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Application of Cloud Point in Spectrophotometric Determination of Drugs, Overview

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ABSTRACT

The technique known as "cloud point extraction," or CPE, involves removing organic and inorganic compounds from chemical or biological systems using safe extractants such as non-ionic surfactants. These extractants have a tendency to separate out of the bulk solution and form clouds when heated to significant temperatures, and the capacity of the surfactants in the aforementioned procedure to concentrate these compounds is well established. The simplicity and speed of the CPE approach get a lot of attention, and the extraction process improves the experimental settings by varying the temperature, surfactant concentration, type of electrolyte, acidity function, and extraction duration. The so-called surfactant-rich phase and the surfactant aqueous phase separate into phases as a result of the surfactant. The cloud point temperature is the result of comparing the greatest temperature with the crucial temperature. It will be the material to be examined is then highly concentrated, with a high preconcentration factor. This article explains the application of CPE method for determination of various medicines utilizing various reactions.

Introduction

In 1978, Watanabe and Tanak (Watanabe & Tanaka, 1978) introduced the CPE technique as a green extraction, which is used as a surfactant agent (Ghasemi, & Kaykhaii, 2016). An analytical method with tremendous potential to increase detection limits is separation and pre-concentration. There are many advantages to using CPE as a pre-concentration process. Some of the features include speed, safety, and low cost. CPE is a simple method that concentrates a wide range of analytes with excellent recoveries and high concentration factors. Results with CPE are equivalent to those acquired using other methods of separation. Therefore, species that interact with the micellar system can be extracted and preprocessed from concentrated solutions either directly (usually through hydrophobic organic compounds) or indirectly through the necessary derivatization reactions (e.g., metal ions after reaction with appropriate hydrophobic ligands).

CPE is divided into three steps: The first three stages are the solubilization of the analyte into micellar aggregates, clouding, and phase separation for analysis.

A surfactant solution swiftly separates into two different phases when heated to a critical temperature. One phase is a surfactant-rich phase, whereas the other phase contains surfactant at a concentration below or equal to the critical micelle concentration (Ojeda & Rojas, 2009). Hydrophobic molecules that were previously confined to micelles in solution are liberated during the surfactant-rich phase.

This impact is noticeable, especially for polyoxymethylene surfactants. The two ethylene oxide fragments in the micelle, which when hydrated repel one another at low temperatures and attract one another at higher degrees due to dehydration, are responsible for

Corresponding author: E-mail: lamyasarsam@uomosul.edu.iq this phenomenon. The theory and related applications of this extraordinary separation technique have been discussed in various reviews (McLntire & Dorsey, 1990; Hinze & Pramauro, 1993; Sanz-Medel et al., 1999; Quina & Hinze, 1999; Stalikas, 2002; Rubio& Pérez-Bendito, 2003; Ferrera et al., 2004; Burguera& Burguera, 2004; Paleologos et al., 2005). And reports on its use in metal determination (Bezerra et al., 2005; Silva et al., 2006).

CPE has been promoted as a desirable substitute for liquid-liquid extraction in recent times. This method is based on the finding that most nonionic surfactants, when heated to their cloud point temperature (Watanabe & Tanaka, 1978), form micelles in aqueous solution and turn cloudy.

In order to separate the two phases, the aqueous supernatant phase and the surfactant-rich phase, in CPE, the appropriate experimental conditions must be met, with the surfactant concentrated near the critical micelle concentration. As a result, temperature change causes two-phase separation in zwitterionic and non-ionic surfactant solutions, In contrast, other factors (such as pH, the addition of an ionic salt, or the presence of an organic solvent) result in two-phase separation in ionic surfactant solutions. Parameters that produce phase separation can limit the types of compounds that can be extracted.

As a result, weakly basic drugs (such as Adrenaline, Codeine, and Atropine) which are ionized in low pH solutions, cannot be analyzed using acidic solutions, while thermo labile chemicals (such as vitamins) cannot be analyzed using CPE at high temperatures. Fig. 1 illustrates the actions needed in each of the five crucial CPE periods (Madej, 2009): (I) treating the sample with a surfactant, (II) keeping the temperature at a tolerable level for a while, (III) centrifuging, (IV) removing the supernatant and (V) correctly handling the surfactant-rich phase.

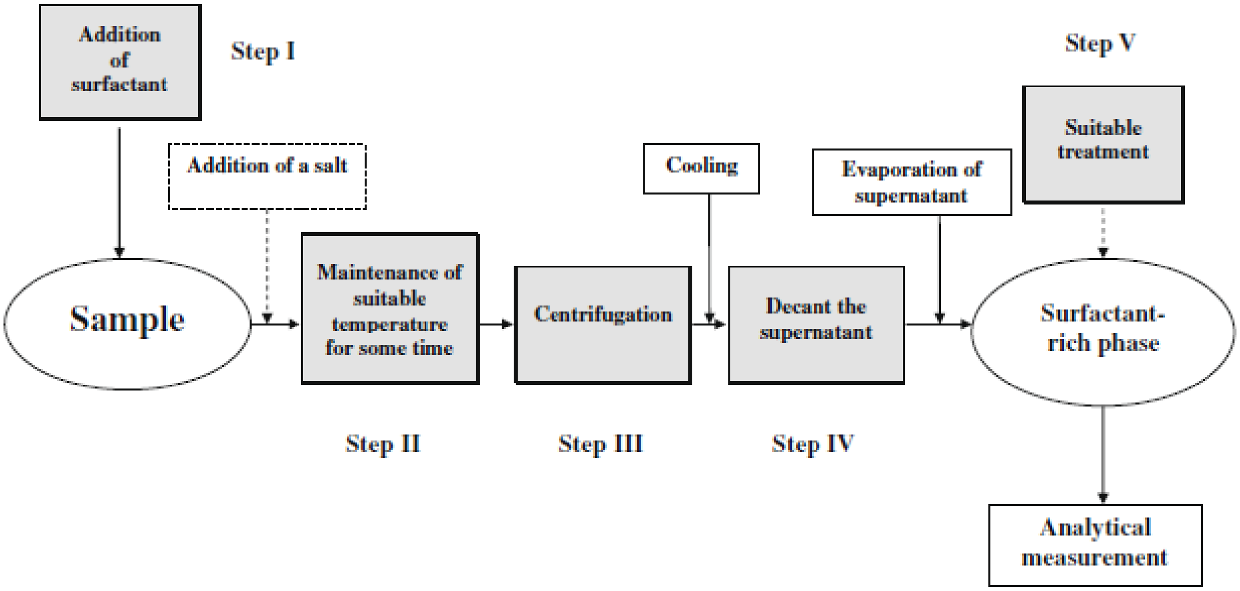

Figure (1) Five key steps in cloud–point extraction (CPE).

If these techniques don't work, you'll need to perform additional cleanup (such as solid-phase extraction (SPE) of the extract being studied) or switch to another detection method.

Ionic strength, temperature, and the kind and concentration of the surfactant are the three most important key variables. When developing a CPE approach, these considerations must be taken into account.

The acidity of the sample solution, similar to liquid-liquid extraction (LLE), is one of the most important factors controlling how well the analyte partitions in the concentrated surfactant-rich phase. The efficiency of maximum extraction of ionized species has been achieved at pH values where the uncharged form of the sample predominates. In micelle-mediated extraction, various surfactants can be used. The three types of surfactants that are most frequently utilized are anionic, double-ionic, and non-ionic.

In general, the effectiveness of CPE increases with the introduction of more hydrophobic surfactants and hydrophobic analytes. The surfactant amount present in the sample solution is an important additional factor affecting the CPE effectiveness of CPE. The recommended range for surfactant concentrations is a pretty narrow band. As the final surfactant volume increases, it is seen that the analytical signal degrades over the optimal range. However, analytical accuracy and reproducibility deteriorate if surfactant concentration is dropped below the values that are recommended.

Dehydration happens when the temperature rises, and the surfactant-rich phase's volume decreases. Researches have indicated that during CPE, two phases, a micelle-rich phase and a water micelle phase, must be maintained for a certain amount of time and at temperatures higher than the cloud point temperature.

. Using ionic compounds creates a repulsive electrostatic effect. This can be explained by the fact that increasing ionic strength usually promotes phase separation and improves recovery. The effect of ionic strength on biological fluids is particularly significant (Madej, 2009).

Spectrophotometry is the most popular and enticing approach since it is simple and less `expensive to use than other instrumental processes (BİŞGİN, 2018).

The measurement of dyes using spectrophotometry can be difficult because of the low dye concentrations and matrix interference in real samples (Bişgin & Narin, 2015). As a result, many analytical methods such as dispersive liquid-liquid microextraction (DLLME), CPE (Karatepe & Soylak, 2017; Pourreza & Zareian, 2009) and others are combined with UV-Vis spectroscopy (Bazregar, et al., 2018).

Solid-phase extraction (SPE) (Yu & Fan, 2016). Has been developed to identify food dyes. For the identification and quantification of trace hazardous chemicals in diverse matrixes, such as dyes and heavy metal ions, CPE, a separation, purification, and enrichment approach, has been widely used (Li, et al., 2017; Nambiar et al., 2017). Phase separation makes it possible to observe two stages in CPE (Shi et al., 2004). The crucial temperature over which the surfactant-containing solution turns turbid and divides into two phases is known as the cloud point temperature. First, the target analyte is present in very small quantities in the surfactant-rich phase. The diluted aqueous phase is at the second stage and has a large volume (Lemos et al., 2007).

The spectrophotometric technique combined with CPE offers appealing qualities in regular examinations of metals and chemical compounds in various matrices as an alternative to using the pricy instruments mentioned above (Surme et al., 2007; Candir et al., 2008; Khammas et al., 2014; Khammas et al., 2013).

The unaided eye is the best tool for finding cloud patches. It is especially suitable when the appearance of the solution changes quickly and noticeably. The cloud point temperature is the point at which a solution begins to get clouded (cloud). However, since eye observation is subject to observer error, especially if the cloudiness is increasing, its assessment is essentially arbitrary (Pincemaille, et al., 2018).

In compliance with standard CPE technique, an aqueous two-phase system known as "ATPS" is utilized. In order to create a surfactant-rich phase containing the target analyte, a PEG-based aqueous solution containing a surfactant or mixture of surfactants was heated and centrifuged.

. In this study, temperature-induced cloud point extraction (TICPE) and a new methodology were used to extract, separate, or elevate flavonoids from *Euonymus alatus* (see Figure 2). To do this, flavonoids were extracted from euonymus by ultrasonically-assisted extraction (UAE) using PEG-water as a homogeneous media system (Mai et al., 2020).

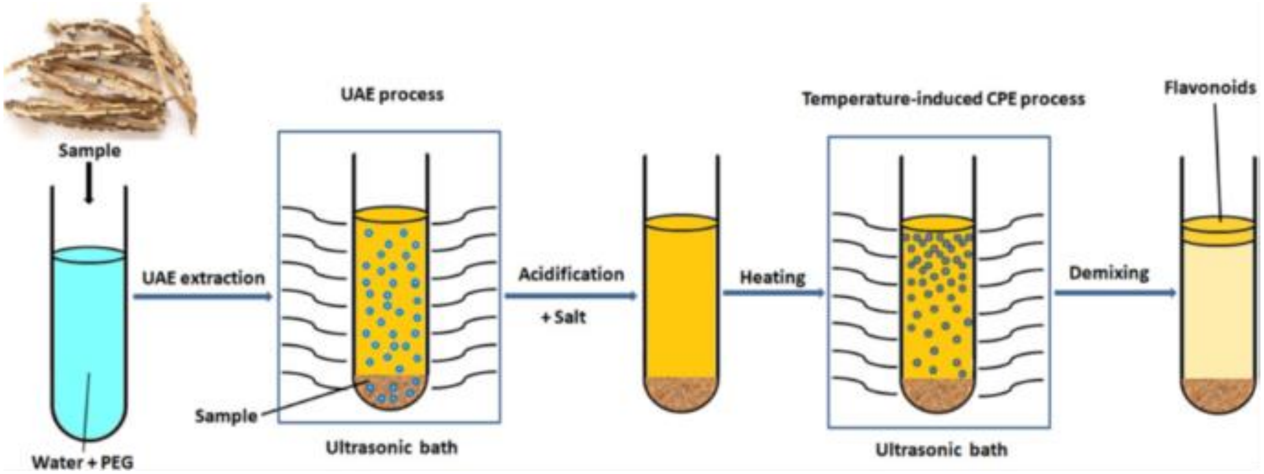

Figure (1) elevate flavonoids from Euonymus alatus.

The CPE method has gradually replaced the conventional liquid-liquid extraction process as the standard. Instead of using harmful organic solvents, CPE uses very small amounts of non-hazardous surfactants.

, it is far healthier and more environmentally sustainable than other kinds of separation processes. CPE is an appealing method that lowers exposure and solvent consumption, which reduces disposal costs and the amount of time required for the pre-concentration of metal ions following the production of sparsely water-soluble complexes (Akl et al., 2021).

To deal with these problems, the micro-cloud point extraction (MCPE) method was put out. The advantages of CPE are maintained, however, MCPE completely does away with the water bath stage and increases the amount of dangerous chemical solvents utilized from a few mL to a few 10 L. They make MCPE an efficient, inexpensive, and ecologically friendly process (Ghasemi & Kaykhaii 2015).

Advantage of CPE

Comparing CPE to conventional liquid-liquid extraction, there are a number of benefits. Water is used in CPE instead of a lot of hazardous and combustible organic solvents, which are used in standard solvent extraction. The capacity of surfactant to reduce analyte losses as a result of its adsorption onto the container can also raise the pre-concentration factors and recovery efficiency of CPE.

Rence Metal ions have been separated and pre-concentrated in a variety of substances employing CPE prior to their detection by analytical techniques.

The new online deployment of CPE into an FIA system has considerable benefits because it does away with all manual work (Ojeda & Rojas, 2009).

The CPE technique (green method) has become the best extraction method due to its advantages over other extraction techniques, including its simplicity, safety, affordability, good recovery, high enrichment factor, minimal need for organic solvents, and capacity to extract a range of chemicals and metals, as well as its ease of use and high efficiency (Kaykhaii & Ghasemi 2016).

Specifically in the extraction and pre-concentration processes, analytical procedures are increasingly using micelles and surfactants. CPE is an environmentally friendly extraction technique when compared to other liquid-liquid extraction techniques. The use of minute amounts of extracted solvents or surfactants in place of toxic organic solvents allowed for the development of CPE-safer procedures and the measurement of a variety of analytes, including organic (Katsoyannos et al., 2012).,inorganic (Shariati & Golshekan, 2014)., and nano-compounds (Majedi & Kelly 2012). Additionally, less solvent is being consumed, which reduces extraction times and costs (Abdullah, 2017). Medicinal substances have been extracted and identified using CPE from a range of matrixes.

Tabrizi proposed employing cloud point extraction and spectrofluorimetry as a quick and efficient method to evaluate thiamine levels in human urine. Thiochrome is produced by oxidizing thiamine with ferricyanide, and it is subsequently extracted into Triton X-114 micelles for spectrofluorimetric analysis. (Tabrizi, 2006). To measure paracetamol using spectrophotometry, cloud point extraction (CPE) was used (PCT). The process is based on the acidic hydrolysis of PCT to PAP, which is then combined with tetrahydroxy-calix [4] arene (CAL4) and an oxidizing agent (KIO_4) to produce a blue-colored product at room temperature. Following formation, the PAP-CAL4 blue dye was captured in Triton X-114's surfactant micelles and detected at 590 nm (Filik, et al., 2006).

According to Khammas (Khammas, 2009), the CPE methodology offers various advantages to those using extraction/preconcentration in analytical chemistry and research. These advantages include robustness, low cost, excellent extraction efficiency, and the ability to use a novel, exciting green chemistry process. Additionally, the ability to conduct online analysis using the majority of instrumental approaches will create a desirable alternative in the field of automated separation techniques. Even though there have been numerous developments in linking CPE with instrumental approaches, it is clear that there will be even more advancements in this field of study during the coming years. To fully comprehend the operation of the parameters governing the behavior of micelle-mediated extraction, additional theoretical foundations about the process of separation and preconcentration are also required.

By creating a charge transfer-ion pair complex with bromothymol blue in an acetate buffer medium, codeine was identified. Triton X-114 was used to extract the compound, and an absorbance measurement at 430 nm was taken **(**Mashhadizadeh & Jafari, 2010).

In an acidic solution, trifluoperazine hydrochloride (TFPH) formed a colored complex with vanadium (V-TFPH), which was then extracted by the surfactant Triton X-114 and spectrophotometrically quantified at a wavelength of 476 nm (Khammas & Rashid, 2015).

In a dilute acidic medium, norfloxacin reacts with Fe(III) ions to form a colored hydrophobic (Fe(III)-NOR) complex. This complex is first extracted as a mediated extractant in micelles of Triton X-114. This is done after NOR and Fe(III) ions are separately measured by spectrophotometry at 432 nm (Khammas, & mubdir, 2015).

Aspirin was extracted and preconcentrated using Triton X-114, a non-ionic surfactant, in the presence of HNO3. At 305 nm, the absorbance of this mixture was measured in comparison to a blank (Kaykhaii, & Ghasemi, 2016).

Amoxicillin and Metoclopramide hydrochloride concentrations in medicines were determined using a method that was provided. The method involves the reaction of diazotized Metoclopramide and Amoxicillin in an alkaline medium to produce an orange-colored and water-soluble product that is readily extractable from micelles in nonionic surfactant (Triton X-114). The two drugs are measured consecutively at 479 nm (Khammas, & Abdulkareem, 2016).

Using spectrophotometry, the three different cephalosporin classes of Cefotaxime (CFX), Ceftriaxone (CFT), and Cefepime (CFM) were identified. The procedures involved creating an azo dye by reacting diazonium salts of CFT, CFX, and CFM with phenol, resorcinol, and α-naphthol in a basic solution. The resulting compounds were then extracted using Triton X-114 and measured at 545, 500, and 515 nm, respectively (Hassan & Al-Rubaiaw, 2017).

Following diazotization and coupling with o-aminobenzoic to produce azo dye, lamotrigine was identified. After that, Tritone X-114 was used to extract the substance, and its absorbance was measured at 424 nm (Dhahir & Mahdi, 2017).

In an acetate buffer media with a pH of 3.5, bromophenol blue and vardenafil HCl formed an ion pair combination. The complex was extracted using Triton X-114, and the surfactant-rich phase from that extraction was diluted with methanol before its absorbance at 420 nm was measured (Hafez, 2017).

Using the cloud point extraction (CPE) methodology, a spectrophotometric approach for clonazepam (CLO) determination in pharmaceutical dosage forms was described. The procedure uses Triton X-114 as a surfactant to recover the product from the oxidative coupling between reduced CLO and phloroglucinol (PHG), which is then measured at 543 nm (Abdullah, 2017).

For the measurement of catecholamine medications (Hassan & Al-hraishawi, 2017) established batch and cloud point spectrophotometric approaches. Cloud-point extraction technique to get the most analytical data and to obviate any potential measurement interference. The batch approach depends on diazotizing 2-aminothiazole and combining it with Dopamine or Adrenaline. The violet-colored dye with Adrenaline has λ_{max} at 565 nm, and the faint violet-colored dye with Dopamine at 555nm. The UV-visible spectrophotometry measures the separation and preconcentration of violet dye in the cloud point extraction procedure. Analytical results obtained from the batch method show that the concentration ranges for dopamine and adrenaline are 1.0-12.5 and 1.0-17.5 µg/ml, respectively, with molar absorptivity values of 1.7 x 104 and 5.51 ×105 l.mol-1.cm-1, Sandell's sensitivity values of 0.0175 and 0.061 µg/cm2, limit of detection of 0.043 and 0.038 µg/ml, and RSDs of 0.65% and 0.91%, respectively. With molar absorptivity values of 4.8×104 and 1.8×105 l.mol-1.cm-1 for dopamine and adrenaline, respectively, the concentration range for the CPE method was 0.25 to 5.0 µg ml-1. Sandell's sensitivity values were 6.1 × 10-3 and 0.01 µg/cm2, and the limits of detection were 0.019 and 0.025 µg/ml, RSD is 0.307 and 0.445, and recovery% were 100.03% and 99.93% respectively. The measurement enrichment factors for Dopamine and Adrenaline are 2.71, and 2.46, as well as the preconcentration factor was 25. Adrenaline and Dopamine measurement in conventional medications and urine using the two approaches was successful alongside catecholamine. Additionally, the cloud-point extraction method was used to invest the colored dye result from the aforementioned reaction in order to collect the most analytical data and to obviate any potential measurement influence. These techniques have been used successfully to estimate catecholamine molecules in medicines and urine.

For the determination of vitamins B1 (thiamine) and B2 (riboflavin) utilizing cloud point extraction-HPLC technology, trace levels based on cloud point extraction were disclosed. The method is based on the complex formation between each vitamin and Ag (I) ions that were removed to nonionic surfactant phase cetyl pyridinium chloride (CPC) in the presence of KNO_3, Tergitol, and Genapol (Ulusoy & Akçay, 2018).

After being diazotized and combined with 4-tert-butylphenol and 2-NPT in a basic medium, cefdinir was identified. Triton X-114 was used to remove the azo dyes, and the measurements for each reagent were made at 490 and 535 nm, respectively (Hassan & Mizher, 2018).

A cloud point extraction approach and a spectrophotometric method are both used to determine the presence of sulphadimidine sodium in Trtion X-114. The procedure involved diazotizing the medication Sulphdimidine Sodium, combining it with α-naphthol in the basic medium to produce an orange-colored product, and then extracting it using a surfactant to measure it at 473 nm (Dhahir et al., 2019).

Streptomycin Sulfate was measured using the cloud point extraction method with Trtion X-114. The procedure involved creating an Ag+1 chelating complex at pH 12 and measuring it at 404 nm (Dhahir & Mohammed, 2019).

Three spectrophotometric techniques have been proposed for the determination of salbutamol and methyldopa (Abood et al., 2019). The first method involved the oxidation of Methyldopa by ferric nitrate and then coupling with thiosemicarbazide, yielding a dark green colored product with an absorbance maximum at 460 nm. In the presence of potassium iodide and sodium hydroxide, salbutamol undergoes a coupling reaction with 4-nitrophenyl hydrazine to produce a violet-colored substance with a maximum 530 nm absorbance. Beer's law is seen between 1 and 50 µg/ml with Sandall's sensitivity of (0.039, 0.073), and molar absorptivity of 0.536×10^4 and 0.327×10^4 $l.mol^{-1}.cm^{-1}$ for Methyldopa and Salbutamol, respectively. The second technique is CPE for estimating the traces of the above medicines that result from the same reaction. This technique allows for accurate drug assessment under the best experimental circumstances, with maximal absorption at 470 and 535 nm, respectively. For Methyldopa and Salbutamol, the concentration range was between 0.25 and 6 µg/ml, the molar absorptivity values were 0.510×10^5 and 0.483×10^5 respectively, and the enrichment factor was between 9.51 and 14.72. The third method is based on using flow injection analysis (FIA) depending on measuring the absorption signal for products produced by the above reaction to determine the phenolic drug content. The stability of the product's color was also studied. The active material for Salbutamol and Methyldopa was detected at maximum wavelengths of 460 and 530nm for each respectively. A total flow injection of 1.5 ml/min was pumped. The provided approaches were successfully used in this case to determine the presence of Salbutamol and Methyldopa in pharmaceutical formulations.

Recently**,** three spectrophotometric methods for the determination of the Cefixime drug have been created (Abood et al., 2019). In method (I), NH_2 in Cefixime was diazotized and coupled with bisphenol A in a basic medium, producing an orange-colored product that had a maximum absorbance at 490 nm. Beer's Law followed the concentration range of 1 to 50 µg/ ml with a limit of detection of 0.157 µg/ml, and the molar absorptivity was 0.866×10^4 $l.mol^{-1}.cm^{-1}$. In method (II), CPE was used to pre-concentrate the Cefixime azo dye for trace amounts. The azo dye was measured at λ_{max} 500 nm. A calibration plot had a molar absorptivity of 0.961×10^5 $l.mol^{-1}.cm^{-1}$, and the concentration ranged from 0.25 to 6 µg/ml. Method (III) was based on the above reaction using FIA and the absorbance of the diazotized orange-colored product was measured at 490 nm.

A rapid and effective cloud point spectrophotometric method was used to quantify the concentrations of salbutamol and methyldopa in both pure and pharmaceutical formulations. The process relied on the ion-pair complex formed with eosin Y dye. The extraction of complexes was driven to Triton X-114 surfactant and measured at 558 and 564 nm for the above drugs respectively (Shihab & Al-Sabha2020).

A rapid and precise approach for enriching and identifying Oxymetazoline (OMZ) in its pharmaceutical matrix was proposed by Wahdan et-al, (Wahdan et al., 2021) using the CPE methodology. The diazotization of OMZ and coupling with metoclopramide in a basic medium is the basis of the procedure. Triton X-114 surfactant was used to extract the azo dye product, which was then measured at 510 nm.

Al-Ward et-al developed a sensitive and exact reaction for the batch and cloud point extraction (CPE) methods of determining vancomycin hydrochloride. The first approach is based on the reaction of diazotized dapsone with vancomycin HCl (VAN) in a basic media, which forms azo dye. By using Triton X-114, a nonionic surfactant, and the cloud point extraction approach (second method), the sensitivity of this reaction was increased. After being removed into the surfactant-rich phase, the azo dye was diluted in ethanol and spectrophotometrically measured at λ_{max} 446 nm. Both batch and CPE procedures (with and without extraction) were used to study the reaction, and a straightforward comparison of the two developed methods was performed. A thorough examination has been done of the factors influencing the extraction process and the approaches' sensitivity. For both batch and CPE methods, the linearity of the calibration curves fell between 3 and 50 and 0.5 and 25 µg.mL-1, respectively, with detection limits of 0.806 and 0.214 µg.mL-1 for VAN. For the two approaches, the relative standard deviation (R.S.D.%) percentage was superior to 2.54% and 2.83%, respectively. Assaying VAN in commercial injection has proven to be an effective use of the suggested methodologies (Al-ward et al., 2023).

The pure form of mesalazine (MEZ) and its medicinal formulation were identified, and a rapid and accurate cloud point spectrophotometric method was proposed. The technique relied on the interaction of mesalazine with brilliant green dye (B.G.), which is extracted with triton x-114 and measured at 361 nm, to generate a yellow ion-pair complex. The experimental conditions for phase separation were optimized. With a precision (RSD) of 1.26, an average recovery % of 100.82, a molar absorptivity of 3.914×10^4 L.mol-1.cm-1, and a concentration range of 0.3 to 3.5 g mL^{-1}, Beer's law was observed. the method was successful in identifying MEZ in its pharmaceutical forms (Jabar et al., 2023). However; applications of the CPE technique for the determination of drugs are described in Table (1).

Table (1) Applications of the CPE technique for the determination of drugs is described

Reference number	Analyte	λmax nm	Linear range	Surfactant	Molar absorptivity L.mol^{-1}.cm^{-1}	RSD %	Application
Tabrizi, 2006	Thiamine	438	2.5-1000 ng.mL^{-1}	Triton x-114		2.42	Human urine
Filik et al., 2006	p-aminophenol (PAP)	590	1.5-12 mg.mL^{-1}	Triton x-114		2.15	Tablets and blood samples
Mashhadizadeh & Jafari, 2010	Codeine	430	100-700 ng.mL^{-1}	Triton x-114		2.15	Tablets and blood samples
Al-Khammas & Rashid, 2015	Trifluoperazine hydrochloride (TFPH)	476	0.5-10 µg mL^{-1}	Triton x-114		0.48-3.40	Pharmaceuticals and the spiked serum samples
Al-Khammas & Mubdir, 2015	Norfloxacin (NOR)	432	2.5-125 µg.mL^{-1}	Triton x-114		0.04-0.66	Biological and pharmaceutical samples
Kaykhaii & Ghasemi, 2016	Aspirin	305	0.05–2 mg.L^{-1}	Triton x-114			Pharmaceuticals
Khammas & Abdulkareem 2016	AMX and MCP	479	0.3-3.0 µg mL^{-1}	Triton x-114		2.35-10.8 and 0.20-3.43	Pharmaceuticals
Hassan & Al-Rubaiawi, 2017	ceftriaxone (CFT), cefotaxime (CFX), and cefepime (CFM)	545, 500, and 515	1 of 2.5 to 62.5 mg. L^{-1}	Triton x-114			Pure and pharmaceutical formulations
Dhahir & Mahdi, 2017	Lamotrigine drug	424	0.5–18 µg mL^{-1}	Triton x-114	2.88×10^{3}	1.62–3.04	
Hafez and et al., 2017	vardenafil HCl (VARD)	420	0.1-2.0 µg mL^{-1}	Triton x-114		1.80	Tablets
Abdullah, 2017	Clonazepam (CLO)	543	0.3-25 µg.mL^{-1}	Triton x-114		2.5	Tablets
Jasim et al., 2017	catecholamine	565	1.0 – 17.5 µg.mL^{-1}	Triton x-114	4.8 x 10^{4}	0.307	Urine and drugs
Ulusoy & Akçay, 2018	vitamins B1 (thiamin) and B2 (riboflavin)		4 - 400 , 1-500 ng.mL^{-1}	Triton x-114		2.90 and 2.20	Baby foods, milk, and cereals.
Hassan & Mizher, 2018	cefdinir (CFD), cephalosporin species	490, 535	3-100 µg.mL^{-1}	Triton x-114	0.6129×10^{4}, 0.3361×10^{4}		Commercial formulation
Dhahir et al., 2019	sulphadimidine sodium (SDMS)	473	1-12 µg.mL^{-1}	Triton x-114		1.3-5.28	pharmaceutical dose
Saadiyah et al., 2019	Streptomycin Sulfate	404	2.5-30 µg. mL^{-1}	Triton x-114		good	Some Pharmaceuticals
Abood et al., 2019	Methyldopa and Salbutamol	460, 530	1-50 µg.mL^{-1}	Triton x-114	0.536×10^{4}, 0.327×10^{4}		Pharmaceutical preparation.
Abood et al., 2019	Cefixime	490	1-50 µg.mL^{-1}	Triton x-114	0.866×10^{4}		Bulk drug and pharmaceutical formulations

Shihab et al., 2022	Salbutamol Sulphate and Methyldopa	558, 564	0.1-20, 0.3-10 µg.mL^{-1}	Triton x-114	4.0×10^{4}, 5. 7×10^{4}	<1.6 >0.3	Pharmaceutical preparations.
Whdan et al., 2021	Oxymetazoline	510	0.05-17.0 µg.mL^{-1}	Triton x-114	2. 7×10^{4}	4.48	Commercial nasals
Al-ward et al., 2022	Vancomycin Hydrochloride	446	0.5-25 µg.mL^{-1}	Triton x-114	7.2071×10^{4}	2.83	Commercial injections
Jabar et al., 2023	Mesalazine	361	0.3 – 3.5 µg.mL^{-1}	Triton x-114	3.914×10^{4}	1.26	Pharmaceutical preparations

The table above clarifies the uses of different types of spectrophotometric methods and chromatography for the determination of drugs by cloud point extraction (CPE) using Triton x-114 as a surfactant and they give good results. That means CPE is a suitable technique to increase detection limits in separation and pre-concentration.

Conclusions

This review describes the cloud point extraction (CPE) technique as an environmentally friendly analytical technique, providing a simple, rapid, inexpensive, and method for preconcentrating and separating trace amounts of substances in aqueous solutions suitable for extraction. CPE is a cost-effective analytical tool. Also; the potential benefits of established technique include time savings, reduction in the amount of reagents used, and minimization of analyst effort.

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