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Analysis of erectile dysfunction drugs and their analogues in counterfeit drugs and herbal medicines by LC-ESI-MS/MS

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Abstract: Distribution of various illegal or counterfeit drugs of seven approved erectile dysfunction drugs and their analogues has been increased, causing health problems such as cardiovascular disorder, tachycardia, headache, or vision disturbance. We used liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) to determine the erectile dysfunction drugs and their analogues in various counterfeit drugs. Eleven erectile dysfunction drugs and their analogues were detected, with sildenafil and its analogues being the most counterfeited compounds (73.8 %), followed by tadalafil and its analogues (25.4 %). The limits of detection (LOD) and the limits of quantitation (LOQ) of liquid-type and solid-type negative samples ranged from 0.1 to 3.3 ng/mL or ng/g and from 0.3 to 10.0 ng/mL or ng/g, respectively. The recoveries ranged from 84.3 to 112.3 % and 83.2 to 110.2 %, respectively. The contents of sildenafil and tadalafil in the various counterfeit drugs ranged from 21.0 to 947.5 mg/g and from 0.2 to 170.2 mg/g, respectively.

Key words: erectile dysfunction drugs and their analogues, illegal or counterfeit drugs, LC-ESI-MS/MS

1. Introduction

Pharmaceutical counterfeiting is a growing problem worldwide. In industrialized countries, phosphodiesterase type-5 (PDE-5) inhibitors, a class of erectile dysfunction (ED) drugs, are one of the most counterfeited drugs. In Korea, the number of patients with ED has been increased with increase in the elderly population, traffic accidents, industrial accidents, environmental pollution, drug abuse, stress, and so on. This has resulted in an increase in the manufacture and trade of counterfeit drugs. Counterfeit drugs are usually sold both online (through websites) and offline (retail) stores.

While sildenafil (Viagra®) was the first drug approved for the treatment of ED, tadalafil (Cialis®), vardenafil (Levitra®), udenafil (Zydena®), mirodenafil (Mvix®), avanafil (Zepeed®) and lodenafilcarbonate (Helleva®) are also approved for similar use in Korea. Misinformation about ingredients or dosage mislabelling may lead to drug abuse or accidental overdose. An overdose of sildenafil, tadalafil, vardenafil, udenafil,

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mirodenafil, avanafil, lodenafilcarbonate and their analogues may cause several side effects such as cardiovascular disorder, tachycardia, cardiac arrest, headache, face flushing, dyspepsia, back pain, or vision disturbance.[1] Several recent reports identified ED drugs and their analogues from illegally adulterated foods, dietary supplements, herbal medicines, and other products,[2-4] using various analytical techniques, including high performance liquid chromatography (HPLC),[7] liquid chromatography-mass spectrometry (LC-MS),[8] Fourier transform near-infrared (FT-NIR) spectroscopy,[9] Raman spectroscopy,[10] and nuclear magnetic resonance (NMR).[11]

Counterfeit drugs are fake drugs which are deliberately and fraudulently made to mimic the medicine. Counterfeit drugs look like approved drugs in terms of their size, shape, colour, etc., but they pose potential risks to public health because their safety, efficacy, and quality cannot be guaranteed.[5-6] The importance of screening for counterfeit drugs has been increased.

Hence, we had analysed from 2009 to the first half of 2013 counterfeit drugs and herbal medicine marketed online or offline stores as ED drugs or advertised as effective in enhancing male sexual performance. We monitored 7 ED drugs, including sildenafil, tadalafil, vardenafil, udenafil, mirodenafil, avanafil and lodenafilcarbodnate, and their analogues, in various samples of counterfeit drugs and herbal medicines. We aim to maintain public health and protect the public from the misuse of counterfeit drugs. We secured 89 counterfeit drugs and herbal medicines, and analysed them by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS).

2. Experimental

2.1. Chemicals

Analytical standards of 7 ED drugs and their analogues were provided by the Ministry of Food and Drug Safety (MFDS, Osong, Korea) (Supplementary data 1). Stock standard and working standard solutions for LC-ESI-MS/MS analysis were prepared in a concentration of ~1 mg/mL in methanol and diluted to the appropriate concentration with methanol (MeOH). The standard solutions were stored at 4 °C. Acetonitrile and methanol (HPLC-grade) were purchased from Merck (Darmstadt, Germany). Formic acid was purchased from Sigma-Aldrich (St. Louis MO, USA). Deionized water was purified (18.2 MΩ·cm) with a Milli-Q system (Millipore, USA).

2.2. Sample preparation

All the samples (89 counterfeit drugs and herbal medicines) sold as ED drugs were secured beginning from 2009 to the first half of 2013 in Korea through both online and offline stores. To extract the target compounds, ~0.5 g of each sample was sonicated with 70 % methanol (25 mL) for 30 min. The extracts were then filtered with a 0.20 μm polyvinylidene difluoride (PVDF) membrane syringe filter (GE Healthcare Life Science, Little Chalfont, UK). Each filtered sample was diluted with methanol to an appropriate concentration for optimal LC-MS/MS analysis.

2.3. LC-MS/MS conditions

The concentration of the 7 ED drugs and their analogues present in the obtained samples was determined using LC-ESI-tandem MS. The analytical system consisted of a Shiseido SP LC (Shiseido, Japan) and an API Triple Quad™ 5500 triple quadrupole mass spectrometer (AB SCIEX, USA). The analytes were separated using a Capcell Pak® MG2 C18 column (2.0 × 100 mm, 3 μm, Shiseido, Japan) at 40 °C. The mobile phases consisted of 0.1 % formic acid in distilled water for solvent A, and 0.1 % formic acid in acetonitrile for solvent B. The flow rate was 0.2 mL/min, and the injection volume was 2.0 μL. The gradient elution was as follows: 0.0–0.5 min, 10 % B; 0.5–8.0 min, 10–50 % B; 8.0–8.5 min, 50–80 % B; 8.5–10.0 min, 80 % B; 10.0–10.5 min; 80–90 % B; 10.5–13.0 min, 90 % B; 13.0–13.5 min, 90-10 % B; 13.5–20.0 min, 10 % B. To identify the target compounds, we selected the ions of each compound for quantitation with the appropriate ionization mode by a continuous infusion of the standard compound. The electrospray ionization

(ESI) source was operated in the positive (+) ion or negative (−) ion mode. The optimized MS conditions were: curtain gas, 25 psi (+, −); collision gas, 9 psi (+, −); ion spray voltage, 5000 V (+) or 4500 V (−); source temperature, 450 °C (+) or 500 °C (−); ion source gas 1, 50 psi (+) or 55 psi (−); and ion source gas 2, 50 psi (+, −).

To analyse more effectively, data acquisition was carried out in the MRM mode as previously reported.[8] The MRM transition parameters for the 52 standards are shown in Supplementary data 2.

2.4. LOD, LOQ, and recovery

Method validation was carried out by establishing the limit of detection (LOD) limit of quantitation (LOQ), recovery, and linearity values. Liquid-type and solid-type blank samples were used, and each sample was spiked with the standard to determine the LOD, LOQ, and recovery values. LODs and LOQs were determined at a signal-to-noise ratio (S/N) of 3 and 10, respectively. Based on the LOD and LOQ of each analyte, the recovery experiment was carried out using a 10 ng/mL concentration of a standard spiked sample. The recoveries were conducted in triplicate. The linearity was determined by a standard calibration curve using points from six different concentration levels for each standard in the range 5–200 ng/mL.

Table 1. LOQ and recovery of 7 erectile dysfunction drugs and their analogues in spiked samples

Compound	r^2	Spiked in Liquid-type Samples				Spiked in Solid-type Samples			
		LOD (ng/mL)	LOQ (ng/mL)	Recovery (%)	RSD (%)	LOD (ng/g)	LOQ (ng/g)	Recovery (%)	RSD (%)
Sildenafil group									
Acetil acid	0.999	0.1	0.3	110.0	4.8	0.1	0.3	110.2	3.1
Benzylsildenafil	0.999	1.0	3.0	98.3	1.5	1.0	3.0	97.3	6.2
Carbodenafil	0.999	0.1	0.3	99.4	6.5	0.2	0.6	96.1	7.8
Chlorodenafil	0.999	0.1	0.3	104.6	3.2	0.1	0.3	104.8	1.9
Cinnamyldenafil	0.999	3.3	10.0	100.4	10.1	3.3	10.0	95.8	6.1
Cyclopentinafil	0.999	0.5	1.5	109.7	7.4	0.5	1.5	97.4	7.2
Demethylhongdenafil	0.999	3.3	10.0	94.7	10.5	3.3	10.0	86.3	6.6
Dichlorodenafil	0.999	0.5	1.5	103.7	2.1	0.5	1.5	105.8	1.7
Dimethylsildenafil	0.999	0.5	1.5	96.7	12.7	0.5	1.5	108.7	10.2
Dimethylthiosildenafil	0.999	3.3	10.0	91.0	4.9	3.3	10.0	97.7	9.8
Gendenafil	0.999	0.5	1.5	103.2	4.0	0.5	1.5	97.3	8.4
Homosildenafil	0.999	1.0	3.0	108.6	11.6	1.0	3.0	97.7	1.5
Hongdenafil	0.999	3.3	10.0	96.9	8.5	3.3	10.0	95.4	5.1
Hydroxychlorodenafil	0.999	0.1	0.3	101.9	1.4	0.1	0.3	105.2	4.3
Hydroxyhomosildenafil	0.999	3.3	10.0	97.0	4.5	3.3	10.0	104.1	3.5
Hydroxyhongdenafil	0.999	3.3	10.0	99.5	2.6	3.3	10.0	106.6	9.4
Hydroxythiohomosildenafil	0.999	3.3	10.0	99.4	8.2	3.3	10.0	103.1	9.5
Imidazosagatriazinone	0.998	0.1	0.3	94.6	3.4	0.5	1.5	101.9	2.1
Methylhydroxyhomosildenafil	0.999	1.0	3.0	96.9	5.3	1.0	3.0	98.9	5.9
Mirodenafil	0.999	1.0	3.0	94.4	4.8	1.0	3.0	100.3	4.5
Nitrodenafil	0.999	0.1	0.3	108.2	7.8	0.1	0.3	99.9	8.9
Norneosildenafil	0.998	0.5	1.5	106.2	7.1	0.5	1.5	96.4	4.8
Oxohongdenafil	0.999	1.0	3.0	84.3	6.4	1.0	3.0	88.0	5.6
Piperidinohongdenafil	0.999	0.5	1.5	104.3	7.3	0.5	1.5	86.7	4.0
Propoxyphenylthioaildenafil	0.999	0.4	1.2	97.0	3.0	0.4	1.2	96.2	2.0
Propoxyphenyl-thiohomosildenafil	0.999	0.2	0.6	98.1	0.3	0.2	0.6	100.9	2.8
Propoxyphenyl-thiohydroxyhomosildenafil	0.999	0.2	0.6	98.5	14.4	0.2	0.6	99.0	4.5

Table 1. Continued

Compound	r^2	Spiked in Liquid-type Samples				Spiked in Solid-type Samples			
		LOD (ng/mL)	LOQ (ng/mL)	Recovery (%)	RSD (%)	LOD (ng /g)	LOQ (ng /g)	Recovery (%)	RSD (%)
Sildenafil group									
Propoxyphenyl-thiosildenafil	0.999	0.4	1.2	98.1	7.4	0.4	1.2	101.3	6.5
Sildenafil	0.999	3.3	10.0	95.4	17.5	3.3	10.0	108.3	0.4
Thiohomosildenafil	0.999	3.3	10.0	86.7	7.0	3.3	10.0	102.8	4.5
Thiosildenafil	0.999	0.5	1.5	99.0	4.5	0.5	1.5	107.8	7.7
Udenafil	0.999	0.2	0.6	112.3	16.1	0.3	0.9	105.1	8.0
Tadalafil group									
Acetaminotadalafil	0.999	2.0	6.0	99.5	15.9	2.0	6.0	100.1	9.4
Aminotadalafil	0.999	2.0	6.0	98.1	6.7	2.0	6.0	102.5	17.4
epi-Aminotadalafil	0.999	2.0	6.0	107.8	4.0	2.0	6.0	105.3	3.7
N-Butyltadalafil	0.999	0.2	0.6	92.8	4.1	0.5	1.5	99.8	11.0
Chloropretadalafil	0.999	0.5	1.5	106.4	13.8	0.5	1.5	102.3	5.7
Demethyltadalafil	0.999	2.0	6.0	85.2	15.1	2.0	6.0	94.1	6.2
N-Octylnortadalafil	0.999	0.2	0.6	94.1	6.2	0.2	0.6	103.2	2.6
Tadalafil	0.999	0.5	1.5	97.8	1.6	0.5	1.5	83.2	5.2
trans-Tadalafil	0.999	0.5	1.5	111.6	4.6	0.5	1.5	99.6	2.6
Vardenafil group									
Acetylvardenafil	0.999	3.3	10.0	105.3	0.6	3.3	10.0	91.6	2.4
Desulforvardenafil	0.999	0.1	0.3	91.5	4.6	0.1	0.3	100.0	2.4
Hydroxyvardenafil	0.999	3.3	10.0	89.1	11.0	3.3	10.0	107.3	4.4
Norneovardenafil	0.999	1.0	3.0	91.3	6.9	1.0	3.0	105.8	12.1
Pseudovardenafil	0.999	0.1	0.3	108.1	9.9	0.1	0.3	110.0	14.4
Vardenafil	0.999	1.0	3.0	104.2	13.1	1.0	3.0	107.4	13.2
Etc.									
Avanafil	0.999	0.1	0.3	100.1	6.7	0.1	0.3	102.5	10.1
Icariin	0.999	0.1	0.3	102.1	0.4	0.1	0.3	108.0	0.4
Thioquinapiperifil	0.999	0.5	1.5	104.7	1.2	1.0	3.0	99.4	1.3
Xanthoanthrafil	0.999	0.2	0.6	100.1	8.5	0.5	1.5	94.5	5.9
Yohimbine	0.999	0.2	0.6	90.1	3.9	0.2	0.6	90.0	4.4

3. Results and Discussion

As shown in Supplementary data 1, with the exception of icariin, the remaining 7 ED drugs and their analogues were observed as their protonated molecular ions $[M+H]^+$. More than two product ions of each compound were selected among the fragmented ions from precursor ions depending on their high intensity. The most abundant product ion was selected for quantitation.

To validate this method, LODs, LOQs, recoveries, and linearity experiments were conducted using standard spiked-negative samples, which had no detectable trace of ED drugs and their analogues. The LODs, LOQs, and recoveries values obtained are shown in the *Table* 1. For the 7 ED drugs and their analogues screened, the LODs ranged from 0.1 to 3.3 ng/mL or ng/g and LOQs ranged from 0.3 to 10.0 ng/mL or ng/g for standard spiked liquid-type and solid-type samples, respectively. With the exception of carbodenafil (0.3 ng/mL and 0.6 ng/g), udenafil (0.6 ng/mL and 0.9 ng/g), *N*-butyltadalafil (0.6 ng/mL and 1.5 ng/g), thioquinapiperifil (1.5 ng/mL and 3.0 ng/g), and xanthoanthrafil (0.6 ng/mL and 1.5 ng/g), the LOQs of both the standard spiked liquid-type and solid-type samples were similar. The

recoveries of each compound were determined by comparing the response of each standard with that of the spiked sample at a concentration of 10 ng/mL. The recoveries of the compounds ranged from 84.3 to 112.3 % and 83.2 to 110.2 % for standard spiked liquid-type and solid-type samples, respectively. These results show that the matrix effect in this method is relatively low. To quantitatively analyse the compounds detected in the samples, calibration curves were obtained using points from six different concentration levels in the range 5–200 ng/mL. The calibration curve had an acceptable linearity with an r^2 between 0.998 and 1 (*Table* 1). Therefore, the results indicate that this method is appropriate for the analysis of the 7 ED drugs and their analogues.

Previously, using HPLC with photodiode array (PDA) or diode array detector (DAD) is employed methods for analysis of ED drugs and their analogues in diverse samples. However, mentioned methods are required more time to analysis than LC-MS analysis, and UV spectra of ED and their analogues are too similar to separate distinctly. Therefore, it is difficult to identify each ED drugs and their analogues.

In this method, LC-MS/MS analysis was performed using ESI operated in positive and negative mode. The HPLC separation was achieved on a C18 reverse-phase column by using mobile phase of 0.1 % formic acid in water and 0.1 % formic acid in acetonitrile of a gradient elution mode. The optimized method was validated for linearity, LOD, LOQ and recovery according to ICH guideline.[12] The developed method was successfully applied to determine ED drugs and their analogues in counterfeit drugs and herbal medicines without any interference. The results demonstrated that the values were within the acceptable range.

This validated method was then applied to determine the concentration of ED drugs and their analogues in counterfeit drugs and adulterated herbal medicines which require the prescriptions of physician. The number of ED drugs detected in counterfeit drugs between 2009 to the first half of 2013 is shown in *Fig.* 1. In 2009 and 2010, 14 samples were detected in a total of 14 samples and 11 samples were

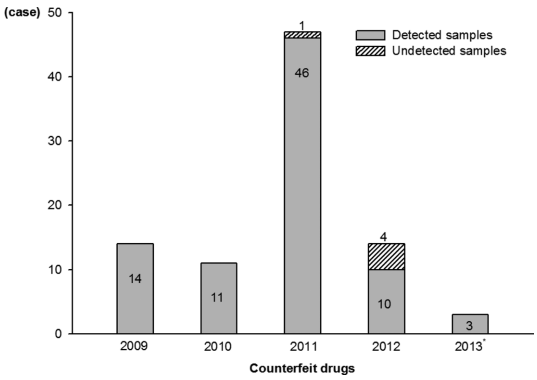

Fig. 1. Numbers of detected and undetected samples from 2009 to the first half of 2013 (n = 89). 2013*, the first half of the 2013.

detected in a total of 11 samples, respectively. In 2011 and 2012, 46 samples were detected in a total of 47 samples and 10 samples were detected in a total of 14 samples, respectively. In the first half of 2013, 3 samples were detected in a total of 3 samples. Based on the results of analyzing from 2009, we conducted surveillance manufacturing and distribution of counterfeit drugs and herbal medicine. As results, unlike tendency of increase from 2009 to 2011, products and detections of counterfeit drugs and herbal medicine were shown decreased.

As shown in *Table* 2, 11 ED drugs were detected, including sildenafil and its analogues (chlorodenafil, demethylhongdenafil, dichlorodenafil, dimethylthiosildenafil, homosildenafil, hydroxychlorodenafil, and oxohongdenafil), tadalafil and its analogue (chloropretadalafil), and vardenafil. The sildenafil group compounds were the most frequently detected (73.8 %), in particular, sildenafil were detected consistently from 2009 to the first half of 2013. The tadalafil group compounds followed (25.4 %) and tadalafil were detected from 2011 to the first half of 2013. Counterfeit drugs are fake drugs which are deliberately and fraudulently made to mimic the medicine. These counterfeit drugs may contain the compounds like medicines and wrong content of ingredient. Most detected products advertising as effective on enhancement male sexual performance were based on counterfeiting Viagra (sildenafil) or Cialis (tadalafil), or adulterating sildenafil or tadalafil illegally. In case of

Table 2. Detected numbers of erectile dysfunction drugs and their analogues in counterfeit drugs and herbal medicines from 2009 to the first half of 2013 (n = 89)

Group	Compounds	2009	2010	2011	2012	2013*
Sildenafil Group (73.8%)†	Chlorodenafil	-	-	4	-	-
	Demethylhongdenafil	-	-	4	-	-
	Dichlorodenafil	-	-	4	-	-
	Dimethylthiosildenafil	-	-	1	-	-
	Homosildenafil	-	-	1	-	-
	Hydroxychlorodenafil	-	-	4	-	-
	Oxohongdenafil	-	-	4	-	-
	Sildenafil	14	11	30	10	3
Tadalafil group (25.4%)†	Chloropretadalafil	-	-	2	-	-
	Tadalafil	-	-	24	3	2
Vardenafil group (0.8%)†	Vardenafil	-	-	1	-	-

Note: 2013*, the first half of 2013
(given number) †, percentage of detection frequency

Table 3. Ranges of detected concentration (mg/g) of erectile dysfunction drugs and their analogues in the counterfeit drugs and herbal medicines from 2009 to the first half of 2013 (n = 89)

Group	Compounds	2009	2010	2011	2012	2013*
Sildenafil group	Chlorodenafil	*n.d.*	*n.d.*	18.0-19.9	*n.d.*	*n.d.*
	Demethylhongdenafil	*n.d.*	*n.d.*	0.04-0.3	*n.d.*	*n.d.*
	Dichlorodenafil	*n.d.*	*n.d.*	37.0-39.8	*n.d.*	*n.d.*
	Dimethylthiosildenafil	*n.d.*	*n.d.*	5.5	*n.d.*	*n.d.*
	Homosildenafil	*n.d.*	*n.d.*	142.2	*n.d.*	*n.d.*
	Hydroxychlorodenafil	*n.d.*	*n.d.*	7.5-8.3	*n.d.*	*n.d.*
	Oxohongdenafil	*n.d.*	*n.d.*	47.7-58.7	*n.d.*	*n.d.*
	Sildenafil	27.9-443.0	173.7-567.9	62.3-947.5	21.0-516.5	122.5-266.9
Tadalafil group	Chloropretadalafil	*n.d.*	*n.d.*	0.1	*n.d.*	*n.d.*
	Tadalafil	*n.d.*	*n.d.*	0.2-170.2	10.7-29.8	2.1-60.4
Vardenafil group	Vardenafil	*n.d.*	*n.d.*	258.1	*n.d.*	*n.d.*

Note: 2013*, the first half of 2013
n.d. not detected (< LOD)

sildenafil, it showed high detection rate than other compounds. In addition, samples of counterfeit Viagra (sildenafil) were contained only tadalafil or sildenafil and tadalafil together. It showed that the Viagra were the main targets of counterfeiting.

The concentration of the 11 ED drugs and their analogues detected in the samples ranged from 0.04 mg/g of demethylhongdenafil (2011) to a high of 947.5 mg/g of sildenafil (2011) (*Table* 3). Thus, a large variation was observed in the concentration of sildenafil and tadalafil in the 89 secured samples. The concentration of sildenafil and tadalafil ranged from 21.0 to 947.5 mg/g and 0.2 to 170.2 mg/g, respectively. The dosage forms for the samples were solids such as tablet, pill, capsule, film, and powder. The type of formulation used for the 89 counterfeit

Table 4. Classification of samples and the number of detected samples according to dosage forms (n = 89)

Formulation	Number of Samples	Number of Detected Samples
Tablet	62	58
Capsule	15	15
Pill	4	3
Film	7	7
Powder	1	1
Total samples	89	84

drugs and herbal medicines is presented in *Table* 4. Vardenafil was identified as an ingredient for one counterfeit drug sample formulated as an oral dissolving film (ODF). At the time of this counterfeit drug sample's secured, ODF was not officially approved as a method for drug delivery.

Illegal distribution of various illicit or counterfeit drugs containing sildenafil and its analogues are secured constantly in Korea. In this study, we developed and validated a method to detect 7 ED drugs, including sildenafil, tadalafil, vardenafil, udenafil, mirodenafil, avanafil and lodenafilcarbonate, and their analogues, to monitor their concentrations in the 89 secured samples. As a result, about 73 % of secured counterfeit drugs and herbal medicines have sildenafil.

These results indicate that consumers were unconsciously exposed to health risks associated with the use of adulterated ED drugs and their analogues.

4. Conclusion

In this study, we secured 89 counterfeit drugs and herbal medicine marketed online or offline as ED drugs from 2009 to the first half of 2013 which require prescription of physician. These samples were analysed by using LC-ESI-MS/MS for ED drugs such as sildenafil, tadalafil, udenafil, mirodenafil, avanafil, and lodenafilcarbonate, and their analogues, and other compounds, including icariin and yohimbine, which were effective against ED. As a result, 11 different ED drugs were detected in 84 counterfeit drugs and herbal medicines. Most of detected products were based on counterfeiting Viagra (sildenafil) or Cialis (tadalafil), or adulterating sildenafil or tadalafil in the herbal medicines illegally. The health of people who have consumed these counterfeit drugs and herbal medicines on a regular basis is potentially threatened. Therefore, in order to protect public health and the safety of consumers, the information obtained through monitoring should be made accessible to the public. Furthermore, it is essential to monitor all existing and newly identified ED drug analogues to maintain and protect public health from the misuse of counterfeit drugs.

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Supplementary Data

Supplementary data for this article is available free of charge via the Journal website.

References

1. M. Alp, M. Coşkun and H. Göker, *J. Pharm. Biomed. Anal.*, **72**, 155-58 (2013).
2. Y. H. Lam, W. T. Poon, C. K. Lai, A. Y. Chan and T. W. Ma, *J. Pharm. Biomed. Anal*., **46**, 804-807 (2008).
3. C.-L. Kee, X. Ge, H.-L. Koh and M.-Y. Low, *J. Pharm. Biomed. Anal.*, **70**, 265-272 (2012).
4. E. S. Lee, J. H. Lee, K. M. Han, J. W. Kim, I. S. Hwang, S. Cho, S. Y. Han and J. Kim, *J. Pharm. Biomed. Anal.*, **83**, 171-178 (2013).
5. P. Zou, S. S. Oh, P. Hou, M. Y. Low and H. L. Koh, *J. Chromatogr. A*., **1104**, 113-122 (2006).
6. S. Singh, B. Prasad, A. A. Savaliya, R. P. Shah, V. M. Gohil and A. Kaur, *Trend in Anal. Chem.*, **28**, 13-28 (2009).
7. S. Park, J. G. Lee, S. H. Roh, G. Kim, C. H. Kwon, H. R. Park, K. S. Kwon, D. Kim and S. W. Kwon, *Food. Addit. Contam.: Part B*, **5**, 29-32 (2012).
8. J. H. Lee, N. S. Kim, K. M. Han, S. H. Kim, S. Cho and W. S. Kim, *Food. Addit. Contam.: Part A,* **30**, 1849-1857 (2013).
9. M. J. Vredenbregt, L. Blok-Tip, R. Hoogerbrugge, D. M. Barends and D. de Kaste, *J. Pharm. Biomed. Anal.*, **46**, 840-849 (2006).
10. S. Trefi, C. Routaboul, S. Hamieh, V. Gilard, M. Malet-Martino and R. Martino, *J. Pharm. Biomed. Anal*., **47**, 103-113 (2008).
11. S., Trefi, V. Gilard, S. Balayssac, M. Malet-Martino and R. Martino, *Magn. Reson. Chem*., **47**, S163-S173 (2009).
12. ICH Q2 (R1); Validation of analytical procedures: Text and methodology; International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical for Human Use, Geneva, Switzerland, 2005.