Potentiometric sensors for the determination of pharmaceutical drugs

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Abstract
Potentiometric sensors based on ion-selective membrane electrodes have continued to get great attention from the scientific community. These sensors have been employed in several applications including medicine, forensic analysis, environmental assessment, industry, agriculture, and pharmaceutical drug analysis. Indeed, these sensors possess several advantages, for example, simple design, fabrication, and manipulation, rapid response time, good selectivity, applicability to colored and turbid solutions, and possible interfacing with automated and computerized systems. On the other hand, therapeutic drug monitoring and the detection of pharmaceutical drugs in their pharmaceutical formulations and biological matrices are highly significant from a medical point of view, especially for drugs with a narrow therapeutic index, such as anticancer drugs, which can cause fatal side effects for patients. Interestingly, potentiometric sensors have been broadly employed as one of the most important electrochemical approaches for pharmaceutical drug analysis. Moreover, the breakthroughs in potentiometric sensors based on ion-selective electrodes (ISEs) make them superior to the other reported methods for pharmaceutical drug analysis in terms of many performance parameters, such as sensitivity, selectivity, low detection limit, and low cost. In this review, we try to offer a summary prologue to the applicability and merits of potentiometric sensors that have been employed for pharmaceutical drug analysis while emphasizing their application for the assay of pharmaceutical drugs in their dosage forms and the in-vivo assay of pharmaceutical drugs in different biological samples such as milk, water, plasma, and urine.

Keywords Potentiometric sensors · Drug · Ion-selective electrode · Biological samples

Introduction
Biosensing technologies are of increasing significance in the fields of healthcare, drug analysis, industrial process control, environmental assessment, and military applications. Therefore, great efforts have been made in the fabrication of versatile, simple, sensitive, and selective biosensing platforms for different targets, employing electrochemical, spectroscopic, and other sensitive approaches. Potentiometric sensors based on ion-selective electrodes (ISEs) is a well-established sensing analytical strategy that has been regularly used for the physiological detecting of key electrolytes [1, 2]. ISEs are capable of identifying a target compound in the sample solution and then producing a response related to the amount of the target compound through a transducer attached to the biosensor device [3]. In another way, potentiometric sensors detect the analyte's concentration by determining potential changes between the working (ion-selective or indicator) and reference electrodes [4]. There are several applications for potentiometric sensors, for example, quality control and quality assurances of drugs, agricultural analysis, metal ions detection, small molecules detection, detection of enzymes, DNA analysis, environmental assessment, industrial analysis, and pharmaceutical drug monitoring (Fig. 1) [5, 6]. Potentiometric sensors
as sensing tools have presented many advantages since they allow the determination of various analytes in a wide range of concentrations, and employ inexpensive measurement equipment. Furthermore, these sensors are characterized by their small size, fast response, ease of use, cost-effectiveness, and resistance to color and turbid interferences. What’s more, the unique features of ISEs provide information about the free-ion concentration (ion activity), which is different from other analytical methods that give the total concentration [7]. Nearly all potentiometric sensors, including glass electrodes, metal oxide-based sensors as well as ISEs, are now commercially available. Many of them could be easily mass-fabricated in device using advanced modern silicon or thick-film technologies [8]. Also, the biomodification of conventional electrodes leads to great advancements in the field of potentiometric biosensors, which significantly broaden the spectrum of analytes detected by potentiometry. The second important advantage of such biomodifications is selectivity improvement, which is attributed to the high specificity of the biomolecular interactions.

The detection of a specific drug concentration in different biological samples involving blood plasma, spinal fluid, tear, saliva and urine is important for recognizing the physiological as well as clinical performance of this drug. Also, drug assessments in body fluids offer critical information, such as drug efficacy, drug therapeutic index, drug bioavailability, drug metabolism, drug pharmacokinetics and pharmacodynamics, drug-drug interactions, and drug toxicity [9–11]. With the recent progress in ISEs, most of the potentiometric sensors that have been utilized for determining pharmaceutical drugs and in therapeutic drug monitoring were relied on using ISEs [12, 13]. Notably, potentiometric sensors have been commonly applied for pharmaceutical drug analysis more than other analytical approaches due to their several merits, such as excellent target selectivity and high sensitivity, fast analysis time, high stability, low LOD, resistant to color and turbid interferences, wide linear range, relatively low cost and ease of usage [14–18]. In the present review, we summarize the potentiometric platforms that were established for the detection of different pharmaceutical drugs in their different dosage forms as well as their biological fluids such as milk, plasma and urine, and discussed their numerous analytical performances, such as linear concentration, LOD, response time, lifetime and their applications.

**Ion-selective electrodes (ISEs)**

An ISE is known to be a membrane-based electroanalytical sensor whose potential reveals the ion activity to be measured in a sample solution. The membrane of ISE comprises either liquids or solid or glass electrolytes that are generally non-conductive under measuring conditions [19]. ISEs allow for the potentiometric determination of particular ion activity in the presence of other ions [20]. The ISEs response towards charged compounds is mainly dependent on the type of the ion-selective membranes, which can be fabricated from various materials, for instance, glass (pH electrode), ceramic, solid crystalline, or polymers [21]. Their selectivity is attained either by employing a material structure or by doping the membrane with definite ion-selective complexing agents. The most known ISE is the glass pH electrode, which is applied for adjusting the pH of any solution. The best commonly utilized selective sensors are polymer membranes-based electrodes.

**ISE with polymeric membranes**

A membrane is a universal term that implies a continual layer, generally involving a semi-permeable material, with a controlled permeability covering a structure, for example, carbon or an inert metal, or separating two electrolyte solutions. The membrane ISE is typically fabricated of a chemical identification material, named ionophore, a solvent mediator that delivers the plastic membrane features, and a polymer that physically supports these membrane components. In certain cases, the membranes also contain compounds that work as lipophilic ionic additives and form the electrodes operating properties. The membrane's composition and relative proportions of the membrane constituents determine the electrode reaction selectivity.

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Fig. 1 Diagram illustrations of the different applications of potentiometric sensors
Applications of potentiometric sensors for the determination of pharmaceutical drugs

Potentiometric sensors have been proposed and established for the determination of several categories of important drugs that rely on the chemical structures of the target drug, often require specific sensor interfaces to realize their full determination potential. New potentiometric sensors are persistently being developed to enhance their detection sensitivity, stability as well as to lower their detection limits. Here we will discuss the recent advances of potentiometric sensors that have been employed for the determination of important drugs in their dosage forms and biological fluids (Table 1).

For example, Elmorsy et al. developed novel disposable potentiometric sensors for the detection of naproxen (NAP) that relied on a single-walled carbon nanotubes-polyvinyl chloride (SWNTs-PVC) composite combined of calix[4]arene as a host–guest molecular identification element [22]. The developed sensors have been applied for the assay of NAP with a fast response time and good stability, which reaches 24 weeks. The fabricated sensors were successfully employed for the selective potentiometric determination of NAP in tablet dosage formulations as well as biological fluids (urine and plasma) applying batch and flow injection analysis (FIA) systems with acceptable average recoveries ranges of 94.9—99.6%. Amr established potentiometric sensors for the assay of melatonin (MLN) as well as oxomemazine (OXM) in urine samples and certain pharmaceutical formulations [23]. The fabricated sensors relied on using a bismuth tetraiodate (BT)–drug ion-pair as a new electroactive substance including a plasticized PVC membrane with o-nitrophenyl octyl ether (o-NPOE) or dioctyl phthalate (DOP) as plasticizers. They have used potentiometric sensors for the rapid and stable assay of MLN (1.0 × 10⁻⁶—1.0 × 10⁻² M) as well as OXM (1.0 × 10⁻⁵—1.0 × 10⁻² M) in the pH ranges of 3.0–6.5 and 3.5–6.0 for MLN and OXM, respectively. The potentiometric sensors have exhibited an excellent selectivity in the presence of various interfering ions and other certain pharmaceutical excipients. Ensafi and coworkers described a potentiometric method for the detection of an anti-vertigo drug, named betahistine (BTH), in pharmaceutical preparations, urine and blood plasma [24]. This sensor has exhibited linearity of 1.0 × 10⁻⁶—1.0 × 10⁻¹ M with a LOD of 5.8 × 10⁻⁷ M; the working pH range was 4.27—9.02. Furthermore, the developed sensor has been characterized by its short analysis time (10 s) and long lifetime (8 weeks). Also, they have validated the results from the established sensor for the assay of BTH in urine, plasma and pharmaceutical samples with the HPLC technique, and noticed there is no significant difference between the results of the two methods (reported and potentiometric methods). Another potentiometric sensor was established by Santini and coauthors for furosemide detection in blood serum, pharmaceutical dosage forms, urine, and bovine milk [25]. The proposed sensor has exhibited a linear range of 5.0 × 10⁻⁷—1.0 × 10⁻² M (LOD = 3.8 × 10⁻⁷ M). The proposed sensor has worked effectively within the pH range of 7.0—9.0. The established sensor has several advantages, such as facile preparation steps, low cost of fabrication, rapid response time (10–20 s) and long life-span stability (around 6 months). The selectivity coefficient of the developed sensor has not been influenced by the existence of other anions in the used sample. The obtained results have been compared and validated with that of liquid chromatography (LC), and non-significant differences were attained, indicating the validity of the proposed sensor for its usage. Ismaeel et al. designed potentiometric sensors for the assay of cyproheptadine in tablet dosage form, human urine and plasma by employing di-butyl phthalate (electrode 1), tris (2-ethylhexyl) phosphate (electrode 2) as well as o-NPOE (electrode 3) as plasticizers [26]. The three mentioned electrodes have limits of detection of 9.0 × 10⁻⁵, 7.5 × 10⁻⁵, and 6.0 × 10⁻⁵ M for electrodes 1, 2, and 3, respectively. Notably, the tris (2-ethylhexyl) phosphate-based electrode has shown the best results. Furthermore, they have found that the most suitable pH ranges for the developed sensors are 3.0—7.0, 4.0—7.0, and 4.0—8.0, respectively.

Two different potentiometric approaches were established for the detection of a local anesthetic drug (lidocaine hydrochloride) in different pharmaceutical formulations, and biological fluids, such as urine and serum [27]. The developed sensors relied on the potentiometric titration of the studied drug by applying modified screen-printed as well as carbon-paste electrodes as end-point indicator sensors. The linear range for the modified screen-printed electrode was 1.0 × 10⁻⁷—1.0 × 10⁻² and for carbon paste one was 6.2 × 10⁻⁷—1.0 × 10⁻² M. The working pH ranges of screen-printed as well as carbon paste electrodes were 2.0—8.0 and 2.0–7.5, and the response times were about 6 and 4 s, respectively. The obtained results using these potentiometric electrodes were compared with British pharmacopeia. A novel automatic flow potentiometric platform was developed for the detection of ofloxacin by Pimenta and coauthors (Fig. 2) [28]. The authors have applied this platform in pharmaceutical samples and biological fluids, such as plasma and urine {[bis(trifluoromethyl)phenyl]borate}}
Table 1 Analytical performance parameters of the developed potentiometric sensors for the analysis of different drug molecules in biological samples

| Target drug     | Concentration range/M | Detection limit/M | pH working range | Response time/s | Slope/mV decade⁻¹ | Life time | Target solutions | References |
|-----------------|------------------------|-------------------|------------------|-----------------|-------------------|-----------|-----------------|-----------|
| Naproxen        | 1.0 × 10⁻⁸ to 1.0 × 10⁻² (Batch) | 1 × 10⁻⁸ (Batch)  | 6–12             | 3               | ~ 61.0 ± 0.0       | 24 weeks | Urine and plasma | [22]      |
|                 | 1.0 × 10⁻⁶ to 1.0 × 10⁻² (FIA) | 1 × 10⁻⁹ (FIA)   | –                | –               | 59.10  | –               |           |           |
|                 | 1.0 × 10⁻⁸ to 1.0 × 10⁻² | 1 × 10⁻⁸         | –                | 4               | 56.70.7           | 18 weeks |                |           |
|                 | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 1 × 10⁻⁷         | –                | 10              | 57.40.3           | 6 weeks   |                |           |
|                 | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 1 × 10⁻⁷         | –                | 6               | 59.70.4           | 12 weeks |                |           |
| Oxomemazine     | 1.0 × 10⁻⁵ to 1.0 × 10⁻² | 7.0 × 10⁻⁵       | 3.0–6.5          | –               | 55.25             | 14 weeks | Urine           | [23]      |
| Melatonin       | 1.0 × 10⁻⁶ to 1.0 × 10⁻² | 7.0 × 10⁻⁶       | 3.5–6.0          | –               | 58.55             | 12 weeks | Urine           | [23]      |
| Betahistine     | 1.0 × 10⁻⁶ to 1.0 × 10⁻¹ | 5.8 × 10⁻⁷       | 4.27–9.02        | 10              | 29.74 ± 1.47      | 8 weeks   | Urine and plasma | [24]      |
| Furosemide      | 5.0 × 10⁻⁷ to 1.0 × 10⁻² | 3.8 × 10⁻⁷       | 7.0–9.0          | 10–20           | ~ 58.4 ± 0.9      | 6 months | Urine and blood serum | [25]      |
| Cyproheptadine  | 1.0 × 10⁻³ to 1.0 × 10⁻² | 9.0 × 10⁻⁵       | 3–7              | 3.9             | 53.10             | 35 days  | Human urine and plasma | [26]      |
|                 | 5.0 × 10⁻³ to 1.0 × 10⁻² | 7.5 × 10⁻⁵       | 4–7              | 5.6             | 58.72             | 42 days  |                |           |
|                 | 5.0 × 10⁻⁵ to 1.0 × 10⁻² | 6.0 × 10⁻⁵       | 4–8              | 4.2             | 57.44             | 2 days   |                |           |
| Lidoconine      | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 3.3 × 10⁻⁷       | 2.0–8.0          | 4               | 58.90 ± 0.68      | 6 months | Urine and human serum | [27]      |
|                 | 6.2 × 10⁻⁷ to 1.0 × 10⁻² | 6.2 × 10⁻⁷       | 2.0–7.5          | 6               | 57.50 ± 0.89      | 4 months |                |           |
| Ofloxacin       | 2.0 × 10⁻⁵ to 5.0 × 10⁻³ | 1.0 × 10⁻⁵       | 2.1–6.6          | –               | 57.4              | 4 months | Biological fluids | [28]      |
| Meclofenoxate   | 1.0 × 10⁻⁶ to 1.0 × 10⁻² | 7.0 × 10⁻⁷       | 3.0–8.0          | <4              | 62.7 ± 0.9        | 300 days | Spiked urine samples | [29]      |
| Clenbuterol     | 1.0 × 10⁻⁷ to 1.0 × 10⁻⁴ | 7.0 × 10⁻⁸       | 7.0–8.5          | 5               | 55.7              | –        | Spiked human urine | [30]      |
| Doxycycline     | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 1.0 × 10⁻⁷       | 2.0–8.0          | 6               | 58.7 ± 0.2        | 5 months | Urine and serum  | [31]      |
|                 | 1.22 × 10⁻⁷ to 1.0 × 10⁻² | 1.22 × 10⁻⁷      | 2.0–7.5          | 7               | 58.0 ± 0.6        | 4 months |                |           |
| Betaxolol       | 1.0 × 10⁻⁶ to 1.0 × 10⁻² | –                | 3.2–8.3          | 25              | 59.0              | 45 days  | Spiked plasma and urine | [32]      |
| Cytarabine      | 1.0 × 10⁻⁶ to 1.0 × 10⁻³ | 5.5 × 10⁻⁷       | 2.8–4.0          | <10             | 52.3 ± 1.2        | –        | Human serum      | [33]      |
| Methylphenidate | 8.0 × 10⁻⁶ to 1.0 × 10⁻³ | 7.5 × 10⁻⁶       | 4.0–8.0          | 25 ± 0.5        | 59.4 ± 0.5        | ~ 8 weeks | Spiked urine     | [34]      |
| Target drug       | Concentration range/M | Detection limit/M | pH working range | Response time/s | Slope/mV decade⁻¹ | Life time | Target solutions                  | References |
|-------------------|-----------------------|-------------------|------------------|----------------|------------------|-----------|----------------------------------|------------|
| Ketotifen         | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 9.81 × 10⁻⁸      | 3.0–6.0          | –              | 52.51 ± 0.2      | 82 days   | Human urine samples              | [35]       |
|                   | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 1.2 × 10⁻⁷       | 2.0–7.0          | –              | 51.51 ± 0.25     | 35 days   |                                  |            |
| Sulfadiazine      | 1.0 × 10⁻⁵ to 1.0 × 10⁻² | 1.0 × 10⁻⁵       | 4.0–5.5          | < 10           | – 57.3 ± 0.1     | –         | Spiked human urine samples       | [36]       |
|                   | 7.5 × 10⁻⁶ to 1.0 × 10⁻² | 7.5 × 10⁻⁶       | 4.8–10.0         | < 10           | – 46.7 ± 0.5     | –         |                                  |            |
|                   | 7.0 × 10⁻⁶ to 3.2 × 10⁻² | 3.2 × 10⁻⁶       | 4.5–8.0          | < 20           | – 65.1 ± 0.2     | –         |                                  |            |
| Diphenhydramine   | 1.0 × 10⁻⁶ to 1.0 × 10⁻² | 9.7 × 10⁻⁷       | 3.0–8.0          | 10             | 55.20 ± 1.0      | 63 days   | Human urine and serum            | [37]       |
|                   | 1.0 × 10⁻⁶ to 1.0 × 10⁻² | 9.8 × 10⁻⁷       | 3.0–7.0          | 16             | 54.70 ± 1.0      | 55 days   |                                  |            |
| Pethidine         | 2.1 × 10⁻⁶ to 1.0 × 10⁻² | 7.3 × 10⁻⁷       | 3.5–6.6          | 5–8            | 54.2             | –         | Spiked urine samples             | [38]       |
| Ketamine          | 2.5 × 10⁻⁶ to 1.0 × 10⁻² | 8.5 × 10⁻⁷       | 2.6–6.4          | ~ 8            | 55.8 ± 0.3       | –         | Urine                            | [39]       |
| Sulpiride         | 1.0 × 10⁻⁶ to 1.0 × 10⁻² | 7.6 × 10⁻⁷       | –                | 5              | 57.1             | 20 weeks  | Human urine and real water samples | [40]       |
|                   | 4.0 × 10⁻⁶ to 1.0 × 10⁻² | 1.58 × 10⁻⁶      | –                | 7              | 56               | 18 weeks  |                                  |            |
|                   | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 8.7 × 10⁻⁸       | 2–8              | 4              | 58.8             | 25 weeks  |                                  |            |
| Lamotrigine       | 5.2 × 10⁻⁷ to 1.0 × 10⁻³ | 3.1 × 10⁻⁷       | –                | 10–15          | 56.4             | 10–12 days | Spiked urine and plasma          | [41]       |
|                   | 5.8 × 10⁻⁷ to 1.0 × 10⁻³ | 9.5 × 10⁻⁷       | –                | 25–30          | 52.3             | 20–25 days |                                  |            |
| Lamotrigine       | 5.2 × 10⁻⁷ to 1.0 × 10⁻³ | 3.1 × 10⁻⁷       | –                | 10–15          | 56.4             | 10–12 days | Spiked urine and plasma          | [41]       |
|                   | 5.8 × 10⁻⁷ to 1.0 × 10⁻³ | 9.5 × 10⁻⁷       | –                | 25–30          | 52.3             | 20–25 days |                                  |            |
| Felbamate         | 1.5 × 10⁻⁶–1.0 × 10⁻³ | 1.9 × 10⁻⁷       | –                | 10–15          | 58.0             | 10–12 days | Spiked urine and plasma          | [41]       |
|                   | 1.8 × 10⁻⁷ to 1.0 × 10⁻³ | 3.5 × 10⁻⁷       | –                | 25–30          | 62.3             | 20–25 days |                                  |            |
| Primidone         | 2.6 × 10⁻⁷ to 1.0 × 10⁻³ | 1.0 × 10⁻⁷       | –                | 10–15          | 60.0             | 10–12 days | Spiked urine and plasma          | [41]       |
|                   | 6.6 × 10⁻⁷ to 1.0 × 10⁻³ | 4.7 × 10⁻⁷       | –                | 25–30          | 54.2             | 20–25 days |                                  |            |
| Lomefloxacin      | 1 × 10⁻⁵ to 1 × 10⁻²  | 6.31 × 10⁻⁶      | 2–6              | 8              | 55.829           | 30 days   | Plasma                           | [42]       |
|                   | 1 × 10⁻⁵ to 1 × 10⁻³  | 5.01 × 10⁻⁶      | 2–6              | 5              | 58.229           |          |                                  |            |
| Ticlopidine       | 1.0 × 10⁻² to 5.0 × 10⁻⁵ | 1.12 × 10⁻⁵    | 3.8–5.4          | ≤ 10           | 58.23            | 4 weeks   | Human serum                      | [43]       |
| Bromazepam        | 1 × 10⁻⁶ to 1 × 10⁻²  | 3.1 × 10⁻⁷      | 2–4              | 20–30          | 44.13            | 4–6 weeks | Plasma                           | [44]       |
| Olanzapine        | 7.5 × 10⁻⁷ to 5.6 × 10⁻⁴ | 5.0 × 10⁻⁷      | 4.5–6.0          | 4              | 59.2             | 2 months  | Serum                            | [45]       |
| Pentoxifylline    | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 4.89 × 10⁻⁶      | 4–6              | 25             | 56.77 ± 0.19     | 30 days   | Urine and serum                  | [46]       |
|                   | 9.0 × 10⁻⁸ to 1.0 × 10⁻² | 3.90 × 10⁻⁶      | 4–6              | ≤ 15           | 55.76 ± 0.71     | 28 days   |                                  |            |
| Desipramine       | 2.2 × 10⁻⁶ to 1.0 × 10⁻³ | 1.2 × 10⁻⁶      | 2.8–7.4          | 12             | 59.2             | –         | Urine and blood                  | [47]       |
Table 1 (continued)

| Target drug | Concentration range/M | Detection limit/M | pH working range | Response time/s | Slope/mV decade⁻¹ | Life time | Target solutions | References |
|-------------|------------------------|-------------------|------------------|-----------------|------------------|-----------|-----------------|------------|
| Atorvastatin | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 7 × 10⁻⁸ | 5–9 | 8 | 60.94 ± 0.2 | 12 weeks | Human plasma | [48] |
| Tolterodine  | 1.0 × 10⁻⁵ to 1.0 × 10⁻² | 6.30 × 10⁻⁶ | 2.0–6.0 | 12 | 58.1 | 6 months | Urine and plasma | [49] |
| Neostigmine  | 4.0 × 10⁻⁷ to 1.0 × 10⁻² | 3.0 × 10⁻⁷ | 3.8–10 | 10 | 62.5 ± 0.5 | – | Spiked urine and plasma | [50] |
| Carvedilol   | 3.0 × 10⁻⁷ to 1.0 × 10⁻³ | 1.5 × 10⁻⁷ | 4.5–7.0 | 9 | 58.7 | 9 weeks | Urine and serum | [51] |
| Venlafaxine  | 5.0 × 10⁻⁵ to 1.0 × 10⁻² | 1 × 10⁻⁵ | 3.5–7.5 | 56 | 45 days | Serum | [52] |
| Venlafaxine  | 8.0 × 10⁻⁶ to 1.0 × 10⁻² | 5.0 × 10⁻⁶ | 3–9 | 10 | 29.4 ± 0.1 | 2 months | Urine and serum | [53] |
| Bambuterol   | 1.0 × 10⁻⁷ to 1.0 × 10⁻² | 2.3 × 10⁻⁸ | 2–8.5 | 5 | 58.8 ± 0.5 | 24 weeks | Surface water, human plasma | [54] |
| Ziprasidone  | 8.5 × 10⁻⁶ to 1.0 × 10⁻² | 4.6 × 10⁻⁷ | 3–7 | 15 | 57.0 | 35–40 days | Spiked urine and serum | [55] |
| Codeine      | 1.95 × 10⁻⁷ to 1.0 × 10⁻² | 1.93 × 10⁻⁷ | 5–7 | 25 | 33.83 ± 1.82 | 6–8 weeks | Human plasma | [56] |
Potentiometric sensors for the determination of pharmaceutical drugs

(KTFPB) has been employed as a molecular identification substance. They fabricated the selective membrane from the dispersion of KTFPB in a PVC matrix of o-NPOE. This system permitted high-throughput drug monitoring of about 50 different samples each hr. The sensor displayed a linear range of $2.0 \times 10^{-5} – 5.0 \times 10^{-3}$ M (the pH range was 2.1–6.6). LOD for the established potentiometric method was estimated to be $1.0 \times 10^{-5}$ M. The authors stated that the sensor was not affected by the existence of inorganic ions as well as famous excipients in biological matrices and pharmaceuticals, respectively.

A dietary supplement called meclofenoxate hydrochloride (MFC) was detected by a potentiometric sensor that relied on β-cyclodextrin/carbon xerogel-based potentiometric screen-printed sensor [29]. They fabricated a nickel-doped carbon xerogel as a novel carbon nanomaterial within the electrode matrix to improve the sensor stability, response time (< 4 s) and extended the sensor lifetime to 300 days. A nickel-doped carbon xerogel (Ni-CX) morphology was characterized by scanning electron microscopy (SEM) (Fig. 3). As shown in Fig. 3, particles of the carbon were spherical and connected in a continuous network. This sensor was described to act in the concentration range from $1.0 \times 10^{-6}$ to $1.0 \times 10^{-2}$ M. Moreover, the established sensor has been effectively employed for assays of MFC in the existence of its degradation products with agreeable recoveries regarding the reported methods for the same drug.

Rong-Ning et al. proposed an ISE for the detection of clenbuterol (CB) in pig urine [30]. The developed sensor used a molecularly imprinted polymer (MIP) as an ionophore for molecular identification, which was fabricated by a precipitation polymerization process utilizing CB as a template substance. The as-prepared CB-MIP is spherical with an average diameter of 0.5–1.0 μm. This fabricated electrode has shown a linear response from $1.0 \times 10^{-7}$ to $1.0 \times 10^{-4}$ M and had a LOD of $7.0 \times 10^{-8}$ M. The proposed MIP ion-selective electrode was featured by its rapid response as well as long-term usage stability.

A report by Ali and coworkers described the establishment of potentiometric sensors that relied on α-cyclodextrin (α-CD) and a multi-walled carbon nanotube (MWCNT) as ionophores for the assay of doxycycline hydrochloride (DOH) biological samples and pharmaceutical preparations.

### Table 1 (continued)

| Target drug | Concentration range/M | Detection limit/M | pH working range | Response time/s | Slope/mV decade$^{-1}$ | Life time | Target solutions | References |
|-------------|-----------------------|-------------------|-----------------|----------------|------------------------|-----------|-----------------|-----------|
| Pregabalin  | $1 \times 10^{-6}$ to $1 \times 10^{-3}$ | $2.23 \times 10^{-7}$ | 6–9 | 30–35 | $53 \pm 1$ | 3 weeks | Spiked human plasma | [57] |
| Torasemide  | $1.0 \times 10^{-5}$ to $1.0 \times 10^{-3}$ | $4.0 \times 10^{-6}$ | 4–8 | 50 | 28.5 | 5 weeks | – | [58] |
| Torasemide  | $1.0 \times 10^{-5}$ to $1.0 \times 10^{-2}$ | $3.5 \times 10^{-6}$ | 3–8 | 30 | 30.1 | 4–6 weeks | – | [58] |
| Torasemide  | $1.0 \times 10^{-6}$ to $1.0 \times 10^{-4}$ | $2.5 \times 10^{-7}$ | 3–8 | 30 | 31.1 | 4–6 weeks | – | [58] |
| Torasemide  | $1.0 \times 10^{-6}$ to $1.0 \times 10^{-3}$ | $2.5 \times 10^{-7}$ | 3–8 | 10 | 29.8 | 4–6 weeks | – | [58] |
| Olopatadine | $1.0 \times 10^{-5}$ to $1.0 \times 10^{-2}$ | $5.0 \times 10^{-6}$ | 3.0–4.5 | 18 | 50.0 | 13 weeks | – | [59] |
| Oxeladine   | $1.0 \times 10^{-5}$ to $1.0 \times 10^{-2}$ | $4.4 \times 10^{-6}$ | 2.5–8.5 | 3 | 60.0 | 13 weeks | Human plasma | [59] |
| Citopolar   | $1.0 \times 10^{-6}$ to $1.0 \times 10^{-2}$ | – | 3.4–7.8 | 30 | 56.83 | 25 days | Spiked plasma and urine | [60] |

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**Fig. 2** Diagram representation of high-throughput flow platform for detection of ofloxacin; GE, ground electrode; RF, reference electrode; Flow cell, ion-selective electrode. Reproduced/Adapted from [28] with permission from JSAC publisher, Copyright 2013
In this work, they employed tricresyl phosphate (TCP) as a plasticizer for electrode I and o-NPOE for electrode II. The proposed electrodes have displayed linearity from $1.0 \times 10^{-7}$ to $1.0 \times 10^{-2}$ as well as $1.22 \times 10^{-7}$ to $1.0 \times 10^{-2}$ M; as well as LODs of $1.0 \times 10^{-7}$ and $1.22 \times 10^{-7}$ M for electrode I and II, respectively. The working pH ranges that have been applied for the two electrodes were 2.0–8.0 and 2.0–7.5, respectively. Interestingly, 6–7 s was the response time for the proposed sensors, while the lifetime was 4–5 months.

Another potentiometric sensor was proposed by Alturiqi for the detection of betaxolol hydrochloride (BT), which relied on a BT-tetraphenylborate (BT-TPB) ion-pair complex form with di-butyl phosphate (DBP) as a plasticizer [32]. They applied this sensor in real human plasma and urine samples. The linearity and pH range for the sensor were found to be $1.0 \times 10^{-6}$ to $1.0 \times 10^{-2}$ M and 3.20—8.30, respectively. The produced sensor showed 25 s of response time and about 45 days of working stability. Kamel et al. established novel liquid-contact potentiometric sensors for an assay of the antileukemic drug (cytarabine) in real samples and various pharmaceutical preparations [33]. They have prepared the sensors by imprinting the cytarabine template with methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA) as a functional monomer and crosslinker, respectively (Fig. 4A). The MIPs were dispersed in a plasticized PVC matrix membrane. SEM was used to examine the surface morphology of the fabricated polymers, either MIPs or NIPs. As revealed in Fig. 4B, the cytarabine imprinted beads were uniform and spherical in shape, with an average diameter of 1.32–2.11 µm. The sensor has exhibited a linear range for the studied drug of $1.0 \times 10^{-6}$—$1.0 \times 10^{-3}$ M, and had a LOD of $5.5 \times 10^{-7}$ M. The authors stated that the sensor presented an excellent specificity toward the studied drug in the existence of several counter ions, and the response time was less than 10 s. Moreover, the obtained results from the established sensor were carefully compared with those from LC, and a non-significant difference was detected, indicating the accuracy and validity of the developed sensors for the quantification of cytarabine in real samples.

The assay of methylphenidate (MP) in market formulations as well as urine samples were achieved potentiometrically by AlRabiah and coauthors [34]. They have utilized β-CD, γ-CD, and 4-tertbutylcalix[8]arene as ionophores in the construction of these potentiometric approaches. The approaches have displayed a linear calibration graph in the range of $8.0 \times 10^{-6}$ to $1.0 \times 10^{-3}$ M and the working pH range was 4.0–8.0. The sensors had a reaction time of 25 s and a life span of about 8 weeks. The researchers have compared the analytical performance of the established approaches to HPLC, and showed that both methods produced equally accurate outcomes. Similarly, ketotifen fumarate was detected in its tablet dosage form and urine samples by using novel potentiometric sensors dependent on a carbon paste electrode (CPE) and PVC membrane electrodes [35]. The sensors have operated in the linear range of $1.0 \times 10^{-7}$ to $1.0 \times 10^{-2}$ M. Their lifetimes were 35 and 84 days, respectively. The electrodes have shown Nernstian slope values of 52.51 ± 0.20 and 51.51 ± 0.25 mV decade⁻¹ for CPE and PVC membrane electrodes at 30 °C, respectively. The findings of these sensors have been shown to have been in good agreement with the results of the reported spectrophotometric method. New PVC membrane electrodes for the detection of sulfadiazine (SDZ) in dosage formulations and biological fluids were fabricated with conventional and tubular configurations with a graphite-based electrical contact and without an internal reference solution [36]. The fabrication of PVC membrane potentiometric sensors relied on bis(triphenylphosphoranylidene) ammonium-SDZ (electrode I), tetraoctylammonium bromide (electrode II) or iron(II)- phthalocyanine (FePC), (electrode III) as electroactive substances. They have applied o-NPOE as a plasticizer in fabricating these sensors. The developed sensors have exhibited linear responses of $1.0 \times 10^{-5}$—$1.0 \times 10^{-2}$, $7.5 \times 10^{-6}$—$1.0 \times 10^{-2}$ and $7.0 \times 10^{-6}$—$3.2 \times 10^{-2}$ M, respectively. They correlated the findings of these approaches with HPLC methods, and concluded that both methods well agree, indicating that the new approaches could be applied for the detection of SDZ in pharmaceutical products and biological samples. SP and CP electrodes were employed for the detection of diphenhydramine hydrochloride (DPH) drug in pure form, dosage forms as well as biological samples.
The proposed SPE and CPE sensors have demonstrated a linear response of $1.0 \times 10^{-6} - 1.0 \times 10^{-2}$ M in the pH range of 3.0—8.0 and 3.0—7.0 with a LOD of $9.7 \times 10^{-7}$ and $9.8 \times 10^{-7}$ M, respectively. Their response times were found to be 10 and 16 s, and their lifetimes were about 8 weeks. They have compared the outcomes with those estimated employing the standard official method, and noticed similar performance utilizing both techniques.

For the detection of pethidine hydrochloride (PDH) in injection dosage form as well as spiked urine samples, a chemically modified CPE (CMCPE) relied on PDH-phosphotungstate (PD–PT) as an ion-pair complex was fabricated. This new sensor has exhibited Nernstian responses over the range of $2.1 \times 10^{-6} - 1.0 \times 10^{-2}$ M and operated effectively in the pH range of 3.5—6.6. The developed sensor was characterized by its fast response (5–8 s) and low detection limit ($7.3 \times 10^{-7}$ M). The analytical features of the established electrode were compared with other reported electrodes, and it has displayed similar results. Shawish and colleagues proposed a new potentiometric sensor dependent on sodium TPB as an electroactive substance for the assay of ketamine hydrochloride in ampoule dosage forms and urine samples. The suggested sensor has operated linearly in the range of $2.5 \times 10^{-6} - 1.0 \times 10^{-2}$ M with a LOD of $8.5 \times 10^{-7}$ M. The pH range of 2.6—6.4 was also shown to be suitable for the sensor action without being influenced by variations in the pH and to have a rapid response (about 8 s). The researchers showed that the sensor and the standard

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**Fig. 4** A Diagram illustrations of the cytarabine imprinting process. SEM photos for B cytarabine-MIP and C NIP beads. Reproduced/Adapted from [33] with permission from MDPI publisher, Copyright 2020
methods had identical performances in the assessment of ketamine hydrochloride.

Khalil et al. fabricated three novel modified CPS that relied on MWCNTs (sensor A), Fe-Co doped TNTs (sensor B) and MWCNTs/Fe-Co doped TNTs composite (sensor C) for the sensitive potentiometric detection of sulphiride (SLP) in real samples [40]. The detection limits for the developed sensors (A, B, and C) were estimated to be 7.6 × 10⁻⁷, 1.58 × 10⁻⁶ and 8.7 × 10⁻⁸ M, respectively. The fabricated sensors have shown that the long-lifetime stability reaches 20, 18, and 25 weeks for sensors (A), (B), and (C), respectively. Interestingly, sensor C has been employed for estimating the SLP concentration in its pure state, dosage forms, human urine, as well as real water samples. The proposed method can be employed as an important monitoring platform in the pharmaceutical industry’s quality control. Gupta and coauthors developed ISEs for the assay of three antiepileptic pharmaceutical drugs, named lamotrigine, felbamate, and primidone, in their pharmaceutical products and biological samples [41]. The established electrodes were dependent on PVC membranes doped with drug-TPB or drug-phosphotungstic acid (PTA) ion-pair complexes as molecular identification substances. The developed electrodes have exhibited rapid Nernstian responses with detection limits of 10⁻⁷ M. The proposed membranes have lifetime stability of about 1 month, and have offered a high selectivity for the three mentioned drugs in the presence of other ions and dosage form excipients. The suggested electrodes were effectively used for the assay of these drugs in their pharmaceutical products in four batches of various expiry dates. For the detection of lomefloxacin hydrochloride, LOM, two potentiometric approaches were proposed through in-house developed ISEs [42]. Various sensors were established by employing a PVC-based membrane, potassium tetrakis(4-chlorophenyl) borate as a cation exchanger, and o-NPOE as a plasticizer (sensor I). To improve the selectivity of sensor I, a specific molecular identification material (2-hydroxypropyl-β-cyclodextrin) was applied as an ionophore (sensor II). The developed potentiometric sensors have exhibited a linear dynamic range of 1 × 10⁻⁵—1 × 10⁻² M, with Nernstian slopes of 55.829 and 58.229 mV/decade for sensors I and II, respectively. The LODs were calculated to be 6.31 × 10⁻⁶ and 5.01 × 10⁻⁶ M for electrodes I and II, respectively. What’s more, the developed platforms have been utilized for the detection of LOM in the pure state, various pharmaceutical products, and human serum samples with high recoveries. An ISE for the assay of ticlopidine (Tic) was developed based on PVC involving Tic-TPB as the sensing component and DOP as a plasticizer [43]. The electrode has shown a linear calibration curve for Tic of 1.0 × 10⁻²—5.0 × 10⁻⁵ M. Interestingly, the electrode response time is very fast (≤ 10 s) and the electrode potential is nearly constant over the pH range 3.8–5.4. The electrode has shown excellent selectivity for Tic detection in the coexistence of a different number of inorganic ions, amino acids as well as some drugs. The sensor has been applied for the assay of Tic in dosage forms and biological fluids.

Nesma et al. proposed a PVC membrane sensor for the detection of a benzodiazepine drug called bromazepam (BMZ) [44]. The sensor was dependent on the application of the ion association complex of BMZ-TPB as ion exchange positions in a PVC matrix plasticized with dibutyl sebathete (DBS). The developed method has given a linear concentration range of 1 × 10⁻⁶—1 × 10⁻² M with a rapid response time (20–30 s) and a long sensor stability of about 4–6 weeks. The sensor was applied for the detection of BMZ in pharmaceutical products and plasma samples. Validation of the proposed method confirmed the suitability of the developed sensor for its application in the quality-control assessment of BMZ. Mina and Ahmed proposed the first potentiometric sensor for the detection of olanzapine (OZ) [45]. The developed sensor was based on using modified CPE with an OZ-tungstophosphate ion pair for the analysis of OZ in real samples. The modified electrode has exhibited a linear range for OZ detection of 7.5 × 10⁻⁷—5.6 × 10⁻⁴ M with a LOD of 5.0 × 10⁻⁷ M. Also, it has shown a fast response of around 4 s and long lifetime stability (2 months). The developed sensor has been utilized for the detection of OZ olanzapine® tablets dosage form and human serum. Two kinds of electrodes (plastic membrane A and coated wire B) were fabricated for the determination of pentoxifylline (PF) dependent on the combination of PF with PTA [46]. By applying the optimized conditions, the electrodes have displayed a linear response for PF concentration ranges of 1.0 × 10⁻⁵—1.0 × 10⁻² and 9.0 × 10⁻⁶—1.0 × 10⁻² M, with limits of detection of 4.89 × 10⁻⁶ and 3.90 × 10⁻⁶ M for electrodes A and B, respectively. The suitable pH range of the proposed electrodes was 4–6. The proposed electrodes have shown suitable selectivity in the existence of different species (metal ions, alkaloids, amino acids, sugars, and dosage form excipients). The developed electrodes were also employed for assessing the PF in its pharmaceutical products and body fluids (urine and serum) with excellent recoveries.

A novel ion-pair complex between desipramine hydrochloride (DH) and TPB has been synthesized and incorporated into a PVC-based membrane sensor for the detection of DH in various pharmaceutical products [47]. The proposed sensor has demonstrated a Nernstian response in the concentration range of 2.2 × 10⁻⁶—1.0 × 10⁻² M (LOD = 1.2 × 10⁻⁶ M). The membrane sensor worked satisfactorily over the pH range of 2.8–7.4 with a rapid response time of 12 s. The developed sensor can tolerate
a non-aqueous content of up to 20%, and can be used for the detection of DH content in its tablet dosage form and in biological fluids, such as urine and plasma samples. Interestingly, DH concentration in the blood sample was higher than in the urine sample, and the authors have clarified this as that most of the DH was digested in the liver before being excreted in the urine. Amr reported for the first time the application of Aliquat 336S-atorvastatin as an electroactive substance in a PVC matrix membrane sensor plasticized with α-NPOE or DOP for the assay of atorvastatin in the biological fluid (human plasma) and in pharmaceutical products [48]. The sensors have displayed a rapid (8–12 s), stable and reproducible response over the concentration range of 1.0 × 10⁻⁷—1.0 × 10⁻² M. Results were achieved with average recoveries of 99.5% and 99.3% for α-NPOE and DOP plasticized based membrane sensors, respectively. The sensor has shown excellent selectivity for atorvastatin detection in the existence of numerous anions, drug excipients as well as diluents. Marwa and Rasha developed two new ISEs of a plastic membrane type for the detection of Tolterodine (Tol) [49]. These electrodes were based on the incorporation of ion-exchangers of Tol with PTA or silicotungstic acid (STA) in a PVC matrix. The developed electrodes have linear ranges of 1.0 × 10⁻⁵—1.0 × 10⁻² and 5.0 × 10⁻⁵—1.0 × 10⁻² M under batch and FIA conditions, respectively. The electrodes have displayed a high selectivity to Tol in the existence of several metal ions, and could be applied for the detection of Tol in real samples (urine and plasma). Novel, facile, fast, and selective potentiometric sensors for estimating neostigmine (Ns) in its pure powder, various pharmaceutical products, and body fluids were developed [50]. The fabricated sensors were dependent on using four modified CPEs. Sensor A relied on an ion-association Ns-TPB, sensor B used an Ns-PTA, sensor C involves a mixture of Ns-PTA + Ns-TPB and sensor D was fabricated utilizing Ns-PT + β-CD. 2-nitrophenyl phenyl ether (2-NPPE) as a solvent mediator has shown a suitable response (1.0 × 10⁻⁷-1.0 × 10⁻² M) and the LOD was calculated to be 6.3 × 10⁻⁸ M. Also, the proper pH range was found to be 3.8–10 for the four sensors. The response time is very short (≤ 10 s). By applying FIA, sensor C has displayed a linear range for Ns detection of 1 × 10⁻⁶ to 1 × 10⁻² M (LOD = 7.5 × 10⁻⁷ M). Compared to sensors A and B, the use of mixed or β-CD additives affected remarkably the sensitivity of sensors C and D. The cited drug has been detected using the potentiometric sensors in the standard authentic powder, various pharmaceutical preparations as well as biological fluids, such as plasma and urine. Ahmed and Mazahar developed a potentiometric CPE dependent on integration of the ion-association complex of the carvedilol-PTA for the detection of carvedilol (CV) in carvedilol® tablets, plasma and urine samples [51]. The electrode has demonstrated a Nernstian slope of 58.7 mV/decade over a wide concentration range of 3.0 × 10⁻⁷—1.0 × 10⁻³ M with a LOD of 1.5 × 10⁻⁷ M. The developed sensor has displayed several advantages, including rapid response, long working stability, and proper selectivity for CV in the presence of several inorganic cations, natural molecules which are founded in the biological fluids, and other β-blockers. The sensor was effectively applied as an indicator electrode in potentiometric titration, as well as in the potentiometric assay of CV in carvedilol® tablets, plasma, and urine samples. The formation of the inclusion complex (IC) between α- and β-cyclodextrin and CV was checked potentiometrically by the developed sensor and the formation constant of the IC was estimated using the proposed method.

For the detection of venlafaxine (VL) in a market product and serum, Marwa et al. proposed potentiometric sensors dependent on applying the ion association complexes of the VL cation with PTA and ST counter anions as ion exchange positions in the plasticized PVC matrix [52]. The electrodes have displayed a rapid response (15 s), long lifetime (45 days), and good correlation coefficient (r² = 0.995), for VL over a linear range of 5 × 10⁻⁵—1 × 10⁻² M. Remarkably the electrodes exhibited excellent selectivity, and reproducibility (RSD < 1%) and also were appropriate for a VL assay in pure powder, a pharmaceutical formulation and a serum biological fluid, without any interference. Another potentiometric sensor for the determination of VL was constructed by Ensafi et al [53]. The potentiometric sensor was based on VL-TPB (ion-pair) as an electroactive substance and DBP as a plasticizer in a PVC matrix. The sensor has shown a linear response for VL detection of 8.0 × 10⁻⁶—1.0 × 10⁻² M (LO D = 5.0 × 10⁻⁶ M) over the pH range 3.0–9.0. The selectivity study for the detection of VL was investigated in the presence of different potential interfering molecules. The sensor was found to be highly selective for VL over a large number of similar molecules. The sensor was characterized by its fast response (10 s), long life span (around 2 months), and good repeatability. The sensor was effectively employed for VL detection in dosage forms, urine and serum samples with acceptable results. Mohamed et al. developed CPEs using flowered-like Mg–Al layered double hydroxides/MWCNTs (FLLDH/MWCNTs) (sensor I), FLLDH/titanate nanotubes (TNTs) (sensor II) and MWCNTs/TNTs (sensor III) nano-composites for bambuterol hydrochloride (BAM) detection [54]. MWCNTs were fabricated by applying chemical vapour deposition (CVD), while TNTs were fabricated by employing the hydrothermal strategy under alkaline conditions. Flower-like LDH was fabricated by dissolving a mixture of Mg(NO₃)₂ as well as Al(NO₃)₃ (ratio, 2:1) in distilled water containing sodium dodecyl sulfate and urea. The developed sensors have displayed high sensitivity with
low LOD values of $2.3 \times 10^{-6}$, $2.5 \times 10^{-7}$ and $7.5 \times 10^{-8}$ M for sensor I, II and III, respectively. The selectivity of the proposed sensors has been checked for the biological blood electrolytes. The proposed potentiometric approach has been effectively employed for BAM detection in pure form, pharmaceutical preparations, surface water, human plasma and urine samples with excellent recoveries (99.62, 99.10 and 98.95%) for sensors I, II and III, respectively.

Other potentiometric sensors for the detection of an important antipsychotic drug (Ziprasidone Hydrochloride, ZD) in pharmaceutical samples, and body fluids were developed by Vinod and coworkers [55]. The sensors were relied on using ZD-TPB, chlorophenyl borate (ZD-CIPB), and ZD-PTA ion association complexes as molecular identification materials dispersed in a PVC matrix with DBP as a plasticizer for the assay of ZD. The three membranes have shown a rapid, stable and linear response for ZD over the concentration ranges of $8.5 \times 10^{-6}$—$1.0 \times 10^{-2}$, $3.9 \times 10^{-6}$—$1.0 \times 10^{-2}$, $7.7 \times 10^{-7}$—$1.0 \times 10^{-2}$ M, respectively. The potentiometric detection of ZD in various pharmaceutical products and body fluids has been obtained without any obstruction from different excipients and diluents frequently applied in the drug dosage form. Validation of the proposed approach confirmed the appropriateness of the developed electrodes for the quality control assessment of ZD. The proposed potentiometric membranes offered the merits of high-throughput detection, facility, precision, automation possibility and applicability to both turbid and colored sample solutions. Hebatallah et al. developed six potentiometric sensors for the detection of codeine phosphate (COD) in the co-existence of ibuprofen drug in pharmaceutical preparations and biological fluids [56]. Sensors 1–3 used the traditional liquid inner contact, and sensors 4–6 are solid-state sensors (gold: sensor 4, modified SPE with MWCNTs: sensor 5 and gold nanoparticles GNPs-SPE: sensor 6). Potassium tetrakis (gold: sensor 4, modified SPE with MWCNTs: sensor 5 and p-chlorophenyl borate. This membrane was typically constructed by incorporating a suitable ion exchanger and solvent mediator into a PVC membrane matrix. The potentiometric response was linear over a drug concentration range of $1 \times 10^{-6}$—$1 \times 10^{-2}$ M. The established electrochemical approach has been effectively employed for the detection of PR in the pure state, pregabalin capsules and human plasma without any interference. For the quality control assessment of torasemide (TOS), four TOS-selective electrodes were established and characterized in PVC matrices [58].

An ISE strategy for the detection of pregabalin drug (PR) in pure powder, dosage form and plasma was proposed [57]. The mechanism for constructing this sensor relied on the fact that PR behaved as a cation in an acidic medium, and could form a precipitate with anionic potassium tetrakis p-chlorophenyl borate. This membrane was typically constructed by incorporating a suitable ion exchanger and solvent mediator into a PVC membrane matrix. The potentiometric response was linear over a drug concentration range of $1 \times 10^{-6}$—$1 \times 10^{-2}$ M. The established electrochemical approach has been effectively employed for the detection of PR in the pure state, pregabalin capsules and human plasma without any interference. For the quality control assessment of torasemide (TOS), four TOS-selective electrodes were established and characterized in PVC matrices [58].

The precipitation-based approach with TPB as an electroactive substance in a PVC matrix was employed for sensor A development without the incorporation of any ionophore. While the 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) based technique with TPB and either DOP, dibutyl sebacate (DBS) or O-NPOE as plasticizer in carboxylated polyvinylchloride (PVC-COOH) matrix were applied for fabricating sensors B, C, and D, respectively. Rapid and stable responses were achieved in concentration ranges of $1 \times 10^{-5}$—$1 \times 10^{-3}$, $1 \times 10^{-5}$—$1 \times 10^{-2}$, $1 \times 10^{-6}$—$1 \times 10^{-4}$, $1 \times 10^{-6}$—$1 \times 10^{-3}$ M for sensors A, B, C, and D, respectively. The sensors display excellent selectivity to the drug in the occurrence of several inorganic and organic interfering species involving acid degradation products of torsemide, related substances and dosage form excipients. Another report has been published by Mahmoud and co-authors for estimating olopatadine hydrochloride (OP) and oxeladin citrate (OL) in pure states, dosage forms, and human plasma [59]. The estimated potentiometric sensors relied on the formation of drug-TPB ion-pairs as electroactive components in plasticized PVC matrix membranes with o-NPOE. The two potentiometric sensors have exhibited Nernstian responses over concentration ranges of $1.0 \times 10^{-5}$—$1.0 \times 10^{-2}$ M and LOD of $5.0 \times 10^{-6}$ and $4.4 \times 10^{-6}$ M for OL and OP, respectively. However, the response times were observed to be 18 and 3.0 s for OL and OP, respectively. The suitable pH ranges were 3.0–4.5 and 2.5–8.5 for OL and OP, respectively. The lifetimes were found to be very long (3 months) for both sensors. The sensors were effectively applied for the monitoring of OL and OP in pharmaceutical products with excellent recoveries. Furthermore, the OL sensor was employed for quantifying the OL in human plasma with an average recovery of 99.49%. An effective ISE for the detection of citapolarm hydrobromide (CT) in pure powder, urine and
plasma was developed [60]. ISE was based on the formation of CT-TPB ion-pair complex as an electroactive substance in the existence of DOP as the plasticizing solvent mediator. The electrode has shown a linear response for detection of CT within the range of $1.0 \times 10^{-6}$—$1.0 \times 10^{-2}$ M. The electrode was used for estimating the CT in pure powder, urine and plasma by standard addition technique.

Conclusion and outlooks

During the past two decades, significant growth has been achieved in the field of polymeric membrane ISEs, while aiming to enhance the system performance, gaining a deeper understanding of their response mechanism, discovering new materials and configurations, and proposing new sensing approaches. Remarkable improvements in the sensitivity, specificity, stability and versatility of potentiometric sensors have been obtained that allow different analytes to be measured with unprecedented precision.

On the other hand, the detection of drug molecules in body fluids and market products is of high significance in several areas involving the analysis of drug metabolism, clinical and environmental monitoring, drug availability, safety assessment, and drug toxicity. Although several analytical methods were reported for the detection of pharmaceutical drugs in real samples, these methods suffered from many disadvantages such as complicated analytical procedures, low sensitivity, and low selectivity. With the recent progress in the fabrication of potentiometric sensors, potentiometric sensors are now hugely employed as sensing biosensors for the detection of different drugs in their market products and body fluids. This is attributed to their several merits, such as excellent selectivity, fast response, high sensitivity, simple instrumentation, and cost-effectiveness. Moreover, the implementations of these sensing platforms.

Due to recent advances in ISEs and the increasing availability of various nanomaterials [61–66], we expect that, much more attention from researchers will be increased concerning the fabrication of selective ISEs and nanomaterials-based potentiometric platforms for pharmaceutical drug analysis in different dosage forms, quality control, and quality assurance of drug molecules, and TDM in biological fluids. We believe that the use of new materials will enhance the LOD, selectivity, sensitivity, biocompatibility, lifetime, and sensor working stability of ISEs. Also, we think in the future the integration of microfluidic-based analytical devices (μPADs) with potentiometric ISEs will be helpful as interesting sensing tools and detection devices for pharmaceutical drug analysis. Moreover, we think that more important potentiometric platforms for several other pharmaceutical drugs will be proposed, and thus spreading the implementations of these sensing platforms.

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