



# Air-assisted liquid–liquid microextraction using floating organic droplet solidification for simultaneous extraction and spectrophotometric determination of some drugs in biological samples through chemometrics methods



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## ABSTRACT

An air assisted liquid–liquid microextraction by applying the solidification of a floating organic droplet method (AALLME-SFOD) coupled with a multivariate calibration method, namely partial least squares (PLS), was introduced for the fast and easy determination of Atenolol (ATE), Propranolol (PRO) and Carvedilol (CAR) in biological samples via a spectrophotometric approach. The analytes would be extracted from neutral aqueous solution into 1-dodecanol as an organic solvent, using AALLME. In this approach a low-density solvent with a melting point close to room temperature was applied as the extraction solvent. The emulsion was immediately formed by repeatedly pulling in and pushing out the aqueous sample solution and extraction solvent mixture via a 10-mL glass syringe for ten times. After centrifugation, the extractant droplet could be simply collected from the aqueous samples by solidifying the emulsion at a lower than the melting point temperature. In the next step, analytes were back extracted simultaneously into the acidic aqueous solution. Derringer and Suich multi-response optimization were utilized for simultaneous optimizing the parameters of three analytes. This method incorporates the benefits of AALLME and dispersive liquid–liquid microextraction considering the solidification of floating organic droplets (DLLME-SFOD). Calibration graphs under optimized conditions were linear in the range of 0.30–6.00, 0.32–2.00 and 0.30–1.40  $\mu\text{g mL}^{-1}$  for ATE, CAR and PRO, respectively. Other analytical parameters were obtained as follows: enrichment factors (EFs) were found to be 11.24, 16.55 and 14.90, and limits of detection (LODs) were determined to be 0.09, 0.10 and 0.08  $\mu\text{g mL}^{-1}$  for ATE, CAR and PRO, respectively. The proposed method will require neither a highly toxic chlorinated solvent for extraction nor an organic dispersive solvent in the application process; hence, it is more environmentally friendly.

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## 1. Introduction

Biological samples include many analytes and impurities at low level. In biological samples, if drugs are low level, they cannot be detected by simple spectrophotometric method. Therefore, spectrophotometric method should be coupled with sample preparation. The typical extraction and preconcentration methods such as liquid–liquid extraction (LLE) [1] and matrix solid-phase dispersion [2] require considerable time for extracting target analytes into sorbents or an organic phase. Therefore, a fast, efficient, and sensitive analytical method would be required. In 2006, the dispersive liquid–liquid microextraction (DLLME) was introduced by Rezaee et al. as a new method for sample preparation [3]. This method affords high values of enrichment factor due to the large extraction solvent contact area. As a disperser, the need for

chlorinated solvents is the main drawback of DLLME [4]. Air-assisted liquid–liquid microextraction (AALLME) was then developed by Farajzadeh and Mogaddam as a novel simple microextraction technique without dispersive solvent [5]. In this approach, the aqueous sample solution mixture and extraction solvent are repeatedly pulled in and pushed out in a conical test tube using a syringe [5–7]. In previous work, we have developed a two steps AALLME to extraction and simultaneous spectrophotometric determination of some preservatives [6]. In a modified AALLME method, the easy and reliable extraction phase collection is possible without a special extraction tube based on the solidification of floating organic droplets (AALLME-SFOD) [8]. It is crucial to investigate low density and low toxic solvent usage which can be easily collected in AALLME-SFOD method that combines both AALLME and DLLME-SFOD advantages. In the AALLME-SFOD method, a low toxic and low density solvent with a melting point about room temperature is used as an extraction solvent. After centrifugation, the extractant droplet is floated on top of the aqueous solution and could be simply

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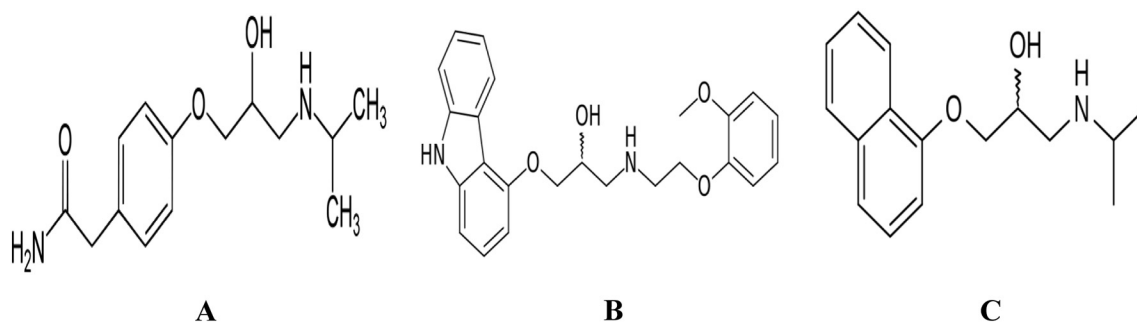


Fig. 1. Chemical structure of the studied compounds: (A) Atenolol, (B) Carvedilol and (C) Propranolol.

collected using solidification at temperatures lower than melting point [8–11].

$\beta$ -Adrenergic blockers show a crucial class of drugs used worldwide for treating different cardiac diseases [12]. Atenolol (Fig. 1A), Carvedilol (Fig. 1B), and Propranolol (Fig. 1C) are  $\beta$ -blocker group forming antihypertensive drugs widely used to treat hypertension and some other disorders [13]. The analysis of  $\beta$ -adrenergic blockers in biological samples such as urine and human plasma provides beneficial data for clinical researches. To perform these studies, specific analytical methods which are efficient, effective, reproducible, and selective would be necessary. Several methods are utilized for sample preparation and determinations of  $\beta$ -blockers [2,14,15]. Chromatographic and capillary electrophoresis methods are beneficial methods employed for determination of  $\beta$ -blockers [12,16–19]. Moreover, spectrophotometric method is considered as one of the bests because of the common availability of the instrumentation and the simplicity of procedures [20–24]. The main disadvantage of this technique is low selectivity which can be attributed to broad band overlapped spectra of species; this may inhibit the determination process. To overcome this problem, one can apply a multivariate calibration method such as partial least squares (PLS), so as to undertake quantitative simultaneous determinations.

Response surface methodology (RSM) is a combination of mathematical and statistical methods beneficial for analyzing and modeling the problems. These methods allow the development of mathematical models that permit assessment of the relevance in addition to the statistical significance of the factor effects being studied, as well as evaluating the interaction effects between the factors. The main objective in RSM is to response surface optimization that is affected by different process parameters. Moreover, the relationship between the obtained response surfaces and the controllable input parameters is quantified by RSM [25]. The procedure for designing response surface methodology is as: (i) design of experiments considering the response of interest, (ii) mathematical model development with the best fittings, (iii) finding the optimum of experimental parameters producing an optimum response value and (iv) showing the interactive and direct effects of process parameters using surfaces or contour plots. Multi-response optimization (MRO) is a branch of response surface methodology that can be applied in modeling and designs optimization. MRO has become a progressively important issue in complex processes, particularly in situations where more than one correlated response must be assessed simultaneously [26–28]. The desirability function approach is one of the most extensively applied methods for optimizing multiple response processes. The goal in desirability function approach is the finding of conditions where the independent variables leading to optimal or nearly response variables optimal values. In this approach, multi responses are condensed to univariate response by linear combination of them. A useful class of desirability function approach was introduced by Derringer and Suich [29]. This approach has the following main steps: i) The experiments are designed using central composite of RSM. ii) The experiments are performed and response models are fitted to all responses. iii) The overall desirability is maximized with respect to the controllable factors.

The purpose of the present study is to use AALLME-SFOD method before simultaneously determining mixtures of Atenolol, Propranolol and Carvedilol via UV–vis spectrophotometry. In the suggested method, two steps were considered for the extraction method. In the first step, analytes from neutral aqueous solution were extracted to organic solvent, using AALLME-SFOD, and in the next step analytes were back extracted simultaneously into the acidic aqueous solution. In this method 1-dodecanol was utilized as the extraction solvent. The high absorption signal of 1-dodecanol was the primary reason to perform this back extraction step. PLS regression was applied for simultaneous quantitative analytes determination. Central composite design (CCD) was used as the experimental design and analysis, then Derringer and Suich method was applied as multi response optimization method to get the best or nearly the best conditions of controllable factors. The presented method was tested for human plasma and urine samples analysis.

## 2. Experimental

### 2.1. Apparatus and Software

Absorbance measurements were performed on a double beam UV–vis spectrophotometer model UV-1601 PC (SHIMADZU, Kyoto, Japan) using 700  $\mu$ L quartz cells with 10 mm path length. Measurements of pH were done with a Metrohm 713 pH-meter using a combined glass electrode (Herisau, Switzerland). Different experimental parameters optimization and PLS were performed with Minitab Statistical Software 14.

### 2.2. Chemicals and Reagents

All experiments were performed with analytical grade chemicals and doubly distilled water (Ghazi Company, Tabriz, Iran). Carvedilol, Propranolol and Atenolol with 98% purity were obtained from Sigma-Aldrich (Denmark). Ba (OH)<sub>2</sub> and ZnSO<sub>4</sub> were kindly supplied by Sigma Aldrich (Denmark) with certified purities of 98% and 99%, respectively. 1-dodecanol as tested extraction solvents and other compounds including sodium chloride, hydrochloric acid and sodium hydroxide were provided from Merck (Darmstadt, Germany).

Using the blank solution as a reference, all spectral measurements were carried out. The analyte-free aqueous solution was extracted using the proposed procedure with optimum parameters and used as reference.

### 2.3. Standard Solutions

Stock standard solutions of Carvedilol, Propranolol and Atenolol were prepared daily in methanol of 50 mg L<sup>-1</sup> concentration. Working standard solutions and more dilute solutions of the three components were made by several dilutions using double distilled water each in the different concentrations of the analyte. These solutions were kept in a refrigerator at 4 °C in the dark. The Ba(OH)<sub>2</sub> and ZnSO<sub>4</sub> solutions

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