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Rapid determination of 88 veterinary drug residues in milk using automated TurborFlow online clean-up mode coupled to liquid chromatography-tandem mass spectrometry

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ABSTRACT

A novel method based on TurborFlow online solid phase extraction (SPE) combined with liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been established for simultaneous screening and confirmation of 88 wide-range veterinary drugs belonging to eight families (20 sulfonamides, 7 macrolides, 15 quinolones, 8 penicillins, 13 benzimidazoles, 4 tetracyclines, 2 sedatives, and 19 hormones) in milk. The preparation method consists of sample dilution and ultrasonic extraction, followed by an automated turbulent flow cyclone chromatography sample clean-up system. The detection was achieved in selected reaction monitoring mode (SRM). The total run time was within 39 min, including automated extraction, analytical chromatography and re-equilibration of the turboflow system. The optimization of different experimental parameters including extraction, purification, separation, and detection were evaluated separately in this study. The developed method was validated and good performing characteristics were obtained. The linear regression coefficients (R^2) of matrix-match calibration standard curves established for quantification were higher than 0.9930. The limits of detection (LOD) were in the range of 0.2–2.0 μg/kg given by signal–noise ratio ≥ 3 (S/N) and the limits of quantification (LOQ, S/N ≥ 10) ranged between 0.5 μg/kg and 10 μg/kg. Average recoveries of spiked target compounds with different levels were between 63.1% and 117.4%, with percentage relative standard deviations (RSD) in the range of 3.3–17.6%. The results indicated that the developed method has great potential for the routine laboratory analysis of large numbers of samples on measuring different classes of compounds. In comparison to traditional procedures, the automated sample clean-up ensures rapid, effective, sensitive analyses of veterinary drugs in milk.

1. Introduction

Veterinary drugs (VDs) such as sulfonamides, macrolides, quinolones, and hormones are increasingly applied to animal husbandry as well as in the animal feed for the prevention and treatment of animal diseases purposefully [1]. These drugs are essential in protecting animals from diseases for large commercial interests. However, the illegal use of these drugs can cause residues in several animal-origin products such as milk, meat, liver and honey. Long terms expose on VDs residues might induce acute poisoning, allergic reaction, and long term antibiotic resistance due to their toxicity [2]. Therefore, European Union Council Directives (96/22/EC, 96/23/EC) [3,4], and the Ministry of Agriculture of the People's Republic of China announcement No 235 [5] have set regulations on monitoring programs and establishing specific maximum residue limits (MRLs) for the vast majority of VDs in various food to monitor the VDs residual level in the products. Owing to the high consumption of milk, the regulation of various VDs residues in milk is extremely strict with the lowest MRLs for consumer's protection. The rigorous regulation and the dramatically increased number of sample analyses require efficient, accurate and sensitive methods for simultaneous detection of multiclass veterinary drugs residues in milk.

The reported methods for measuring VDs residues mainly included immunoassay [6], capillary electrophoresis (CE) [7], high performance liquid chromatography with diode array detection (HPLC-DAD) [8] or fluorescence detection (FLD) [9], and liquid chromatography-tandem mass spectrometry (LC-MS/MS) [10,11], liquid chromatography coupled with high resolution mass spectrometry [12]. Immunoassay is widely used because it is quick, inexpensive, and selective while fulfilled with the basic requirements. Jiang, et al. [13] developed a multiplex flow-through immunoaffinity chromatography test for screening sulfonamide and quinolone residues in milk. However, the lack of structural

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Table 1
The CAS and mass parameters of 88 veterinary drugs.

No.	Family	Compounds	CAS#	Product (m/z)	Daught ion (m/z)	CE (eV)	Tubelens
1	Sulfonamides	Sulfamonomethoxine	1220-83-3	281.1	156.0[a]	16	76
					126.1	19	76
2	Sulfonamides	Sulfamethoxypyridazine	80-35-3	281.1	156.0[a]	16	76
					126.1	19	76
3	Sulfonamides	Trimethoprim	738-70-5	291.2	123.0	28	101
					230.0[a]	22	101
4	Sulfonamides	Benzenesulfonamide	526-08-9	315.0	131.0	45	95
					158.1[a]	29	95
5	Sulfonamides	Sulfaquinoxaline	59-40-5	301.0	92.0	31	108
					156.0[a]	16	108
6	Sulfonamides	Sulfapyridine	144-83-2	250.0	155.9[a]	15	84
					184.1	17	84
7	Sulfonamides	Sulfathiazole	72-14-0	256.1	92.1	27	98
					156.0[a]	14	98
8	Sulfonamides	Sulfisoxazole	127-69-5	268.0	113.1	18	95
					156.0[a]	15	95
9	Sulfonamides	Benzenesulfonamide	729-99-7	268.0	113.1	18	95
					156.0[a]	15	95
10	Sulfonamides	Sulfadimethoxine	122-11-2	311.2	108.1	22	93
					156.0[a]	15	93
11	Sulfonamides	Sulfadoxine	2447-57-6	311.2	108.1	21	93
					156.0[a]	15	93
12	Sulfonamides	Sulfamethazine	57-68-1	279.0	124.1	21	74
					186.0[a]	16	74
13	Sulfonamides	Benzenesulfonamide	515-64-0	279.0	124.1[a]	21	74
					186.0	16	74
14	Sulfonamides	Sulfamerazine	127-79-7	265.1	156.0	15	87
					172.0[a]	16	87
15	Sulfonamides	Sulfamethoxazole	723-46-6	254.2	108.1	23	89
					155.9[a]	15	89
16	Sulfonamides	sulfachlorpyridazine	80-32-0	285.1	156.0	15	92
					129.9[a]	20	92
17	Sulfonamides	Sulfaclozine	102-65-8	285.2	108.1	28	92
					155.9[a]	15	92
18	Sulfonamides	Succinylsulfathiazole	116-43-8	356.0	108.0	27	116
					255.9[a]	16	116
19	Sulfonamides	Sulfabenzamide	127-71-9	277.1	108.0	22	91
					155.9[a]	12	91
20	Sulfonamides	Benzenesulfonamide	144-82-1	271.0	92.018	27	80
					155.9[a]	13	80
21	Macrolides	Erythromycin	114-07-8	734.4	158.2[a]	29	136
					576.2	18	136
22	Macrolides	Kitasamycin	1392-21-8	772.4	109.1	38	150
					174.0[a]	30	150
23	Macrolides	Spiramycin	8025-81-8	843.4	141.9	32	175
					174.2[a]	35	175
24	Macrolides	Clindamycin	18323-44-9	425.0	126.1[a]	30	110
					377.1	18	110
25	Macrolides	Tilmicosin	108050-54-0	869.4	132.0	39	183
					174.1[a]	40	183
26	Macrolides	Vlrglnlamycin	11006-76-1	526.1	354.9[a]	17	128
					508.0	11	128
27	Macrolides	Tiamulin	55297-95-5	494.3	119.0	36	110
					192.0[a]	19	110
28	Quinolones	Enoxacin	74011-58-8	321.1	206.0[a]	25	106
					303.1	15	106
29	Quinolones	Fleroxacin	79660-72-3	370.0	269.0[a]	25	111
					326.1	17	111
30	Quinolones	Marbofloxacin	115550-35-1	363.0	72.1.0	23	104
					320.0[a]	14	104
31	Quinolones	Orbifloxacin	113617-63-3	396.1	295.0[a]	23	111
					352.0	16	111
32	Quinolones	Danofloxacin	112398-08-0	358.0	283.0	22	110
					314.0[a]	17	110
33	Quinolones	Ciprofloxacin	85721-33-1	332.1	288.0[a]	17	115
					314.0	19	115
34	Quinolones	Difloxacin	98106-17-3	400.0	298.9[a]	27	118
					355.9	17	118
35	Quinolones	Pefloxacin	70458-92-3	334.2	233.0[a]	25	105
					290.0	16	105
36	Quinolones	Sparfloxacin	111542-93-9	393.1	291.9	24	117
					349.0[a]	17	117
37	Quinolones	Ofloxacin	82419-36-1	362.1	261.0[a]	25	109
					318.0	17	109
38	Quinolones	Enrofloxacin	112732-17-9	360.1	245.0	24	109