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Stir bar sorptive extraction and high performance liquid chromatographic determination of carvedilol in human serum using two different polymeric phases and an ionic liquid as desorption solvent

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ABSTRACT

This article presents a method employing stir bar coated with a film of poly (methyl methacrylate/ethyleneglycol dimethacrylate) (PA-EG) and polydimethylsiloxane (PDMS) in combination with liquid desorption (LD) using ionic liquid, followed by high performance liquid chromatography (HPLC) equipped with ultraviolet (UV) detection for the determination of carvedilol in human serum samples. Stir bar sorptive extraction (SBSE) variables, such as desorption and extraction time and temperature, desorption solvent and pH of the matrix were optimized, in order to achieve suitable analytical sensitivity in a short period of time. Also, the concentration effect of 1-methyl-3-octylimidazolium tetrafluoroborate [Omim][BF4] ionic liquid on the efficiency of LD was investigated. A comparison between PA-EG/SBSE and PDMS/SBSE was made by calculating the experimental recovery and partition coefficient (K), where PA-EG phase demonstrated to be an excellent alternative for the enrichment of the carvedilol from serum samples. The effect of [Omim][BF4] on carryover was studied and no carryover was observed. Under optimized experimental conditions, the analytical performance showed excellent linear dynamic range, with correlation coefficients higher than 0.999 and limits of detection and quantification of 0.3 and 1.0 ng mL^{-1}, respectively. Intra- and inter-day recovery ranged from 94 to 103% and the coefficients of variations were less than 3.2%. The proposed method was shown to be simple, highly sensitive and suitable for the measurement of trace concentration levels of carvedilol in biological fluid media.

1. Introduction

Carvedilol, 1-(carbazolyl-4-oxy)-3-[2-(O-methoxyphenoxyethyl)amino]-2-propranol, is a non-selective β-adrenergic antagonist which is universally utilized in the treatment of hypertension, angina and congestive heart failure [1]. Several chromatographic methods have been developed for the determination of carvedilol in biological fluids [2–4]. In the majority of published methods, liquid–liquid extraction (LLE) is used as sample preparation step [5,6]. Nevertheless, this technique is laborious, time-consuming, and uses toxic and expensive solvents. In addition to this technique, different sorptive extraction methods have become popular such as solventless approaches for enrichment purposes namely including solid phase microextraction (SPME) and liquid phase microextraction (LPME).

Recently, stir bar sorptive extraction (SBSE) has been proposed as a novel sample preparation method for the enrichment of priority organic compounds from food, environmental and biomedicinal aqueous matrices at trace level [7–11]. The extraction mechanism and the advantages of SPME and SBSE are identical, whereas the enrichment factor of SBSE is ~100 times higher than that of SPME. In SBSE, a glass tube with a magnetic core, coated with a layer of special polydimethylsiloxane (PDMS) tubing is used to stir aqueous samples. After a certain time, the captured molecules on the bars can be desorbed either thermally for gas chromatography or into a solvent for liquid chromatography.

A problem associated with SBSE is the limitation of the SBSE coatings available; because this analytical approach makes use of PDMS, which are polymeric phases with high affinity for non-polar compounds. To overcome this problem, several authors have proposed new coatings, such as polymeric phase based on polyurethane [12,13], poly(vinylpyridine/ethylene dimethacrylate) [14], poly(phthalazine ether sulfone ketone) [15], polydimethylsiloxane/polypyrrole [16] and poly(methyl methacrylate/ethyleneglycol dimethacrylate) (PA-EG) [17] in order to extract more polar compounds.

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Another limitation of SBSE method is the presence of memory effect (carryover) during desorption step using organic solvent. Recently, room-temperature ionic liquids (ILs) have been used especially as environmentally friendly solvents in different sample preparation methods [18] such as LLE [19,20], LPME [21,22], single drop microextraction (SDME) [23] and SPME [24]. There are several advantages for ILs over organic solvents to be used in sample preparation step. ILs have negligible vapor pressure, wide liquid range, good thermal stability, tunable viscosity and miscibility with water and organic solvents, as well as good solubility and extractability for various organic compounds. On top of that, ILs were used as intermediary solvent in three-phase liquid–liquid–liquid solvent bar microextraction (SBME) method [25] so that it would be expected for them to be used as desorption solvents in SBSE of organic compounds, but as far as we are concerned, there are no reports of this application.

The aim of this work is the application of SBSE using PA-EG and PDMS coatings followed by high performance liquid chromatography (HPLC) with ultraviolet (UV) detection for the determination of carvedilol in human serum matrix. SBSE variables, such as solvent, temperature and time for desorption step and pH of matrix, temperature and time for extraction step were optimized in order to achieve suitable analytical sensitivity in a short period of time. The novelty of this work is the application of imidazolium-based ionic liquid as modifier in desorption solvent and the investigation of its effect on carryover. Optimization of the extraction method was performed by evaluating the effect of [Omim][BF4] concentration on the efficiency of liquid desorption (LD). Finally, the performance of the proposed methodology was evaluated in terms of precision, linearity and detection limit. The recovery yields were investigated and the estimated distribution coefficients (K) of PA-EG and PDMS sorptive phases were compared.

2. Experimental

2.1. Chemicals and materials

Standard racemic carvedilol was obtained from Food and Drug Research Center (Tehran, Iran). HPLC grade solvents used throughout the work were obtained from Caledon (Georgetown, Canada). The 1-methyl-3-octylimidazolium tetrafluoroborate ([Omim][BF4]) ionic liquid was purchased from Kimia Exir Chemical Co. (Tehran, Iran). Tris(hydroxymethyl)aminomethane hydrochloride (Tris–HCL), boric acid, sodium hydroxide, acetic acid, sodium acetate and hydrochloric acid were obtained from Merck (Darmstadt, Germany). The water used throughout the study was purified using a Milli-Q water purification system (Millipore, St. Quentin, France). Drug-free human serum was obtained from the healthy volunteers.

2.2. Instruments and chromatographic conditions

A HPLC system containing a Kontron Model 420 pump, a valve injector Rheodyne (Rohnert Park, CA, USA) equipped with a 20-μL loop and a Kontron Model 432 detector was used with a Chromgate software (Knauer, Berlin, Germany) for data acquisition. The separation was performed on a C_{18} column (3 μm, 4.6 mm i.d. × 250 mm, Knauer, Berlin, Germany). The mobile phase was composed of acetonitrile:acetate buffer (pH 4.0; 0.1 M) (45:55, v/v) being used in an isocratic mode with a flow rate of 1.0 mL min^{-1}. The experiments were carried out at wavelength of 285 nm for the optimization steps and 242 nm for analytical method validation and comparison studies.

2.3. Stir bar sorptive extraction device

The lab-made stir bar coated with PA-EG film was prepared according to our previous work [17]. The procedure of preparation, pretreatment, chemical modifications and coating of the glass bar was described completely in this reference. This prepared device is a 19 mm length glass-encapsulated magnetic stir bar, externally coated with PA-EG. This layer is 1.0 mm thick which approximately corresponds to a volume of 41 μL of PA-EG. In order to compare PDMS and PA-EG results, a PA-EG stir bar with 11 mm length and approximately 21 μL film volume was used. Between successive extractions, the used stir bar was placed in a vial containing 1.0 mL of methanol and treated for 5 min with sonication. Then the solvent mixture was discarded and the procedure was repeated three times. The stir bar was dried in a desiccator at room temperature.

The commercial Twister stir bars (Gerstel GmbH, Mulheim an der Ruhr, Germany) are coated with 10 mm in length and 0.5 mm film thickness of PDMS which corresponds to a volume of 24 μL. Prior to the first use, the stir bar was placed into a vial containing an acetonitrile:methanol solution (80:20, v/v) and conditioned for 24 h under agitation. Between successive extractions, the used stir bar was cleaned in methanol for 30 min at 50 °C, under magnetic stirring rate of 1200 rpm, followed by a drying step using a lint-free tissue.

2.4. Preparation of standard solutions

A 1 mg mL^{-1} stock solution of carvedilol was prepared in methanol. Carvedilol working standard solutions were prepared by diluting the stock solution by water to a proper volume. At the optimization step, the experiments were carried out with an aqueous solution spiked by carvedilol at 500 ng mL^{-1} concentration level. The spiked serum samples by therapeutic level of carvedilol were used for analytical method validation and for efficiency comparison between two different sorptive phases.

2.5. SBSE procedure

The SBSE procedure was carried out by introducing either the PA-EG or the PDMA stir bars into 10 mL screw-cap vials and throughout the experiment these were stirred at constant speed (1000 rpm). At the extraction step, 5 mL of sample was stirred for a selected period of time at controlled temperature. At the desorption step, the stir bar was removed using a clean tweezers, rinsed slightly with MilliQ water (1.0 mL), dried with lint-free tissue, and placed in a glass vial containing 350 (150 μL at comparison step) and 150 μL of the desorption solvent for PA-EG and PDMS stir bars, respectively ensuring the total immersion. Desorption was performed by ultrasonic treatment during a selected period of time at controlled temperature. After desorption process, the stir bar was removed by means of a magnetic rod and the solvent was evaporated to dryness. The dry residue was re-dissolved in 150 μL of the mobile phase, and 20 μL of this extract was injected into the HPLC system.

Several parameters that could influence the extraction efficiency of PA-EG and PDMS stir bars were investigated by coupling SBSE to HPLC-UV. To obtain the best desorption condition: desorption solvent (acetonitrile, mobile phase, methanol), desorption temperature (30 and 45 °C) and desorption time (15, 20 and 30 min) were all individually evaluated. In order to optimize the extraction step, the pH of the matrix was assessed using different pH values from 3.7 to 10.0 (buffer solutions, 0.05 mol L^{-1}). Extraction temperature (30, 40, 50, 60, 70 °C), extraction time (30, 45, 75, 100, 120 min) and ionic strength of the matrix solution (NaCl addition) were also evaluated. Finally, [Omim][BF_4] ionic liquid was used as modifier in desorption solvent (methanol) for the first time and the

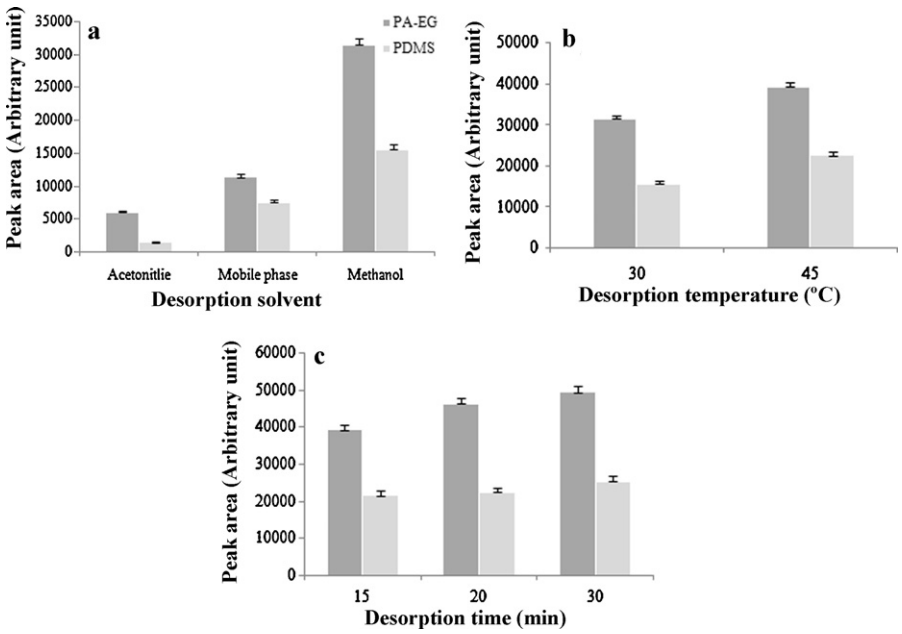

Fig. 1. The effect of (a) desorption solvent, (b) desorption temperature and (c) desorption time on the extraction efficiency of carvedilol (expressed as peak area).

effect of its concentration (0.02–0.4 M) on extraction recovery and carry over was investigated.

2.6. Method validation

For quantitative analysis, 0.5 mL of serum samples spiked by drug standard solutions at concentrations in therapeutic level were diluted with 4.5 mL of buffer solution in a glass vial and extracted as described in previous section. Calibration curve was prepared using PA-EG sorptive phase with 7 calibrators over a concentration range of 1.0–120.0 ng mL^{-1} for carvedilol in serum matrix and constructed by plotting peak areas against the respective concentrations. The linearity was evaluated by the least-squares regression method, which was used to calculate the R^2-value, *y*-intercept, and slope of the regression line. The limit of quantification (LOQ) was calculated as the lowest concentration analyzed.

Accuracy and precision of the method were determined for the drug through analyzing standard quality control (QC) samples at three concentration levels of carvedilol (35, 65 and 85 ng mL^{-1}). Accuracy was established by the recovery percent values. Precision was established by three replicate injections of the standard QC samples at each concentration level for the intra-day precision and on 3 days for the inter-day precision. The precision was expressed in terms of coefficient of variation (CV, %) of the recoveries.

3. Results and discussion

3.1. Optimization of the SBSE procedure

During the development of the present methodology, in order to obtain the highest extraction efficiency for carvedilol using PA-EG and PDMS sorptive phases, factors affecting desorption step including solvent, temperature and time were investigated. Also, the extraction variables such as pH of the matrix, temperature, time and ionic strength were evaluated so as to reach the drug partition equilibrium in shorter analyses times, and to obtain adequate sensitivity to work in therapeutic levels. For both stir bars, the sample volume, stirring speed and ultrasonic power were maintained constant during the optimization process.

3.1.1. Optimization of the desorption condition

The obtained results for optimization process of desorption step using two sorptive phases are shown in Fig. 1. Performing a complete back-extraction process depends on the different parameters especially desorption solvent which must have enough power to promote the best stripping of the target compounds from the polymeric phases, and can be accelerated through ultrasonic treatment [7]. During the present study, a few solvents such as acetonitrile, mobile phase solution (acetonitrile:sodium acetate, 45:55, v/v) and methanol were studied in order to assess the desorption efficiency. The data (Fig. 1a) showed that the best efficiency (expressed as peak area) is obtained when methanol is used as desorption solvent for both of the sorptive phases, and this can be related to its polar protic characteristic.

Probing the temperature effect at desorption step, as illustrated in Fig. 1b, when the temperature was increased from 30 °C to 45 °C, the desorption efficiency also raised and therefore 45 °C was selected as the optimum desorption temperature. Finally, desorption time was also evaluated for the target compound by studying different sonication periods. The desorption time profile is shown in Fig. 1c. The best desorption times were obtained at 20 and 15 min for PA-EG and PDMS sorptive phases, respectively.

3.1.2. Optimization of the extraction condition

The characteristics of the sample matrix, such as its pH is an important parameter that may have a substantial effect on the SBSE efficiency. The effect of sample pH on the extraction efficiency of carvedilol was investigated in the range of 3.7–10.0. As shown in Fig. 2a the extraction efficiency improved significantly when the pH value increased from 3.7 to 8.5, but decreased when the pH values were altered from 8.5 to 10.0 for both of the sorptive phases. As an explanation of the above changes, carvedilol is definitely a basic compound which means that its nonionic form occurs in basic media in a way that it can be extracted by the polymeric phases [26]. Therefore, setting the pH value of matrix at 8.5 was recommended for analyzing carvedilol in serum matrix with SBSE.

The extraction temperature profile is shown in Fig. 2b. As it is clearly observed, the extraction efficiencies are improved with the increase of extraction temperature. By using the same extraction time period, the sorption-time profile should be closer to that of the

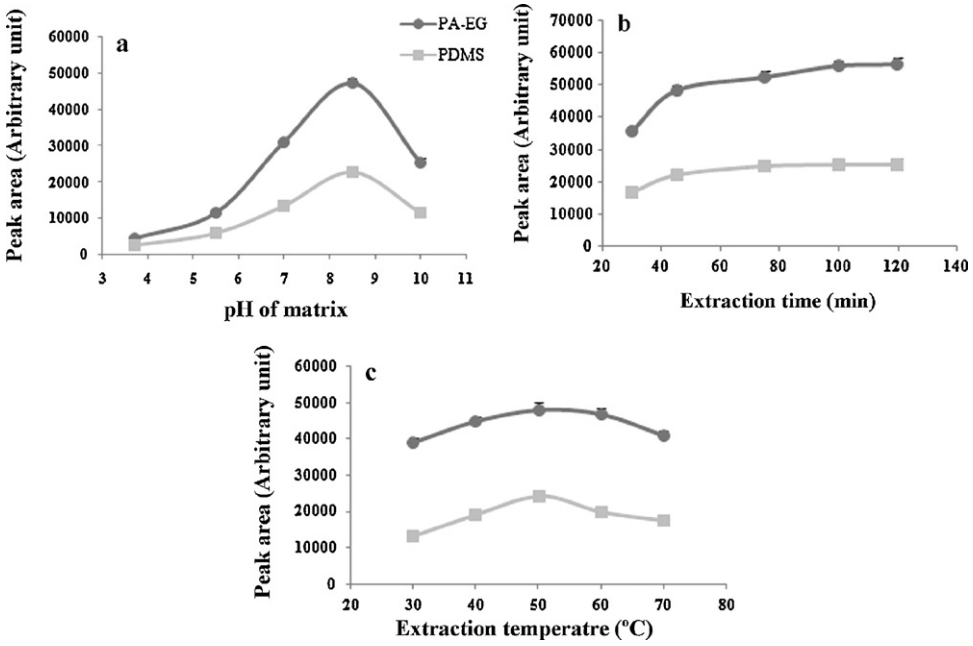

Fig. 2. The effect of (a) pH of matrix, (b) extraction time and (c) extraction temperature on the extraction efficiency of carvedilol (expressed as peak area).

equilibrium and thus more material would be extracted. However, the SBSE efficiency for carvedilol, decreased above 50 °C because of a decline in sorption distribution coefficient between the coating and the sample. Thus, 50 °C was selected as the optimum temperature for both sorptive phases.

The extraction time is a very important parameter because it influences the partition of the solutes between the matrix and the polymer [11]. Based on the obtained results (Fig. 2c), the equilibrium times were established after 100 min and 75 min for PA-EG and PDMS stir bars, respectively. Balancing the sensitivity on one hand and the time consumed on the other hand, extraction time of 45 min was selected for further studies of both sorptive phases.

The addition of NaCl increases the ionic strength which leads to a decrease in the amount of the extracted carvedilol using both PA-EG and PDMS sorptive phases. This phenomenon was also reported by the other authors [27,28] and occurres probably due to an increase in the electrostatic interactions between the drug and the salt ions in solution. This in turn decreases the ability of the drug to be absorbed into the extraction phases, causing a reduced recovery. Therefore, all the subsequent experiments were conducted using samples without NaCl.

3.1.3. *The effect of [Omim][BF_4] ionic liquid on extraction efficiency*

The ionic liquid properties encouraged us to examine [Omim][BF_4] as modifier for desorption solvent (methanol) in SBSE method for the first time. The obtained results showed that the recovery of carvedilol increases significantly when [Omim][BF_4] is added at concentration levels up to 0.1 M and remains constant at higher concentrations.

Final comparison using PA-EG and PDMS sorptive phases was carried out on serum samples spiked at the 300 ng mL^{-1} concentration level of carvedilol under optimized conditions. Fig. 3 shows the obtained results using methanol with and without [Omim][BF_4] ionic liquid as modifier at different concentration levels in desorption solvent. As it is apparent, the peak area when using PDMS coating and methanol as desorption solvent is the lowest of all. Moreover PA-EG sorptive phase that was used to desorb carvedilol using methanolic solution of 0.1 M ionic liquid can provide the greatest peak area and consequently the least LOD value.

In order to obtain carryover values of each sorptive phase and desorption solvent, an stir bar already used for the extraction of a spiked serum sample (300 ng mL^{-1}) of carvedilol was desorbed again. The obtained chromatograms using PA-EG sorptive phase are shown in Fig. 4. Our results were shown that for both of the sorptive phases when [Omim][BF_4] methanolic solution was used as desorption solvent, there was no evidence of carryover, ensuring the effectiveness of the procedure. But when using methanol as desorption solvent for both PA-EG and PDMS sorptive phases carryover was observed (about 11% of initial desorption step).

3.2. *PA-EG stir bar versus commercial PDMS stir bar*

In order to calculate the partition coefficient of carvedilol between the sorbent phase (either PA-EG or PDMS) and water, various concentrations of carvedilol (1–10 μg mL^{-1}) were directly injected to HPLC, the calibration curve was constructed and the corresponding regression equation with the correlation coefficient higher than 0.999 was obtained. Then, the amount of the extracted materials from each sorptive phase were calculated through placing peak area of extracted serum sample containing 1.5 μg of carvedilol (300 ng mL^{-1}) in direct regression equation. Finally, the experimental recovery was calculated as the ratio of the obtained amount of

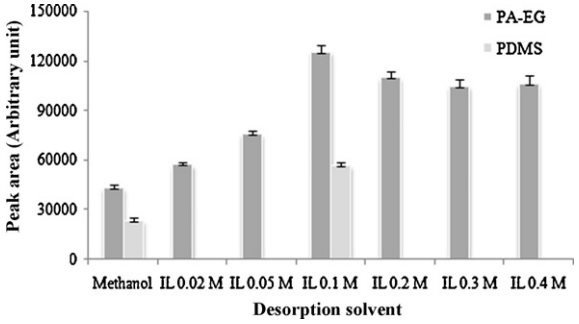

Fig. 3. The comparison of carvedilol extraction efficiency for spiked serum sample at concentration level of 300 ng mL^{-1} using PA-EG and PDMS sorptive phases and [Omim][BF_4] ionic liquid (IL) as modifier in desorption solvent.

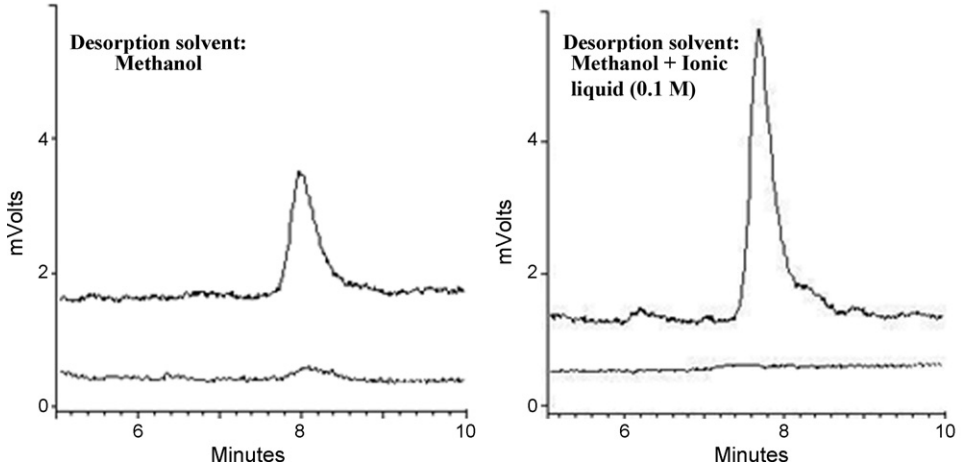

Fig. 4. The obtained chromatograms from spiked serum sample at 300 ng mL^{-1} concentration level of carvedilol using PA-EG/SBSE method after the first (up) and the second (down) desorption step.

Table 1
Experimental recoveries and estimated partition coefficients (K) for the carvedilol (300 ng mL^{-1}) in serum sample obtained by PA-EG/SBSE and PDMS/SBSE using methanol with or without ionic liquid as desorption solvent followed by HPLC-UV, under optimized experimental conditions.

Sorptive phase	Desorption solvent	Initial amount of carvedilol (μg)	Obtained extracted amount of carvedilol (μg) ± SD[a] (n = 3)	Average experimental recovery (%)	K[b]
PA-EG	Ionic liquid solution	1.50	1.39 ± 0.04	93	3162
PA-EG	Methanol	1.50	0.52 ± 0.04	35	–[c]
PDMS	Ionic liquid solution	1.50	0.71 ± 0.04	47	185
PDMS	Methanol	1.50	0.33 ± 0.04	22	–[c]

[a] Standard deviation.
[b] Partition coefficient.
[c] Desorption process was incomplete.

the extracted materials over the known amount of carvedilol in serum sample ($m_{\text{sorbent phase}}/m_0$).

Based on the SBSE theory [7], factors regarding recovery ($m_{\text{sorbent phase}}/m_0$), partition coefficient between the sorbent phase and water ($K_{\text{sorbent phase/w}}$) and phase ratio ($\beta = V_w/V_{\text{sorptive phase}}$) are related together according to the following equation (Eq. (1)):

$$\frac{m_{\text{sorbent phase}}}{m_0} = \frac{(K_{\text{sorbent phase/w}})/\beta}{1 + (K_{\text{sorbent phase/w}}/\beta)} \quad (1)$$

where the sorbent phase is PA-EG or PDMS and w is water. Based on this equation, it was possible to estimate the K values for the carvedilol by the use of the experimental recoveries achieved only when the ionic liquid methanolic solution was used as desorption solvent. Because under this condition, no carryover effect was observed and back-extraction process was carried out completely. The volume of aqueous phase was 5 mL (V_W) and the volume of sorptive phases ($V_{\text{sorbent phase}}$) were 21 μL and 24 μL for PA-EG and PDMS, respectively. The obtained amount of the extracted materials, experimental recovery and calculated partition coefficient values of carvedilol are shown in Table 1. The figures of merit in this table clearly indicate the superiority of PA-EG over PDMS. Also, addition of ionic liquid to desorption solvent improved the figures of merit of SBSE method for the extraction of carvedilol from serum matrix.

3.3. Method validation

Under the optimum conditions, a calibration graph was obtained through extraction of spiked serum samples ranging from 1.0 to 120.0 ng mL^{-1} using PA-EG SBSE and 0.1 M ionic liquid methanolic solution as desorption solvent according to the procedure described in Section 2.

The values of the slope, intercept and correlation coefficients for linear calibration plot are 311, 3120 and 0.999, respectively.

Table 2
Intra- and inter-day accuracy and precision for quality control (QC) samples of carvedilol in serum sample.

QC[a] samples	Added concentration a (ng mL^{-1})	Obtained mean concentration (ng mL^{-1}) (n = 3)	Accuracy (recovery, %)	Precision (CV[b], %)
Intra-day (n = 3)				
High	85.0	87.5	103	2.4
Middle	65.0	65.1	100	2.8
Low	35.0	32.4	94	3.2
Inter-day (n = 3)				
High	85.0	86.1	101	2.1
Middle	65.0	67.4	103	3.1
Low	35.0	33.7	97	3.2

[a] Quality control.
[b] Coefficient of variation.

The standard error (SE) of the slope and intercept were 4 and 305, respectively. Furthermore, the lowest experimental concentration that was analyzed in serum matrix (1.0 ng mL^{-1}) is introduced as limit of quantification (LOQ). The theoretical limit of detection (LOD) was obtained by 0.3 ng mL^{-1} according to equation of LOQ = 3.3 LOD.

The intra-day accuracy and inter-day accuracy were calculated from the QC samples for carvedilol at three concentration levels. The intra-day precision was evaluated by performing three determinations ($n = 3$) at the same concentration in a day under the same experimental conditions, and the inter-day precision was evaluated by comparing the assays on three different days. The obtained results are summarized in Table 2. Results indicate that good recoveries were obtained for assay (94–103%) with the coefficient of variation less than 3.2%.

4. Conclusion

In the present work, we applied PA-EG polymeric phase which was introduced in our previous work as a novel coating for SBSE, for the extraction and LD/HPLC-UV determination of carvedilol in human serum sample and its comparison with PDMS-coated stir bar. The application of ionic liquid as modifier in desorption solvent was also investigated for the first time and methanolic solution of [Omim][BF_4] proved to be the best solvent for desorption step under sonification treatment, ensuring the elimination of carry-over.

The experimental recoveries were obtained and employed for estimation of partition coefficient values. They clearly indicated that carvedilol has a better affinity for PA-EG phase than PDMS. Under optimized experimental conditions, remarkable recovery, repeatability, linear dynamic range and detection limit at therapeutic level were attained. The PA-EG/SBSE/HPLC-UV method with liquid desorption using [Omim][BF_4] ionic liquid is highly sensitive, precise and accurate, so that allowing the quantification of carvedilol in the human serum. Thus, the proposed method can be a useful tool for therapeutic drug monitoring.

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