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Molecularly imprinted polymers based biomimetic sensors for mosapride citrate detection in biological fluids

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ABSTRACT

Computational modeling was applied to study the intermolecular interactions in the pre-polymerization mixture and find a suitable functional monomer to use in the design of a new molecularly imprinted polymer (MIP) for mosapride citrate which is considerably a large molecule (as the citrate ion is also included in calculations as it has centers that can take part in interaction with monomer via hydrogen bonding). Based on these calculations, methacyrlic acid (MAA) was selected as a suitable functional monomer. Mosapride citrate selective MIP and a non-imprinted polymer (NIP) were synthesized and characterized using FTIR, TGA and SEM and then incorporated in carbon paste electrodes (CPEs). The designed modified sensor revealed linear responses in the ranges of 1×10^{-4}–8×10^{-7} and 8×10^{-7}–8×10^{-8} mol L^{-1} with a limit of detection (LOD) of 2.6×10^{-8} mol L^{-1}. The results of the sensor exhibited high selectivity over interfering species and could be applied for the determination of mosapride citrate in pure solutions, pharmaceutical preparations, urine and human serum samples.

1. Introduction

Molecularly imprinted polymers (MIPs) are synthetic polymers that have tailor-made selectivity for their templates. They are prepared by the complexation of a target compound (template) and a functional monomer, through either covalent or non-covalent bonds, followed by polymerization with an excess of cross-linker to form a highly cross-linked polymer network. After polymerization, template molecules are removed from the polymer network leaving specific recognition binding sites which are complementary to the template in terms of their size, shape, and function [1].

MIPs have several advantages including ease of preparation, storage stability, high mechanical strength, durability against heat and pressure, cost effectiveness and applicability in harsh chemical conditions. MIPs have a wide range of applications including drug delivery systems [2], stationary phases for chromatography [3], capillary electrochromatography [4], solid phase extraction [5] and electrochemical sensors [6,7].

Computational studies aid in avoiding time-consuming experimental trials performed to select the best monomer-type and ratio for synthesis of molecular imprinted polymers so as to achieve highest selectivity and re-binding capacity to the template, besides being a complementary tool for understanding prevalent molecular interactions [8]. Commonly, computational studies of pre-polymerization complexes are performed for templates with low molecular weight since the process of optimization will not be complicated and can be easily performed [9]. This work reports the first attempt for optimization of template, namely, mosapride citrate, having a considerably high molecular weight (614.02 g/mol) and contains the citrate group that might take part in hydrogen bonding interactions.

Mosapride citrate (MC) is chemically designed as 4-amino- 5-chloro-2-ethoxy-N-[[4-[(4-fluorophenyl) methyl]-2-morpholinyl] methyl]-benzamide-2-hydroxy-1, 2, 3-propanetricarboxylate [10]. MC is a benzamide derivative that possesses a gastrointestinal prokinetic activity as a gastroprokinetic agent that acts as a selective $5HT_4$ agonist. MC is used for short-term treatment of erosion and ulceration of the esophagus caused by the gastroesophageal reflux disease and dyspepsia.

Literature reports the use of HPLC [11], UPLC–MS/MS [12], spectrophotometry [13], spectrofluorimetry [14], electrochemical sensor [15] for the determination of MC, Yet, application of molecularly imprinted polymer of MC as a modifier in its electrochemical sensors is not reported before.

In the present work, MIPs were synthesized using methacrylic acid (MAA) and 4-vinylpyridine (4-VP) as functional monomers, divinyl benzene (DVB) as a cross-linker and dimethyl sulfoxide (DMSO) as porogen based on the findings of computational studies. The performance of the MIPs was then evaluated using equilibrium rebinding

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assay then the MIP with highest binding capacity was incorporated in carbon paste sensors as recognition material for the determination of MC in real samples (urine, serum and pharmaceutical preparations).

2. Experimental

2.1. Reagents and materials

All chemicals were of analytical grade and used without further purification, the MC reference standard was provided by Western Pharmaceutical Industries, Egypt. The pharmaceutical preparation mosapride (5 mg/tablet) was purchased from the local market. Methacrylic acid (MAA), 4-Vinylpyridine (4-VP), Divinylbenzene (DVB), 2, 2′-azobisisobutyronitrile (AIBN), graphite powder (<20 μm), Dimethyl sulfoxide (DMSO), paraffin oil, boric acid and phosphoric acid were purchased from Sigma-Aldrich, Germany.

2.2. Computational optimization and energy calculations

The structures of monomer, template and template-monomer complexes were optimized via the Gaussview software, applying Hartree Fock theory with 6-31G (d) basis set. Based on which, the binding energy of template–monomer complexes, ΔE, was calculated via the following relation:

$$\Delta E = E\,(\text{template–monomer complex}) - E\,(\text{template}) - n\,E\,(\text{monomer}) \quad (1)$$

Consequently, the increase of the interaction energy between two molecular moieties indicates an increased stability of the complex formed between them.

The polarizable continuum model (PCM) was applied to calculate the energy of complex, where the effect of solvent should be considered during energy calculations as it leads to changes in stability and energy of the template monomer complexes in solvent phase compared to gaseous phase [16].

The counterpoise (CP) correction was applied to avoid the basis-set superposition error (BSSE) resulting from interaction of two molecules on approaching each other, where the energy of the system falls not only because of the favorable intermolecular interactions, but also because of the basis functions on each molecule provides a better description of the electronic structure around the other molecule as previously recommended for better accuracy of interactions involving ab-initio methods [17,18].

2.3. Apparatus

Voltammetric measurements were performed in a three electrode cell using a CHI 802 B electrochemical analyzer (CH instruments, Inc., USA). CHI 150 saturated Calomel electrode was used as a reference electrode, platinum wire 1.0 mm diameter was used as a counter electrode and a modified carbon paste was used as working electrode. Jenway pH-meter 3310 (England), Infrared spectra (4000–200 cm^{-1}) were recorded in KBr pellet using FTIR-460 plus, Jasco, Japan. UV-spectroscopic measurements were performed using Jasco V-530 UV/Vis spectrophotometer (Japan). Incubation of MIPs with MC solutions was done in an Eppendorf Thermomixer® (Germany). TGA measurements were performed using TA Instruments, TGA Q5000, USA. SEM images were taken by Scanning Electron Microscope Phenom Pro X desktop, Belgium.

2.4. Preparation of the molecularly imprinted polymers

The MIPs were synthesized according to the procedure described elsewhere [19]. Briefly, 0.5 mmol of MC and the appropriate amount of functional monomer were dissolved in 5 mL of DMSO in a screw capped glass tubes and then the cross-linker (DVB) and initiator (AIBN) were added. The polymerization mixture was degassed with argon for 2–5 min. Finally, the glass tubes were sealed and transferred to an oil-bath at 60 °C for 24 h for polymerization to take place. The resulting MIPs were grounded in a mortar with a pestle and sieved into particles below 45 μm diameter. For template extraction, the polymer particles were incubated while stirring with a mixture of methanol and acetic acid (9:1, v/v) for different time intervals till complete removal of template (confirmed by UV/Vis spectrophotometer at 274 nm) then the particles were left to dry at room temperature. Non-imprinted polymers (NIPs) were prepared under the same polymerization conditions in absence of the template (MC), and were treated in the same way as the corresponding imprinted polymers.

2.5. Equilibrium binding assays

The MIP binding efficiency was tested by adding 20 mg of the prepared MIPs and their corresponding NIPs to 2 mL of 100 μmol L^{-1} solution of MC prepared in methanol in 2 mL Eppendorf tubes followed by 20 h shaking at room temperature. The solution was then centrifuged at 14,000 rpm for 5 min and the resulting supernatants were further filtered through a 0.22 μm PTFE syringe filter and used to determine the remaining MC spectrophotometerically at 274 nm [19].

The binding capacities can then be calculated by subtracting the unbound amount from the initial amount used. The binding capacities (B, mmol g^{-1}) for MIPs and NIPs are calculated according to Eq. (2):

$$B = \frac{(C_i - C_f)\,V}{W} \quad (2)$$

where C_i is the initial solution concentration (mM), C_f is the solution concentration after adsorption (mM), V is the volume of solution (mL), and W is the weight of the polymer particles.

The imprinting factor of the polymer was determined by comparing the binding capacities of the imprinted polymers with those of their non-imprinted counter part according to Eq. (3):

$$IF = \frac{B(MIP)}{B(NIP)} \quad (3)$$

2.6. Electrode fabrication

The bare carbon paste electrode was papered by mixing graphite powder and paraffin oil in, a 79:21 (w/w %) ratio. The chemically modified carbon paste electrode (MIP-CPE) was prepared by mixing MIP, graphite powder and paraffin oil with different specified percentages (w/w/w %) as shown in Supplementary Table 1(S). Each mixture was mixed in a mortar for 10 min to homogenize then packed into one end of a plastic syringe of diameter 5 mm and an electrical contact was made using a copper wire. The external electrode surface was smoothed with filter paper. The NIP modified CPE (NIP-CPE) was prepared by following the same procedure at the optimum composition obtained for (MIP-CPE) [7].

2.7. Analytical evaluation

The electrochemical measurements of MC were recorded in the potential range of (0.4–1.3 V) at a scan rate of 0.1 Vs^{-1} after 175 s of accumulation time at open circuit potential with continuous stirring at 400 rpm. Afterwards, the stirring was stopped and after 5 s the cyclic (CV) or linear sweep (LSV) voltammograms were recorded. All solutions were purged with argon gas for 2 min before measurements at room temperature (25 ± 2 °C). After each measurement, the electrode was washed using water/methanol (95:5 w/w %).