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Using The GMDH Neural Network Model in Carbon Paste Electrodes Modified with Different Metal Oxide Nanoparticles for the Electrochemical Measurement of Tramadol and Acetaminophen

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Abstract

Various nanoparticles, such as metal oxide nanoparticles, are extensively applied in the field of producing electrodes related to electrochemical processes. The present study uses the GMDH neural network model in carbon paste electrodes modified with different metal oxide nanoparticles for the electrochemical measurement of tramadol and acetaminophen. Thus, nanoparticles of zinc oxide, copper oxide, and titanium dioxide were synthesized by sol-gel method and then inserted into carbon paste through a process to obtain the working electrodes for the electrochemical process. The results of the GMDH neural network in the previous model showed that the impact of the input parameters on the objective function can be concluded by counting the number of repetitions of that variable. The results revealed that the initial concentration of the pollutant and temperature with 8 repetitions, pH with 7 repetitions, and gram of catalyst material and time with 6 repetitions indicate the level of effect on the target function.

Keywords: Sensor, Nanoparticle, Detection, Acetaminophen, Tramadol, Carbon paste.

Introduction

The simultaneous measurement of two or more substances without initial separation is one of the significant problems in drug analysis. Various methods have been introduced to determine each of the substances alone or in different combinations. Each method has been examined by different researchers [1]. Acetaminophen is one of the most extensively used pharmaceutical substances. Thus, it can be detected in human urine or blood plasma individually or with other active compounds using different methods including high-performance liquid chromatography, electrochemical methods, spectrophotometry, titrimetry, spectrofluorometry, current injection analysis, etc. [2-5]. Acetaminophen (AP) is extensively used as an antipyretic to reduce fever symptoms and an analgesic to relieve pain. AP is prescribed as an alternative to aspirin and phenacetin in many countries. However, its overconsumption leads to the accumulation of toxic metabolites, resulting in liver and kidney disease.

AP is also used in animal care to treat fever and also as an analgesic. Fast and sensitive methods for the detection of AP in animal tissue and edible meat are necessary to protect consumers [6]. Many methods are currently used to determine acetaminophen in different environments, including high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry, spectrometry, capillary electrophoresis, and electrochemical methods. Most of these methods are not completely ideal since they use expensive tools for production and efficiency and require a long analysis time (due to the preparation of the required sample before analysis and identification). For this reason, researchers are looking for quick and cheaper methods. A technique should be adopted to measure the value of this substance in meat and other consumer products prepared from these animals since acetaminophen is not only used to treat humans but also often to treat colds and fevers in livestock, poultry, and other animals [7].

Electrochemical methods have many advantages over conventional analytical techniques for the detection of acetaminophen thanks to relatively low capital cost and short analysis time. Tramadol, also known by the brand

names Tramal, Tramed, Biomadol, Piralgin, and Alapin, is an opioid analgesic drug prescribed for the relief of moderate to severe pain [8]. Tramadol's analgesic effect begins after about an hour of taking it orally [9]. Tramadol as a generic drug is produced by various pharmaceutical companies worldwide. It is a very strong reuptake inhibitor of serotonin, dopamine, and norepinephrine. With more than 19 million prescriptions, this drug was the 35th most commonly used prescription drug in the United States in 2019. Its mechanism of action is in two ways. First, like other opioid drugs (opium derivatives), it is an agonist of Mu (μ) receptors. However, the binding property of tramadol to "μ" opioid analgesic receptors is very weak. After taking tramadol, it is converted by the CYP2D6 enzyme into the active metabolite o-desmethyl tramadol, which has about 6 times more capability to bind the "μ" receptor than tramadol. The primary analgesic effect of this drug depends on this metabolite and the effect of inhibiting the reuptake of serotonin and norepinephrine depends on the mother element.

Some people have lower amounts of CYP2D6 enzyme in their body due to genetic reasons. For this reason, they do not benefit from the analgesic properties of tramadol. On the pharmacokinetic scale, the analgesic power of tramadol is about 10 times weaker than morphine, and its capability to bind the μ receptor is 600 times less than morphine**.** The measuring method with electrochemical technique is one of the most extensively used techniques for measuring and identifying pharmaceutical substances especially acetaminophen in different environments due to less trouble, low costs, ease of setting up the pilot, and frequent use of the prepared pilot. Different electrochemical electrodes can be used in this technique. It is one of the newest methods to increase the efficiency of modification of these electrodes using different nanomaterials.

The modified electrodes are obtained to increase the sensitivity. Thanks to their suitable and new features, they can increase the efficiency of the whole electrochemical cell. The modified electrodes have a higher detection rate compared to the unmodified electrodes. Nanocomposites, nanoparticles, nanotubes, nanoplates, and other forms of nanomaterials are a turning point for enhancing the efficiency of electrochemical sensors in analytical chemistry. Metal oxide nanoparticles, carbon nanotubes (CNTs), polymer films, graphene, and graphene oxide (GO) nanocomposites in various combinations are extensively used in the fabrication of nanocomposites as modifiers in electrochemical sensors to determine various compounds [10].

In electrosynthesis processes, some parameters including electrode potential, type and structure of electrodes, concentration of electroactive species, and conditions of electrosynthesis environment such as type of solvent, carrier electrolyte, pH, temperature, and the design of the reaction vessel are effective in the final efficiency of the process. The start of electrosynthesis of organic compounds was related to the electro-oxidation of alcohols in 1801. Many different electrochemical reactions have been examined since then, ranging from the reduction of aromatic compounds to the electropolymerization of organic monomers. Additionally, the electrosynthesis of aliphatic and aromatic compounds has expanded industrially so reactions such as the conversion of nitrobenzene to azobenzene, maleic acid to succinic acid, and acrylonitrile to adiponitrile are commercially performed currently in the industry by electrochemical method [8].

Electrochemical decomposition techniques include the measurement of electrical quantities such as flow, potential, and charge and their relationship with chemical parameters. Such use of electrical measurements for decomposition purposes leads to a wide range of applications including environmental investigations, industrial quality control or biomedical decompositions. Unlike many chemical measurements performed in homogeneous solutions, electrochemical processes are located at the electrode-solution interface. Two basic types of electrochemical decomposition measurements include potentiometric methods and controlled potential methods. In potentiometry, the potential of an electrochemical cell is measured under static conditions, and the current passing through the cell is zero or very small. Controlled potential methods study the charge transfer process at the electrode-solution interface under dynamic conditions (non-zero current). Here, the potential applied to the electrode leads to the electron transfer reaction.

The study by Săndulescu et al. (2000) [11] investigated the measurement of ascorbic acid and acetaminophen using spectroscopic and electroanalytical methods. To conduct this study by electroanalytical method, they used an electrochemical electrode made of carbon paste modified by AgCl. A chromatographic method for measuring acetaminophen and ascorbic acid in combined drugs was used in the study by Gioia et al. (2008) [12]. This study

revealed that it is possible to know the amount of AA and acetaminophen in different substances using HPLC analysis, and there is no need for more specialized equipment and tests. In the study by Afrasiabi et al. (2013) [13], an electrochemical sensor using carbon modified with nanocomposite was used to measure the amount of ascorbic acid, acetaminophen, and uric acid. The primary goal of this study was to measure the mentioned substances in the urine of human samples. Their results revealed that the prepared sensor could be effective for this measurement.

In the study by Zare et al. (2016) [14], an electrochemical electrode was used to measure the amount of acetaminophen, ascorbic acid, adrenaline, and tyrosine. This chemical electrode was prepared based on carbon nanotubes. The results revealed that this electrode can be very efficient for the detection of ascorbic acid and adrenaline at a pH of 5. In the study by Sharifian and Nezamzadeh (2016) [15], an electrochemical sensor prepared with carbon paste modified with magnetic iron nanoparticles was used for the simultaneous detection of amounts of acetaminophen and ascorbic acid. The results revealed that the prepared sensor has a high capability to find ascorbic acid, while it requires a more complex and difficult function to detect acetaminophen. In the study by Chen et al. (2016) [16], Au-ZnO hybrid nanocatalyst along with graphene was used for the simultaneous measurement of acetaminophen and ascorbic acid. This nanocatalyst, used for the first time to measure both acetaminophen and ascorbic acid, indicated a suitable capability. The results of the mentioned study indicated that using graphene can improve the detection power of the mentioned materials by 10% due to the increase in the oxidation property of the nanocatalyst.

The study by Taei and Sadegh (2017) [17] used a voltammetric sensor for the simultaneous detection of ascorbic acid and Acetaminophen. In this study, glassy carbon electrodes modified by poly trypan blue were produced for the simultaneous determination of ascorbic acid and acetaminophen. Based on the researchers, the glassy carbon electrode alone has limitations in solving the oxidation current of these compounds and cannot identify these compounds well. According to the obtained results, the electrode prepared in this study can be used to identify the mentioned compounds in human and pharmaceutical samples. Mousazadeh et al. (2023) [18] conducted a study on recent advances in electrochemical sensors based on nanomaterials for tramadol analysis. They reported that electrochemical methods have attracted much attention for the quantification of this drug due to the demonstrated potential for fast response, real-time measurements, selectivity, and high sensitivity. In this review, we highlighted the recent advances and applications of nanomaterial-based electrochemical sensors for the analysis and detection of tramadol, which are vital to demonstrating effective diagnostics and quality control analyses to protect human health.

Additionally, the primary challenges in the development of electrochemical sensors based on nanomaterials for the determination of tramadol will be discussed. Finally, this review provides prospects for future studies and development needed for modified electrode sensing technology for tramadol detection. Shahinfard et al. (2023) [19] conducted a study on an electrochemical sensor based on CuO-reduced graphene nanoribbons (rGNR) and ionic liquid for simultaneous determination of tramadol, olanzapine, and acetaminophen. This study used a new electrochemical sensor based on a carbon paste electrode for the simultaneous determination of tramadol, olanzapine, and acetaminophen for the first time. Nanocomposites of CuO-reduced graphene nanoribbons (rGNR) and 1-ethyl-3-methylimidazolinium chloride as ionic liquid (IL) were used as modifiers.

The electro-oxidation of these drugs on the surface of the modified electrode was evaluated using cyclic voltammetry (CV), differential pulse voltammetry (DPV), electrochemical impedance spectroscopy (EIS), and chronoamperometry. Various techniques such as scanning electron microscopy (SEM) with energy dispersive X-ray analysis (EDX), X-ray diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR) were used to validate the structure of CuO-rGNR nanocomposites. This sensor displays excellent electro-catalytic oxidation activity and good sensitivity. In optimal conditions, the results revealed a line in the concentration range of 0.08-900 μM and the limit of detection (LOD) of 0.05 μM. The proposed method was effectively used for the determination of tramadol in pharmaceutical samples and human serum. For the first time, the present study indicated the synthesis and use of porous nanocomposites to fabricate a unique and sensitive electrode and ionic liquid for electrode modification for joint measurement of these drugs.

A chemical electrode is a device that converts a physical or chemical environmental change into a measurable signal and provides quantitative or qualitative information about those environmental conditions. Each chemical electrode includes a selectable layer to prevent the interference of other disturbances, a converter to convert the response into a detectable signal, and a device to read this signal [7]. Compared to visual, mass, and thermal sensors, chemical sensors are very attractive thanks to their remarkable sensitivity, ease of preparation, and relatively low cost. These cases have made them find a special status in areas such as medicine, industry, environment, and agriculture. Nanomaterials are becoming important in this area due to the development of electrodes with improved performance [20].

The use of electrodes modified with different nanoparticles with electro-catalytic properties in the design and manufacture of sensors and biosensors often reduces the excess potential of reactions, increases their reversibility characteristics, and increases the oxidation current compared to non-modified electrodes. Additionally, in some cases, the selectable electro-catalytic role of nanomaterials also provides the possibility of designing and manufacturing selectable sensors. Various nanomaterials in various forms are used in the improvement and modification of electrochemical electrodes including carbon nanotubes, various nanoplates, nanoparticles, and various nanocomposites, used for electrode improvement depending on the application of each nanomaterial. A large part of chemical electrode modifiers include metal oxide nanoparticles, including titanium dioxide nanoparticles, zinc oxide, copper oxide, magnetic iron oxide nanoparticles, etc. [21]. Thus, the present study uses the GMDH neural network model in carbon paste electrodes modified with different metal oxide nanoparticles for the electrochemical measurement of tramadol and acetaminophen.

Methods

In this study, the sol-gel method was used to synthesize the desired nanoparticles. The sol-gel process, also known as chemical solution deposition, is a wet chemical method (bottom-up approach) used extensively in materials science and ceramic engineering for the synthesis of various nanostructures. The sol-gel method is a cheap method that nanoparticles (production of particles of the same size) with high quality and high purity that can be prepared with this method due to the low temperature of the reaction. This process involves a series of irreversible chemical reactions that ultimately lead to the production of the final product. In other words, these reactions cause the transformation of the initial homogeneous solution molecules as sol, into an unlimited, heavy, and three-dimensional polymer molecule as gel.

This method is mostly used to produce materials, for example, metal oxides, starting from a colloidal solution (sol), which is a precursor for an interconnected network (gel) of discrete particles or network polymers. Common precursors include metal alkoxides and salts (such as chlorides, nitrides, and acetates) undergoing various hydrolysis and stepwise deposition reactions. The sol-gel method is a reliable method for preparing nanoparticles, especially metal oxides, and nanocomposites based on metal oxides [22]. In this method, nanoparticles and nanocomposites are generally prepared on a nanoscale. One of the crucial advantages of this method is the capability to add different materials during synthesis.

The sol-gel method has been used for the synthesis of the desired nanoparticles. The sol-gel process, known as chemical solution deposition, is a wet chemical method (bottom-up approach) used extensively in materials science and ceramic engineering for the synthesis of various nanostructures. The sol-gel method is a cheap method that nanoparticles (production of particles of the same size) with high quality and high purity that can be prepared with this method due to the low temperature of the reaction. This process involves a series of irreversible chemical reactions that ultimately lead to the production of the final product. In other words, these reactions cause the transformation of the initial homogeneous solution molecules as sol, into an unlimited, heavy, and three-dimensional polymer molecule as gel. This method is mostly used to produce materials, for example, metal oxides, starting from a colloidal solution (sol), which is a precursor for an interconnected network (gel) of discrete particles or network polymers. Common precursors include metal alkoxides and salts (such as chlorides, nitrides, and acetates) undergoing various hydrolysis and stepwise deposition reactions. The sol-gel method is a reliable method for preparing nanoparticles, especially metal oxides, and nanocomposites based on metal oxides [22]. In

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The sol-gel method was also used for the synthesis of this nanoparticle. For this purpose, an aqueous solution of copper sulfate (0.1 M) was prepared using distilled water. Then, the concentrated NaOH solution was added to the copper sulfate solution until the pH of the solution reached 7. In this case, the amount of sediment formed started to dissolve again until the pH increased to 8, and a blue deposit of Cu (OH) 2 copper hydroxide was formed. At this time, the obtained deposit was filtered and washed several times with distilled water to remove impurities. Then, the resulting Cu (OH) 2 deposit was placed in an electric furnace at a temperature of 400 C° for 1 hour. Finally, a black deposit of copper oxide (CuO) was formed [23]. FiϽure 1 illustrates the image of the final material.

Figure 1: Final copper oxide nanoparticle

Synthesis of zinc oxide nanoparticles

The sol-gel method was used for the synthesis of zinc oxide nanoparticles for the reasons mentioned in this study. For the synthesis and in the initial step, we prepared a 1 M solution of zinc acetate with ethanol in a volume of 50 ml as a solvent (according to stoichiometric calculations). Then, this solution was stirred for 10 minutes on the stirrer by a magnet and magnetic stirrer. Figure 2 illustrates the image of the initial stages of the synthesis [24].

Figure 2: Image of the initial stages of nanoparticle synthesis

After making the initial solution of zinc acetate, we add 5 ml of MEA substance in the previous solution gently and drop by drop (almost for 5 minutes). This addition should be done on the stirrer and after the addition is finished, stirring should continue for another 15 minutes. After completing the stirring process, we placed the final solution in the ultrasonic bath for 10 minutes as it will make the ingredients mix better. After completing these steps, we add 250 µl of 65% nitric acid to the solution using the sampler and let the solution stir for 15 minutes again on the stirrer. In this step, the solution reached the final step of synthesis and we gave an opportunity of

about 72 hours to remove its excess solvent. However, this should be done in the same way that we place the final solution in the same 150 ml beaker from which we started the synthesis, cover it with parafilm, and make holes on the parafilm with scissors so its excess solvent is removed from the holes. This will prevent contamination from entering to the solution. After this step, the desired material becomes a white dry mass, which must be placed in the furnace for the calcination process. Thus, we scrape the material with a spatula, pour it into the porcelain crucible, and place it in the electric furnace for 30 minutes until the calcination process is complete.

Synthesis of titanium dioxide nanoparticles

For the synthesis, we first pour 50 ml of ethanol into a 250 ml beaker and place it on a magnetic stirrer. The speed of the stirrer will be set to 1000 rpm in all stages. The stirrer temperature is set at 50 C° in the initial steps to prepare the best nanocomposite structurally [25]. First, we add 5 ml of TTiP to ethanol and place this solution on the heater stirrer for 15 minutes to mix. Then, we gently add 300 µl of nitric acid to the ethanol and TTiP solution and let the solution be stirred for 15 minutes on a magnetic stirrer until the initial network of nanoparticles begins to form. Figure 3 shows the material prepared in this step.

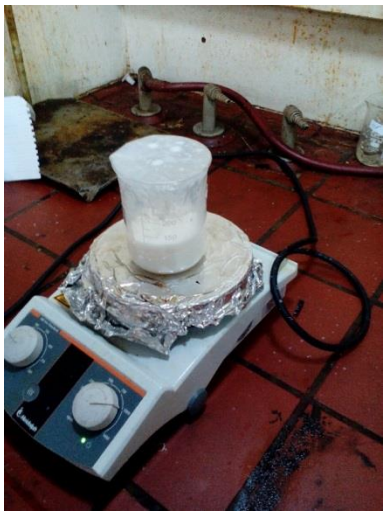


Figure 3: Initial cell prepared on a magnetic stirrer

In the next step, the final cell is covered with parafilm, and holes are made in the parafilm with the tip of scissors. This solution is kept at room temperature for 48 to 72 hours until the excess solvent (ethanol) evaporates. Then, the final material becomes a white material, as seen in Figure (4).

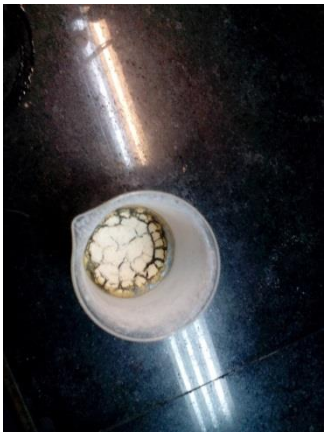


Figure 4: Dried material before calcination

After performing these laboratory steps, the material is ready for calcination. Calcination is a term in materials and chemistry that refers to heating materials for pyrolysis, removing moisture, forming intermediate compounds,

performing solid-state reactions, and permeation [26]. For this study, the calcination temperature for the synthesis of titanium dioxide nanoparticles was selected to be 400 C°.

Results

The 34 data series obtained from the discontinuous elimination experiment were used to model this process. The superior chromosome for predicting the residual concentration in the solution is shown in Table 1. Each number belongs to an input variable whose order is as follows:

1. PH

2. Gram of inserted nanomaterial

3. The initial concentration of the pollutant

4. Temperature

5. Time

Table 1- Superior chromosome for pollutant identification process by combined state

Optimal chromosome obtained by multi-objective GMDH neural network model	Test error	Training error
34331121141355232245141342543543 54	0.0710585	0.1654757

As stated, the impact of the input parameters on the objective function can be concluded by counting the number of repetitions of that variable. In this model, the initial pollutant concentration, temperature with 8 repetitions, pH with 7 repetitions, and grams of catalyst substance and time with 6 repetitions indicate the level of impact on the target function.

Figure (5) shows the proposed structure of the GMDH neural network for the pollutant identification process by the hybrid method.

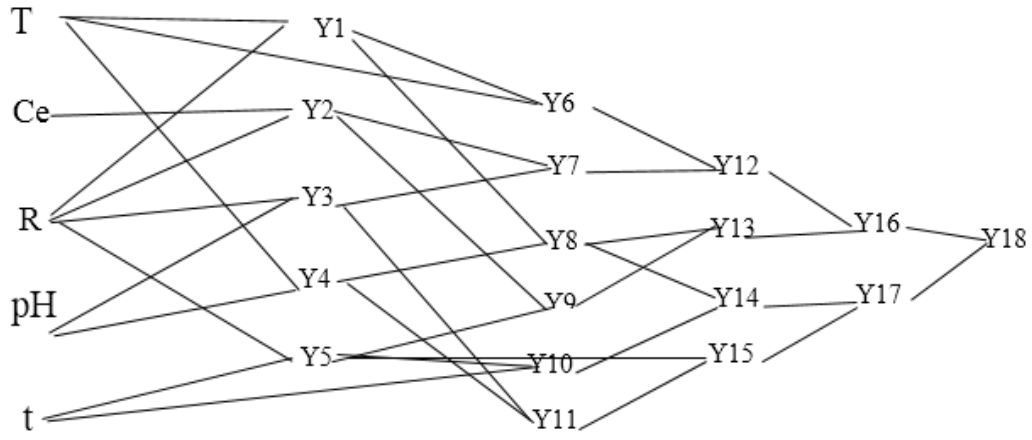
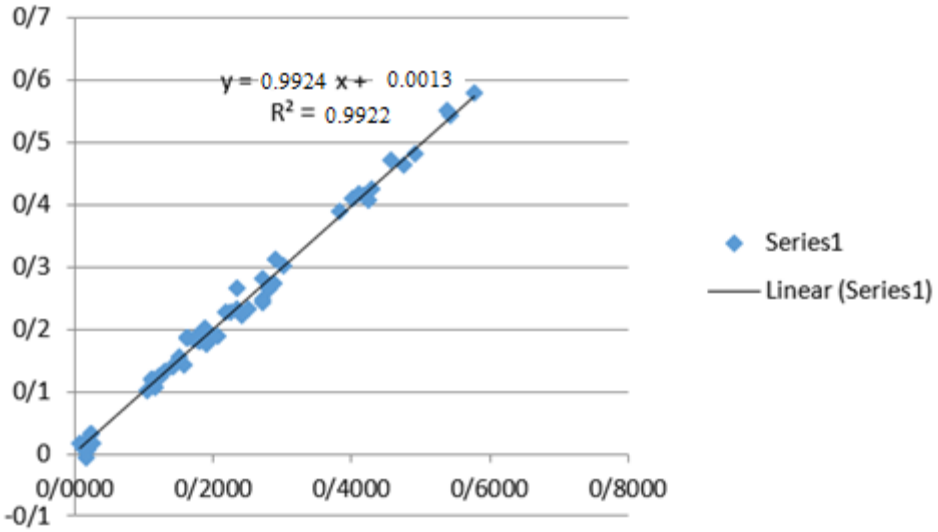


Figure 5: The proposed structure of the multi-objective GMDH model for the pollutant identification process by the hybrid method

After obtaining the proposed model, the experimental data is compared with the results of modeling, as shown in Figure (6).

Figure 6: Comparison of experimental data and modeling output with GMDH multi-objective pollutant identification by combined method

Based on figures (5) and (6) that compared the data obtained from the model with the experimental data and based on the coefficient of determination R2 value, it can be concluded that these models have a good fit with the experimental data, and the results indicate the reliability of these models.



Conclusion

Electrochemistry is a branch of chemistry that studies electrical and chemical processes. A large part of this branch studies the chemical changes caused by the passage of electric current and the creation of electric energy by chemical reactions. Among the electrochemical techniques, voltammetry with modified electrodes has attracted the attention of many experts thanks to its high sensitivity, the capability to detect very small amounts of analyte, the ease and speed of operation, the low cost of preparing the electrode, the renewability of the electrode surface, and the low residual current in recent years. Many compounds are oxidized or reduced at high potentials, or display a weak electrochemical response on the unmodified electrode surface, leading to a reduction in sensitivity.

According to the GMDH neural network, as mentioned in the previous model, the level of impact of the input parameters on the objective function can be concluded by counting the number of repetitions related to that variable. In this model, the initial pollutant concentration and temperature with 8 repetitions, pH with 7 repetitions, and grams of catalyst substance and time with 6 repetitions indicate the level of impact on the target function. Based on the results of using synthesized nanoparticles in this study as a carrier of cancer drugs and the drug release rate, it is recommended to use synthetic nanoparticles to identify organic compounds in surface and underground water and investigate the improved polymer nanocomposites with different nanoparticles to identify different compounds in aqueous solutions.

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