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Full Paper

A New Efficient Agarose Gel based Electro-membrane To Extract, Preconcentrate, Clean-up and Quantify Nilotinib in Biological Samples

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Abstract- For the first time, this study used agarose gel as a membrane in electro membrane extraction (AG-EME) without using any organic solvent to preconcentrate and clean up nilotinib in biological samples, following: its spectrofluorometric determination. Optimal conditions were: agarose concentration (w/v) 3.0%, acetic acid concentration in membrane (v/v) 0.2%, applied electric voltage 50V, pH of the donor phase (pH_d) 4, pH of the acceptor phase (pH_a) 3, and extraction time of 30 min. Limits of detection (LOD) and quantification (LOQ) were 15 and 50 ng mL^{-1}, and the analytical curve was linear at the range of 50–5000 ng mL^{-1}. The proposed validation method was compared with the other electro-membrane extraction techniques. Our proposed method is fast; it uses little sample and possesses a short extraction time. The developed procedure could be utilized successfully to determine the total amount of nilotinib, an anticancer drug, as a routine analysis in the biological samples.

Keywords- Agarose gel; Clean up; Electro-membrane extraction; Preconcentration; Nilotinib

1. INTRODUCTION

Today, treating some types of cancer has changed from conventional chemotherapy drugs to chronic treatments by purposeful molecular methods [1]. Cancer-based therapies such as tyrosine kinase inhibitors (TKIs) are known as small molecular drugs that prevent the growth and spread of cancerous tumors by preventing intracellular signals that cause them to multiply in many malignant cells [2]. Tyrosine kinase inhibitors are extensively (<95%) bound to serum proteins and tissues, and only a tiny percentage are freely released into the cell for their pharmacological activities Infiltrate. On the other hand, research has shown that very small amounts of tyrosine kinase inhibitors can penetrate the central nervous system through the blood-brain barrier, and the concentration of tyrosine kinase inhibitors is less than 1% of their plasma concentration. In order to determine the TKIs in real samples like plasma, some kind of treatment is necessary as an analytical technique, because these types of measurements are often not responsive to analytes in their current form and interfering species, leading to distortion of the results of the analysis [3]. Therefore, developing a selective analytical method should be considered for the determination of vitally important anti-cancer drugs.

These kinds of chemical analyses require several developed sample preparation methods, such as solid-phase extraction (SPE) and liquid-liquid extraction (LLE), to be utilized [4-9]. Although these methods provide accurate and reliable results, most use toxic organic solvents that are not available in routine laboratories. Also, finding organic solvents with suitable extraction capacity for the drug in the LLE method is usually time-consuming and tedious. In the case of SPE, finding the suitable solvent for selective washes of the analyte has its obstacles [10].

Electro-membrane extraction (EME) is one of the sample preparation techniques which function based on the distribution of two species between two aqueous phases, also presented by Pedersen-Bjergaard and Rasmussen in 2006 [11] in which the presence of an electric field causes an increase in extraction efficiency, shortening extraction time. EME has gained considerable attention due to its advantages over other microextraction techniques, including compatibility, versatility, high efficiency, and fast extraction time [10-14]. It is a miniaturized extraction procedure in which charged analytes (either positive or negative) are extracted from the donor phase (DP) according to the polarity of an applied field through an organic solvent immobilized by capillary forces in the pores of a porous polymeric membrane, into an acceptor phase (AP) of a few microliters in volume placed in the lumen of hollow fiber [11, 15-18]. The principle of EME is based on the transport of ionized analytes by the electric field from aqueous solution through the supported liquid membrane (SLM) following their emergence into the aqueous acceptor phase. Before performing the extraction, the pH of the sample solution should be adjusted so that the corresponding analyte exits in an ionized form.

Up to now, most of EME experiments have been designed with a supported liquid membrane (SLM), a porous polypropylene polymer. Polypropylene polymers are a group of artificial membranes most of which are commercially available only in limited sizes and forms. Thus, there is restrictions on using these materials as support for the SLM in different setups of EME [16]. Crown ethers have been used as a SLM for the extraction of potassium ions [19]. Further improvement in EME methods occurred with the use of nanoparticles in the SLM [20-22]. Another modification on the EME method was the introduction of ionic liquids as a new solvent in the SLM [23]. It has been reported that ion-pairing reagents such as di-(2 ethylhexyl) phosphate (DEHP) is capable of controlling the selectivity in EME [24]. In another study, agar films containing silver nanoparticles (AgNPs) were used as SLM, with dihexyl ether (DHE) being immobilized, as an extracting solvent [25]. Polyacrylamide gel as a membrane in EME developed by Tabani et al. [26] have been used to extract three basic drugs following their HPLC-UV detections with no need for an organic solvent and carrier agents.

In the present research, agarose gel based EME procedure was used without any organic solvents or ion-pairing reagents. Agarose, as hydrogel, has found numerous applications in gel EME procedure for extraction and identification of different analytes [27-29]. Agarose is very stable in a varied range of pHs and temperatures which makes it as an ideal medium for diffusion and electro-kinetic migration of several compounds [30]. The preparation of agarose gel is easily feasible in virtually every laboratory, as only a mixture of agarose and water are used to make a gel membrane. Regarding the analyte, nilotinib, which is a basic drug, was selected as the target used to validate the applicability and efficiency of the proposed EME setup. The findings were then compared to those obtained by conventional EME.

2. EXPERIMENTAL

2.1. Reagents and Instrumentations

Agarose was acquired from Cina Gen Company (Tehran, Iran). Double distilled deionized water (DDW) was provided by a Milli-Q® system (Millipore, Milford, MA, USA) and was used to prepare all the solutions. Transfer pipettes were supplied from a company in Wertheim, Germany. Nilotinb (purity > 99%) were purchased from Tofigh Daru Pharmaceutical Company (Tehran, Iran) and was used without further purification. Acetic acid was purchased from Merck (Darmstadt, Germany). The model PV-300 DC power supply with programmable voltage in the range of 0–600 V provided by Paya Pajohesh Pars, Tehran, Iran and was used to supply currents in the range of 0-1.0 mA along with two platinum wires of 0.2 mm in diameter as electrodes. Stirring of the solutions was carried out by a Heidolph MR 3001 K magnetic stirrer (Schwaben, Germany) equipped with 1.5 mm×8 mm magnetic bars.

2.2. Standard and real sample solutions

A stock solution (1000 mg L^{-1}) of drug was prepared in DDW, protected from light and stored for one month at 4 ºC with no evidence of decomposition. All required standard solutions were daily prepared from it and were diluted with DDW. The pH of the sample solutions was adjusted using HCl (1.0 M) and NaOH (1.0 M) solutions. Plasma and urine samples were provided by the Imam Reza hospital laboratory (Birjand, Iran). The samples were stored at -4 ºC, thawed and shaken before use.

2.3. Fabrication of the agarose gel based electro-membrane

Fig. 1 illustrates steps to fabricate the membrane. 5 %(w/v) agarose and 0.2 %(v/v) of acetic acid were dispersed in the boiling DDW to complete dissolution following homogenization. Then, the desired amount of it was quickly transferred into a micro vial using a disposable micropipette and stored at 4 ºC for 2 hours. After that, the end of the micro vial was carefully cut to form a membrane having thickness of 5 mm and with upper space as a compartment for holding the acceptor phase [31,32].

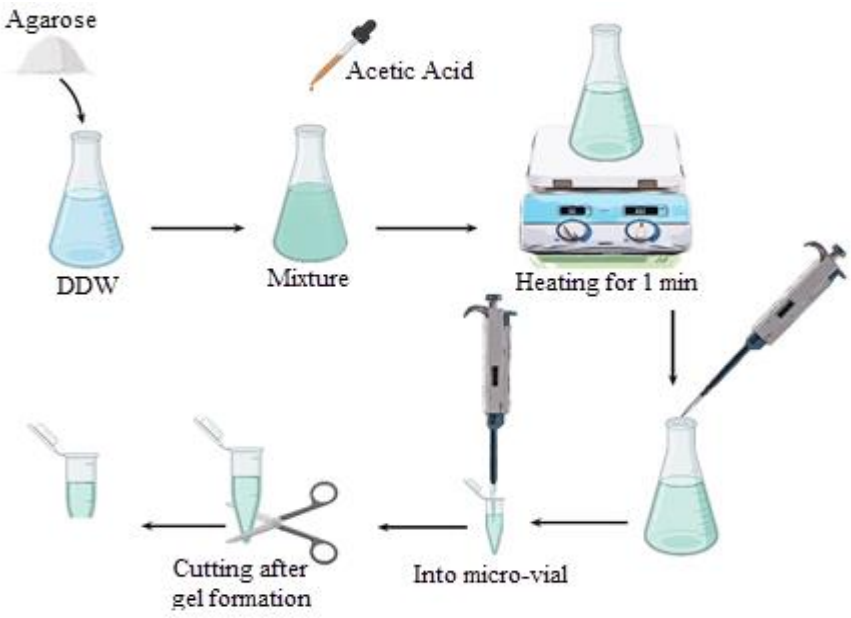

Fig. 1. Schematic illustration of the membrane preparation

2.4. Proposed AG-EME procedure

As shown in Fig. 2, the equipment used to implement the proposed AG-EME procedure. The DC power supply used was a model PV-300 (Mobtaker Aryaei J., Zanjan, Iran) with

programmable voltage in the range 0-600 V which provides currents in the range 0-0.5 A. Platinum electrodes (0.2 mm in diameter) were purchased from Pars Pelatine (Tehran, Iran). The stirring of the solutions was carried out by a Heidolph MR 3001 K magnetic stirrer (Schwabach, Germany) equipped with 1.5 mm × 8 mm magnetic bars.

The sample (4.5 mL at pH = 4.0) containing the target drug was introduced into a six mLglass vial. 150 µL of the aqueous AP (pH = 3.0) was introduced, by a micropipette, into the tube containing agarose gel as the membrane. The negative electrode (cathode) was introduced into the tube, with the positive electrode (anode) inserted into the sample solution (Fig. 2). The electrodes had their ends ring-shaped to create a larger electric field near the membrane and keep inter-electrode spacing constant during the extraction process. A voltage of 50 V was turned on, and the extraction was performed for 30 min while the sample solution was agitated at 900 rpm. After the extraction time, the acceptor phase was collected by micropipet and given to the UV-Vis spectrophotometer for measurement.

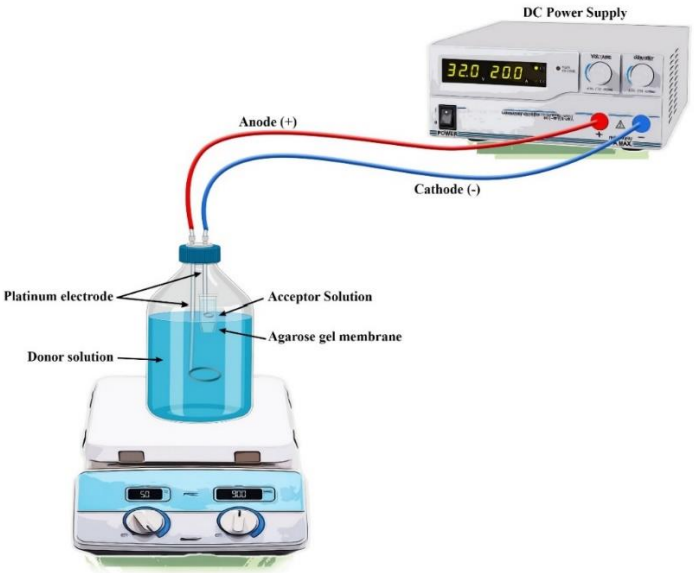

Fig. 2. Schematic illustration of the proposed EME setup

3. RESULTS AND DISCUSSION

3.1. Optimization of AG-EME procedure

3.1.1. Effect of agarose gel concentration

The effect of the agarose content in membrane gel on the extraction efficiency was investigated in the range 1-5% (w/v). The results showing that EME efficiencies improved with increasing

agarose concentration to up to 3% (w/v), and then the efficiencies decreased (Fig. 3). This behavior can be qualified to the fact that, at low concentrations, the agarose gel was not stable, so that it tended to be destroyed during the extraction time. Also, the membrane with 2 % agarose allowed water to flow from the DP to the AP via so-called electroosmotic flow (EOF). EOF is the motion of liquid induced by an applied potential across a porous material, capillary tube, membrane, or any other fluid conduit. This phenomenon is most significant when occurred in small channels.

On the other hand, at concentrations higher than 3%, the membrane was tough to prepare because the solidification time of the gel was concise. Also, at high concentrations of agarose gel, the extraction percentage was low due to the hardness of the gel. Therefore, the agarose gel's 3% (w/v) was chosen as the optimal agarose concentration for membrane fabrication.

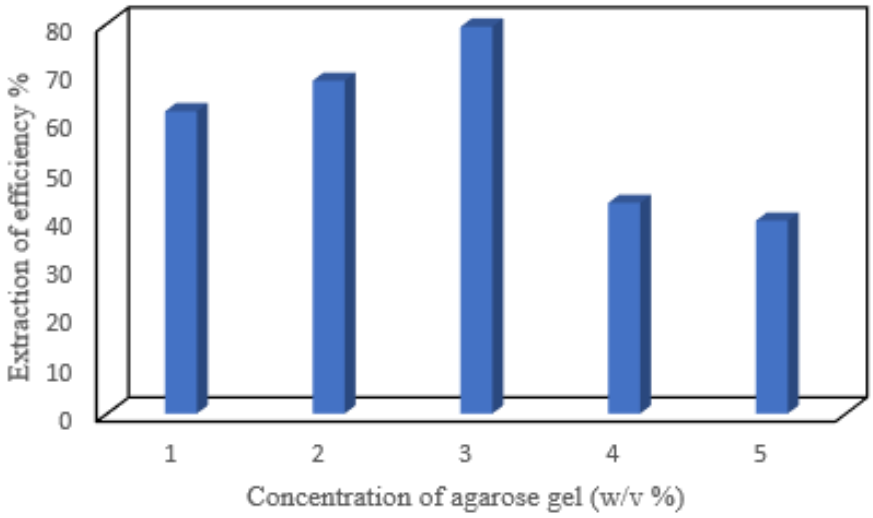

Fig. 3. The effect of the agarose concentration on the extraction efficiency; extraction conditions: concentration of the acetic acid: 0.10% (w/v); pH of the DP: 7.0; pH of the AP: 3.0; Applied voltage: 60 V; Extraction time: 30 min; Stirring rate: 900 rpm

3.1.2. Effect of acetic acid concentration on membranes

In order to increase the extraction efficiency in AG-EME, the pH of the gel membrane was also investigated using acetic acid. Because the analyte first passes through the gel before reaching AP, to maintain the ionic state and increase the extraction efficiency [33, 34], the pH of the agarose gel membrane is 0-0.25% (v/v) was investigated. As it could be observed from (Fig.4), an increase in the percentage of acetic acid up to 0.20% (v/v) enhances extraction efficiency, but beyond that, the extraction percentage decreases. By using the higher volume due to electrode reactions and electrolysis, extraction efficiency decreases [35]. Electrolysis causes a change in pH, forming bubbles in donor and acceptor solutions and converting the ions into neutral molecules, all leads

to extraction efficiency reduction. As a result, the optimal amount of 0.2% (v/v) acetic acid was selected.

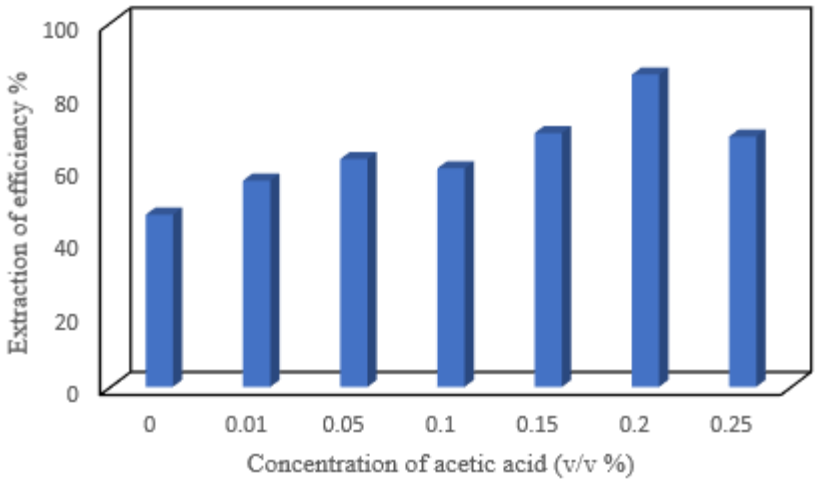

Fig. 4. The influence of the acetic acid concentration on the extraction efficiency; extraction conditions: concentration of the agarose: 3 % (w/v); pH of the DP: 7.0; pH of the AP: 3.0; Applied voltage: 60 V; Extraction time: 30 min; Stirring rate: 900 rpm

3.1.3. Effect of acceptor phase pH

The pH of a sample solution determines the nature of the analyte (ionic or molecular). In an AG-EME process, the charged analyte is extracted from an aqueous sample solution. Nilotinib solution exhibit different charge in acidic and basic pH. Thus, for its extraction, the acceptor solution should have acidic pH so that it can be converted into its ionized form (cation) to enable it to migrate through the electric field. Several experiments were performed to investigate the effect of the acceptor solution's pH in the range of 2-5. As illustrated in (Fig. 5), the best result was obtained at pH 3. The findings showed that a decrease in electromigration of the analyte with increasing pH of the AP has occurred. During the extraction, the pH of the AP increased gradually due to electrolysis via the following reactions [14].

AP (negative electrode): $2H^{+}+2e \rightarrow H_2$ (1)

DP (positive electrode): $H_2O \rightarrow 2H^{+} + 1/2O_2 + 2e$ (2)

The small volume of the AP somewhat intensified this effect. Therefore, the pH of the AP should be sufficiently low (pH 3.0) to maintain the analyte in ionized form and prevent it from being back-extracted. Thus, the pH of the AP was adjusted to 3.0 in further analyses.

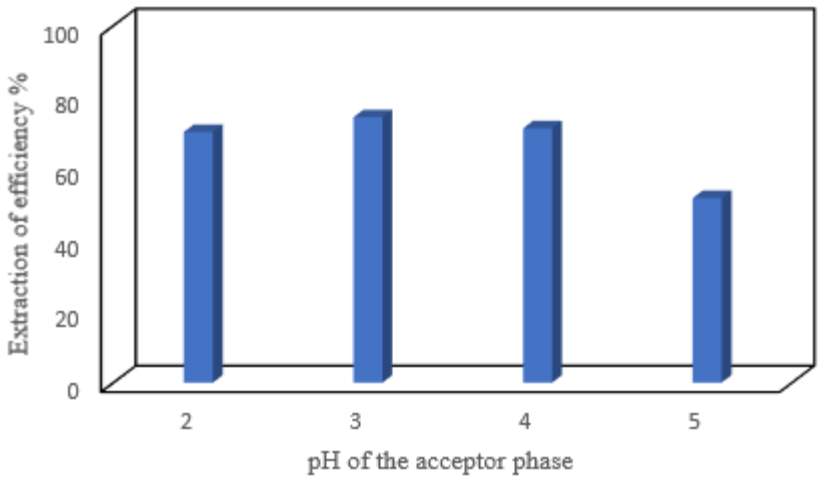

Fig. 5. Effect of the pH of the AP on the extraction efficiency; extraction conditions: concentration of the agarose: 3 % (w/v); Concentration of the acetic acid: 0.2% (w/v); pH of the DP: 7.0; voltage: 60 V; extraction time: 30 min; stirring rate: 900 rpm

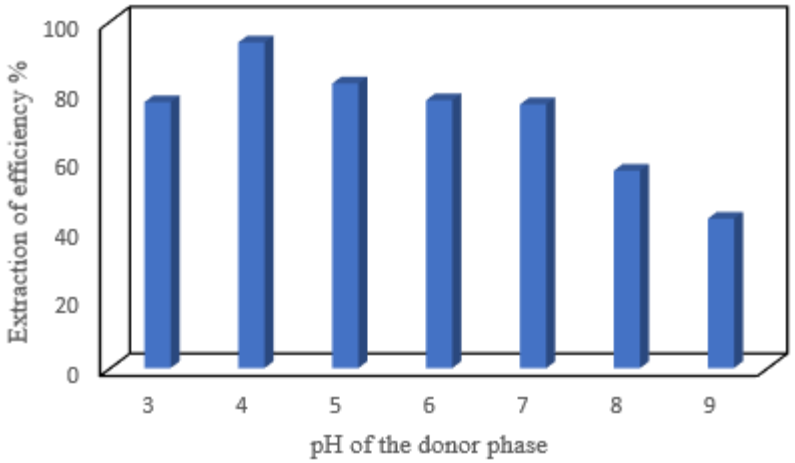

Fig. 6. Effect of the pH of the DP on the extraction efficiency; extraction conditions: concentration of the agarose: 3 % (w/v); concentration of the acetic acid: 0.2% (w/v); pH of the AP: 3.0; voltage: 60 V; extraction time: 30 min; stirring rate: 900 rpm

3.1.4. Effect of sample pH

The sample solution's pH plays an essential role in the AG-EME process because it should be adjusted so that the analyte maintains its ionic form. A range of pH from 3.0 to 9.0 was considered, while the pH of the acceptor phase was set at 3.0. As predicted by the corresponding theoretical

model [36], the maximum response at the most negligible value of χ could be obtained. The results showed that by raising the pH of the donor phase to 4.0 due to lessening of the χ value, extraction efficiency of the drug increased significantly (Fig. 6). As a result, a pH of 4.0 was regarded as the optimum pH for the donor phase.

3.1.5. Effect of applied voltage

In AG-EME, the electrical field stimulates the transfer of analytes through the SLM into the acceptor solution. Thus, mass transfer depends on the applied electrical field, and the extraction efficiency is expected to be enhanced by increasing the applied voltage. This study conducted a series of experiments at various extraction voltages (20–80 V) to estimate the most appropriate voltage (Fig. 7).

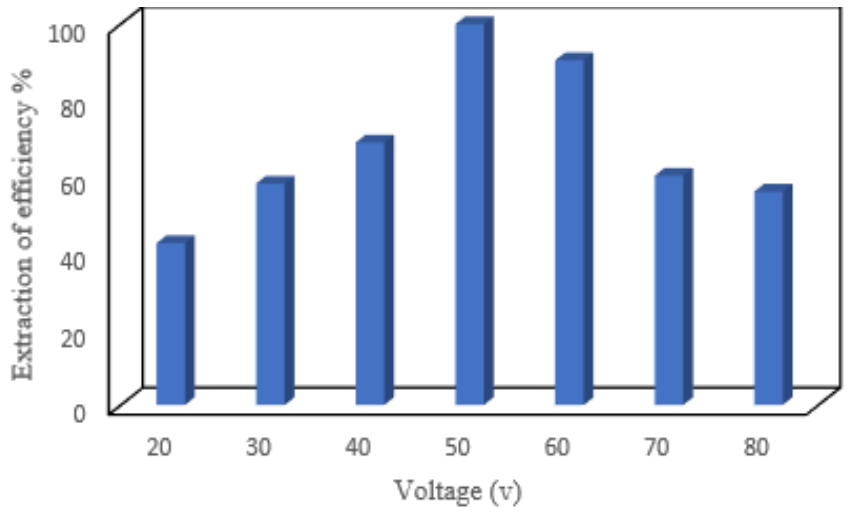

Fig. 7. Effect of the voltage on the extraction efficiency; extraction conditions: concentration of the agarose: 3 % (w/v); concentration of the acetic acid: 0.2% (w/v); pH of the AP: 3.0; pH of the DP: 4.0; extraction time: 30 min; stirring rate: 900 rpm

The results showed that by increasing the voltage from 20 to 50V, the extraction efficiency increased. According to the Nernst–Planck equation [36], by increasing the potential difference between electrodes, an improvement in analyte flux is observed. Nevertheless, a further increase in voltage from 50 to 80 V led to the decreased extraction performance, related to the bubbles formed at the electrodes by electrolysis [37].

Furthermore, the value of electrical current passing through the membrane was continuously measured by applying different voltages. The results showed that the electrical current increased

with higher applied voltage. Relying on this fact that the larger current magnitudes resulted in lower extraction recoveries [38]. Therefore 50 V was chosen as the optimal potential voltage.

3.1.6. Effect of extraction time

Extraction time is also pivotal to determine the total amount of analytes transported from the DP (sample) to the AP [39]. Thus, extraction time was tested in the range of 5−40 min. (Fig. 8), indicates that extraction efficiency improved with an increase in the extraction time to up to 30 min; beyond that, the extraction efficiency decreased. At extraction times longer than 30 min, the agarose gel becomes unstable so that it tends to be destroyed. Also, at long extraction times, the bubbles formed by electrolysis at the electrodes could destabilize the migration of analytes, thus affecting the extraction efficiency negatively [17]. Eventually, 30 min was selected as the optimum extraction time for further analyses.

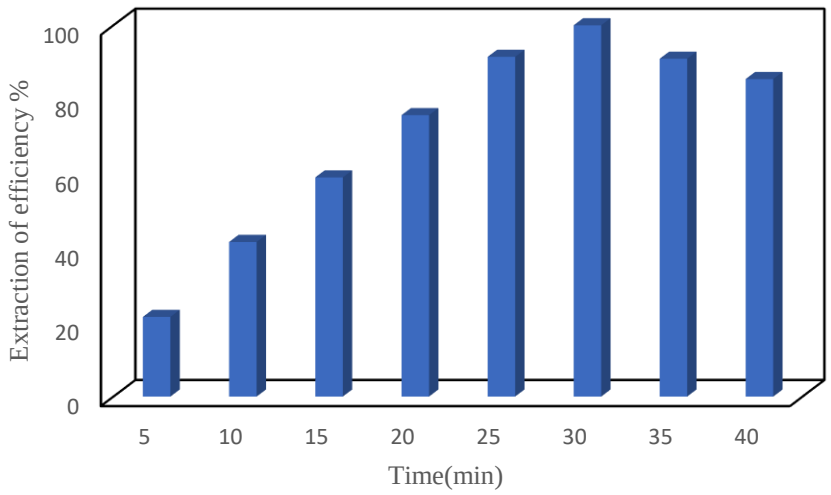

Fig. 8. Effect of the extraction time on the extraction efficiency; extraction conditions: concentration of the agarose: 3% (w/v); Concentration of the acetic acid: 0.2% (w/v); pH of the AP: 3.0; pH of the DP: 4.0; Voltage: 50; stirring rate: 900 rpm

3.1.7. Effect of salt

According to reported articles [40,41], ionic species at high concentration could increase the degree of ionic balance, $\chi 2$, in the system causing the reduction in analyte flux. Ionic balance is the ratio of total ions concentration in donor phase to total ions concentration in acceptor phase [36]. Indeed, with increasing concentration of non-analytes ions, competition between analyte ions and interfering ions for migrating toward the acceptor phase and passing through the membrane rises. In addition, with rising passing ions through the membrane, membrane decomposition and

increase in electrolysis may occur, conflicting undesired effect on efficiency and reproducibility of the extraction process. Using sodium chlorate.001% and 0.4% (w/w) in the the donor phase, this salt effect was studied. It was seen that adding analytical grade NaCl salt, even in small quantities (0.005%), to the donor solution resulted in extremely high electrical currents and decreased extraction efficiencies. Therefore, the experiments were performed in the absence of salt.

3.2. Method validation

In order to estimate the performance of the proposed method, the reproducibility, and limit of detection were studied using standard target analyte solutions in DDW, summarized in Table 1. The calibration curves in the span of 50 to 5000.0 ng mL^{-1} analyte produced excellent value for R^2 (R^2 > 0.998). LOD (SNR =3) and LOQ were found to be 15 and 50 $ngmL^{-1,}$ respectively. An extraction recovery percent of 100% and enrichment factor of 30 were obtained.

Table 1. Figures of merit of the optimized AG-EME method

LOD[a] (ng mL^{-1})	**LOQ[b] (ng ml^{-1})**	**LDR[c] (ng ml^{-1})**	**R^2**	**EF[d]**	**R[e] (%)**
15	50	50-5000	0.998	30	100

[a]Limit of detection
[b]Limit of quantification
[c]Dynamic linear range
[d]Enrichment factor
[e]Recovery

The proposed method for extracting nilotinib anticancer drug has been compared with other methods for extracting and measuring anticancer drugs in Table 2. Ours has a wide dynamic range, low detection limit, high sensitivity, and low volume of sample consumption. High enrichment factor, fairly good precision, facile and rapid makes our developed method for determination of nilotinib to be valid and reliable.

3.3. The analysis of the real sample

To examine the matrix effect and the application of the proposed method in actual samples analyses Table 3. Plasma and urine diluted 1:10 and 1:4 with DDW respectively, their pH was adjusted to 4.0. The drug was spiked to samples in three different concentrations of 100, 500, and 1000 $ngmL^{-1}$, then three replicates of the EME method in both samples, spiked and unspiked, were

conducted under proposed optimum conditions. The extraction percentage was in the acceptable range of 70-97%. These results show that the recoveries are not significantly affected by the matrix effect in real samples.

Table 2. Comparison between AG-EME and reported method for preconcentration and extraction of TKIs

Method	LOD (ng ml^{-1})	LOQ (ng ml^{-1})	Linear range (ng ml^{-1})	EF	Ref.
EME	15	50	50-4000	37	This study
HPLC–MS protein precipitation extraction	20	62.5	-	-	[42]
UHPLC/MS/MS	2500		2500-9000		[43]
HPLC-MS	50		100-12000		[44]

Table 3. Real sample analysis results

Sample	Spiked concentration (ng mL^{-1})	RR[a] ±SD[b]
Plasma	100	83.5 ± 2.97
	500	86.54 ± 5.2
	1000	70.26 ± 2.3
Urine	100	97.67 ± 2.6
	500	89.66 ± 2.77
	1000	75.97 ± 4.9

[a]Relative recovery
[b]Standard deviation

4. CONCLUSIONS

The applicability of agarose gel as a membrane for the extraction of nilotinib anticancer drug in the EME technique was investigated. The developed preconcentration method (AG-EME) is more comfortable to work with than conventional hollow fiber-based EME methods. The other advantages include adjustable membrane thickness, easy fabrication, and facile operation, requiring no organic solvent, and having a tunable acceptor phase volume range. Moreover, it is inexpensive and benign. It also has low LOD and LOQ with and wide dynamic range. Finally, the developed method was successfully used in plasma and urine samples resulting in reasonable recoveries with improved preconcentration and clean-up.

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Declarations of interest: None

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