

A REVIEW OF THE DETERMINATION OF DICLOFENAC SODIUM WITH ELECTROCHEMICALLY MODIFIED SENSORS IN VARIOUS BIOLOGICAL, PHARMACEUTICAL AND WATER SOURCES

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Diclofenac sodium (DCF) has attracted much attention because it is one of the most common pharmaceuticals in water matrices and can potentially harm aquatic life. Although most techniques used to analyze it are expensive and require highly trained professionals to operate such equipment, it is possible to detect DCF with electrochemical sensors. Despite being able to identify this contaminant in different samples (tablets, blood, urine), only a few articles have been reported regarding the testing of DCF in wastewater. Therefore, the papers selected in this review were organized according to the type of modifier used in the working electrode. Furthermore, recent improvements in the detection of diclofenac by electrochemical techniques in pharmaceutical formulations, biological fluids and environmental materials are discussed along with a brief description of the results and methods employed in research.

Keywords: diclofenac sodium, wastewater, modifier, electrochemical detection

1. Introduction

Over recent decades, industry and the global population have been growing rapidly, leading to an increase in the anthropogenic emission of contaminants into the environment, especially into water sources, which has greatly increased over the past few years [1]-[2]. As a result, different types of contaminants in water sources are gradually becoming more common. Even if only at trace levels, they are harmful to the environment, animals and human health [3]-[4], perhaps causing several toxic side effects such as changes in behavior, the inhibition of cell proliferation and reproductive damage. Furthermore, studies have shown that high concentrations of antibiotics cause several changes to the structure of bacteria, bringing about resistance to many strains and greatly affecting the food chain, which may contaminate sources of drinking water [5]-[6]. Among these antibiotics, diclofenac sodium (DCF), which is a commonly used human and veterinary pharmaceutical prescribed to reduce inflammation and manage pain, has attracted much interest because it is one of the most common pharmaceuticals in water matrices and has the

potential to harm aquatic life [7]-[8]. It enters the water bodies through wastewater treatment plants, whereas most diclofenac residues in animals are released directly into the ecosystem [9]. Moreover, unused and expired diclofenac from households is disposed directly into water sources down sinks or toilets [9].

Consequently, several analytical methods have been developed to quantify the concentration of DCF in pharmaceutical and biological samples such as chromatographic methods (liquid chromatography (LC), gas chromatography-mass spectrometry (GC-MS)), tandem mass spectrometry, capillary zone electrophoresis (CZE), spectrophotometry [11]-[12] and spectrofluorimetry [13]-[14], which are very sensitive with low limits of detection (LOD) but require organic solvents, costly apparatus and highly qualified specialists, moreover, sample preparation is mandatory prior to analysis, making them unsuitable for screening [10]. In comparison, potentiometric sensors are environmentally friendly, simply designed, portable for in situ monitoring, require tiny samples as well as yield sensitive and reliable results cheaply [10].

In addition, one of the most important developments to enhance drug detection and increase the

electron transfer rate on the surface of the electrode is electrode modification, which can be achieved by designing a highly electroconductive, stable modifier equipped with a high-degree molecular recognition system, an active area, large surface binding sites and excellent catalytic activity [15]. A good example of this are TiO₂ nanoparticles which are versatile compounds extensively applied as a catalyst in various fields [56]. Their properties and characteristics contribute towards its effectiveness in catalytic reactions, moreover, can be used as a modifier in electrochemical sensing.

However, since the novel determination techniques have not been widely studied for analyzing the concentration of DCF in sources of wastewater, they may be developed and applied in this respect to improve the precision of measurements and reduce costs. In this study, the most promising and viable methods for creating electrochemically modified sensors to assess the concentration of DCF in various sources (blood, urine, wastewater, groundwater) are presented based on performance characteristics such as pricing, limit of detection, preparation technology, linear range and selectivity/chemical interference (Figure 1).

These methods are illustrated in the form of tables and graphs. Finally, in the future, the compiled information will be expanded to prepare electrochemically modified sensors to determine the concentration of DCF in groundwater, wastewater and municipal water, providing an easy, fast and cheap way of measuring this contaminant globally, particularly in, for example, South America and Africa, where the technology to perform the cited analytical methods is lacking.

2. Experimental

2.1. Literature review - theoretical methodology

This analysis included publications from Scopus, ScienceDirect and the Web of Science (WoS) database as well as searched for using Google Scholar. Except for a few additional publications due to their academic value, articles published between 2015 and 2022 were preferred. In terms of the literature review and selection of articles, at least two key phrases in search strings were evaluated. The first word refers to the material the working electrode is composed of (glassy electrodes, glassy carbon electrodes (GCEs), multiwalled carbon nanotubes (MWCNTs), carbon nanotubes (CNTs), single-walled carbon nanotubes and metals), while the second refers to surface modification techniques (imprinted, coating and cyclic voltammetric techniques). Only literature published in English up until October 10, 2022 was evaluated. A systematic review and meta-analysis using published simulated data [16] were used to assess the manual examination of the published studies selected.



Figure 1: Various modified electrodes for the electrochemical determination of DCF in different sources

2.2. Qualification analysis of the literature

The considered publications were downloaded in a separate folder in order of the authors and entitled after the material the working electrode is composed of as well as the method used to make it. The titles and abstracts of these publications were selected based on their primary content. Finally, the core idea and key findings of each study were extracted and compared to the other articles published.

2.3. Data extraction and analysis

The data from the publications were separated into two groups according to the baseline data they contain, as stated in the preceding sections. Literature based on characteristics such as the accessible technology in the electrochemistry laboratory at Babes-Bolyai University, year of publication, place of origin, nature of the study, type of article, study area and study design were prioritized. Afterwards, the type of low-cost working electrode and electrochemical surface modification technique(s) used, modification category, in-depth discussions on the surface characterization techniques applied (Electrostatic Force Microscopy (EFM), Energy Dispersive X-Ray Analysis (EDX), Fourier-transform Infrared Spectroscopy (FTIR), analysis of Cyclic Voltammograms (CV), Electrochemical Impedance Spectroscopy (EIS)) as well as sample preparation were the most popular criteria for searching and extracting data from the chosen publications. The important data from the analysis were originally organized in a table to examine it clearly and statistically. IBM SPSS statistical software version 17.0 (IBM Corp., TX, USA, 2021) was employed to analyze the collected data. Hungarian Journal of Industry and Chemistry provided a limited amount of disk space to distribute electronic supporting information.

3. Results and analysis

3.1. Statistical results

100 valuable published studies were retrieved following a thorough statistical analysis, the majority of which were from WoS-indexed journals. 40 studies were eliminated because of duplicated downloads, reducing the number to 60. 20 more publications were eliminated from this total of 60 owing to a lack of importance and in-depth analysis. Furthermore, 12 records were temporarily omitted because of a lack of information and their years of publication, resulting in just 28 articles being considered. The importance of the research published in these studies was briefly reviewed below and the results classified according to their field of development and year of publication.

3.2. Electrochemical sensors to determine the diclofenac concentration

Electrochemical sensors are by far the most commonly used type of sensor because of their advantages, which include limits of detection as low as picomoles, rapidity and the low-cost equipment used for sensing. The analytical information in electrochemical sensors is derived from the electrical signal produced by the interaction between the target analyte and recognition layer [54]. The following focuses on potentiometric sensors that analyze specific interactions between sensors and analytes. When no current is allowed to flow through the system, a Nernstian equilibrium is formed at the sensor interface, providing information about the concentration of the analyte.

In this regard, it is critical to account for the chemical reaction that will occur on the surface of the electrode in order to detect diclofenac. Previously, the oxidation mechanism of the drug (see *Figure 2*) was studied in which the oxidation peak that occurs between 0.65 and 0.70 V that is sensitive to changes in the pH of the electrochemical system is clearly visible [34]. Furthermore, in the presented mechanism, DCF is irreversibly oxidized to 5-hydroxydiclofenac in a process of losing $2e^-$ and $2H^+$ giving rise to an oxidation peak at ~ 662 mV when the sweep was initiated in the positive direction. 5-hydroxydiclofenac is reduced as a result of the successive cathodic sweeps to diclofenac 2,5-quinone imine. During the second anodic sweep, a new oxidation peak was observed relating to the oxidation of diclofenac 2,5-quinone imine, involving $2e^-$ and $2H^+$ [45].

Therefore, it is necessary to create a surface that allows the reaction mechanism to occur beneath its surface. It is also necessary to determine what surface characteristics are preferable and their level of importance in influencing the peak potential, thereby changing the sensing characteristics. As a result, the information compiled in the following sections is divided according to how the surface electrode was modified and the characteristics of the sensors.

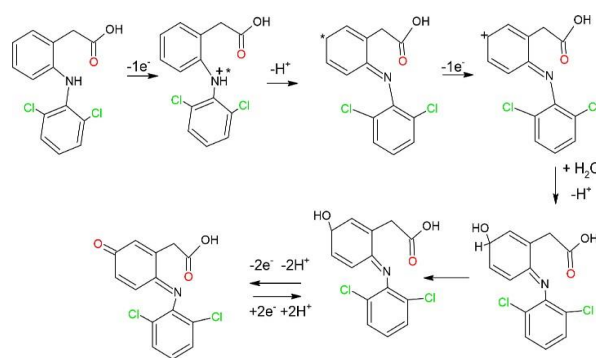


Figure 2: Oxidation mechanism of DCF proposed by [45] at pH 7.0 under a GCE modified with MWCNTs

3.3. Diclofenac detection using CNTs as a modifier

Several studies were conducted using a GCE modified with carbon nanotube composites as a working electrode for determination. Furthermore, the working electrode was modified by incorporating f-MWCNTs which provide a larger surface area, a high degree of mechanical strength and improved electrical conductivity. Diclofenac is found in different sources, namely commercial tablets and human biological fluids [17]-[28], due to its low cost and easy fabrication as well as techniques available to fabricate the sensors. As a result, these types of electrodes are still the most commonly used. Furthermore, the broad range of pH, from acidic to basic environments (4-8), facilitates different applications, thereby ensuring their robustness.

The mechanism cited in Section 3.1 can occur at the surface of the modified electrochemical sensor using GCE/CNT sensors, ensuring accurate identification of the drug present in different samples. For example, the GCE was modified using nanocellulose/MWCNTs prepared by drop-casting techniques and the contaminant was tested using differential pulse voltammetry (DPV) [49]. The working concentration range reported by this sensor was $0.1 - 0.5 \mu\text{M}$ with a LOD of $0.0012 \mu\text{M}$. The applicability of the sensor was tested on samples of human blood and urine obtained from different patients. In contrast, GCE sensors that were not modified reported a low limit of detection when the tables were analyzed within a linear range and LOD equal to $0.01 - 0.05 \mu\text{M}$ and $0.0053 - 1.6 \mu\text{M}$, respectively [27]. Although the concentration of diclofenac was determined using the same technology (DPV) in all tests, the pH varied allowing how the pH affects the extent of the reaction to be observed. Furthermore, modified GCEs have a large electroactive surface area, ensuring that the reactions can occur in the sensor. In addition, working electrodes modified by MWCNTs have piqued the interest of researchers due to their unique properties such as increased surface area, sharp electrochemical response, good adsorption capacity, improved chemical stability, significant electrical conductivity and increased mechanical strength.

Table 1: Principal outcomes in the determination of the diclofenac concentration in different sources using CNTs as a modifier in working electrode

Modifier	Method	Linearity (μM)	LOD (μM)	Ref.
NC-fMWCNTs-CuN/GCE	SWV	0.05 - 80	0.00048	[48]
MWCNTs	DPV	0.047 - 12.95	0.017	[30]
NC-fMWCNTs-CuN	SWV	0.05 - 80	0.00014 - 0.00048	[49]
MWCNTs-Chitosan	SWV	0.3 - 200	0.021	[25]
Nanocellulose/f-MWCNTs	CV	0.05 - 50.00	0.2	[26]
Cellulose/f-MWCNTs	DPV	0.05 - 1.00	0.0012	[49]
Non-Modifier	DPV	0.01 - 0.05	0.053 - 1.6	[27]

The majority of the current trends in the preparation of sensors modified by MWCNTs is summarized in *Table 1* in which the major parameters used to describe the differences between the various manufactured sensors, that is, the modifier, electrochemical technique used for determination, linearity, LOD and source of the analysis, are presented. Furthermore, since fabrication of these modified sensors is simple, large-scale production, the use of relatively low-cost materials and the potential to be used over a wide concentration range of DCF is possible.

In addition, this type of sensor can ensure accurate analyses within seconds as fast scan rates can be used without the need for bulky expensive equipment, solvents and special gases. When the baseline correction (the moving average) is performed in a high potential region, interference with the peak height of the analyte occurs due to the presence of high background currents following the onset of oxygen evolution and possibly carbon oxidation reactions, making the determination of compounds above +0.8 V unreliable. Finally, the modified sensors demonstrate remarkable electrocatalytic activity in the electro-oxidation of DCF by dramatically lowering the oxidation overpotential and increasing peak currents. To detect DCF concentrations, the modified electrodes demonstrated a low LOD, wide linear concentration range and quick response as well as high degree of stability and repeatability [21].

3.4. Diclofenac detection using GO as a modifier

Researchers have shown much interest in graphene and its derivative graphite because of its remarkable electrical characteristics resulting from the arrangement of carbon

atoms in a perfect honeycomb lattice. The backbone is comprised of hybridized sp^2 orbitals which are important in sensing applications because they allow graphene-based materials to interact with their environment and convert these interactions into a readable electrical signal [45]. Furthermore, within the internal structure of graphene and its derivatives, a phenomenon known as ballistic transport occurs in which electrons travel less than a micrometer without scattering. As a result, graphene-based sensors are extremely electrically robust [46]. Nevertheless, under ambient conditions, the mobility of charge carriers is still limited by impurity scattering which decreases the sensing ability in wastewater samples [46]. On the other hand, thanks to a strong ambipolar electric field effect, graphene can be electrically doped by transferring the charge carriers between electrons and holes. This is critical in the field of water quality monitoring since selectivity for the desired analyte is essential and graphene may be readily doped with a wide variety of compounds [47].

For example, the performance of the sensor was improved by adding carboxyl-functionalized graphene oxide to it [23]. Under normal conditions, the LOD of the sensors was low, that is, equal to 0.09 μM which was 10 times lower than that of the graphene sensors prepared without a modifier, when tested in urine [29].

To summarize, graphene oxide-modified electrodes are resilient because of the electrical properties of graphene and a key feature is the ability of graphene to be doped by p- and n-doping, facilitating the inclusion of chemically sensitive diclofenac. The price of the prepared sensors, on the other hand, is the key hurdle in the implementation of this type of sensor in the industry. However, if it is possible to integrate low-cost analyses, the demand for wastewater analysis will skyrocket. Finally, the pencil graphite electrode (PGE)-modified sensors offered a high degree of sensitivity and low LOD, moreover, can be used to determine diclofenac concentrations at trace levels. These characteristics make them an appropriate type of sensor for determining the concentration of DCF in aqueous solutions (*Table 2*).

3.5. Diclofenac detection using nanoparticles of metals or metal oxide particles as a modifier

Metals and alloys have been widely studied in the construction of sensors to identify different contaminants in water. The metals gold and titanium in particular have a huge range of applications due to their high electrocatalytic activity and mechanical properties (see *Table 3*). Consequently, a new electrochemical sensor based on Au-Pt bimetallic nanoparticles supported on MWCNTs which have a large specific surface area, exhibit high electrical conductivity and can significantly facilitate the electron transfer process of the redox probe on the electrode surface was produced [41]. Furthermore, a linear calibration curve within the concentration range of 0.5 to 1000 μM was obtained. The LOD of the prepared sensor was 0.3 μM . Finally, the presence of interfering species in the solution had no significant

Table 2: Principal outcomes regarding the determination of the diclofenac concentration in different sources using graphite oxide as a modifier in working electrode

Modifier	Method	Linearity (μM)	LOD (μM)	Ref.
GO/COOH	CV, LSV	1.2 - 400	0.09	[23]
Non-Modifier	DPV	0.80 - 9.5	0.76	[29]
GO/ZnO	SWV	18.01 - 1	5.06	[31]
GO/ Co(OH) ₂ / CNF	CV, SWV	3.7 - 140	0.05	[27]
GO/Ag/ZnO	DPV	0.025 - 200	0.02	[27]
GO/Cu	CV	20 - 400	0.08	[52]

effect on the DCF current response and the changes in peak current were $< 5\%$.

Additionally, iron oxide nanoparticles functionalized with ionophoric polymer β -CD were applied to detect diclofenac in wastewater [42]. The sensor achieves an LOD equal to $0.11\ \mu\text{M}$ as well as the highest degree of selectivity towards DCF anions in the presence of organic compounds and some inorganic anions that may exist in pharmaceutical dosage forms which are likely to be present in wastewater. Finally, the results of dosage-form and wastewater analysis showed the applicability of the sensors in terms of both quality control and environmental studies without the need for sample treatment beforehand.

The application of metal-decorated particles in contaminant sensing is evident as a result of the electrochemical performance of the electrode, which is determined by its electrical conductivity and accessible surface areas. Therefore, the electrochemical performance of sensors can be improved by building composites from mixing highly electrocatalytically active materials with outstandingly conductive substances to change the electrode surface. Furthermore, the modification of metallic electrodes is one of the most important developments to increase drug detection and the electron transfer rate at the electrode surface [47].

3.6. Diclofenac detection using polymers as a modifier

One of the most successful potentiometric sensors in use today, primarily in clinical analysis and quality control, is based on conductive polymeric membranes with ionophores incorporated directly into the polymeric matrix [33]. Furthermore, some polymers can modify the internal structure of the working electrodes (*Table 4*). For

Table 3: Principal outcomes in the determination of the diclofenac concentration in different sources using nanoparticles of metals or metal oxides as a modified in working electrode

Modifier	Method	Linearity (μM)	LOD (μM)	Ref.
CeO ₂	DPV	0.4	0.4 - 1.6	[20]
AuNPs/ MWCNTs	CV	0.03 - 200	0.02	[21]
GO/Cu/ Doped Zeolite	DPV	3.01 - 15	0.3	[36]
MoS ₂	CA	0.05 - 600	0.03	[37]
Ru/TiO ₂	CV	0.291	11.48	[38]
Au/MWCNTs/ GO	CV	0.4 - 1000	0.09	[39]
Hg/GO	CV	0.002 - 5	0.32	[40]
Au-Pt/ MWCNTs	CV	0.5 - 1000	0.3	[41]
Fe ₃ O ₄ / iontophoretic polymer	CV	0.001 - 0.1	0.11	[42]
C ₃ N ₄ /CuAl	DPV	0.5 - 60	0.38	[53]

example, an imprinted electrochemical sensor based on a polyaniline nanocomposite was prepared [32]. The electrochemical studies of the prepared sensor demonstrated a change in the peak-to-peak separation equal to $0.248\ \text{V}$ due to a more reversible charge-transfer process on the polyamide-printed electrode than that on the PGE electrode which may be attributed to a possible catalytic effect of the added nanocomposite on the carbon paste [46]. In addition, the evaluated surface areas of the PGE and Polyamide-PGE electrodes were found to be 0.013 ± 0.001 and $0.019 \pm 0.002\ \text{cm}^2$, respectively, an enhancement in the active surface area of the modified electrode of about 46% when compared to the unmodified PGE electrode. Furthermore, the calculated average concentration ($22.7 \pm 2.0\ \text{mg L}^{-1}$ of DCF) demonstrated that the proposed sensor can be appropriately reproduced. Finally, the tolerance limit was determined as the concentrations of foreign substances, yielding an error of less than $\pm 5\%$. The variation in the peak height observed for DCF in the presence of the tested species (ascorbic acid, glucose and urea) in the

Table 4: Principal outcomes in the determination of the diclofenac concentration in different sources using polymers as a modifier in working electrode

Modifier	Method	Linearity (μM)	LOD (μM)	Ref.
MAA/EGDMA	CV	Not reported	5	[24]
TiO ₂ /PEDOT	CV	0.715 - 1.62	0.02 - 0.03	[28]
GO/Polyamide	CV	1.61	1.2	[32]
GO/Polypyrrole	CP	0.011 - 0.310	19	[33]
PDMS/PC	CV	1.01 - 5.01	5	[43]
PVC	CV	0.005 - 0.5	0.32	[44]
MIP	CV	Not Reported	0.077	[32]

ratios of 1:1–1:1000 (DCF to interfering substances in mol L⁻¹) confirms that the presence of different interfering species did not significantly affect the efficiency of the sensor, even when their concentration was 1000 times greater than that of the analyte [32].

3.7. Diclofenac detection using ionic liquids as a modifier

Potentiometric methods using ionic liquid electrolytes (ILE) are appealing alternatives to drug detection because they require simple procedures and low-cost electrodes in addition to offering a good degree of selectivity and sensitivity [34]. Recently, ILEs have been used as the paste binders for fabricating carbon composite electrodes (*Table 5*), which provide an obvious increase in the electrochemical response of electroactive substrates and reduce the overpotentials of some organic substances [35]. In this sense, a sensor based on the combination of MWCNTs and Butyl-imidazole, Propargyl bromide used as an ionic liquid [34]. The aforementioned sensor achieves a LOD equal to 0.018 μM and a linear range equal to 0.05 - 50 μM . Furthermore, the stability of the proposed electrode was evaluated by measuring the decrease in CV current of DCF after having been stored for one month. The CV response decreased by only 5 %, indicating that MWCNTs-IL is sufficiently stable. The author concluded that the main advantage of using the MWCNTs-IL is facile and quick surface renewal after each use, moreover, the MWCNTs-IL composite-modified carbon ceramic electrode exhibits high electrocatalytic activity with regard to the oxidation of DCF.

Table 5: Principal outcomes in the determination of the diclofenac concentration in different sources using ILs as a modifier in working electrode

Modifier	Method	Linearity (μM)	LOD (μM)	Ref.
MWCNTs-IL	DPV	0.05 - 50	0.018	[34]
GO/[bpim][dcbf]	DPV	3.18 - 0.318	0.015	[35]
MWCNTs/ Cu(OH) ₂ nanoparticles/ IL nanocomposite	DPV	0.18 - 119	0.04	[52]

4. Conclusions

This review includes the most inexpensive technologies for preparing electrochemically modified sensors to determine the diclofenac concentration in different samples (urine, blood, tablets). The different technologies were differentiated by the type of modifier that the different researchers used to construct the sensors which improve their performance and ensure the oxidation reaction of diclofenac during the analysis of the sample. A significant development was reported when graphene was used as a modifier. As these types of sensors can be doped by p-dopants or n-dopants, in the matrix of the sensor, different types of chemicals can be added to improve the oxidation reaction. In this sense, the most selective sensors were prepared with GCE and MWCNTs by imprinted technologies, reporting an LOD equal to 0.017 μM . The other type of sensors cannot achieve these LOD values. On the other hand, not many sensors were prepared with metallic electrodes because the selected electrodes are quite expensive, exceeding the estimated budget for our project.

Furthermore, continuous monitoring of the DCF concentration in real-time samples will be more useful than batch detection and efforts to build continuous systems are encouraging. Most of the sensors were evaluated using real-world samples such as pharmaceuticals, biological fluids and environmental samples. Furthermore, the examples discussed are represented over a range of suggested electrochemical methodologies, which are mostly based on voltammetric and, to a lesser extent, on amperometric techniques.

Finally, the current review provides a comprehensive picture of the scope and complexity of the preparation of various electrochemical sensors. The selectivity and sensitivity of electrochemically modified sensors can also be ensured by adjusting their various characteristics. Although not much information on wastewater sensors was found, several technologies should be adapted in the laboratory to develop low-cost and sensitive sensors that can be utilized for continuous monitoring of riverwater or different water sources.

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Nomenclature

AuNP: gold nanoparticle
 CA: chronoamperometry
 CNF: carbon nano-flakes
 CNT: carbon nanotube
 CP: chronopotentiometry
 CuN: copper nanoparticles
 CV: cyclic voltammograms
 CZE: capillary zone electrophoresis
 DCF: diclofenac sodium
 DPV: differential pulse voltammetry
 EDX: energy dispersive X-ray
 EFM: electrostatic force microscopy
 EGDMA: ethylene glycol dimethacrylate
 EIS: electrochemical impedance spectroscopy
 FTIR: Fourier-transform infrared spectroscopy
 GCE: glassy carbon electrode
 GC-MS: gas chromatography-mass spectrometry
 GO: graphene oxide
 GO-COOH: carboxyl-functionalized graphene oxide
 IL: ionic liquid
 ILE: ionic liquid electrolyte
 LC: liquid chromatography
 LOD: limit of detection
 LSV: linear sweep voltammetry
 MIP: molecularly imprinted polymer
 MWCNT: multi-walled carbon nanotube
 NC: nanocellulose
 PC: polycarbonate
 PDMS: poly(dimethylsiloxane)
 PEDOT: poly(3,4-ethylene dioxythiophene)
 PGE: pencil graphite electrode
 PVC: polyvinyl chloride
 SWV: square wave voltammetry technique
 WoS: Web of Science
 [bpim][dcf]: associate of diclofenac with an imidazolium moiety

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