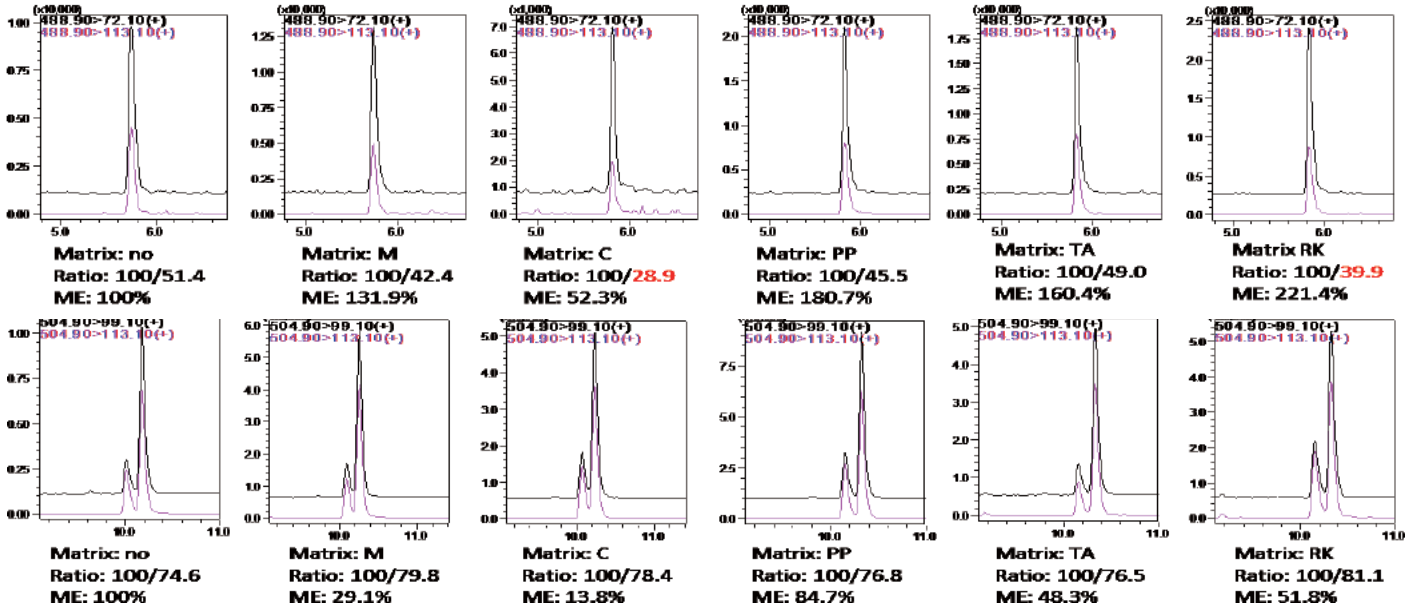

Fig. 3: Comparison of peak intensity ratios and matrix effect values for vardendafl (top) and thiodimethylsildenafl (bottom) in different sample matrixes.

Conclusions

A MRM targeted screening method has been developed for sensitive and reliable screening analysis of thirty-two synthetic PDE-5 inhibitors and analogues in health products. In consideration of matrix effect using spiked samples in fve health products selected randomly, the detection limits of the method are estimated at 0.1~4.0ppb for different compounds in solutions. The quantitation limits are at 0.4~13.4ppb in solutions. Further study on extract recovery of the method is needed.

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