Establishment and validation of analytical methods for 15 hazardous drugs by UPLC-Q/Orbitrap-HRMS

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Background: Cytotoxic drug residues in pharmacy intravenous admixture services (PIVAS) have always been a major problem for pharmaceutical workers and the PIVAS environment,which is not only pollutes the PIVAS environment, but also causes serious harm to the life and health of the staff. This study aimed to establish an ultra-high performance liquid chromatography quadrupole orbitrap high resolution mass spectrometry (UPLC-Q/Orbitrap-HRMS) method for the rapid detection and monitor of 15 cytotoxic drugs.

Methods: UPLC-Q/Orbitrap-HRMS method was used to establish a rapid detection method for 15 cytotoxic drugs such as cytarabine, gemcitabine and so on. The daily precision and accuracy of this method were verified by injecting four concentrations of standard solution on the same day, and the same four concentrations of standard solution were injected within three days respectively to verify the daily precision of this method. The signal-to-noise ratio (SNR) of 10:1 was calculated as the limit of quantity. The mixed standard solution of 15 cytotoxic drugs with concentrations of 0.5, 1, 3, 10, 30, 100, 300, and 1,000 ng/mL was configured and detected by this method for linearity and range.The stability of this method was investigated using a mixture of 15 drugs (15MIX) standard solutions at high concentration (300 ng/mL) and low concentration (10 ng/mL) at room temperature for 12 and 24 hours, respectively. A standard solution of each drug, 15MIX and blank solution were taken to verify the exclusivity of the method.

Results: The results showed that the method had good specificity, and the intraday precision of all drugs was less than 10% and the intraday precision was less than 15%. At the same time, the standard curve had good linearity, R^2 was greater than 0.99, and the limit of quantification of most drugs was about 1 ng/mL.

Conclusions: In this study, an UPLC-Q/Orbitrap-HRMS method was established for the rapid detection of 15 cytotoxic drugs, providing technical support for the monitoring of cytotoxic drug residues in PIVAS, which is of great significance for environmental contamination mornitoring as well as occupational exposure alert.

Keywords: Ultra-high performance liquid chromatography quadrupole orbitrap high resolution mass spectrometry (UPLC-Q/Orbitrap-HRMS); pharmacy intravenous admixture services (PIVAS); cytotoxic drugs; environmental monitoring

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Introduction

As a severe public health problem that threatens human health (1), cancer is a leading cause of mortality worldwide, accounting for nearly 10 million, or almost one in six deaths, in 2020 (2). While traditional treatments include surgery, chemotherapy and antineoplastic drugs (3), and radiation therapy (4), new approaches such as immunotherapy have come of age in recent years, although cytotoxic drugs remain the mainstay (5). Increasing concern has been raised regarding the safety and health of health-care practitioners who are occupationally exposed to hazardous chemotherapy drugs. Activities that create most of the significant risks of occupational exposure are preparing and administering antineoplastic agents, managing chemotherapy spills, and handling patients (6).

In 2004, the National Institute for Occupational Safety and Health (NIOSH) presented a standard precautions or universal precautions approach to safely handling hazardous drugs (HDs) (7) which included drugs with apparent occupational health hazards (8). The American Society of Health-System Pharmacies (ASHP) published its Guidelines on Handling Hazardous Drugs in 2006 to harmonize with both the NIOSH alert and the United States Pharmacopeia (USP) general chapter 797 (Pharmaceutical Compounding-Sterile Preparations) (8-10), and although the ASHP definition of HDs differed from that of the NIOSH, the USP adopted the NIOSH HD list. HDs may enter the body through inhalation, dermal absorption, accidental injection, ingestion of contaminated foodstuffs, or mouth contact with contaminated hands. Inhalation is no longer considered the main route of exposure due to protections such as personal protective equipment (PPE) and primary engineering controls (PEC), and dermal absorption via direct contact is probably the most direct route. Surface contamination transferred to hands may be ingested via the hand-to-mouth route, and contaminated hands may transfer HD residue to other surfaces and other workers (11-15). As almost all cytoxic drugs are classified as HDs, the periodic environmental monitoring of HD contamination is beneficial to ensure the safety of personnel, the environment, and preparations.

Usually, several index cytotoxic drugs are subjectively selected for measurement of contaminants, and the problem is not comprehensive. Recently, a quick analysis of chemical contamination by HDs was performed with a BD (Becton Dickinson and Company) HD Check semi-quantitative device, although only methotrexate, doxorubicin, and cyclophosphamide samples could be analyzed (16). Due to the low concentration of contaminants, the detection limit and quantification limit of the corresponding analytical method should be significant. Therefore, it is urgent to establish an analytical method that can be used for the simultaneous determination of multiple HDs for environmental contaminating samples while meeting the requirements of sensitivity and accuracy. Q-Orbitrap enables fast, sensitive and reliable detection and identification of small molecules without considering the relative ion abundance; it also has an extremely fast scanning speed, and the front body ions and product ions provide high-quality measurement results (17). In addition, UPLC, which is specifically advantageous for applications that require separation by columns with small particle sizes and under ultra-high pressure, maintains the basic principles of traditional high-performance liquid chromatography system but demonstrates improved separation efficiency and speed over other liquid chromatography techniques (18).

The current study was designed to develop a simultaneous sensitive and accurate method to determine the most commonly used chemotherapy agents by UPLC-Q/Orbitrap-HRMS.

Methods

Chemicals and reagents

Cyclophosphamide, etoposide, ifosfamide, and epirubicin were obtained from Macklin Biochemical Co., Ltd. (Shanghai, China), and daunorubicin, pirarubicin, pemetrexed, cytarabine, homoharringtonine, gemcitabine, irinotecan, paclitaxel, doxorubicin, docetaxel, idarubicin, raltitrexed, and methotrexate were obtained from Meilun Biotechnology Co., Ltd. (Dalian, China). Methanol and acetonitrile were purchased from Merck KGaA (Darmstadt, Germany), and HPLC-grade formic acid (99%) was purchased from Anaqua Chemicals Supply (Wilmington, USA). Purified water was obtained from a Merck Milli-Q HR Water Purification System (Darmstadt, Germany).

Chromatographic and mass spectrometry conditions

In this project, separation of the target compounds was performed on a Thermo Hypersil GOLD (2.1 mm × 100 mm, 3 μm) column using a Dionex Ultimate 3000 UPLC system. The mobile phase contained 0.1% aqueous formic acid (A) and acetonitrile (B), the mobile phase flow rate was

Table 1 Chromatographic and mass spectrometry conditions

Retention (min)	Flow (mL/min)	A (%)	B (%)
0	0.2	10	90
3	0.2	10	90
14	0.2	30	70
15.5	0.2	90	10
17.5	0.2	90	10
18	0.2	10	90
21	0.2	10	90

A: 0.1% aqueous formic acid; B: acetonitrile.

0.3 mL/min, and the injection volume was 5 µL. The gradient program is shown in *Table 1*.

Acquisition was performed in selective ion monitoring mode, and all MS spectra were acquired and analyzed using Xcalibur 4.0 software (Thermo Fisher Scientific). Mass spectrometry conditions were as follows: full MS/TSIM, electrospray ion source (HESI), positive and negative ion scanning at the same time, capillary temperature at 320 ℃, volume flow of sheath gas of 15 psi (1 psi ≈ 6.9 kPa), and a volume flow of auxiliary gas of 2 psi. Spray voltage for positive ion mode and negative ion mode were 3.5 and 2.5 kV, respectively, the lens voltage was 55 kPa, and the probe heater temperature was 300 ℃. The maximum spray current was set at 100 V, and the NEC was 10, 30, 50. The quality scanning range was m/Z 150–2,000, and the quality resolution is 70,000.

Preparation of standard solutions

By adding 1 mg of each of the 15 standard cytotoxic drugs to 1ml methanol, 15 standard solutions with a concentration of 1 mg/mL were achieved. 50 µL of each of the 15 standard solutions were mixed with 250 µL methanol to obtain a mixture of 15 drugs (15MIX) with a concentration of 50 µg/mL, which was filtered with a 0.22 µm organic filter membrand for later use. The standard curve was established with a standard working solution of 0.5, 1, 3, 10, 30, 100, 300, and 1,000 ng/mL.

Practical sampling methods for cytotoxic drugs in PIVAS

The plate was wiped twice by 1/4 of the glass fibre filter paper wet with a 50 µL desorption solution [methanol: acetonitrile: water (1:1:2, v/v/v)], and the wiping procedures were performed with a vertical motion followed by a horizontal motion. The two pieces of glass fibre filter paper were transferred to a 1.5 mL centrifuge tube, and 900 mL of desorption solution was added subsequently. The sample was immediately vortexed for 20 minutes, sonicated for 10 min, and centrifuged at 12,000 rpm for 10 min. Finally, 100 µL of supernatant mixed with 10 µL of internal standard at a concentration of 5 µg/mL was transferred to the autosampler for further analysis.

Statistical analysis

Quantification data were expressed as means ± standard deviation (SD). One-way analysis of variance (ANOVA) was carried out on the quantitative data, using Microsoft Excel 2010 at a significance level of $P<0.05$. The data of mass spectrometry were processed by using Xcalibur 4.0 software (Thermo Fisher Scientific, USA).

Results

Accuracy and precision

We measured the precision and accuracy of this recovery method by setting up four concentrations and each was tested five times in parallel on the same day. Results showed that the relative sandard deviation (RSD) of each group was less than 15%, and the error between the measured value and theoretical value was less than 5%. At the same time, four concentrations were set for continuous injection for three days, and each was tested five times in parallel. The RSD of each group was less than 15%, and the comparison error between the measured and theoretical values was less than 10%. These data (*Table 2*) suggested the method had good precision and accuracy.

Specificity

Each of the above mentioned 15 cytotoxic drugs of 1 mg was dissolved in 1 mL solvent (methanol/water/acetonitrile 1/2/1) and further diluted to 50 ng/mL as an exclusive solution. The blank solution (methanol/water/acetonitrile 1/2/1), 15MIX solution, and appropriate amount of specific solution were then injected and analysized. The retention time of each chemotherapy drug is shown in Figure S1, and other drugs in blank solvent and mixed solvent did not interfere with the principal component, indicating the method had good specificity.

Table 2 Accuracy and precision

Component	QC (ng/mL)	Inter-day (%)		Intra-day (%)			
		RSD	RE	RSD	Day 1-RE	Day 2-RE	Day 3-RE
Cytarabine	1	6.73	2.14	6.67	8.53	8.91	4.06
	3	1.74	0.66	6.25	−7.71	−0.90	1.56
	80	10.35	−5.55	4.26	−13.19	−11.24	3.50
	250	8.87	−1.43	7.93	−11.53	2.24	3.27
Gemcitabine	0.5	7.86	−0.89	7.44	−3.27	3.22	−2.57
	1	0.30	−2.09	7.21	−5.27	−11.33	4.88
	15	3.87	3.77	5.31	7.48	6.16	4.85
	80	7.26	−3.63	7.19	−7.70	1.91	−9.55
Methotrexate	5	7.78	3.19	5.24	0.69	9.64	5.55
	10	12.39	1.11	4.79	−7.63	−10.09	8.07
	150	8.21	2.23	4.34	−1.95	−0.43	6.69
	800	11.37	1.50	5.71	6.23	10.75	9.02
Homoharringtonine	0.5	19.97	−1.97	7.45	−8.71	−13.71	5.94
	1	14.31	−1.11	6.25	−9.76	−5.92	6.32
	15	11.65	2.35	5.28	−8.37	−3.26	5.15
	80	6.31	−0.27	1.18	−5.19	−8.04	3.74
Raltitrexed	10	9.34	−0.43	8.49	11.93	−10.55	9.52
	30	2.97	−6.14	4.42	−8.41	−0.35	−9.92
	150	11.05	−1.88	6.55	−4.82	−2.11	10.57
	800	4.36	−0.36	5.44	1.56	1.88	−12.15
Isophosphamide	0.5	13.52	−1.25	5.42	−1.98	−7.91	4.61
	1	14.12	−3.79	6.40	−10.24	−14.04	8.23
	15	10.03	1.88	6.27	−9.49	−3.74	6.36
	80	11.37	0.28	5.80	−4.71	−7.95	3.19
Cyclophosphamide	0.5	0.47	1.18	4.26	0.04	−0.63	0.75
	1	3.50	−0.13	7.02	−11.49	10.35	−4.76
	15	3.45	3.24	7.03	−1.15	−11.21	4.64
	80	9.82	−1.11	4.87	−3.60	−8.86	6.76
Doxorubicin	1	5.28	3.01	8.33	9.37	8.49	5.25
	3	4.43	3.69	6.25	7.56	−8.07	7.47
	150	6.84	0.74	4.60	−7.23	5.70	−3.99
	800	0.73	−2.56	6.85	4.12	8.53	0.41

Table 2 (*continued*)

Table 2 (*continued*)

Component	QC (ng/mL)	Inter-day (%)		Intra-day (%)			
		RSD	RE	RSD	Day 1-RE	Day 2-RE	Day 3-RE
Epirubicin	1	15.00	3.28	6.85	−3.27	1.18	14.55
	3	7.21	3.33	5.40	−3.34	7.51	13.15
	150	10.24	1.12	5.35	−7.44	2.52	−2.09
	800	2.18	−1.54	7.04	2.95	13.38	2.19
Etoposide	5	8.60	7.04	4.50	10.97	6.71	8.52
	10	8.50	3.67	4.88	5.28	8.77	6.52
	150	4.40	3.88	4.56	5.27	9.66	6.02
	800	3.42	4.67	6.77	9.81	9.86	9.62
Daunorubicin	1	8.00	1.49	7.17	1.81	1.07	5.46
	3	8.01	2.16	6.98	−6.95	−13.32	−2.25
	150	6.58	4.49	2.87	1.64	11.98	4.44
	800	6.66	1.97	5.91	4.56	5.51	7.42
Pirarubicin	1	6.27	1.00	8.63	−12.31	−2.33	−4.26
	3	8.43	−1.41	5.38	−2.89	2.28	−7.93
	150	8.87	0.21	4.19	−6.35	3.83	3.33
	800	2.62	0.23	7.54	4.56	6.46	3.15
Idarubicin	1	4.75	2.78	8.96	3.26	−7.66	4.44
	3	9.44	−3.19	8.24	11.76	−2.35	−9.43
	150	3.11	4.75	4.85	5.00	9.85	5.71
	800	6.67	0.43	7.23	3.53	7.91	3.23
Docetaxel	30	8.58	−1.73	8.51	2.91	−2.66	−12.82
	80	9.85	−3.24	4.99	−8.45	−7.81	4.86
	250	1.26	−4.78	4.49	−2.85	−7.64	−9.72
	800	4.51	−0.23	5.25	5.83	7.60	−0.74
Paclitaxel	1	5.80	−1.67	7.56	0.25	−9.58	8.25
	3	8.46	2.83	8.07	6.59	7.13	9.93
	150	13.77	1.16	5.60	−5.98	−10.77	5.42
	800	1.29	−2.29	8.01	5.67	7.71	−1.51

QC, quality control; RSD, relative standard deviation; RE, relative error.

Linearity and range

The mixed standard solution of 15 cytotoxic drugs with concentrations of 0.5, 1, 3, 10, 30, 100, 300, and 1,000 ng/mL was configured and detected by the UPLC-Q/Orbitrap-HRMS method established in this study. The standard curve was drawn with the mass concentration of each drug (X axis) as the horizontal coordinate and the mass spectrum response intensity (Y axis) as the vertical coordinate (as shown in *Table 3*). The correlation coefficient R^2 of each component was ≥0.994, and the linear range is depicted in the following

Table 3 Linearity and range

Component	Regression curve	R^2	Quantitative range (ng/mL)
Cytarabine	$Y = -8.76\times10^{-5}+3.72\times10^{-4}\times X$	0.9992	1–300
Gemcitabine	$Y = -1.40\times10^{-4}+2.35\times10^{-4}\times X$	0.9955	0.5–100
Methotrexate	$Y = -6.71\times10^{-5}+4.59\times10^{-4}\times X$	0.9953	5–1,000
Homoharringtonine	$Y = 1.83\times10^{-5}+1.98\times10^{-4}\times X$	0.9984	0.5–100
Raltitrexed	$Y = -2.87\times10^{-4}+1.31\times10^{-4}\times X$	0.9963	10–1,000
Ifosfamide	$Y = 9.76\times10^{-5}+9.86\times10^{-4}\times X$	0.9936	0.5–100
Cyclophosphamide	$Y = 5.47\times10^{-5}+8.77\times10^{-4}\times X$	0.9975	0.5–100
Doxorubicin	$Y = -3.03\times10^{-5}+1.25\times10^{-4}\times X$	0.9957	1–1,000
Epirubicin	$Y = -2.93\times10^{-5}+2.59\times10^{-4}\times X$	0.9970	1–1,000
Etoposide	$Y = -2.10\times10^{-7}+5.78\times10^{-5}\times X$	0.9969	5–1,000
Daunorubicin	$Y = 1.03\times10^{-5}+1.88\times10^{-4}\times X$	0.9957	1–1,000
Pirarubicin	$Y = -5.99\times10^{-5}+2.90\times10^{-4}\times X$	0.9973	1–1,000
Idarubicin	$Y = -1.52\times10^{-5}+2.88\times10^{-4}\times X$	0.9987	1–1,000
Docetaxel	$Y = -4.91\times10^{-5}+1.08\times10^{-5}\times X$	0.9961	30–1,000
Paclitaxel	$Y = 1.44\times10^{-5}+1.89\times10^{-4}\times X$	0.9948	1–1,000

Table 4 Stability

Component	QCL/%		QCH/%	
	12 h	24 h	12 h	24 h
Cytarabine	5.14	3.79	5.71	15.86
Gemcitabine	14.96	15.23	18.85	25.27
Methotrexate	0.20	–4.51	4.07	–4.62
Homoharring tonine	7.49	–2.48	4.87	–1.03
Raltitrexed	–0.46	–5.83	–34.84	–42.77
Isophosphamide	2.07	–3.36	4.60	–6.20
Cyclophosphamide	4.98	–6.98	–1.56	2.93
Etoposide	–15.61	–19.73	–49.20	–58.16
Doxorubicin	–1.63	0.45	–0.30	2.33
Epirubicin	–8.18	–4.94	5.37	4.77
Daunorubicin	–4.08	–0.55	–4.18	–14.43
Pirarubicin	–2.26	–2.85	10.21	–0.82
Idarubicin	6.87	–3.83	7.54	–1.53
Docetaxel	–3.20	1.24	0..20	–2.01
Paclitaxel	6.05	6.47	9.22	16.36

QCL, low concentration quality control; QCH, high concentration quality control.

table which shows the standard curve is established accurately and can be used for subsequent quantification.

Determination of limit of quantitation/limit of detection (LOQ/LOD)

The signal-to-noise ratio (SNR) of 10:1 was calculated as the limit of quantity (LOQ). As shown in the table above, the minimum amount of each component detected by this method was in the range of 0.5–30 ng/mL. Only docetaxel had a minimum quantitation limit of 30 ng/mL, and the rest were within the concentration range of 0.5–10 ng/mL, which show this method has high sensitivity and can be used in practical detection.

Stability test

The stability of this method was investigated using 15MIX standard solutions at high concentration (QCH, 300 ng/mL) and low concentration (QCL, 10 ng/mL) at room temperature for 12 and 24 hours, respectively. *Table 4* shows the results compared with the control solution, which were considered stable if the changes of the high or low concentrations within 24 hours were within 15%.

Table 5 Results of wipe sampling in PIVAS

Sampled surface	Gemcitabine (ng/cm^2)	Ifosfamide (ng/cm^2)	Cyclophosphamide (ng/cm^2)	Irinotecan (ng/cm^2)	Epirubicin (ng/cm^2)	Docetaxel (ng/cm^2)	Paclitaxel (ng/cm^2)
Production area							
Operating table of BSC	2.150	0.901	5.702	0.014	<0.008	<0.24	0.066
Lateral wall of BSC	1.702	0.385	3.416	0.004	<0.008	<0.24	0.055
Drug placement desk	0.462	0.009	0.138	<0.004	<0.008	<0.24	<0.008
Chair	7.010	0.341	1.396	0.355	0.011	0.521	0.098
Door handle	1.454	0.429	2.064	0.223	<0.008	0.443	0.218
Storage area							
Desk	<0.004	<0.004	0.023	<0.004	<0.008	<0.24	<0.008
Phone	<0.004	<0.004	<0.004	<0.004	<0.008	<0.24	<0.008
Checking area							
Desk	<0.004	0.036	0.794	<0.004	<0.008	<0.24	<0.008
Production area (after targeted cleaning)							
Operating table of BSC	0.024	0.022	0.913	<0.004	<0.008	<0.24	0.045
Lateral wall of BSC	0.020	0.009	0.224	<0.004	<0.008	<0.24	0.013
Drug placement desk	0.108	0.080	1.025	<0.004	<0.008	<0.24	0.023
Chair	0.378	0.214	6.340	<0.004	<0.008	<0.24	0.047
Door handle	2.813	0.689	2.685	0.077	<0.008	<0.24	0.285

BSC, biological safety cabinets; PIVAS, pharmacy intravenous admixture services.

Application to surface of different regions in PIVAS

To investigate the applicability and suitability of our method to actual samples in PIVAS, the residues of 15 cytotoxic drugs were wiped and evaluated after standard cleaning procedures (as shown in *Table 5*). The main susceptible-exposed surfaces in the cytotoxic production area, including the operating table and lateral wall of biological safety cabinet, drug placement area, the surface of chair, door handle, and several regions in the storage and checking room, were evaluated according to "wiping recovery validation". We finally detected seven of the 15 cytotoxic drugs, including gemcitabine, ifosfamide, cyclophosphamide, irinotecan, epirubicin, docetaxel, and paclitaxel, which may be related to the stability and specification of different component. It should be noted that gemcitabine, ifosfamide, and cyclophosphamide were the the main residual components in the cytotoxic production area, and only some traces of cytotoxic drugs were detected in the storage and checking room. A targeted cleaning operation was then performed for the high residue regions in the cytotoxic production area, and a significant reduction was observed for the most residual components. These results revealed that the method we established can be used as an effective means to monitor cytotoxic drug residues in PIVAS to reduce the potential risk of cytotoxic drug exposure to pharmaceutical practitioners.

Discussion

Occupational exposure to antineoplastic drugs and its association with adverse health effects has been well documented and established over 3 decades (19,20). As continuous exposure to cancer drugs in the workplace may lead to cancer, prevention is required (21,22), and methods validate and ensure surface contamination detection reliability must be developed. However, despite following published guidelines, workplace contamination persists, leaving healthcare workers exposed to chemotherapeutic agents. The use of new technologies, compounding robots, and other similar automation breakthroughs to

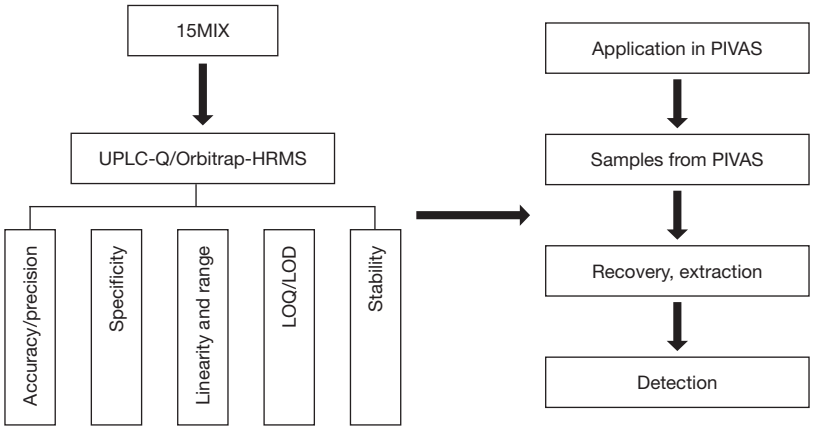

Figure 1 The research process. 15MIX, a mixture of 15 drugs; UPLC-Q/Orbitrap-HRMS, ultra-high performance liquid chromatography quadrupole orbitrap high resolution mass spectrometry; PIVAS, pharmacy intravenous admixture services; LOQ, limit of quantity; LOD, limit of detection.

prepare them may result in a safer compounding process but does not eliminate contamination in the whole process of handling cytotoxic drugs, especially inside hospital pharmacies (23). Efforts need to be maintained, emphasizing continuous monitoring exposure levels for cytotoxic contamination.

In this primary investigation, we set up tests to evaluate whether we are doing enough in daily tasks. We established a cytotoxic drug detection method which laid a foundation for the follow-up monitoring of cytotoxic drug residues, and compared with existing methods itcould simultaneously determine 15 cytotoxic drugs and expand the scope of drug detection. Through continuous optimization of liquid and mass spectrometry conditions, the detection time was within 21 min, which might significantly improve the detection efficiency. In the investigation of accuracy and precision, four concentrations of mixed standard solution were set, and five times parallel injections were carried out. The final RSD values were all below 15%, while the deviation between the measured and theoretical values was about 5%, indicating this method had good accuracy and stability while being fast and efficient.

In addition, this method also had the characteristics of sensitive detection, and except for docetaxel, the minimum quantification limit of whichwas 30 ng/mL, other drugs were below 5 ng/mL, among which gemcitabine and another 5 drugs had the minimum quantification limit of 0.5 ng/mL. These results indicate the method can be used for the actual detection of cytotoxic drugs and protect the life and health of staff.

Conclusions

A fast and simultaneous detection method with a UPLC-Q/Orbitrap-HRMS method was developed to determine 15 cytotoxic drugs on different surfaces of the cleanroom. Method validation parameters included selectivity, linearity, sensitivity, precision, recovery, and stability (as shown in *Figure 1*). The method was successfully applied to monitor the cytotoxic drug residues and optimize cleaning procedures. We hope these results provide practical tools to improve the operation process and specification for the safe handling of cytotoxic drugs.

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Footnote

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2330/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2330/coif).

The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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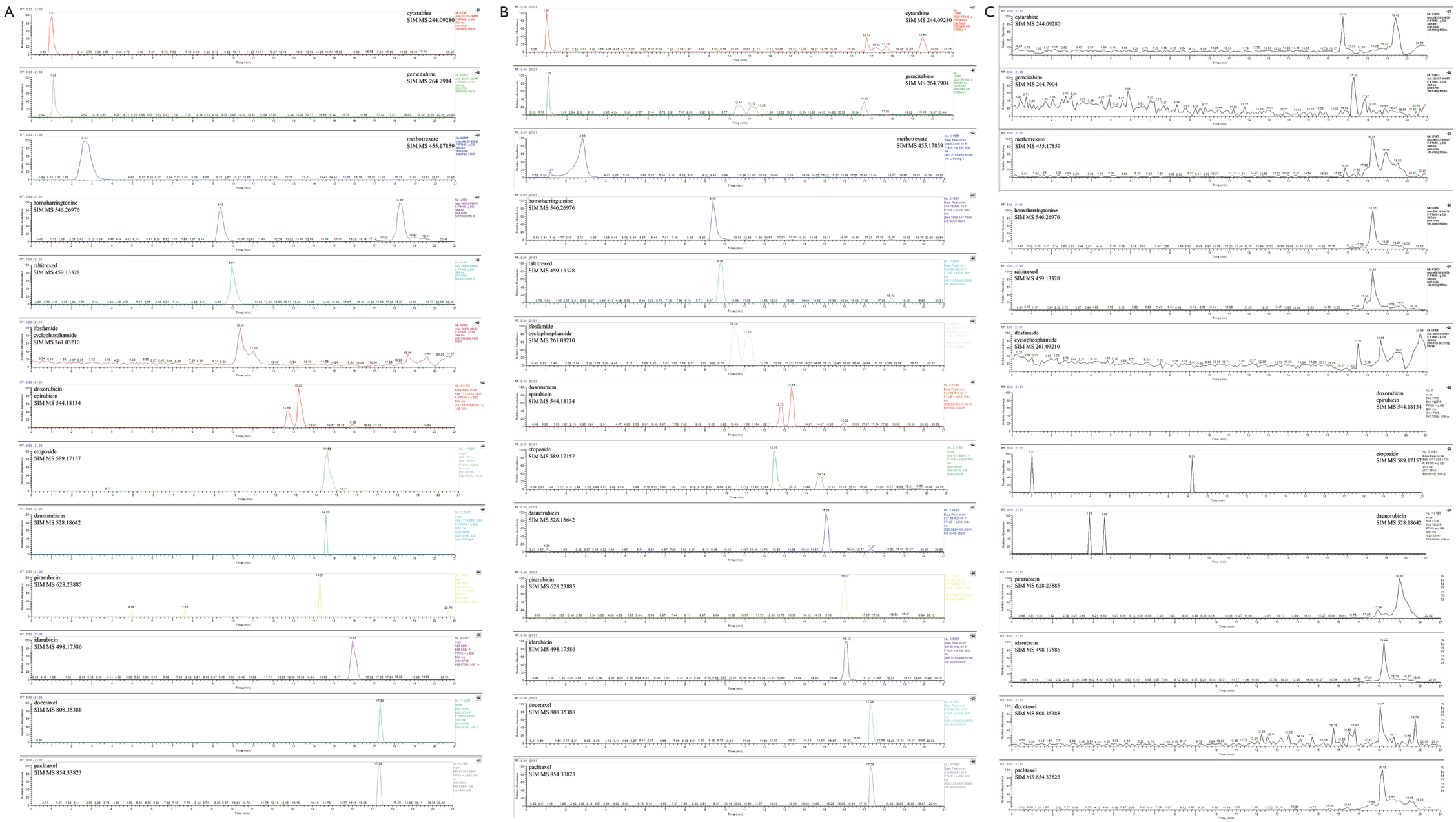

Figure S1 Chromatograms of 15 cytotoxic drugs in the blank solution (methanol/water/acetonitrile 1/2/1), a mixture of 15 drugs (15MIX) solution, and appropriate amount of specific solution. (A) Chromatogram of 15 cytotoxic drugs in the appropriate amount of specific solution; (B) chromatogram of 15 cytotoxic drugs in the 15MIX solution; (C) chromatogram of 15 cytotoxic drugs in the blank solution.