

Simultaneous determination of 20 disperse dyes in foodstuffs by ultra high performance liquid chromatography–tandem mass spectrometry

Weiguo Liu^{a,b}, Jun Liu^{c,*}, Yu Zhang^d, Yinguang Chen^{a,d}, Xiaodong Yang^{a,b}, Luchun Duan^f, Rajarathnam Dharmarajan^f, Xiyuan Wang^{a,b}, Lan Li^e

^a College of Resources and Environment Science, Xinjiang University, Urumqi, China

^b Key Laboratory of Oasis Ecology, Ministry of Education, Xinjiang University, Urumqi, China

^c Department of Technology, Xinjiang Entry-Exit Inspection and Quarantine Bureau, Urumqi, China

^d School of Environment Science and Engineering, Tongji University, Shanghai, China

^e Key Laboratory of Oil & Gas Fine Chemicals, Ministry of Education, Xinjiang University, Urumqi, China

^f Global Centre for Environmental Remediation, Faculty of Science, The University of Newcastle, Callaghan, NSW 2308, Australia

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ABSTRACT

A reasonable, high sensitive and accurate analytical method for the determination of 20 allergenic disperse dyes in foodstuffs was developed and validated. The obtained results showed that an ultra high liquid performance chromatography system – equipped with tandem quadrupole mass spectrometry (UHPLC–MS/MS) proved to be ideal for the selected method enabling multidimensional processing of the samples. Under optimized conditions, validation results showed excellent linearity (5–1000 µg/L, $r^2 \geq 0.997$), limits of detection (LODs, 1.1–10.8 µg/kg), recoveries (60.2–110.3%) and precision (RSDs $\leq 12.6\%$) for the twenty disperse dyes under investigation. The developed method was successfully applied to the analysis of 20 disperse dyes in real foodstuffs demonstrating the validity and applicability of the current method for continuing monitoring of the selected dyes. The proposed UHPLC–MS/MS is thus proved to be a convenient, effective, sensitive and timesaving method for the isolation and determination of allergenic disperse dyes in edible packaging and other foodstuffs.

1. Introduction

The color of food is one of the critical properties that makes it appealing people to purchase. In some cases, synthetic colorants, such as disperse dyes have been added to the foodstuffs and edible packaging to improve its appearance and reduce cost, (Ahlström, Eskilsson, & Björklund, 2005; Timberlake, Bridle, & Walford, 1980). However, exposure of synthetic dye additives in food is dangerous and must be controlled and regulated. The presence of residues with unstable disperse dyes in food products is a matter of concern for public health. Research indicates that it can form aromatic amines (Rafii, Hall, & Cerniglia, 1997) which can cause headaches in adults (Hawley & Buckley, 1974), apart from their neurotoxicity (Nagaraja & Desiraju, 1993), carcinogenicity (Khehra, Saini, Sharma, Chadha, & Chimni, 2006) as well as genotoxicity (Karthik, Meyyanathan, & Nageswara, 2016). In order to protect the potential effect of dyes on Human Health, the European Commission (EC, Commission Regulation 231/2012/EC, 257/2010/EC and 1333/2008/EC), the Council of Europe (CoE) resolution on the Use of colorants for food contact plastics AP(89)1 and

the Chinese government have published regulations on the Using Standard of Food Additives (GB 2760-2014, 2014; Lok, Chung, Benzie, & Woo, 2010) against azo dyes. Nevertheless, miscellaneous synthetic dyes have been illegally abused in foodstuffs to improve the acceptability of the products, making the color brighter and fixation stronger (Zhao et al., 2016).

While it is inevitable to neglect many disperse dyes when taking single or some different disperse dyes as detect objects, one-by-one detecting is expensive and time-consuming (Zhao et al., 2016). Therefore, establishment of a highly practicable and effective method for detecting multiple target dyes simultaneously is urgently needed. Methods of detection and monitoring dyes added in the foodstuff through effective extraction methods followed by HPLC technique has received much attention and been tried extensively. Among them, HPLC system coupled with various detectors, such as diode array detector (DAD) (Liu, Qi, & Zhang, 2018; Qi, Zeng, Wen, Liang, & Zhang, 2011; Sun, Sun, Li, Zhang, & Yang, 2013; Tang et al., 2014), variable wavelength detector (VWD) (Alves, Édira Castello Branco de Andrade, & Netto, 2008; Wu et al., 2013), mass spectrometry (MS) (Gosetti et al.,

* Corresponding author at: Xinjiang Entry-Exit Inspection and Quarantine Bureau, No116, Nanhu North Road, Shui District, Urumqi 830063, China.

E-mail address: junliuxj@126.com (J. Liu).

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Table 1
MS parameters for the analysis of 20 dyes.

NO.	Analyte	Retention Time (min)	Ion source	Parent ion (<i>m/z</i>)	Daughter ion (<i>m/z</i>)	Cone voltage (V)	Collision energy (eV)
1	Acid red 26	0.42	ESI-	217.15	136.3 [*] 141.9	25	20 30
2	Direct red 28	0.59	ESI-	325.51	81.0 152.1 [*]	30	30 23
3	Disperse blue 1	0.96	ESI+	269.18	106.8 160.9 [*]	30	35 25
4	Basic red 9	1.04	ESI+	288.44	168.3 195.3 [*]	30	40 30
5	Disperse blue 7	1.92	ESI+	359.35	283.3 [*] 314.3	35	30 20
6	Disperse yellow 1	2.26	ESI-	274.21	226.2 [*] 244.2	20	20 20
7	Disperse red 11	2.46	ESI+	269.21	226.2 254.1 [*]	40	25 25
8	Disperse blue 3	2.49	ESI+	297.25	235.2 252.2 [*]	25	30 20
9	Disperse red 17	4.00	ESI+	345.33	164.0 [*] 177.1	35	25 30
10	Disperse blue 106	4.61	ESI+	336.24	146.8 178.1 [*]	25	35 20
11	Disperse orange 11	5.07	ESI+	238.16	165.1 [*] 195.1	45	30 30
12	Disperse orange 3	5.34	ESI+	243.20	91.7 121.8 [*]	30	25 20
13	Disperse yellow 3	5.57	ESI+	270.32	106.8 [*] 149.9	25	25 15
14	Disperse brown 1	7.11	ESI+	433.10	185.0 197.1 [*]	40	30 25
15	Disperse red 1	7.43	ESI+	315.32	133.9 [*] 255.2	45	25 30
16	Disperse blue 35	7.48	ESI+	285.19	169.1 270.2 [*]	40	45 20
17	Disperse blue 124	8.12	ESI+	378.27	86.8 [*] 220.3	25	25 15
18	Disperse yellow 49	8.17	ESI+	375.32	163.9 238.3 [*]	25	20 20
19	Disperse orange 37	8.81	ESI+	392.20	323.2 351.2 [*]	25	30 25
20	Disperse orange 1	9.08	ESI+	319.30	122.0 [*] 169.2	45	25 30

^{*} corresponds to quantification ion.

2013; Murty, Sridhara Chary, Prabhakar, Prasada Raju, & Vairamani, 2009), were widely applied and methods evaluated.

Based on these HPLC techniques, though methods are reported for the determination of range of mixed colorants (3–40) in foodstuffs such as water, textile, drinks, chilli products, bread, etc. But the scopes of application are narrow (García-Falcón & Simal-Gandara, 2005; Dossi, Toniolo, Susmel, Pizzariello, & Bontempelli, 2006; Ma, Luo, Chen, Su, & Yao, 2006; Miniotti, Sakellariou, & Thomaidis, 2007; Yoshioka & Ichihashi, 2008; Noguerol, López-Vilariñ, Fernández-Martínez, Barral-Losada, & González-Rodríguez, 2008; Feng et al., 2011) because gelatin in foodstuffs affects the columns. Although method using HPLC equipped with VWD or DAD are of low cost, it is less selective with poor sensitive, especially for samples comprising complex matrices. On the contrary, HPLC-MS is proved to be highly efficient and accurate technique for the identification and quantification of disperse dyes where in the drawbacks being it is an expensive system with high running cost. Consequently, to monitor the multi-residues of disperse dyes in foodstuffs, it is urgently required to develop a time-saving, highly effective and practicable method for the analysis of the target 20 disperse dyes.

Most of currently available HPLC–MS methods are focused on liquid samples, or fruit jellies, confectioneries and jams and thus not fully suitable to adopt directly for complex matrices such as edible packaging. In addition, most researches were reported for the determination of illegal dyes (González, Mercedes, & Valcárcel, 2003; Tavakoli, Hajimahmoodi, & Shemirani, 2014), such as Sudan dyes, Rhodamine B, Para red in foodstuffs based on HPLC-MS technique (Alesso, Bondioli,

Talío, Luconi, & Fernández, 2012; Enríquez-Gabeiras, Gallego, Garcinuño, Fernández-Hernando, & Durand, 2012; Zhou, Shi, Liu, Lv, & Xu, 2016; Zou, He, Yasen, & Li, 2013). However only a limited attention was paid to analyse disperse colorants present in pharmaceutical capsules and oblatum.

Pharmaceutical capsules, fruit, pickled vegetables and oblatum are very complex matrices, such as high concentrations of gelatin, fats, proteins, etc., which often cause interferences in the confirmation of color additives. Thus beside, the appropriate instrumental technique, effective pretreatment procedures to isolate and enrich analytes are crucial prior to analysis. Many pretreatment approaches have been developed, such as liquid–solid extraction (Rebane, Leito, Yurchenko, & Herodes, 2010), liquid–liquid micro extraction (Khanavi et al., 2012; Long, Zhou, & Peng, 2011; Saad, Bari, Saleh, Ahmad, & Talib, 2005), ultrasonic-assisted extraction (Hong yuan, Jindong, Hui, Gengliang, & Kyung Ho, 2011) and solid-phase extraction (Bonan, Fedrizzi, Menotta, & Elisabetta, 2013; Chen et al., 2014; Tang et al., 2014) and others etc (Shen, Zhang, Prinyawiwatkul, & Xu, 2014; Sun et al., 2013). At present, only few studies were focused on the methods of detecting dispersible dyes in complex matrices (Karthik et al., 2016). In this work, a highly sensitive and accurate UHPLC-MS/MS method was developed to simultaneously screen 20 disperse dyes in pharmaceutical capsules, oblatum, fruit and pinked vegetables. The composition of mobile phases and the mass spectrometric parameters for disperse dye were optimized. Extraction procedures for the target analytes utilizing different solvent were performed and evaluated in this study. The

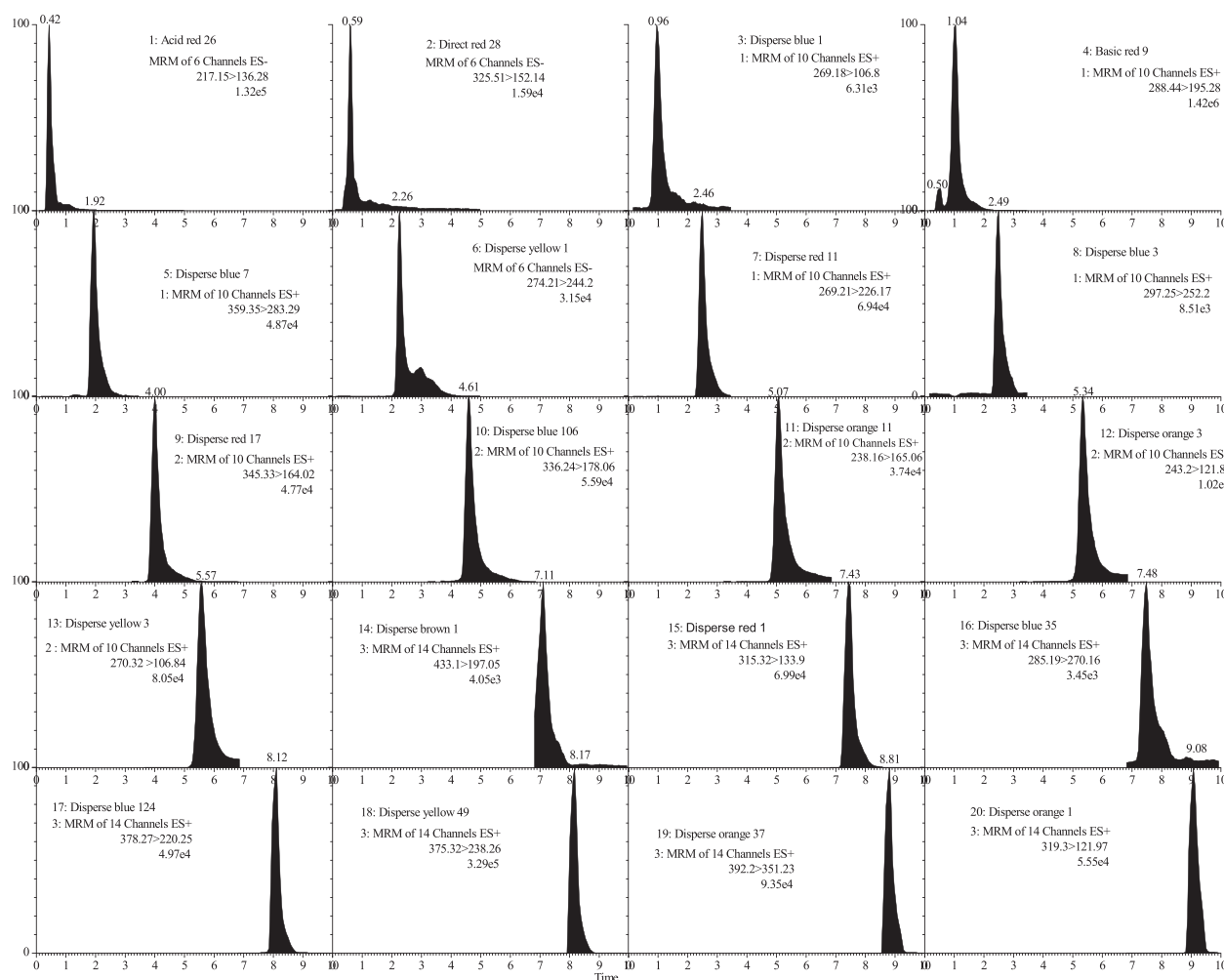


Fig. 1. Selected ion chromatograms of 20 dyes in MRM.

developed method has been successfully applied to monitor disperse dyes in real samples, ensuring food safety, in soft drinks and also can be applied to other foods samples / packages that available in the market.

2. Materials and methods

2.1. Reagents and chemicals

Ammonium acetate, chloride-diethyl, ether formic acid, acetone, acetonitrile, methanol, all LC-MS grade, were purchased from Merck (Darmstadt, Germany); Anhydrous sodium sulfate (analytic grade) was purchased from Zhiyuan Chemicals Reagent Company (Tianjin, China). Certificated reference materials of the 20 types of dye standards, which include, Disperse Blue 1 (CAS: 2475-45-8), Disperse Blue 3 (CAS: 2475-46-9), Disperse Blue 7 (CAS: 3179-90-6), Disperse Blue 35 (CAS: 12222-75-2), Disperse Blue 106 (CAS: 12223-01-7) Disperse Blue 124 (CAS: 61951-51-7), Disperse Orange 1 (CAS: 2581-69-3), Disperse Orange 3 (CAS: 730-40-5), Disperse Orange 11 (CAS: 82-28-0), Disperse Orange 37 (CAS: 13301-61-6), Disperse Red 1 (CAS: 2872-52-8), Disperse Red 11 (CAS: 2872-48-2), Disperse Red 17 (CAS: 3179-89-3), Disperse Yellow 1 (CAS: 119-15-3), Disperse Yellow 3 (CAS: 2823-40-8), Disperse Yellow 49 (CAS: 54824-37-2), Disperse Brown 1 (CAS: 23355-64-8), Basic Red 9 (CAS: 569-61-9), Acid Red 26 (CAS: 3761-53-3), Direct Red 28 (CAS: 573-58-0) were obtained from Dr. Ehrenstorfer GmbH (Augsburg, Germany).

2.2. Standard solutions

Individual stock standard solutions of each disperse dye (1000 µg/mL) were prepared in methanol and stored at 4 °C in dark. The stock mixture standard solution (1000 µg / mL) was prepared by diluting the first stock standard solutions and a series of working standard solutions (5, 10, 20, 50, 100, 200, 500, 1000 µg/mL) were prepared from it by dilution with methanol. Matrix-matching calibration standard solutions were prepared by adding desired volume of individual stock standard solutions into negative samples (blank matrix, matrix that experienced extraction described in Section 2.4).

2.3. Sample preparation

All of foodstuff samples such as pharmaceutical capsules, oblatum, juice and pinkled vegetables were purchased from local markets, the local export inspection, and social commission. The manufacturers or distributors declared that these products didn't contain any disperse dyes additives. Prior to analysis, the sample were mixed homogeneously and stored in 50 mL PTFE centrifuge tubes at −20 °C. Spiked samples were prepared in a 50 mL centrifuge tube by mixing 2.0 g of homogenized samples with a series of the 20 disperse dyes standard solutions at various concentrations.

All matrices were homogenized by blender before use. Various solvent including acetone, methylene chloride-diethyl ether (1: 2, v/v), acetonitrile and methanol were selected as extraction solvents to test the recovery rates in all foodstuffs. Through which, extraction

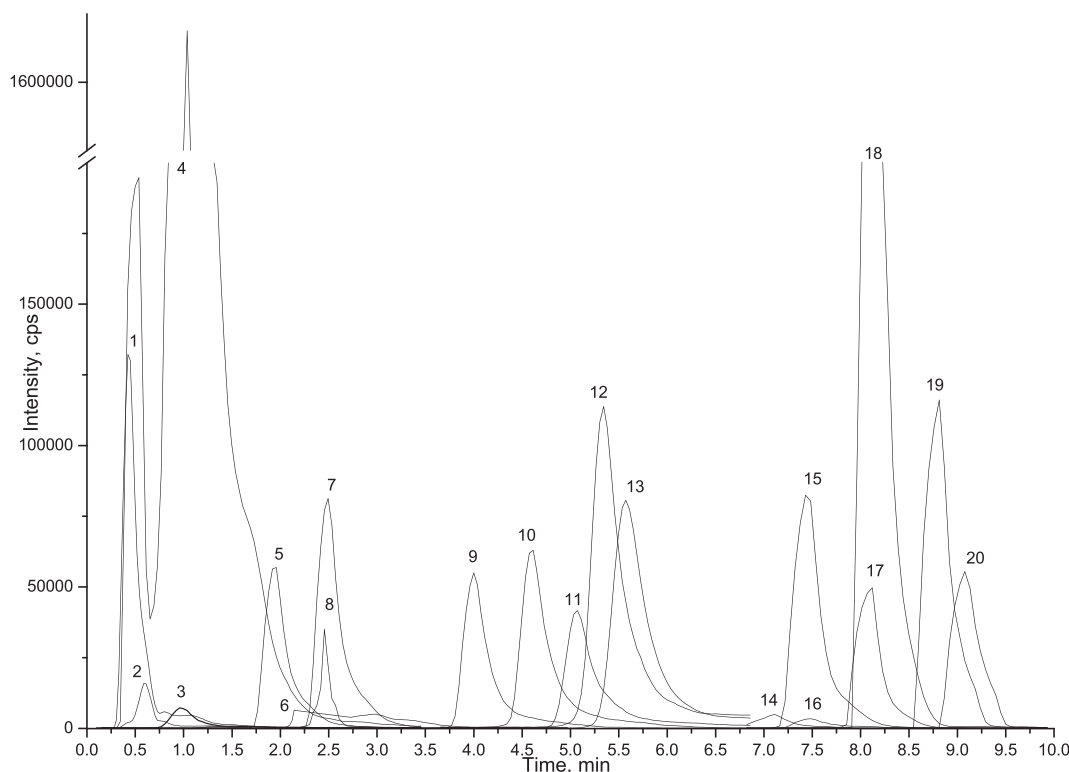


Fig. 2. All ion chromatograms of 20 dyes.

Table 2

Optimization of mobile phase combinations.

Ionization method	Different system	Mobile phase (A)	Mobile phase (B)
ESI [−]	a	Acetonitrile	Water
	b	Methanol	Water
ESI ⁺	a'	Acetonitrile	0.1% Formic acid, pH 2.7
	b'	Acetonitrile	5 mmol/L Ammonium acetate, 0.1% Formic acid, pH 3.2
	c'	Methanol	0.1% Formic acid, pH 2.7
	d'	Methanol	5 mmol/L Ammonium acetate, 0.1% Formic acid, pH 3.2

efficiency of each extraction solvent was compared and optimized for sample extraction.

In general, 1.00 g of sample and 2.00 g of anhydrous sodium sulfate were added into a 50 mL PTFE tube following which 10 mL of methanol–ammonia–water (1:2, v/v) was added. The sample was vortexed for 1 min followed by extraction in an ultrasonic bath at 40 °C for 10 min. The upper-extracts were collected. The above procedure was repeated for twice. The upper-extracts were pooled and evaporated to dryness by rotary evaporator at 40 °C. The residues of extracts were reconstituted in 1 mL methanol and filtered through a 0.22 µm PTFE syringe filter before UHPLC–MS/MS analysis.

2.4. UHPLC–MS/MS analysis

2.4.1. Chromatographic conditions

The detection of disperse dyes analysis was performed on an Ultra high performance liquid chromatography system (ACQUITY RTM Ultra Performance LC, Waters Corporation, USA) coupled with triple quadrupole mass spectrometer system (Quattro Premier XE MS-MS, Waters Corporation, USA) with atmospheric pressure electrospray ionization–tandem mass spectrometry (ESI-MS/MS) detector. The chromatographic separation was performed on an Acquity BEH C₁₈ column (2.1 × 50 mm, 1.7 µm, Waters, Milford, MA) equipping with a G1311A quaternary pump system. Both acetonitrile and methanol were tested as

mobile phase A for ESI⁺ (in combination of 5 mmol/L ammonium acetate in water containing 0.1% formic acid (pH 3.2 or 2.7) as solvent B), acetonitrile and methanol were respectively tested as mobile phase A for ESI[−] (in combination of water as solvent B). Results shown in Section 3.2.

After optimization the mobile phase for ESI⁺ was made up of acetonitrile solvent (solvent A), and 5 mmol/L ammonium acetate in water (containing 0.1% formic acid, solvent B). The gradient used was 28–39% mobile phase A at 0–2 min, 39–39% mobile phase A at 2–6 min, 39–90% mobile phase A at 6–9 min, 90–28% mobile phase A at 9–9.5 min, 28% – 28% mobile phase A at 9.5–10 min. The mobile phase for ESI[−] was made up of acetonitrile (solvent A) and water (solvent B). The gradient used was 28–39% mobile phase A at 0–2 min, 39–39% mobile phase A at 2–4 min, 39% – 28% mobile phase A at 4–4.5 min, 28% – 28% mobile phase A at 4.5–5 min. The flow rate was 0.3 mL/min. The injection volume was 5 µL.

2.4.2. Detection conditions

Mass spectrometry analysis was performed using an atmospheric pressure electrospray ionization source in both positive ion (ESI⁺) and negative ion (ESI[−]) modes. The operation conditions were as follow: electrospray capillary voltage, 3.0 kV for both ESI⁺/ESI[−]. The ion source temperature was maintained at 110 °C and the turbo spray gas temperature, 350 °C and 680 L/h. The cone flow was set at 50 L/h.

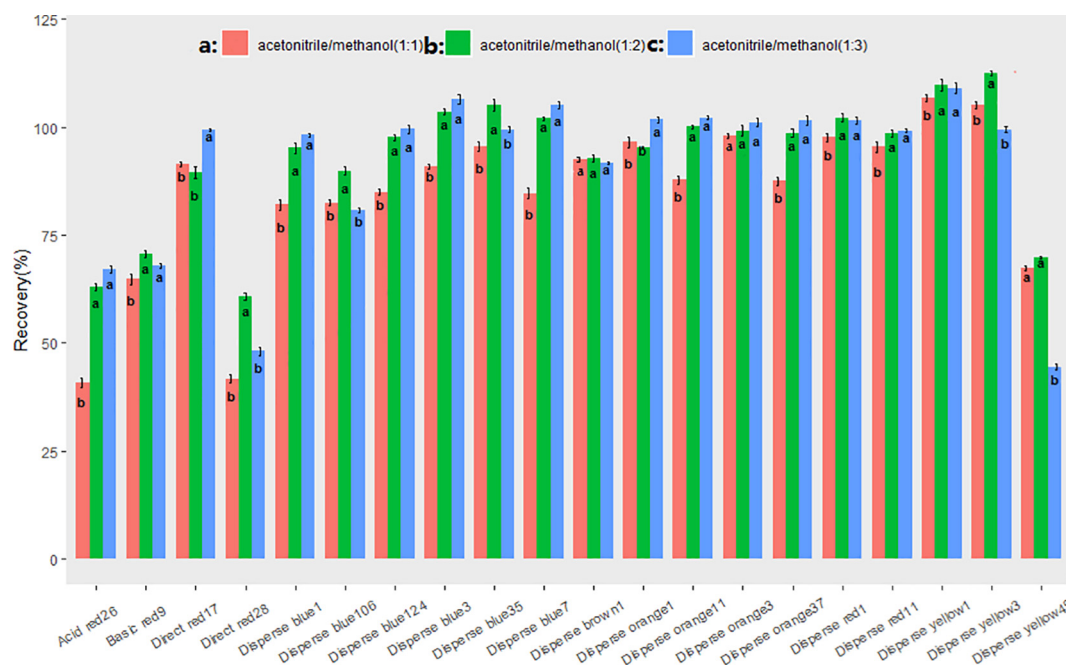


Fig. 3. Average recovery of each color additives using different extract solutions: (a) acetonitrile – methanol, 1: 1 (V/V); (b) acetonitrile – methanol, 1: 2 (V/V); (c) acetonitrile – methanol, 1: 3 (V/V).

Qualitative analysis was performed in Multiple Reaction Monitoring Mode (MRM) for each compound.

3. Result and discussion

3.1. Optimization of MS/MS procedures

The complexity of the disperse dyes matrices pose challenges for quantifying analysis procedure. The development of an efficient optimization of MS / MS procedures was critical for accurate determination of disperse dyes in pharmaceutical capsules, fruit, vegetables and oblatum. Prior to analysis flow injection analysis for each dye was performed to optimize the detector conditions. Dyes showed mixed response with the optimized quasi-molecular ion peaks, for Acid Red 26, Direct Red 28 and Disperse Yellow 1 observed at negative ion mode ionization and all other rest of the dyes in positive ion mode ionization. Then ion mass spectrometry (Daughter scan) scans were performed with the excimer ion as the parent ion to optimize the collision energy. Two ions with higher abundance were selected as the characteristic ions, of which the most abundant ion was the quantitative ion. In positive ion mode ionization, in order to ensure the sensitivity of the target dye, 17 kinds of dyes were divided into 4 channels at different time (The monitoring time of 4 channels were 0–3.5 min, 3.5–6.5 min and 6.5–10 min, respectively). Monitoring to control the dwell time and number of ions in each period to ensure that all target dyes had enough data collection point. After the initial optimization through flow injection analysis, the excimer (precursor) ions are selected for each dye and were subjected to further fragmentation in the collision chamber (octupole reactor system), to obtain daughter ions to be mass filtered using the 3rd quadrupole mass analysis. High sensitive and consistent ions were identified further for each dye to act as quantifier and qualifier ions (Table 1). In the MRM mode, the 20 selected dye ion flow diagrams were shown in Fig. 1 and one ion chromatogram including 20 dyes in Fig. 2.

3.2. Optimization of UHPLC conditions

For optimization of chromatographic conditions both positive/

negative ion modes were employed to evaluate the influence in the composition of mobile phase on the separation performance and also the response of dye under different ionization modes. For negative ion mode ionization, it was easy to form $[M-H]^-$ molecule ion peaks, hence addition of formic acid or acetic acid to the mobile phase would result in instability causing low abundancy for the relevant molecular ion peak. On the other hand for the positive ion mode, $[M+H]^+$ molecular ion peaks will be formed and thus the addition of appropriate amount of formic acid and ammonium acetate to the mobile phase would promote the ionization of the target substance and enhance its sensitivity. The corresponding mobile phase compositions designed for different ionization modes were shown in Table 2.

The results showed that the acetonitrile-water response of mobile phase system (a) was higher than that of mobile phase system (b) methanol-water when anion mode was ionized. The response of 0.1% formic acid mobile phase system (a') and (c') was higher than that of 5 mmol/L ammonium acetate, 0.1% formic acid mobile phase system (b') and (d'). And a buffer system was formed with formic acid to promote pH stability, thereby improving separation performance and ensuring reproducibility of retention time. The response of (d') was higher than that of (d') in the mobile phase system (b'), but the chromatographic peak was not pure and there was interference from extraneous peaks. Therefore, a combination of mobile phase system (b') acetonitrile and 5 mmol/L ammonium acetate-0.1% formic acid aqueous solution was chosen as the mobile phase for positive ion mode ionization.

3.3. Optimization of sample extraction

Sample extraction involves a variety of procedures due to complex composition of synthetic dyes. This necessitates an effective extraction procedure to isolate and enrich analytes which is crucial prior to analysis. In this work, a compound extraction technique was adopted since the analytes have varied polarities. Since most of the dyes under study contained hydrophobic functional groups, such as amino-, cyano- and hydroxyl groups, the selected extraction solvents were acetone, methylene chloride-diethyl ether (1: 2, v/v), acetonitrile and methanol. Through the evaluation of the recovery rate of 20 dyes, the extraction

Table 3

Analytical figures of merit in pharmaceutical capsule (A), oblatum (B), juice (C) and vegetable (D).

Compound	Analyte	Linear dynamic range (µg/L)	Calibration curve	Determination coefficient (r^2)	LOD (µg/kg)	LOQ (µg/kg)
Acid red 26	A	5–1000	$Y = 10.686X - 26.574$	0.9999	0.10	0.24
	B		$Y = 26.932X - 72.400$	0.9992	0.12	0.35
	C		$Y = 15.432X - 24.123$	0.9993	0.11	0.32
	D		$Y = 9.632X - 17.712$	0.9994	0.15	0.51
Direct red 28	A	5–1000	$Y = 2.2868X - 13.279$	0.9999	1.01	4.00
	B		$Y = 2.6766X - 19.928$	0.9993	1.10	3.80
	C		$Y = 2.3871X - 10.542$	0.9995	1.07	3.56
	D		$Y = 1.8973X - 66.671$	0.9984	1.28	4.26
Disperse blue 1	A	5–1000	$Y = 1.5692X - 32.800$	0.9992	1.20	4.73
	B		$Y = 0.6743X - 8.2927$	0.9981	1.45	5.00
	C		$Y = 1.1559X - 40.368$	0.9992	1.35	4.50
	D		$Y = 0.4256X - 6.6733$	0.9983	1.58	5.24
Basic red 9	A	5–1000	$Y = 181.18X + 30.334$	0.9999	0.71	2.39
	B		$Y = 689.73X - 3656.9$	0.9997	0.65	2.00
	C		$Y = 268.32X + 45.198$	0.9991	0.69	2.30
	D		$Y = 128.53X + 23.635$	0.9986	0.86	2.86
Disperse blue 7	A	5–1000	$Y = 23.351X + 5.4617$	0.9998	0.24	0.85
	B		$Y = 24.798X - 25.263$	0.9999	0.20	0.76
	C		$Y = 20.538X + 4.8631$	0.9994	0.21	0.82
	D		$Y = 16.451X - 10.319$	0.9989	0.31	1.04
Disperse yellow 1	A	5–1000	$Y = 15.819X - 18.370$	0.9994	0.79	2.37
	B		$Y = 9.5984X + 6.0785$	0.9993	0.90	2.80
	C		$Y = 10.5521X + 6.317$	0.9985	0.86	2.72
	D		$Y = 6.7539X + 4.6725$	0.9993	1.23	4.78
Disperse red 11	A	5–1000	$Y = 31.383X + 48.649$	0.9999	0.82	2.47
	B		$Y = 32.765X - 130.72$	0.9998	1.52	4.70
	C		$Y = 34.353X + 46.895$	0.9999	0.79	2.35
	D		$Y = 20.719X - 89.324$	0.9985	1.89	6.28
Disperse blue 3	A	5–1000	$Y = 2.6544X + 1.0709$	0.9994	0.70	2.32
	B		$Y = 3.0346X - 31.124$	0.9988	0.80	2.50
	C		$Y = 2.8952X - 9.8734$	0.9978	0.75	2.46
	D		$Y = 1.4525X - 8.3562$	0.9979	0.97	3.25
Disperse red 17	A	5–1000	$Y = 23.351X + 5.461$	0.9998	1.14	3.26
	B		$Y = 41.710X - 366.08$	0.9996	0.75	2.27
	C		$Y = 30.315X + 8.978$	0.9995	0.98	3.15
	D		$Y = 16.425X + 17.846$	0.9975	1.23	3.78
Disperse blue 106	A	5–1000	$Y = 50.291X - 17.506$	1.0000	1.03	3.43
	B		$Y = 54.224X - 513.38$	0.9993	1.45	4.83
	C		$Y = 52.634X - 16.784$	0.9999	1.01	3.33
	D		$Y = 35.578X - 234.43$	0.9989	1.89	6.23
Disperse orange 11	A	5–1000	$Y = 22.649X + 42.221$	0.9995	0.76	2.50
	B		$Y = 25.700X - 278.74$	0.9988	0.83	2.80
	C		$Y = 23.673X + 50.452$	0.9995	0.80	2.64
	D		$Y = 15.652X + 24.854$	0.9983	1.32	4.36
Disperse orange 3	A	5–1000	$Y = 57.623X - 8.3024$	0.9997	1.48	4.80
	B		$Y = 69.409X - 638.02$	0.9992	1.60	5.00
	C		$Y = 63.625X - 7.893$	0.9973	1.51	4.98
	D		$Y = 40.532X - 45.673$	0.9987	1.84	6.07
Disperse yellow 3	A	5–1000	$Y = 42.397X + 188.47$	0.9999	1.25	4.10
	B		$Y = 48.672X - 338.36$	0.9991	1.13	3.80
	C		$Y = 45.463X - 50.452$	0.9992	1.26	4.15
	D		$Y = 30.536X - 145.53$	0.9989	1.65	5.45
Disperse brown 1	A	5–1000	$Y = 2.3118X - 2.3862$	0.9996	1.35	4.76
	B		$Y = 2.1748X - 31.992$	0.9990	1.16	3.86
	C		$Y = 2.2445X - 6.7578$	0.9997	1.24	4.08
	D		$Y = 1.5621X - 1.6436$	0.9993	1.64	5.41
Disperse red 1	A	5–1000	$Y = 64.962X + 172.22$	0.9997	1.20	3.90
	B		$Y = 64.143X - 510.82$	0.9994	0.80	2.70
	C		$Y = 65.663X + 325.45$	0.9998	1.28	4.23
	D		$Y = 40.573X - 124.56$	0.9995	1.64	5.42
Disperse blue 35	A	5–1000	$Y = 2.7585X - 1.5579$	0.9977	1.47	4.90
	B		$Y = 3.1696X - 32.796$	0.9994	1.60	4.95
	C		$Y = 3.5863X - 42.452$	0.9995	1.55	5.13
	D		$Y = 1.5235X - 2.647$	0.9973	1.89	6.35

(continued on next page)

Table 3 (continued)

Compound	Analyte	Linear dynamic range ($\mu\text{g/L}$)	Calibration curve	Determination coefficient (r^2)	LOD ($\mu\text{g/kg}$)	LOQ ($\mu\text{g/kg}$)
Disperse blue 124	A	5–1000	$Y = 12.669X + 36.224$	0.9996	0.56	1.87
	B		$Y = 17.853X - 123.55$	0.9995	0.41	1.38
	C		$Y = 18.967X + 45.854$	0.9989	0.58	1.94
	D		$Y = 9.8577X + 41.452$	0.9995	0.68	2.24
Disperse yellow 49	A	5–1000	$Y = 100.92X + 532.22$	0.9996	0.02	0.08
	B		$Y = 124.50X - 1159.6$	0.9990	0.04	0.12
	C		$Y = 117.53X + 489.98$	0.9964	0.02	0.08
	D		$Y = 87.743X - 346.54$	0.9985	0.06	0.19
Disperse orange 37	A	5–1000	$Y = 33.033X + 63.139$	0.9978	0.30	1.00
	B		$Y = 40.694X - 326.81$	0.9977	0.25	0.80
	C		$Y = 36.852X + 34.733$	0.9987	0.28	0.92
	D		$Y = 23.742X - 45.268$	0.9986	0.42	1.38
Disperse orange 1	A	5–1000	$Y = 26.525X - 153.03$	0.9987	0.01	0.05
	B		$Y = 35.128X - 514.59$	0.9966	0.03	0.10
	C		$Y = 28.756X - 104.57$	0.9978	0.01	0.05
	D		$Y = 20.537X - 58.962$	0.9976	0.06	0.19

efficiency of each extraction solvent was compared and assessed. When acetone and methylene chloride-diethyl (1: 2, v/v) was used as extraction solvent, two out of the 20 dyes (direct red 28 and acidic red 26) were not detected, while the recoveries of others were all over 60%. This could be due to strong binding between direct red 28 and acid red 26 with the protein in the capsule shell (or wafer), resulting in lower recovery. Recoveries of these two dyes were less than 32% when acetonitrile was used, with similar recoveries for the other dyes (all > 60%). With methanol as the extraction solvent, the recoveries of 20 target dyes were all greater than 70%, except for Disperse Blue 106 (47%) and Disperse Yellow 49 (18%). Considering the shortcomings of each extraction of acetonitrile and methanol, further investigation of the extraction efficiency of combined acetonitrile-methanol solution at different volume ratios were performed. Results were shown in Fig. 3. The highest recoveries for all 20 target dyes (all above 60%) was using of acetonitrile to methanol at the volume ratio at 1: 2. Therefore, the volume ratio of acetonitrile – methanol solution as the extraction solvent was selected in this experiment.

To validate the recovery of 20 disperse dyes, an analysis of variance (ANOVA) was performed, seeing in the Fig. 3. First, the Direct red 28, Disperse blue 106, Disperse blue 35 and Disperse yellow 3 were no significant difference between c and a ($p > 0.05$), and both of them were significantly lower than b ($p < 0.05$). Disperse yellow 49 were no significant difference between b and a ($p > 0.05$), and both of them were significantly greater than c ($p < 0.05$). Second, only Disperse orange 1 and Direct red 17 were no significant difference between b and a ($p > 0.05$), and both of them were significantly lower than c ($p < 0.05$). Third, only Disperse orange 3 and Direct brown 1 were no significant difference among a, b and c ($p > 0.05$). Finally, the others Disperse dyes were no significant difference between b and c ($p > 0.05$), and all of them were significantly greater than a ($p < 0.05$). So, the best recoveries of 20 disperse dyes were obtained with the proposed pretreatment technique. Except for Direct red 28 (60.2%), Acid red 26 (65.4%), Disperse red 1 (70.3%) and Basic red 9 (71.1%), the recoveries of others were all over 90% (see the Fig. 3).

3.4. Method development

After review of the reports and performance requirement of the anticipated method, tandem mass spectroscopy was selected as the mode of detection. To avoid the interference of the sample matrix effect, this experiment used the matrix matching external standard method for quantitative analysis. Negative (negative ion mode) samples were selected and the matrix matching standard curve solution was prepared according to Section 2.2. Then, the instrument was running according to the conditions aforementioned in Section 2.4. The linear

regression was performed by taking the peak area as the ordinate (Y) and the corresponding mass concentration as the abscissa (X). The dye has a good linearity in the range of 5–1000 $\mu\text{g/L}$ with the correlation coefficient of 0.9966–1.0000.

The limit of detection (LOD) was set at the minimum peak area to have a reasonable repeatability. The limit of quantification (LOQ) was defined as the concentration corresponding to the lowest standard in the linearity range. These limits were calculated by spiking the matrix with small amounts of the analytes. The detection limit and the limit of quantification of each analyte was defined based on the signal-to-noise ratio ($S/N = 3$) and ($S/N = 10$), respectively. The results were shown in Table 3. The limit of detection and the limit of quantification of the 20 dyes were ranged 0.01–1.48 $\mu\text{g/kg}$ and 0.05–4.90 $\mu\text{g/kg}$, respectively in pharmaceutical capsule (A), 0.03–1.60 $\mu\text{g/kg}$ and 0.10–5.00 $\mu\text{g/kg}$, respectively in oblatum (B), 0.01–1.55 $\mu\text{g/kg}$ and 0.05–5.13 $\mu\text{g/kg}$, respectively in juice (C), 0.06–1.89 $\mu\text{g/kg}$ and 0.19–6.35 $\mu\text{g/kg}$, respectively in vegetable (D).

3.5. Validation of the UHPLC–MS/MS method

The analytical characteristics of the UHPLC–MS/MS method in terms of recovery and RSD were examined under the aforementioned optimized conditions to evaluate the efficiency and precision of application to determine twenty disperse dyes in actual samples. In the negative samples (pharmaceutical capsules, fruit, vegetables or oblatum), three concentration levels (0.05, 0.1, 0.2 $\mu\text{g/g}$) of the mixed standard solution were added, according to aforementioned (2.3 and 2.5), processing of samples and apparatus under the conditions of determination, each plus the standard parallel determination of 6 times, the results were illustrated in Table 4.

The obtained recoveries of 20 dyes were from 60.2 to 110.3% in all foodstuffs, indicating that the recovery was reliable. Precision of the method was estimated by the RSDs of recovery of Dyes in pharmaceutical capsules, glutinous rice paper, fruit and vegetables. The obtained RSDs were in the range from 2.7 to 10.9% for pharmaceutical capsules, from 1.1 to 10.8% for glutinous rice paper, from 1.6 to 112.6 for juice and from 3.2 to 11.7 for vegetables, indicating that the reproducibility was satisfactory.

3.6. Verification of the proposed method

To further validate the feasibility of the proposed method, it was used for the analysis of the real samples, a great variety of preserved matrices, such as pharmaceutical capsules, oblatum, fruit juices and pickled vegetables samples from the local export inspection, social commission were analyzed. Among 135 pickled vegetables samples

Table 4

Recoveries and relative standard deviations (RSDs) of 20 dyes in gelatin capsule, oblatum, juice and vegetable.

Analyte	Spiked levels (µg/g)	gelatin capsule		oblatum		juice		vegetable	
		Recovery (%)	RSD (%)	Recovery (%)	RSD (%)	Recovery (%)	RSD (%)	Recovery (%)	RSD (%)
Acid red 26	0.05	80.8	5.8	65.3	7.9	69.8	8.5	71.8	9.8
	0.1	96.5	4.3	62.4	9.9	70.7	6.5	89.9	9.5
	0.2	63.6	10.2	64.4	9.2	81.1	2.7	97.4	5.6
Direct red 28	0.05	80.4	4.9	80.0	9.5	99.8	5.9	87.4	3.6
	0.1	95.2	4.6	69.3	3.0	68.9	4.6	92.0	6.8
	0.2	72.9	7.9	74.3	8.3	96.7	9.8	73.7	9.5
Disperse blue 1	0.05	75.1	9.1	62.1	4.3	76.1	10.3	61.8	10.1
	0.1	62.0	3.8	63.9	5.1	81.2	6.8	72.9	8.1
	0.2	69.5	5.4	60.5	5.9	72.2	11.1	70.9	6.0
Basic red 9	0.05	65.8	8.9	65.2	7.8	77.7	10.0	69.2	7.6
	0.1	62.1	4.7	68.1	9.4	74.3	6.3	77.7	6.1
	0.2	60.6	7.4	62.1	2.7	70.7	8.6	65.4	5.3
Disperse blue 7	0.05	81.9	8.2	65.6	2.0	85.3	8.5	98.2	7.9
	0.1	83.9	7.8	64.4	2.6	74.7	10.7	77.9	6.4
	0.2	86.4	6.7	62.2	6.9	79.5	11.9	81.5	10.1
Disperse yellow 1	0.05	84.2	10.2	60.5	5.3	84.1	2.4	73.8	9.1
	0.1	100.8	5.9	86.6	2.6	78.2	5.9	91.2	10.5
	0.2	72.0	8.9	87.7	4.8	69.3	12.6	89.4	7.6
Disperse red 11	0.05	84.0	6.9	62.9	8.2	65.6	5.1	79.9	11.9
	0.1	80.2	8.6	69.4	9.3	87.4	11.9	97.5	6.5
	0.2	86.6	6.1	60.6	5.2	81.7	7.2	88.1	8.5
Disperse blue 3	0.05	76.1	10.9	66.4	5.7	80.4	6.7	72.1	11.2
	0.1	83.9	2.9	71.5	3.6	78.8	6.5	62.1	8.7
	0.2	84.7	4.6	68.1	10.2	88.7	7.9	85.2	10.4
Disperse red 17	0.05	78.5	9.8	78.5	7.1	77.6	5.3	72.4	7.7
	0.1	67.8	2.7	79.8	9.7	65.3	1.6	69.5	10.9
	0.2	84.9	3.3	73.6	8.6	76.6	11.3	77.4	7.7
Disperse blue 106	0.05	66.5	3.2	62.9	10.1	80.5	7.0	97.5	11.4
	0.1	60.2	10.3	75.1	9.9	68.2	9.1	73.1	8.7
	0.2	66.3	2.8	65.9	2.0	80.5	7.1	93.2	6.4
Disperse orange 11	0.05	90.2	9.4	72.8	4.7	75.6	5.2	82.1	9.3
	0.1	76.0	8.9	80.6	6.7	92.9	7.5	103.6	10.2
	0.2	85.1	4.3	81.2	2.7	76.5	7.7	92.5	11.7
Disperse orange 3	0.05	80.4	9.4	60.4	9.4	80.6	11.3	82.6	9.4
	0.1	76.6	8.0	66.1	3.7	76.6	6.7	79.3	5.5
	0.2	84.7	3.6	63.6	5.3	75.8	6.8	94.8	11.8
Disperse yellow 3	0.05	88.9	4.5	70.3	3.8	70.4	5.4	70.9	6.2
	0.1	78.9	10.3	78.9	9.9	74.6	3.7	79.2	6.7
	0.2	86.4	5.4	75.9	8.5	89.6	7.8	86.2	5.7
Disperse brown 1	0.05	83.9	3.0	94.0	5.7	70.6	10.5	79.5	9.8
	0.1	62.6	8.2	90.7	10.8	81.6	3.9	77.6	7.9
	0.2	102.0	6.2	93.7	9.7	76.4	3.8	64.3	8.2
Disperse red 1	0.05	89.9	7.7	65.5	8.0	91.1	8.7	87.6	6.3
	0.1	66.3	4.0	77.6	6.3	88.1	5.7	64.8	4.5
	0.2	84.8	3.8	71.3	4.5	86.0	10.9	84.8	3.2
Disperse blue 35	0.05	73.1	8.3	68.1	8.3	79.2	3.1	74.3	3.8
	0.1	74.6	9.1	68.2	1.7	66.1	4.3	81.7	8.1
	0.2	79.4	7.9	64.1	9.7	91.2	4.9	64.0	8.5
Disperse blue 124	0.05	81.7	5.8	80.1	2.9	85.8	8.8	70.9	6.2
	0.1	65.4	8.4	74.9	9.7	89.4	6.6	79.2	6.7
	0.2	71.9	2.7	82.1	1.1	92.2	7.8	86.2	5.7
Disperse yellow 49	0.05	62.2	6.3	81.2	5.8	102.4	9.7	77.3	10.6
	0.1	66.0	9.1	85.1	3.1	84.5	11.3	98.3	8.7
	0.2	67.9	10.7	83.3	4.7	72.0	3.2	83.1	8.5
Disperse orange 37	0.05	81.7	10.3	90.5	5.5	82.7	6.3	97.8	7.4
	0.1	89.9	7.6	83.9	8.3	85.3	3.2	94.8	5.8
	0.2	87.0	6.6	95.6	9.0	97.8	3.1	93.6	8.5
Disperse orange 1	0.05	110.3	2.7	77.9	7.2	86.4	11.5	85.9	7.5
	0.1	90.1	6.1	76.9	8.1	91.8	9.2	82.8	6.0
	0.2	89.7	7.9	89.2	9.5	74.9	4.3	97.9	9.6

analyzed, illegal presence of Basic red 9, Acid red 26, Direct red 28 were identified. The colorant concentrations of Basic red 9 were 1.47 µg/kg and 5.42 µg/kg, 1.24 µg/kg and 4.85 µg/kg of Acid red 26 and 0.93 µg/kg, 1.13 µg/kg and 2.70 µg/kg in Direct red 28, respectively. Presence of Disperse orange1 and Direct red 28 were detected in 125 fruit samples, the concentrations are 2.16 µg/kg and 7.65 µg/kg, 1.45 µg/kg and 3.46 µg/kg, respectively. Meanwhile the other allergenic disperse dyes were not detected because of lower than the LODs of the proposed method in the analyzed samples.

3.7. Comparing with other reported methods

The proposed developed method based on UHPLC–MS/MS was compared to other reported methods. LODs of the present method were lower than most reported methods, and LOQs of the present method were lower than most reported methods. Besides, a short extraction time (only 9 min), wide linear region (5–1000 µg/L) and good recoveries (60.2–110.3%) were obtained with the proposed pretreatment technique. Comparing with the detection limits reported in literatures,

Table 5

Comparison of the proposed method with other reported methods for the detection of disperse dyes.

Analytical Method	Range (µg/L)	LoDs (µg/kg)	LoQs (µg/kg)	Times (min)	References
LC-MS/MS	10–140	1–20	10–40	11	Martin, Oberson, Meschiari, and Caroline (2016)
HPLC-MS/MS	1.5–10000	0.1–500	Not given	30	Feng et al. (2011)
HPLC-MS/MS	10–1000	2.3–22	7.6–71	9	Qi et al. (2015)
HPLC-MS/MS	20–10001	4.54–14.3	15.0–47.6	26	Noguero et al. (2008)
UHPLC-MS/MS	2500–50000	20–1000	100–2000	6	Zhou et al. (2014)
UHPLC-MS/MS	5–1000	0.01–1.89	0.05–6.35	10	This work

the detection sensitivity was improved more than 10 times (see Table 5), showing that the UHPLC-MS/MS as an ideal method in view of disperse dyes in real foodstuffs. In a word, the developed method gives a faster and simpler way for extraction of 20 allergenic disperse dyes in samples and provides relatively lower LOQs.

4. Conclusion

In summary, a significant and effective method was proposed for the simultaneous determination and control of twenty disperse dyes of varying polarities in complex pharmaceutical capsules, oblatum, juice and pickled vegetables by using UHPLC-MS/MS technique. The developed method showed good accuracy, sensitivity and satisfactory recovery under complex matrixes. The lack of interference from matrix effects demonstrated the broad applicability of the current UHPLC-MS/MS method which was eventually validated. The method thus prove to be applicable for the routine analysis of such complex mixture of dyes in pharmaceutical and foodstuffs. In addition, this method has determined the illegal dyes in fruit and pickled vegetables, indicated that there is still dyes contamination in foodstuffs, came from local export inspection, social commission, with the level of 5.18% and 3.2% in analysed samples, respectively. Through practice tests, the result showed that an optimized method is suitable for the simultaneous quantitative determination of the foodstuffs.

Declaration of Competing Interest

None.

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