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Determination of Cefixime inclusion complex with 2-hydroxypropyl-β-cyclodextrin and extraction using DLLME and SIHLLME

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ABSTRACT

Micro-extraction techniques with UV-Vis measurement have been developed and validated for the analysis of Cefixime (CFX) in pure and pharmaceutical form. In this work, the DLLME and SIHLLME methods were employed for the extraction, enrichment and evaluation of CFX in pure form and pharmaceuticals using UV-Vis spectroscopy at 274 and 282 nm, respectively. The type of dispersive and extraction solvents and their volumes, pH, the amount of salt, and the centrifuging time were among the experimental variables that were accomplished. Under the perfect conditions, the procedures were linear in the range of 5.0-100.0 and 1.0-15.0 µg/mL, with a correlation coefficient of determination (R^2) of 0.9963 and 0.9984 for DLLME and SIHLLME, respectively, LOD was 3.7 and 0.11 µg/mL. Recovery of the target analyte in pharmaceuticals was 96.5%-102.4%. The method can be easily applied to CFX concentrations above this value, but needs further improvements before it can be used in pharmacokinetic studies where more sensitive methods can be found. A simple, inexpensive, accurate, and precise spectrophotometric assay of CFX in pharmaceutical formulations was developed and validated following DLLME and SIHLLME for routine analysis.

1. INTRODUCTION

Cefixime(CFX) is known (6R,7R)-7-{(2-(2-Amino-1,3- thiazol-4-yl)-2-(Carboxy-methoxyimino)acetyl) amino } – 3 – ethenyl – 8 – oxo – 5 – thia – 1 - azabicyclo(4 . 2. 0) oct – 2 – ene – 2 - carboxylic acid, Chemical formula ($C_{15}H_{13}N_5O_7S_2$), and molecular weight (439.42 g/mol), figure.1 . It belongs to the cephalosporin class, which is an antibiotic drug against bacterial infections[1]. Cefixime is utilized in the treatment of gonorrhea, urinary system and middle ear infection and respiratory diseases[2]. A literature review indicated that methods such as spectrophotometry[3-5], high-performance thin-layer chromatography (HPTLC)[6,7], high-performance capillary electrophoresis[8,9], high-performance liquid chromatography (HPLC)[10-13], liquid chromatography-mass spectrometry (LC-MS)[14,15], and fluorescence spectrophotometry[16-18], were available for the analysis of CFX. Dispersive Liquid-Liquid Micro-Extraction (DLLME) and Salt-Induced Liquid-Liquid Micro-Extraction (SIHLLME) have many advantages such as speed, low cost and safety[19-23]. The aim of the study was the simultaneous determination of CFX using inclusion complex with 2-hydroxypropyl-β-cyclodextrin as a reagent in combination with the DLLME and SIHLLME as extraction methods. For the evaluation and quality control of pharmaceutical formulations, an established methods must have certain properties such as simplicity, speed and sensitivity.

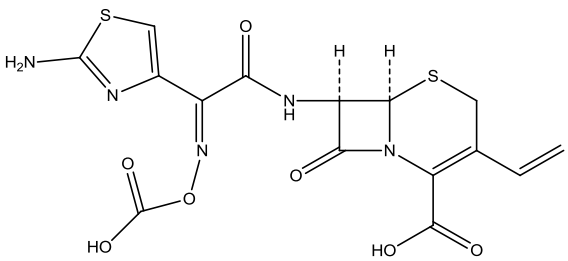

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Fig.1: Cefixime Structure

2. EXPERIMENTAL

2.1. Apparatus.

For absorption measurements, a UV-VIS spectrophotometer (cintra 5), with 1.0 cm matched quartz cells, was used. A pH meter (DW-9421 from the Philips instrument) and a hermle Z-300 centrifuge (Germany, Wehingen) were also used.

2.2. Materials and methods.

Samara-Iraq(SDI), the state company for pharma industries and medical equipment, gave away samples of cefixime (CFX, purity 99.8%). We purchased 2-hydroxypropyl-β- cyclodextrin (2-OHPY-β-CD) from Sigma-Aldrich. To make 1000 mg. L^{-1}, a stock solution of (CFX) 0.250 gm was weighed and diluted in 250 mL of 0.1N HCl solution. To prepare a stock solution (1000 mg. L^{-1}), 0.250 g of 2-OHPY-β-CD was dissolved in 250 mL of D.W. in the volumetric flask. By diluting the stock solution with the same solvent, working standard solutions were produced. The buffer's solution was made in accordance with the reference [24].

2.3. Assay procedure for dosage forms.

To obtain 4000 mg. L^{-1}, Six capsules of CFX, 400 mg (Winex, sudia & Brufix, India) were weighed. The weighed quantity was dissolved in the volumetric flask's 100 mL of (0.1 N) HCl solution. To get removal of the insoluble chemicals, the material was thoroughly mixed and filtered using filter paper.

2.4. Procedure of DLLME.

A 5.0 - 100.0 mg. L^{-1} of CFX solution was added to a volumetric cup stoppered tube (10 mL) containing 2 mL 2-OHPY-β-CD solution (1000 mg. L^{-1}) and topped up the volume with D.W. up to 10 mL. The combination was shaken for 10 min, then warmed at 35 °C for 25 min. Rapidly inject 600 µL of $CHCl_3$ as the extraction solvent, and 900 µL of ETOH as the dispersing solvent into the solution using a microsyringe, resulting in a cloudy solution. Centrifuge the mixture at 4000 rpm (5 min). The inclusion complex was obtained using a microsyringe, and and measure the absorbance at 274 nm compared to the blank.

2.5. Procedure of SIHLLME.

A 1.0 – 15.0 mg. L-1 of CFX standard solution was placed in a volumetric flask stoppered tube (10 mL). For the SIHLLME method, 1 mL of phosphate buffer(pH=6) and 800 µL of 2-octanol were added to the mixture to form a homogeneous mixture. Vortex the resulting mixture for 30 s and achieve phase separation by adding 0.8 g NaCl to a closed volumetric tube, then centrifuge at 3000 rpm for 4 min. The upper phase was dissolved in the 1 mL of ETOH and was conveyed to a UV–Vis spectrophotometer, and its absorbance was measured at 282 nm.

3. RESULTS AND DISCUSSION

In DLLME, Cefixime (CFX) forms inclusion complex, in an acidic media, with 2-OHPY-β-CD. The spectrum of the quantitatively extracted complex CFX-2OHPY-β-CD into $CHCl_3$ showed the maximum absorbance at 274 nm, figure.2. Whereas in SIHLLME, the spectrum of the quantitatively extracted cefixme(CFX) into 2-octanol showed the maximum absorbance at 282 nm, figure.3.

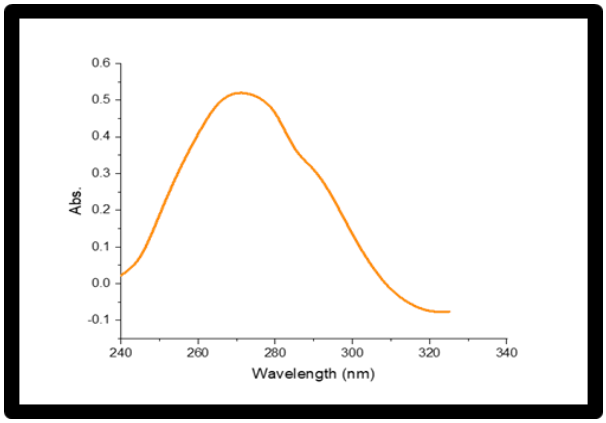

Fig.2: Spectrum of the resulting inclusion complex (CFX-2-OHPY-β-CD)

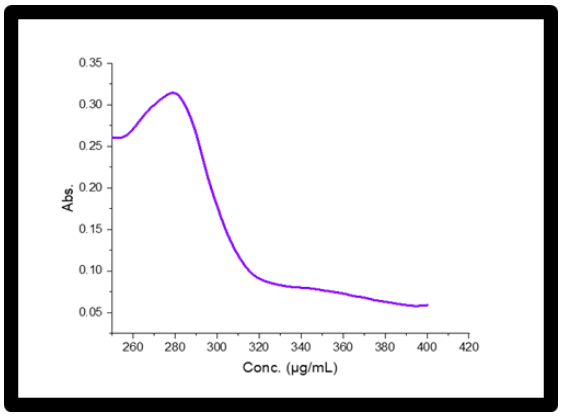

Fig.3: Spectrum of the CFX drug extracted by SIHLLME

3.1. Optimization of dispersive liquid-liquid microextraction..

DLLME microextraction procedure was achieved for the evaluation and pre-concentration of Cefixime. Pure CFX standard solutions in their pure form and pharmaceuticals were utilized to obtain various experimental variables to find the perfect conditions for (DLLME). DLLME has utilized a variety of extraction solvents, including chloroform, dichloromethane, and carbon tetrachloride. After optimizing the type of extraction solvent and its volume (results shown in Tables 1 and 2), 600 µL $CHCl_3$ was suitable for DLLME.

Table. 1: Extraction solvent effect

Solvent type	Abs.
$CHCl_3$	0.519
CH_2Cl_2	0.091
CCl_4	--

Table.2: Effect of extraction solvent volume

volume of extraction solvent µL	Abs.
200	0.020
300	0.052
400	0.068
500	0.102
600	0.510
700	0.242

A good dispersion solvent for DLLME should be miscible with both the aqueous and organic phases and form a cloudy state that increases the contact area between the two phases.We examined methanol, ethanol, and acetone as dispersants. Ethanol was found to produce the best absorbance signal (Table 3), hence it was selected as the dispersing solvent for the subsequent study. Next, the volume range of the dispersion solvent from (500-1500 µL) was tested. The results obtained showed a higher response to 900 µL of ethanol, figure.4.

Table. 3: Dispersive solvent effect

Type of dispersive solvent	Abs.
Ethanol	0.511
Methanol	0.091
Acetone	0.072

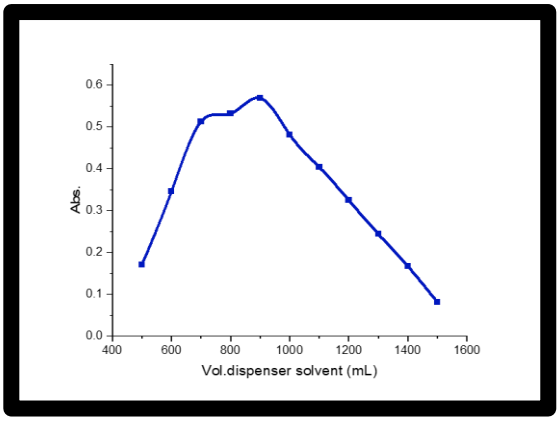

Fig. 4: Effect of ethanol volume used as dispersive solvent

The 0.25–3.0 mL reagent volume influence was accomplished. The outcomes (figure 5) demonstrated that the analytical signal was first made stronger by adding a specific volume of reagent before being decreased by adding more reagent. Therefore, 2.0 mL was selected as the optimal reagent volume for the DLLME procedure. The effect of centrifugation speed and time was seen in this investigation at speeds between 1000 and 4000 rpm and times between 1.0 and 5.0 min, as shown in figures 6 and 7. Due to the large surface area between the extraction solvent and the aqueous phase, DLLME was found to result in a quicker transfer of the analyte from the aqueous phase to the extraction phase. Based on the findings, a centrifugation speed and time of 4000 rpm and 5 minutes, respectively, were chosen. Many saccharides

were tested at as potential interfering agents to estimate the presence of Cefixime(CFX) in pharmaceuticals. The results are shown in the table. 4.

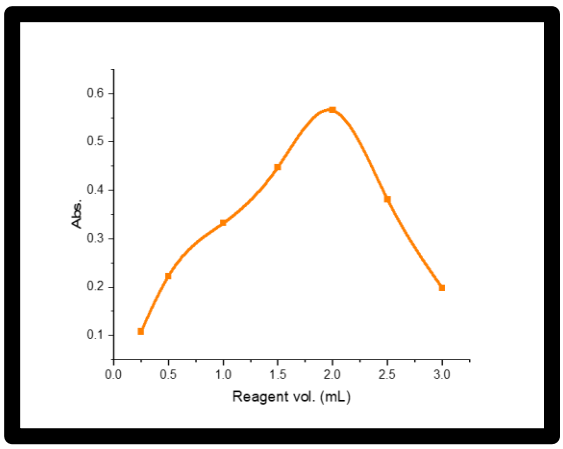

Fig. 5: Effect of reagent volume

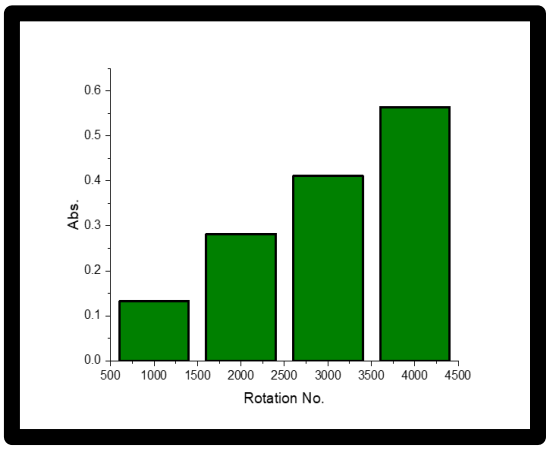

Fig. 6: Effect of rotation number

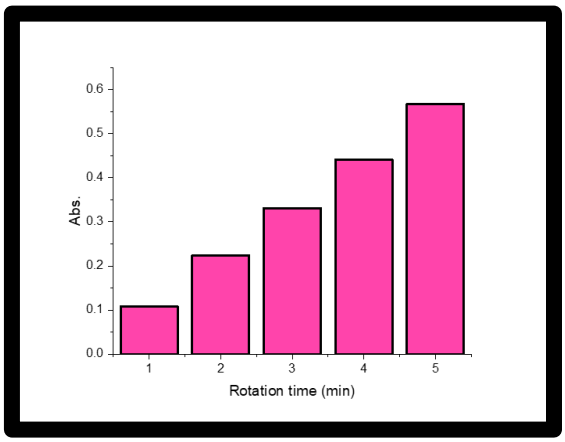

Fig. 7: Effect of the rotation time

Table.4: Effect of excipients on the extraction of CFX

Rec. %	Comp.
96.9	Galactose
96.4	Maltose
96.6	Sucrose
98.9	Glucose
96.4	Talic acid
97.7	Ribose
93.9	Starch

3.1.1. Linearity and range.

Table 8 lists the proposed approach's Beer's law range, regression equation, molar absorption coefficient, Sandell's sensitivity, and correlation coefficient. The peak absorbance at maximum and the CFX drug concentration in the range (5.0–100.0) mg/mL for the DLLME method were found to be linearly related (figure 8). The largest strong correlation after regression analysis can be seen in the Beer's Law plot. The resulting high molar absorption of the inclusion complex shows the sensitivity of the technique.

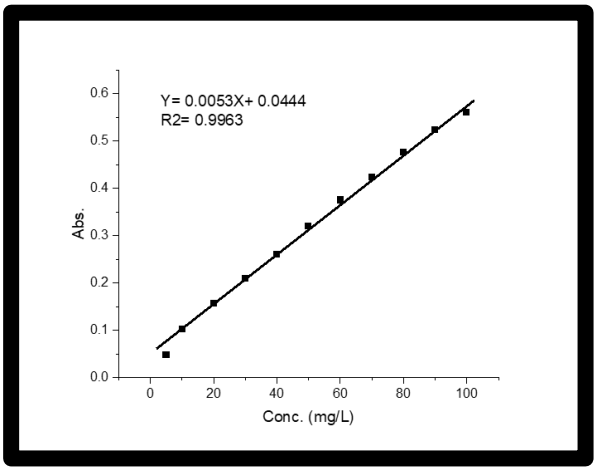

Fig. 8: Calibration curve of CFX using DLLME

3.2. Optimization of salt-induced homogenous liquid-liquid microextraction.

In this study, SIHLLME combined with UV-Vis spectrophotometry was developed for the quantification and pre-concentration of Cefixime(CFX) and the optimization process executed utilizing one variable at a time method. In order to

achieve high extraction efficiency, several effective parameters such as extraction type and volume, pH value, type of buffer solution, salt amount and number and time rotation have been fully estimated and optimized.

In this approach, pH is the most important extraction parameter when the analyte is acidic or basic. The influence of aqueous solution pH was examined in the pH range of 5.0 to 11.0 using either (0.1N) HCl or NaOH solutions for adjusting the pH. The findings of the response surface design demonstrated that high efficiencies are possible at pH 6.0, figure.9. The phosphate buffer is the best among the investigated buffer solutions (KH_2PO_4+NaOH, KH_2PO_4+diethyl amine, and Na_2HPO_4+ Citric acid), Table.5.

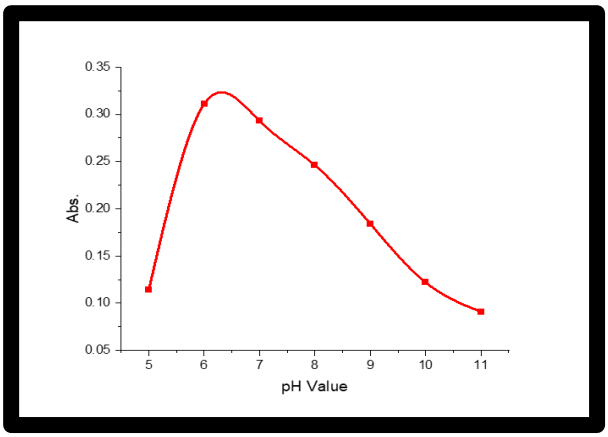

Fig.9: Effect of pH value

Table.5: buffer type effect

Buffer type	Abs.
KH_2PO_4+NaOH	0.481
KH_2PO_4+diethyl amine	0.639
Na_2HPO_4+ Citric acid	0.320

Pure CFX standard solutions was utilized to obtain various experimental parameters to find the perfect conditions for SIHLLME. Many extraction solvents such as 2-octanol, butanol, Isopropanol, and cyclohexanol have been used for SIHLLME. After optimizing the type of extraction solvent and its volume (results shown in Table. 6 and figure.10), 800 µl 2-octanol was suitable for SIHLLME.

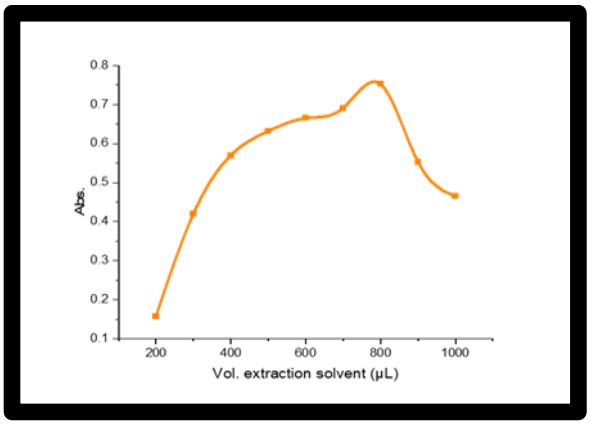

Fig.10: Effect of extraction volume

Table. 6: Extraction solvent effect

Extraction solvent type	Abs.
2-octanol	0.634
butanol	-----
Isopropanol	-----
Cyclohexanol	0.107

When salt is added to a water sample, the extraction process may be affected in one of three ways: salting-in, salting-out, or not at all. The solubility of organic compounds in water is typically reduced by the addition of salt, which is typically employed to increase CFX extraction recovery. Various tests were conducted in the presence of varying quantities of NaCl (0.2-2.0 gm) in order to evaluate the influence of salt concentration on the performance of the SIHLLME. Figure.11 depicts the response surfaces. Due to the salting-out effect, the results demonstrated an improvement in extraction recovery for cefixime at 0.8 grams of NaCl. In addition to increasing the extraction recovery, adding salt to SIHLLME has the additional benefit of preventing foaming, which leads to a proper phase separation following centrifugation and allows the extraction solvent to be quantitatively collected at the tube's top.

The effect of centrifugation speed and time was seen in this investigation at speeds between 1000 and 4000 rpm and times between 1.0 and 5.0 min, as shown in Figures 12 and 13. Because there is a lot of surface area between the extraction solvent and the aqueous phase in SIHLLME, there is a quicker transfer of the

analyte from the aqueous phase to the extraction phase. Based on the findings, a centrifugation speed and time of 3000 rpm and 4 min, respectively, were chosen. To check for the presence of Cefixime(CFX) in pharmaceutical formulations, a variety of saccharides were evaluated as potential interfering agents. The table.7 summarizes the results of the experiment.

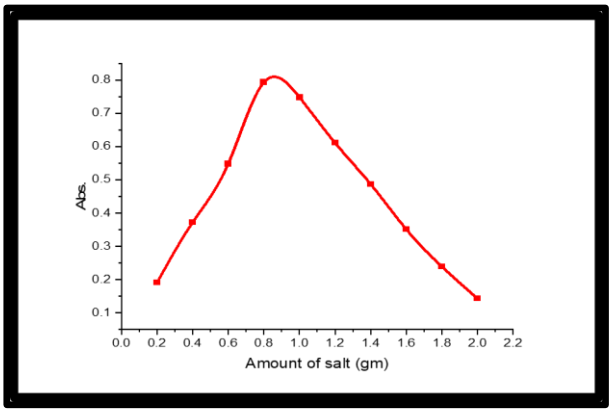

Fig.11: Effect of salt amount

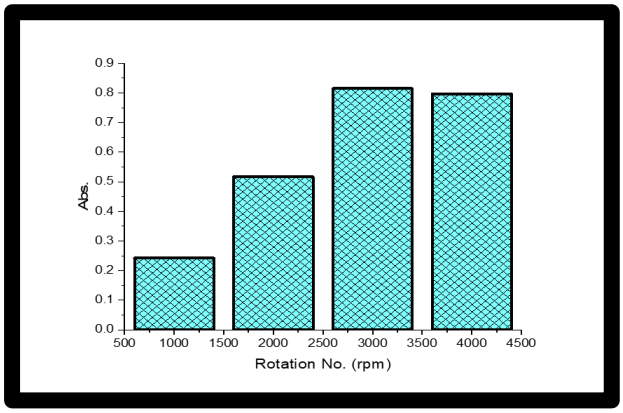

Fig.12: Rotation number effect

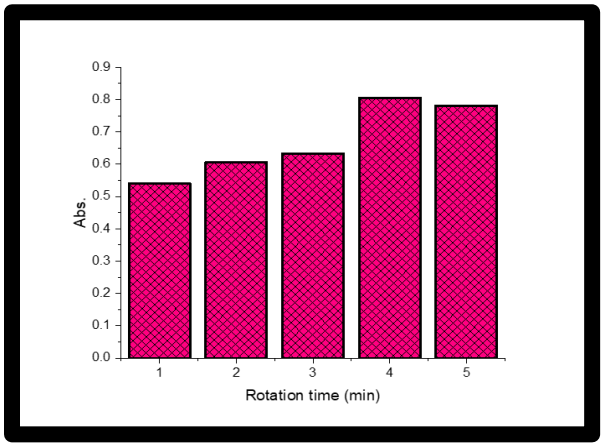

Fig.13: Rotation time effect

Table.7: Effect of excipients on the extraction of CFX

Rec. %	Comp.
98.1	Galactose
97.7	Maltose
96.2	Sucrose
97.7	Glucose
97.3	Talic acid
98.5	Ribose
96.0	Starch

3.2.1. Linearity and range.

Table 8 lists the proposed approach's Beer's law range, regression equation, molar absorption coefficient, Sandell's sensitivity, and correlation coefficient. A linear association between the peak absorbance at maximum and the CFX drug concentration in the range (1.0–15.0) mg/mL was established for the SIHLLME technique (figure.14). The largest strong correlation after regression analysis can be seen in the Beer's Law plot. The resulting high molar absorption of the inclusion complex shows the sensitivity of the technique.

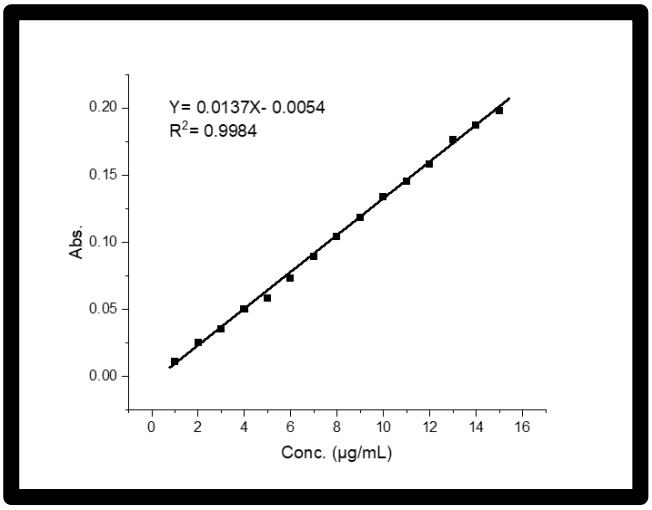

Fig. 14: Calibration curve of CFX using SIHLLME

3.3. Validation of the method.

The utility of both approaches to analyzing CFX in pure and pharmaceutical form has been achieved. The

results obtained for the pure drugs are presented in the table. 9. Testing of three replicates of the drug confirmed the accuracy and precision of the procedures. Low relative standard deviation (RSD%) values represent the best accuracy and reproducibility of procedures. The outcomes of the dose form analysis are presented in Table 9. The results were repeatable, and the RSD% values were low. The methods used were accurate, as indicated by the quantitative average percent recoveries (Rec.%) (96.5%–102.4%).

Table. 8: Analytical and statistical parameters of DLLME and SIHLLME

Parameter	*DLLME*	*SIHLLME*
λ_{max}(nm)	274	282
Color	Colorless	
linearity range (mg/L)	5.0-100.0	1.0-15.0
Molar absorptivity, (L.mol^{-1} cm^{-1}), Ɛ	2.4×10^3	6.2×10^3
Sandell's sensitivity (µg/cm^2)	0.10	0.073
Correlation coefficient (R^2)	0.9963	0.9984
Regression equation	Y= 0.0053X+0.0444	Y= 0.0137X+0.0054
Slope(b)	0.0053	0.0137
Intercept(a)	0.0444	0.0054
LOD(mg /L)	3.7	0.11
LOQ(mg/L)	11.1	0.34
C.L. for the slope at (95%)	$0.0053\pm1.08\times10^{-4}$	$0.0137\pm1.5\times10^{-4}$
C.L. for Intercept at(95%)	0.0444± 0.0064	0.0054± 0.00136
*C.L. for the X1 (mg/L) at 95%	30.248± 1.18	3.99± 0.224
*C.L. for the X2 (mg/L) at 95%	51.05 ± 0.56	7.95± 0.248
*C.L. for the X3 (mg/L) at 95%	69.79 ± 1.62	11.85 ± 0.326

*DLLME (X1=30, X2=50, X3=70), SIHLLME (X1=4, X2=8, X3=12)

Table. 9: Application of the suggested methods (D LLME & SIHLLME) for the estimation of CFX

drug	DLLME					
	Conc. of drug µg/mL^{-1}		Relative Error%	Reco. %	Average Reco.%	RSD% (n=3)
	Taken	Found				
Winex (sudia)	30	30.73	2.4	102.4	100.9	2.4
	50	50.98	1.9	101.9		1.1
	70	70.73	-1.3	98.6		0.66
Brufix (india)	30	30.29	0.98	100.9	101.1	2.2
	50	50.74	1.48	101.4		1.8
	70	70.8	1.13	101.1		0.81
SIHLLME						
Winex (sudia)	4	3.91	-2.08	97.8	99.3	4.5
	8	8.05	0.70	100.6		1.4
	12	11.94	-0.28	99.5		1.8
Brufix (india)	4	4.04	1.00	96.5	98.6	2.9
	8	7.98	-0.20	99.7		1.5
	12	11.97	-0.08	99.7		0.38

4. Conclusion.

A quick, low-cost, and confirmed DLLME extraction method has been developed to evaluate cefixime (CFX) in pharmaceuticals and pure form. The final results have been compared with the SIHLLME strategy. The suggested approach is comparable to other documented methods. A significant benefit of this study is its simple UV-Vis detection technique. To the best of our knowledge, there aren't many methods for evaluating cefixime, and this methodology offers a quick way to figure out how much CFX is in prescription medications. The findings indicate that the indicated strategy has produced a successful recovery. Since CFX may be quantitatively analyzed in pure materials and pharmaceutical preparations, this approach can be employed in a routine examination.

Table. 10: Comparison of the linearity, and LOD with previous studies

Method	Linearity mg/L	LOD mg/L	Ref.
UV Spectrophotometry	10-80	-	[25]
UV Spectrophotometry	1-20	0.1090	[26]
Spectrofluorometric method	0.2-40	0.0024	[27]
RP-HPLC	0.1-0.6	0.037	[28]
UV-Visible Spectroscopy	10-45	0.914	[29]
FIRST DERIVATIVE SPECTROPHOTOMETRIC	2.5-35	0.28	[30]
HPLC-UV Method	0.039-20	0.0195	[11]
Cloud point Extraction	10-160	0.06680	[31]
Ion-Pair Reaction	10–130	1.08	[32]
RP-HPLC Method	0.1-80	-	[33]
Cloud point extraction	2.5-30	0.456592	[34]
DLLME	5.0-100.0	3.7	Present work
SIHLLME	1.0-15.0	0.11	Present work

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تقدير معقد تضمين السيفكسيم مع 2–هيدروكسي بروبيل بيتا سايكلودكسترين و استخلاصه باستخدام DLLME و SIHLLME

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الخلاصة:

تم تطوير تقنيةالاستخلاص المايكروي و المدعومة بالقياس الطيفي في تقدير و تحليل عقار السيفكسيم بالشكل النقي و المستحضرات الصيدلانية. في هذا البحث، تم استخدام تقنيتي DLLME و SIHLLME في فصل واغناء و تقدير السيفكسيم بالشكل النقي و المستحضرات الصيدلانية عند طول موجي 274 و 282 نم على التوالي. هنالك عدة عوامل تم دراستها منها نوع و حجم مذيب الاستخلاص و التشتت و قيمة الاس الهيدروجيني و كمية الملح و عدد ووقت دورات جهاز الطرد المركزي. تحت الظروف المثالية كانت النتائج خطية في نطاق 5–100 و 1–15 مكغم/مل مع معامل ارتباط 0.9963 و 0,9984 لل DLLME و SIHLLME على التوالي. بالاضافة الى ذلك فان حد الكشف للطريقيتين كان 3,7 و 0,11 مكغم/مل و الاسترجاعية كانت بين 96,5 الى 102,4 % . يمكن تطبيق هذه الطريقة بسهولة على تركيزات CFX أعلى من هذه القيمة ، ولكنها تحتاج إلى مزيد من التحسينات قبل استخدامها في دراسات الحركية الدوائية حيث يمكن العثور على طرق أكثر حساسية .بعد طريقيتي DLLME و SIHLLME ، تم القياس بطريقة طيفية مباشرة وبأسعار معقولة ودقيقة ومظبوطة لـ CFX في المستحضرات الصيدلانية والتحقق منها لإجراء التحليلات الروتينية.

الكلمات المفتاحية: الاستخلاص المايكروي، السيفكسيم، DLLME, SIHLLME ، التضمين.