Analytica Chimica Acta 924 (2016) 86–98

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Computational design and multivariate optimization of an electrochemical metoprolol sensor based on molecular imprinting in combination with carbon nanotubes

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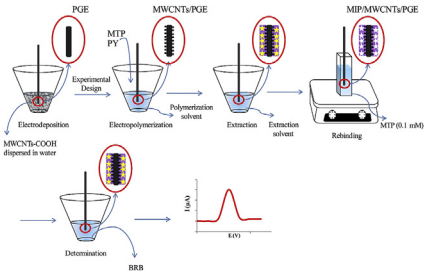
HIGHLIGHTS

- DFT method was used to select functional monomers of MIP by calculating ΔE.
- Experimental design was used for the optimization of MIP process.
- A MIP/MWCNTs/PGE sensor for MTP was fabricated by electro-polymerizing of PY.
- The sensor was used for analysis of MTP in serum and pharmaceutical samples.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 6 February 2016
Received in revised form
9 April 2016
Accepted 14 April 2016
Available online 21 April 2016

Keywords:
Molecularly imprinted polymer
Electrochemical sensor
Metoprolol
Multivariate optimization
Density functional theory
Carbon nano-tubes

ABSTRACT

This work describes the development of an electrochemical sensor based on a new molecularly imprinted polymer for detection of metoprolol (MTP) at ultra-trace level. The polypyrrole (PPy) was electrochemically synthesized on the tip of a pencil graphite electrode (PGE) which modified whit functionalized multi-walled carbon nanotubes (MWCNTs). The fabrication process of the sensor was characterized by cyclic voltammetry (CV) and the measurement process was carried out by differential pulse voltammetry (DPV). A computational approach was used to screening functional monomers and polymerization solvent for rational design of molecularly imprinted polymer (MIP). Based on computational results, pyrrole and water were selected as functional monomer and polymerization solvent, respectively. Several significant parameters controlling the performance of the MIP sensor were examined and optimized using multivariate optimization methods such as Plackett–Burman design (PBD) and central composite design (CCD). Under the selected optimal conditions, MIP sensor was showed a linear range from 0.06 to 490 μmol L^{-1} MTP, a limit of detection of 2.88 nmol L^{-1}, a highly reproducible response (RSD 3.9%) and a good selectivity in the presence of structurally related molecules. Furthermore, the applicability of the method was successfully tested with determination of MTP in real samples (tablet, and serum).

1. Introduction

One class of drugs, which aids in preventing cardiac attack, is β-blockers. β-Blockers are clinically important drugs and are used in

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http://dx.doi.org/10.1016/j.aca.2016.04.017
0003-2670/

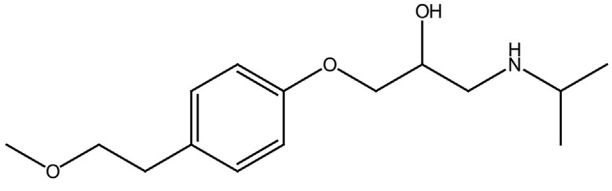
the treatment of disorders, such as hypertension, angina pectoris, myocardial infarction, arrhythmia, and other related diseases [1,2]. Metoprolol (MTP), 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol (Scheme 1), belongs to the class of β-blockers. It is so sensitive that even a small oral dose of the drug gives sufficient blockade and an overdose of such β-blocker can lead to bradycardia, bronchospasm, hypoglycemia, fatigue, hypotension, and provocation of cardiac failure [3]. Because of sedative effect of MTP, the International Olympic Committee [4] has added this drug to the list of forbidden drugs. Therefore, development of a simple, rapid, sensitive, and selective analytical method for MTP determination in both tablets and biological fluids is highly desirable.

Various analytical methods have been described for MTP quantification in pharmaceutical dosage forms as well as in biological fluids individually or simultaneously with other drugs. These methods consist of spectrophotometry [5,6], atomic absorption spectroscopy and spectrophotometry [7], capillary electrophoresis [8], flow-injection chemiluminescence [9], and various techniques of chromatographic methods [10–29].

Although these methods have been successfully employed, they require long and tedious steps for the sample pretreatment. Since these techniques need relatively expensive instrumentation and running costs, the use of simpler, faster, and low cost, but still sensitive method to determination of MTP in both tablets and biological fluids is of great importance. Electrochemical techniques can be an interesting alternative.

Although electrochemical methods have been widely demonstrated to be greatly useful for the detection of both environmentally and biologically relevant analytes [30] due to several related advantages as low cost and simplicity, reduced time analysis, possibility of in-situ measurements, there are only a few works available on the electrochemical detection of MTP [31–33]. These electroanalytical methods were quite sensitive, but some of them showed poor selectivity. Furthermore, MTP was prescribed with other drugs simultaneously, and its detection should be carried out selectively in biological fluid samples and pharmaceuticals. Therefore, it is necessary to seek a facile, cheap, stable, and highly selective method to determine MTP in biological samples. This problem can be solved by adapting a high selective chemical interface when preparing sensors. MIPs revealed to be good candidate as selective sorbent materials for these purposes and can be used in sample pretreatment protocols for the analysis of MTP in real samples matrix.

In order to prepare MIPs, cross-linkers and functional monomers are polymerized with template molecules by covalent and non-covalent methods. After polymerization, the template molecules are removed, providing binding sites ideally complementary in size, shape, and functionality to the template, so that the template preferentially rebinds to the cavity [34–38]. Electrochemical methods, especially electrochemical MIP based sensors, have attracted more attention in recent years for reasons of their recognition properties, simplicity, high sensitivity, good stability, high selectivity, low cost, fast response, and real time detection [39–42].



Scheme 1. Chemical structure of MTP.

Tehrani et al. (2010) reported a PVC membrane based on MTP–MIP coated directly on graphite electrode for determination of MTP in real samples (tablets, human urine, and plasma) [43]. This kind of potentiometric sensors achieved wide linear range (2.0×10^{-7}–8.0×10^{-3} M), but the LOD for sensor exceed 1.26×10^{-7} M. In the other hand, the selectivity of reported sensor was not investigated in present of compounds that have similar molecular structure to MTP or other drugs that prescribed with MTP simultaneously.

Electropolymerization can be used to obtain thin MIP films, but the sensitivity of these sensors is limited. The amount of effective imprinted sites can be increased by increasing the thickness, but this can lead to slow diffusion of the analytes to the recognition sites and inefficient communication with the transducers [44]. This drawback can be overcome by using nanomaterials. Integration of nanomaterials into the sensing systems has several advantages, such as increase of the surface area, mass transport, conductivity and improving the signal-to-noise ratio [39]. Carbon nanostructures are ideal for sensor preparation for molecularly imprinted electropolymer films [45].

Formation of a complex between the template molecule and functional monomers by self-assembly process in polymerization solvent is the first step in the preparation of MIPs. The most advanced approaches available for the selection of appropriate functional monomers and polymerization solvents include combinatorial and computational methods. In combinatorial approaches, it is needed to synthesize a wide range of polymers with trial and error, and during experiments, the hazardous compounds are so harmful for people's health [46]. Besides, in the synthesis of MIPs, most of the standard templates are expensive. Due to this limitation, the use of computational methods as an alternative approach for the rational design of MIPs is very interested. In this regards the density functional theory (DFT) method was widely used to select functional monomers or porogenic solvents among a set of traditional chemicals by calculating the energy difference (ΔE) [47].

One of the major problems in MIP design is the choice of optimal conditions for the development of MIPs. This is mainly because of the need to select and optimize a multitude of variable parameters affecting the polymer synthesis, template extraction, analyte rebinding and analytical determination. Experimental designs are being frequently used for the optimization of different operating conditions of MIP processes [48]. Theoretically, a number of factors have simultaneous effect on a MIP process. Multivariate optimization methods have several advantages over univariate (one-at-a-time) method. One-at-a-time method requires greater amounts of reagent and time to be accomplished. In addition, possible interactions among variables are not considered. In contrast, the multivariate optimization methodology considers the possible interactions and is faster, more effective, and economical. Simultaneous optimization of several variables is also possible in this approach [48,49]. Among the experimental design methodologies, Plackett–Burman employs a design, which allows screening the largest number of effective factors with the least number of observations. In addition, CCD as a response surface methodology (RSM) was useful in modeling and optimizing the effective parameters on the process performance.

Considering the advantages of the electrochemical method, the molecular imprinting technique, electrode surface modification, computational methods, and experimental design, the key idea of the present work is to construct an electrochemical sensor with high sensitivity and selectivity for MTP detection in real sample matrix.