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Low-Level Quantification of Cefdinir and Cefixime in Human Plasma Using Ultrasound-and Magnetic-Assisted Dispersive Micro-Solid-Phase Extraction (MSPE) Based upon Carbon Quantum Dots (CQDs) Combined with High-Performance Liquid Chromatography (HPLC)

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ABSTRACT

A promising and reusable nanohybrid based on carbon quantum dots (CQD) was fabricated as a sorbent for ultrasound- and magnetic-assisted dispersive micro-solid-phase extraction (US-M-A-DMSPE) followed by high-performance liquid chromatography with ultraviolet detection (HPLC-UV) for simultaneous trace determination of cephalosporins (Cefdinir & Cefixime) in human plasma. The structure of the prepared sorbent was characterized by x-ray diffraction (XRD), Fourier transform-infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). Under the optimized conditions, the nanosorbent provided high adsorption and selectivity toward the analytes. The limits of detection and the coefficients of determination (r^2) with dynamic ranges for cefdinir & cefixime were estimated. The method was used for quantifying cefdinir & cefixime in plasma samples to evaluate the pharmacokinetic aspects,including the half-life ($T_{1/2}$), the time to reach the maximum concentration (T_{max}), the maximum plasma concentration (C_{max}), area under the curve (AUC_{0-24}) and area under the curve at infinite time ($AUC_{0-\infty}$). Reliable reproducibility as the intra- assay and inter-assay together with reasonable accuracy were obtained.

Keywords

Carbon quantum dots (CQDs), dispersive micro-solid phase extraction (MSPE), high performance liquid chromatography (HPLC)

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1. Introduction

cefdinir & cefixime are recently developed agents in order to inhibit bacterial cell wall synthesis. These drugs belong to a category of oral broad-spectrum third-generation and are widely utilized to work against gram-positive and gram-negative bacteria to reduce mild to moderate infections (Abbas et al. 2011). Drug evaluation in plasma at trace levels is significant for pharmacokinetic assessment, considering the bioequivalence of the tablet formulation, and developing and optimizing novel dosage forms and the dosage regimen in combination therapy (Purificación et al. 2013). Many analytical techniques have been reported for the quantification of cefdinir & cefixime in human plasma such as liquid chromatography followed by tandem mass spectrometry (LC–MS–MS) (Jin et al. 2020), RP-HPLC with ultraviolet detection (Rajeev & Keisham & Nimisha 2007 2007), and electrochemical methods (Haixia et al. 2018). Ultrasound- and magnetic-assisted dispersive micro-solid-phase extraction (US-M ADMSPE), as a new and powerful technique, has received increasing attention for screening in various real media. In US-M-A-DMSPE, the dispersion and isolation of the sorbent in aqueous media is done using ultrasonic irradiation and an external magnet which reduces the extraction routes and the cost and significantly enhances the mass transfer rate (Fatemeh et al. 2019). The introduction of new sorbents to provide superior performance for trace monitoring is a main investigation area. Carbon quantum dots (CQDs)

are classified as semiconductor nanoparticles. Due to their properties, such as water dispersibility, high sensitivity and selectivity, low toxicity, and good biocompatibility, they have received attention in recent years. The CQDs have been applied in biosensing, bioimaging, and photocatalytic degradation (Monikankana et al. 2020). Due to the presence of oxygen-containing groups on the surface, the small size (10 nm), high surface-to-volume ratio, and high adsorption capacity, these carbon-based materials have been considered to be innovative sorbents (Dongqiang et al. 2020). In this study, the merits of extraction based on CQDs were evaluated to fabricate promising and easy-to-recycle hybrid materials for enrichment. The synthesized nanosorbent was used in ultrasound-and magnetic-assisted dispersive micro-solid-phase extraction (US-M-A-DMSPE) combined with HPLC-UV for quantifying cefdinir & cefixime in biological media. The main variables that influence the extraction were optimized. Lastly, the feasibility of the present protocol was examined by analyzing the pharmacokinetic data of cefdinir & cefixime in human plasma following combination oral therapy.

2. Materials and methods

In all synthesis, the analytical grade of each material was utilized without extra purification. Citric acid was obtained from Sigma-Aldrich. Ethanol, urea,

25% ammonia solution, and acetonitrile (ACN) were purchased from Merck Chemicals. The cefdinir & cefixime standards were obtained from Darupakhsh. Ultrapure water was employed in all experiments (Millipore, Bedford, MA, USA). For separation experiments, HPLC grade methanol, acetonitrile, and potassium dihydrogen phosphate were obtained from Merck.

2.1.Instrumentation

X-ray diffraction (XRD) spectra were recorded and investigated by applying Kα radiation (1.54 Å) from Cu using a D8 Advance instrument (Bruker, Germany). Fourier transform infrared (FT-IR) spectra were obtained using a Perkin Elmer spectrometer (RXI, Germany). Transmission electron microscopic (TEM) images were recorded using a HT7800 (Hitachi, Japan). Scanning electron microscopy (SEM) and (Jena, Germany).

2.2.Chromatographic condition

Chromatographic assessments were performed using an HPLC with a Waters 2487 dual wavelength detector and a C18 TMS end capping/reversed-phase column (Luna 5 mm C18 100A 250 | 4.6mm id). The operating temperature was 30 °C. The wavelength and the injection volume were 280nm and 20 ml. An isocratic mode was used and the mobile phase was a combination of acetonitrile-methanol-phosphate buffer pH 3.0 (30:20:50). The flow rate was 1.5mL min^{-1}. A 0.2 mm polytetrafluoroethylene membrane filter was utilized for filtration of the mobile phase that was degassed every single day.

2.3.Clinical samples

Fresh blood plasma samples were obtained from Iranian Blood Transfusion Organization (Tehran, Iran). Ethical approval for the study was received from the Ethics Committees of the Department of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences prior to the collection and analysis of human blood samples. Written informed consent was obtained from all participants before sampling. The plasma samples were stored at -18 °C.

2.4.Synthesis of CQDs

The CQDs were synthesized via the hydrothermal method. Initially, 3 g citric acid and 1 g urea were treated with 20mL deionized water, stirred for 5 min at room temperature, and heated in an autoclave at 200 °C for 6 h. After cooling to room temperature, the black CQD powder was produced (Sarkar et al. 2020).

2.5.Preparation of human plasma

Protein precipitation is crucial to remove possible interfering substances. Plasma obtained after centrifugation of blood was placed in the tubes containing EDTA and stored at -18 °C until analysis. The frozen samples were transferred to a test tube, thawed at room temperature (25 °C), and transferred into centrifuge tubes. Acetonitrile was used as the deproteinizing agent to precipitate proteins in the plasma. 1.9 mL of plasma was spiked with 100 µl of the working standard to obtain desirable concentrations of each drug and 2 mL acetonitrile was added. All samples were vortexed for 5 min and centrifuged for 6 min at 4000 rpm at room temperature. The remaining acetonitrile was evaporated using nitrogen and transferred into 4.0

mL of pH 5.0 buffer. 5.0 mL of the sample was subjected to the extraction protocol for analysis.

2.6.Calibration curve and quality control samples (QCs)

In order to minimize matrix effects, standards for the calibration curve were prepared using real samples. 100.0 mg L^{-1} stock solutions of CFX and CFD were prepared weekly in HPLC-grade methanol. The stock solutions were diluted with distilled water to obtain the working standard solutions. Human plasma samples were spiked with the working standard solutions to prepare calibration solutions. To evaluate the accuracy and reproducibility of the method, quality control samples of the targets were prepared at 5, 100,500, and 1250 ng mL^{-1} for each drug and stored in darkness at -18 °C. All stored samples were thawed just before measurement.

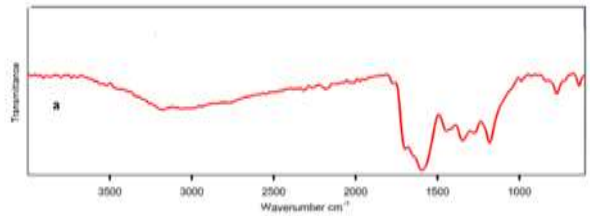
2.7.General procedure for US-M-A-DMSPE-HPLC-UV

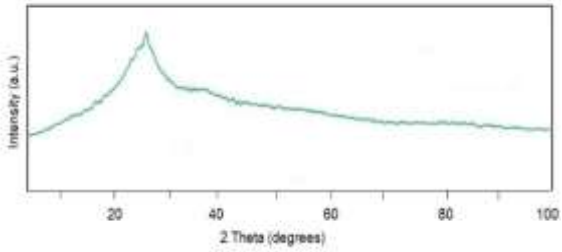
5.0 mL of the prepared plasma at pH 3.0 were treated with 25.0 mg of CQD and sonicated to disperse the magnetic nanosorbent throughout the sample. The analytes were extracted from the aqueous media by the sorbent. For effectual separation and collection of the drug-loaded nanocomposite, the sample vessel was exposed to a magnet that provided a 0.8 Tesla field. During the collection of the nanosorbent, the supernatant was removed. The analytes were desorbed and washed with 2mL acetonitrile with sonication for 3 min. 1mL of acetonitrile was used in every washing step and 1.5 min in each elution. The application of Nd–Fe–B–Nd was repeated to collect of the sorbent. The remaining acetonitrile was removed by heating under nitrogen. Eventually, the residue was dissolved in 50 mL of HPLC mobile phase and 20 mL was injected into the instrument for analysis.

3. Results and discussion

3.1. Characterizations

In order to characterize the fabricated sorbent, FTIR, XRD, and SEM were applied. Figure 1 shows the FTIR spectra of CQD. The broad peaks from 3100 to 3300 cm-1 are due to the stretching vibrations of hydroxyl groups in the CQDs. The broad peaks are due to hydrogen bonds with the solvent. Additionally, absorption bands due to C=O and the aromatic C=C were recorded at 1593 cm-1 and 1444 cm-1, respectively. Furthermore, the peak at 1182 cm-1 was assigned to stretching vibrations of epoxy C-O. The results show that CQD has been correctly synthesized. The synthesized CQDs was characterized by XRD as shown in Figure 2. The CQDs exhibit a broad peak centered at 2θ=25° which confirms the presence of an amorphous carbon structure (Haixia et al. 2020). The morphology and particle size of the nanoporous composite were evaluated using SEM and TEM. Figure 3 shows SEM and TEM images of the CQDs. The transmission electron microscopic (TEM) image of CQD (Figure 3a) indicates the dispersion of spherical-like particles with an average particle size of less 9 nm with the layered morphology of CQD (Honghong et al. 2017). Figure 3b shows the CQD nanosheets are layered with large numbers of residues of hydroxyl and carboxyl groups on the CQDs (Arumugam, et al. 2021).





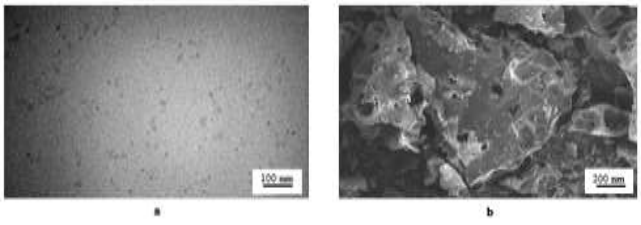


Figure 1. Fourier transform infrared spectra of (a) CQD

Figure 2. X-ray diffraction patterns of CQD

Figure 3. Transmission electron microscopy image of (a) CQDs. Scanning electron microscope image of (b) CQDs

3.2.Optimizations of parameters

In order to obtain the best separations, the mass of sorbent, pH, extraction time, volume of desorbing solvent, and desorption time was optimized for the extraction efficiency.

3.3.Influence of the mass of magnetic nano-sorbent

Nanosorbents offer high surface-area-to-volume ratios with high extraction capacity and efficiency compared to traditional sorbents and hence lower masses may be employed. Therefore, the sorbent mass is an essential parameter influencing the performance and subsequent analysis (Mohammad & Kamran & Gholamreza 2018). Quantities of CQD between 2 and 45 mg were utilized to obtain the best analytical response and reproducibility. Figure 4a shows the highest signal was achieved using 25 mg of sorbent. At larger masses, the extraction effectiveness decreased slightly and subsequently remained almost constant. The decrease may be due to the agglomeration of nanosorbent particles. Hence, 25 mg of CQD was deemed to be the optimum mass of sorbent.

3.4.Influence of pH

The pH controls the type of interactions of the analyte with the sorbent and the charges on the sorbent surface (Nurullah et al. 2011). The pH was varied from 1.0 to 10.0 using 0.01M HCl and NaOH. Figure 4b shows extraction efficiencies were highest from pH 1 to 3. At low pH in which the analytes are in their molecular form, extraction is performed well due to the hydrophobic nature of CQD. In order to optimize the reproducibility, pH 3.0 was deemed to be optimum.

3.5.Influence of extraction time

It is desirable to achieve adsorption in extraction techniques in the shortest time. In the present work, ultrasound was utilized for dispersing the nanosorbent which increased the extraction yield and mass transfer (Qiuhua et al. 2021). Various sonication periods were employed to optimize the enrichment as shown in Figure 4c. The extraction efficiency improved up to 5 min

and decreased at longer periods. Hence, 5 min was selected to be optimal.

3.6.Desorption conditions

Methanol, acetonitrile, and acetone were investigated for desorption of the analytes from the magnetic nanosorbent. Acetonitrile was superior compared to the other solvents with better sensitivity and precision (Figures 4e) and was employed in subsequent experiments. 2.0mL of acetonitrile was sufficient to elute the targets as the results were nearly constant at larger volumes. The best precision was obtained by 2 elution of 1.0 ml. The desorption time was evaluated from 2 to 7 min. 3 min corresponding to 1.5 min for each elution with vortex mixing provided the best sensitivity and precision.

3.7.Reusability

The reusability of the fabricated sorbent was evaluated to characterize its cost. After application of the CQD, it was washed with 2.0mL acetonitrile and 1.0mL double-distilled water with sonication for 6 min, and again subjected to the extraction protocol. After 10 cycles of isolation and enrichment, only a 7% decrease in extraction recovery was observed. Hence, CQD has satisfactory reusability.

3.8.Analytical figures of merit

The analytical figures of merit for cefdinir & cefixime were evaluated by the developed extraction followed by HPLC-UV as shown in Table 1. Figure 5 shows HPLC chromatograms of unspiked and spiked human plasma. The plasma samples did not degrade the performance of the extraction procedure.

3.9.Precision and accuracy

Intra-assay (within 1 day) and inter-assay (within 3 days) precision and accuracy of USM-A-DMSPE-HPLC-UV were assessed by determining the targets in quality control (QC) samples. The precision and accuracy were expressed as the relative standard deviation (RSD) of intra-day and inter-day assays and the relative error (RE), respectively. The results are summarized in Table 2.

3.10.Pharmacokinetic study

To quantify cefdinir & cefixime in human plasma, five samples from healthy volunteers aged 25 to 37 years were analyzed. The developed strategy was utilized to evaluate the pharmacokinetic data. Blood samples were collected 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h after administration. Each sample was centrifuged at 4,000 rpm for 6 min and stored at -18 °C until analysis. Each sample was subjected to the developed optimized method conditions and the mean analyte concentrations were plotted versus sampling time. Pharmacokinetic parameters, such as the maximum plasma concentration (Cmax), the curve from zero to last hour measurable concentration (AUC0-t), the area under the curve from zero to infinity (AUC0-∞), the time to reach the maximum concentration (Tmax), and the half-life (T1/2), were estimated and the results are presented in Table 3. It can be concluded that low level quantification of cefdinir & cefixime by US-M-A-DMSPE-HPLC–UV is suitable for pharmacokinetic analysis.

3.11.Comparison with other methods

The analytical figures of merit for this study were compared with the literature for the determination of cefdinir & cefixime in biological samples (Table 4). The current method is comparable on the bases of limits of detection and quantification**.** Furthermore, the results show

comparable relative standard deviations with rapid extraction. In addition, US-M-A-DMSPE-HPLC–UV is cost-effective, has an easily recyclable sorbent, and provides good precision. US-M-A-DMSPE-HPLC–UV has been demonstrated to be suitable for pharmacokinetic studies**.**

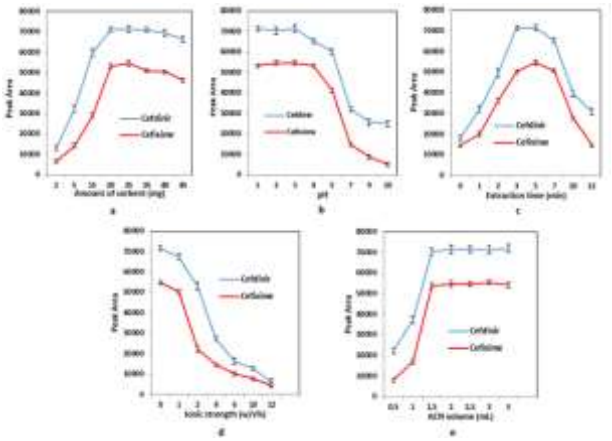


Figure 4. Factors that influence the extraction efficiency: (a) the mass of nanosorbent, (b) pH, (c) Extraction time, (d) ionic strength, and (e) volume of acetonitrile. Conditions: 250 ng ml^{-1} cefdinir & cefixime sample volume, and 3 min desorption time.

Table 1 Analytical features of the presented US-M-A-DMSPE-HPLC-UV

Analyte	cefdinir	cefixime
Linear dynamic range LDR (ng mL^{-1})	0.2-1500	0.5-1750
Linear equation	Y=285X + 291	Y=218X + 157
Coefficient of determination	0.990	0.993
Limit of detection (ng mL^{-1})	0.04	0.15
Limit of quantification (ng mL^{-1})	0.2	0.5
Enrichment factor (EF) % (n=3)	36.7±2.7	35.1±1.7
Extraction recovery (ER) % (n=3)	91.7±2.7	87.7±3.3

Linear dynamic range, Linear equation, Coefficient of determination, Limit of detection, Limit of quantification, Enrichment factor, and Extraction recovery were defined for analyzing 250 ng mL^{-1} of each drug through three independent measurements.

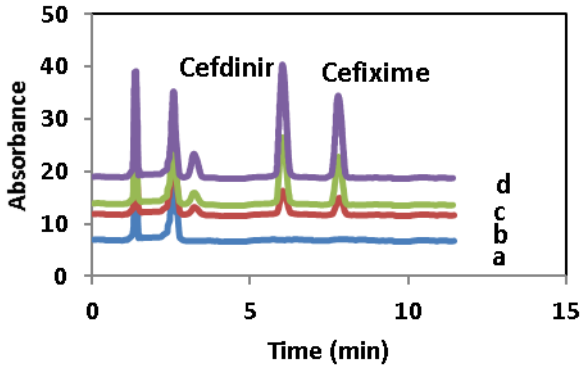


Fig. 5 HPLC–UV chromatograms of cefdinir & cefixime in human plasma: (a) blank; spiked human plasma with concentration level of each drug at (b) 125 ng mL^{-1}, (c) 250 ng mL^{-1} and (d) 375 ng mL^{-1}

Table 2. Intra- assay and inter- assay precisions and accuracies in analysis of cefixime and cefdinir in biological media

Drug	Concentration (ng mL^{-1})	Intra-assay, n = 12[a]			Inter-assay, n = 12[b]		
		Found value ± Standard deviation (ng mL^{-1})[c]	Relative standard deviation[d] (%)	Accuracy[e] (%)	Found value ± Standard deviation (ng mL^{-1})	Relative standard deviation (%)	Accuracy (%)
cefdinir	Low QC (5.0)	4.7 ± 0.2	4.3	-6.0	4.6 ± 0.4	8.7	-8.0
	Medium 1 QC (100)	107.2 ± 6.5	6.1	+7.2	94.5 ± 5.9	6.2	-5.5
	Medium 2 QC (500)	519.9 ± 25.9	5.0	4.0	528.3 ± 41.0	7.8	+5.7
	High QC (1250)	1321 ± 63.4	4.8	5.7	1139.8 ± 59.5	5.2	-8.8
cefixime	Low QC (5)	5.3 ± 0.3	5.6	+6.0	5.3 ± 0.4	7.5	+6.0
	Medium 1 QC (100)	95.5 ± 6.0	6.3	-4.5	91.8 ± 7.1	7.7	-8.2
	Medium 2 QC (500)	473.0 ± 18.4	3.9	-5.4	541.9 ± 46.0	8.5	+8.4
	High QC (1250)	1333.7 ± 71.5	5.4	+6.7	1344.2 ± 76.9	5.7	+7.5

[a] Intra-assay precisions were determined within one day; [b] Inter-assay precisions were determined within three days.[c] The average of three independent measurements. [d]

Table 3 Pharmacokinetic features considarations for cefdinir and cefixime after a combination threapy

Pharmacokinetic parameters	Mean ± SD	
	cefdinir	cefixime
T_{max} (h)	3.20 ± 0.46	5.53 ± 0.57
C_{max} (μg mL^{-1})	1.55 ± 0.39	5.37 ± 0.44
AUC_{0-24} (μg h mL^{-1})	7.98 ± 1.64	33.85 ± 3.51
$AUC_{0-\infty}$ (μg h mL^{-1})	8.14 ± 2.31	35.42 ± 4.20
$T_{½}$ (h)	5.77 ± 1.30	8.32 ± 0.83

4. Conclusions

Sustainable CQD was employed with US-M-A DMSPE for the determination of cefdinir & cefixime in human plasma. The designed sorbent in combination with HPLC provides a reliable approach for trace monitoring. The optimized conditions offer a suitable dynamic range with reasonable sensitivity and accuracy.

Table 4 Comparison of US-M-A-DMSPE-HPLC–UV with other methods for determination cefdinir & cefixime in different real media

Extraction Method	Extraction phase	Drug	Limit of detection ($ngmL^{-1}$)	Limit of quantification (ng mL^{-1})	Extraction time (min)	Matrix	Coefficient of determination	Relative standard deviation (%)	Detection system	Reference
SPE[a]	ZnMOF@ magnetic graphene oxide	cefixime	0.11	0.37	10	Urine sample	0.9994	2.86–4.21	HPLC- PDA[f]	(Habibeh et al. 2021)
SPE	C_{18}	cefdinir	-	50	4	Beagle dog plasma	0.9995	<7.23	HPLC-UV	(Ji et al. 2012)
LLE[b]	Chloroform	cefixime	6.68	23	9.45	Waste water	>0.999	<3	HPLC-UV	(Thi Thanh Tranet al. 2014)
LLE	Chloroform	cefdinir	5	25	7.5	Rat plasma	0.9996	-	HPLC-UV	(Krishnat & Ravindra 2021)
US-M-A-DMSPE	CQD/Fe_3O_4/ ZIF-71/PPy	cefdinir & cefixime	0.15 0.04	0.5 0.2	5 5	Human plasma	0.993 0.990	<8.5 <8.7	HPLC-UV	This work

[a] Solid phase extraction; [b] Liquid-Liquid extraction; [c] Three phase dispersive liquid- liquid microextraction; [d] Solid-phase microextraction; [e] Graphene oxide-reinforced hollow fiber; [f] HPLC with photodiode array detection.RSD (%) measured as 100 × SD/mean; e Relative error as accuracy (%) was defined through the following equation 100 × (mean concentration found - known concentration)/ (known concentration)

The analytical figures of merits for the method were characterized for pharmacokinetic analyses. The prepared sorbent offers efficient mass transfer, appreciable reusability, reduced use of toxic solvents, and rapid extraction. The pretreatment provided a notable improvement in accuracy. Hence, the reported sorbent with HPLC offers a robust protocol for the analysis of human plasma.

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