



# Highly selective electrode for potentiometric analysis of methadone in biological fluids and pharmaceutical formulations



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## ABSTRACT

In order to develop a fast and simple procedure for methadone analysis in biological fluids, a graphite paste electrode (GPE) was modified with the ion-pair of methadone–phosphotungstic acid, and multiwalled carbon nanotubes (MWCNTs). Optimized composition of the electrode with respect to graphite powder:paraffin oil:MWCNTs:ion pair, was 58:30:8:4 (w/w%). The electrode showed a near-Nernstian slope of  $58.9 \pm 0.3$  mV/decade for methadone in a wide linear range of  $1.0 \times 10^{-8}$ – $4.6 \times 10^{-3}$  M, with a detection limit of  $1.0 \times 10^{-8}$  M. The electrode response was independent of pH in the range of 5–11, with a fast response time ( $\sim 4$  s) at 25 °C. The sensor showed high selectivity and was successfully applied to the determination of sub-micromolar concentrations of methadone in human blood serum and urine samples, with recoveries in the range of 95–99.8%. The average recovery of methadone from tablets (5 mg/tablet) by using the proposed method was 98%. The life time of the modified electrode was more than 5 months, due to the characteristic of GPE which can be cut off and fresh electrode surface be available. A titration procedure was performed for methadone analysis by using phosphotungstic acid, as titrating agent, which showed an accurate end point and 1:1 stoichiometry for the ion-pair formed (methadone:phosphotungstic acid). The simple and rapid procedure as well as excellent detection limit and selectivity are some of the advantages of the proposed sensor for methadone.

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## 1. Introduction

Methadone (MET; Fig. 1), is a synthetic analgesic drug which is widely used for the treatment of opioid dependence since the mid-1960s [1]. The treatment replaces a short-acting opioid (heroin) with a long-acting one (MET) [1,2]. MET is a full  $\mu$ -opioid receptor agonist and can produce cross-tolerance with heroin or other opioids. This may in turn diminish withdrawal symptoms in affected individuals and enable patients who have recently stopped taking opioids to perform and maintain normal daily functions [3]. MET represents the most often used drug in opioid substitution treatment, but has been used also for the relief of moderate-to-severe pain [4,5].

Like other pharmaceutical compounds, MET has a therapeutic concentration range in biological fluids. Below this concentration, MET is not effective, while excessive concentrations of MET will produce side effects such as anxiety, nervousness, sleep problems (insomnia), weakness, dry mouth, nausea, and diarrhea. In order to determine MET residuals in biological fluids (blood serum or plasma, and urine), chromatographic method is the first choice [6–9]. In addition to its high cost, chromatographic experiment is time-consuming, needs skilled operator, pretreatment of the samples (e.g. preconcentration) for low levels of the drug, etc. Alternative analytical methods have been

proposed by researchers, such as capillary electrophoresis [10], voltammetry [11,12], and potentiometry [13,14].

The last is one of the simplest analytical methods, although it can be highly efficient. Potentiometry based on ion selective electrodes (ISEs) is based on the measurement of potential difference ( $\Delta E$ ) between reference and indicator electrodes. Ion selective electrode (ISE) is an indicator electrode which selectively responds to the ion of interest. In order to be so, the presence of ionophore in the ISE composition is usually necessary. Moreover, the use of nanomaterials in ISEs has improved their analytical characteristics, effectively [15–17]. Well-prepared ISEs show high selectivity and sensitivity to the ion of interest, fast response and long lifetime. They are inexpensive and their operation is very simple. Many ISEs have been constructed for determination of various inorganic [18–27] and organic [28,29] compounds. Graphite paste electrode (GPEs) is one of the indicator electrodes that have been successfully used for determination of various species [30,31]. Compared to other types of ISEs (e.g., PVC-based ISEs), GPEs possess advantages of simple preparation and regeneration, stable potentiometric response, long lifetime, absence of inner reference solution, and easy to store [32].

In order to improve the performance of ISEs, nanostructured materials have been used in their composition [16,17]. Nanomaterials, due to their physical and chemical properties, such as large surface area/volume ratio, good conductivity, excellent electrocatalytic activity and high mechanical strength, have been used in the construction of sensors and biosensors, extensively [33–35].

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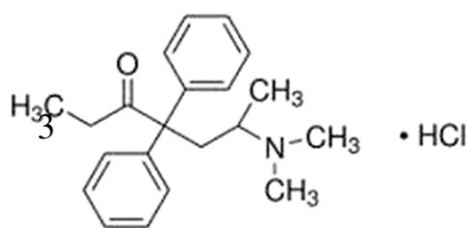


Fig. 1. Chemical structure of MET·HCl.

Among various nanomaterials, carbon nanotubes (CNTs), including single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs), show hydrophobicity and chemical stability, other than the abovementioned properties [36,37]. These properties are favorable for acting as solid contacts [15,38–40]. The aqueous layer between the ion-selective membrane and the electronic conductor was absent in ISEs modified with CNTs [17], which is supposed to improve the detection limit of the sensor [41–44].

In the present work, a GPE was modified with the ion-pair of MET-phosphotungstate and MWCNTs, and used in the potentiometric determination of MET. The modified GPE exhibited a wide linear range for calibration curve and low detection limit for MET and also excellent selectivity to this drug in human blood serum and urine samples without prior separation steps.

## 2. Experimental

### 2.1. Chemicals and reagents

Pure powder of MET·HCl was a gift kindly provided by TEMAD Co. (Tehran, Iran). Phosphotungstic acid (PTA), MWCNTs (diameters within 10–20 nm), graphite powder and paraffin oil were purchased from Merck (Darmstadt, Germany). All other reagents were of analytical grade, and used without further purification. Double distilled deionized water was used throughout the experiments.

Stock solution of MET·HCl ( $1.0 \times 10^{-2}$  M) was prepared by dissolving 0.346 g of the drug in 100 mL double distilled water. It was used for the preparation of more dilute solutions.

### 2.2. Apparatus

The potentiometric measurements were carried out with a Jenway 3345 digital pH/mV meter (Dunmow, Essex, UK) with Ag/AgCl/KCl (saturated) reference electrode. All emf measurements were carried out with the following cell assembly:

Ag/AgCl, KCl (saturated) | test solution | modified GPE.

The performance of the modified electrode was investigated by measuring the potential difference ( $\Delta E$ ) between indicator and reference electrodes which were immersed in MET solution. Each solution was stirred thoroughly, and the potential reading was recorded when it became stable, then the potential values were plotted against log [MET].

### 2.3. Preparation of the ion-pair

MET is a basic compound ( $pK_a = 9.2$ ), and exists as a cation in aqueous solution ( $pH < 9$ ). A bulky anion was needed to precipitate MET as an ion-pair in aqueous solutions. PTA was used for this purpose which was added (150 mL of  $5.0 \times 10^{-3}$  M) to a solution of MET·HCl (150 mL of  $1.0 \times 10^{-2}$  M) drop wise. The white precipitate (MET-PTA) was washed several times with distilled water to remove excess reagents, dried at ambient temperature and used as the active substance for preparing a GPE selective to MET.

### 2.4. Preparation of the modified electrode

The modified graphite paste was prepared by thoroughly mixing weighed amounts of MET-PTA (8%), MWCNTs (4%), graphite (58%), and paraffin oil (30%) in a Petri dish until a uniformly oily paste was obtained which was used for sensor construction. Electrode bodies were 1-mL polypropylene syringes (3 mm i.d.), the tips of which had been cut off. The prepared graphite paste was packed into the end of the syringe. Electrical contact to the instrument was established by using a copper wire. A fresh electrode surface was obtained by squeezing out a small amount of paste and scraping off the excess, then polishing the electrode on a smooth paper to obtain a shiny surface. The resulting GPEs were conditioned in MET solution ( $1.0 \times 10^{-3}$  M) for 24 h before use.

### 2.5. Preparation of real samples

#### 2.5.1. Preparation of urine and blood serum samples

MET was added to blood serum (or urine) of healthy volunteers and the recovery of the drug was obtained by the proposed method. In order to remove proteins, methanol (5 mL) was added to 5.0 mL of blood serum (or urine) sample. After vortexing of the sample for 2 min, the precipitated proteins were separated by centrifugation (3 min at 5000 rpm). The clear supernatant layer was filtered through a millipore filter (0.45  $\mu$ m), and its volume was adjusted to 50 mL by phosphate buffer solution (0.01 M, pH 7.5). 10 mL of this solution was transferred into a 50 mL beaker. Different amounts of MET standard solution were spiked into the sample solution,  $\Delta E$  was recorded. MET content was then determined by using calibration curve and standard addition methods.

#### 2.5.2. Preparation of tablet sample

10 tablets of MET (5 mg/tablet) from Darou Pakhsh Pharmaceutical Mfg. Co (Tehran-Iran), were finely powdered and dissolved in distilled water (~40 mL). After centrifugation, the supernatant was filtered and diluted to the mark in a 50 mL calibrated flask by phosphate buffer solution (0.01 M, pH 7.5). The sample was diluted to a proper concentration and its MET content was determined by potentiometry, using the modified GPE as ISE.

## 3. Results and discussion

### 3.1. Optimization of electrode composition

The ionophore (or ion carrier) is the most important sensing component in an ISE. It selectively binds the target ion while discriminating against interfering ions. Ionophores should have rapid exchange kinetics and adequate formation constants. In addition, they should have good solubility in the electrode matrix, but sufficient lipophilicity to prevent leaching into the sample solution. In order to provide these characteristics, phosphotungstic acid (a bulky anion) was used for the

Table 1  
Optimization of GPE ingredients.

| Electrode no. | Graphite | Paraffin oil | Ion pair | MWCNTs | Slope | Linear range (M)                            |
|---------------|----------|--------------|----------|--------|-------|---|
| 1             | 70       | 30           | –        | –      | 21.8  | $5.0 \times 10^{-6}$ – $2.9 \times 10^{-4}$ |
| 2             | 66       | 30           | –        | 4      | 30.9  | $5.0 \times 10^{-7}$ – $7.9 \times 10^{-6}$ |
| 3             | 67       | 30           | 3        | –      | 33.5  | $5.0 \times 10^{-7}$ – $1 \times 10^{-5}$   |
| 4             | 64       | 30           | 6        | –      | 42.1  | $5.0 \times 10^{-7}$ – $1.1 \times 10^{-5}$ |
| 5             | 62       | 30           | 8        | –      | 56.5  | $1.0 \times 10^{-7}$ – $1.3 \times 10^{-5}$ |
| 6             | 61       | 30           | 9        | –      | 48.9  | $1.0 \times 10^{-7}$ – $1.3 \times 10^{-5}$ |
| 7             | 60       | 30           | 8        | 2      | 41.8  | $1.0 \times 10^{-7}$ – $5.4 \times 10^{-4}$ |
| 8             | 59       | 30           | 8        | 3      | 45.5  | $1.0 \times 10^{-7}$ – $4.4 \times 10^{-4}$ |
| 9             | 58       | 30           | 8        | 4      | 58.9  | $1.0 \times 10^{-8}$ – $4.6 \times 10^{-3}$ |
| 10            | 56       | 30           | 8        | 6      | 53.6  | $5.0 \times 10^{-8}$ – $1.6 \times 10^{-4}$ |

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