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Paratiroid Hormon Tayinine Yönelik IrO_2 Nanopartikül Tabanlı Yatay Akış İmmünosensör Geliştirilmesi

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Yatay akış immünosensör, Kağıt-bazlı biyosensör, İridyum oksit nanopartikül, Paratiroid hormon.

ÖZET

Biyosensörlerin hayatımıza getirdiği kolaylıklar, biyosensör teknolojisinin gün geçtikçe gelişmesini sağlayacak yeni çalışmaların önünü açmaktadır. Optik sensörler ile birçok alanda kalitatif ve kantitatif analizler yapılmaktadır. Bu alanlar arasında sağlık sektöründe önemli olan hormon testleri de dikkat çekmektedir. Bu çalışmada, kandaki kalsiyum dengesini koruyarak bazı metabolik faaliyetlerde önemli bir role sahip olan paratiroid hormonunun (PTH) kağıt bazlı yatay akış testi (LFA) ile tayin edilmesi amaçlanmıştır. Kandaki PTH seviyesi birçok paratiroid kaynaklı hastalık ve kanser teşhisi için önem arz etmektedir. Geliştirilen iridyum oksit nanopartikül (IrO_2NPs) esaslı LFA ile PTH tayini ve tespiti gerçekleştirilmiştir. Aynı zamanda, PTH tespiti için IrO_2NPs kullanılarak LFA geliştirilen ilk çalışmadır. PTH tayini için tasarlanan IrO_2NPs bazlı LFA'nın teşhis ve tayin alt sınırı (LOD ve LOQ) sırasıyla 3,92 ng/mL ve 11,88 ng/mL olarak hesaplanmıştır.

Development of IrO_2 Nanoparticles-Based Lateral Flow Immunosensor for Determination of Parathyroid Hormone

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ABSTRACT

The conveniences that biosensors bring to our lives pave the way for new studies that will enable biosensor technology to develop day by day. Qualitative and quantitative analyses are conducted in many areas with optical sensors. Among these areas, hormone tests, which are important in terms of health, also attract attention. This study aims to detect parathyroid hormone (PTH), which has an important role in some metabolic activities by maintaining calcium balance in the blood, by paper-based lateral flow analysis. PTH levels in the blood are important for the diagnosis of many parathyroid-related diseases and cancer. PTH was determined by the developed iridium oxide nanoparticles-based (IrO_2NPs) LFA. At the same time, this is the first study to develop an LFA for the detection of PTH using IrO_2NPs. The limit of detection and quantification (LOD and LOQ) of IrO_2NPs-based LFA designed for PTH determination were calculated as 3.92 ng/mL and 11.88 ng/mL, respectively.

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INTRODUCTION

Parathyroid hormone (PTH), a single-chain peptide hormone consisting of 84 amino acids, is synthesized by parathyroid primary cells [1]. Its half-life is short, between 2-4 days. PTH increases the amount of calcium in the blood by triggering the formation of calcium from the bone and ensuring its reabsorption [2]. PTH generally helps the body absorb calcium from the kidneys, excrete phosphorus, and increase the formation mechanism of vitamin D. This hormone is also called "intact parathyroid hormone" and it plays a key role in metabolic activities in the liver and kidneys of the body [2–6].

Determination of PTH levels in blood is used to monitor parathyroid diseases such as osteoporosis and malignant hypercalcemia. PTH levels in blood are also important in determining some types of cancer, such as prostate cancer and breast cancer. When breast cancer and prostate cancer metastasize to the bone, an increase in the levels of PTH in the blood is observed. Therefore, determining the PTH levels is important and various analytical approaches were developed by using fluorometric, electrochemical and chromatographic [7] methods for PTH detection. Since PTH has a short half-life, the PTH levels in the blood decrease from its normal levels of 11-54 pg/mL in a short time after the parathyroid tissue is removed [8–10]. Therefore, rapid test kits are important to detect the PTH level in a short time.

Lateral flow assay (LFA) is a simple paper-based platform offered in strip format. LFA is one of the broadly used point-of-care technologies (POCT) because it provides robustness, high sensitivity, and easy and fast performance [11,12]. LFA consists of a chromatographic system that occurs through the separation of the components in the mixture resulting from differences in their movements in the reaction membrane and the specific antibody-to-antigen immunochemical reaction [13,14]. LFA consists of four parts: sample pad, conjugate pad, reaction pad (test membrane) and adsorbent pad [14,15]. This POCT platform provides results in a few minutes and is obtained with end-user intervention. It is preferred in many fields such as food safety, biomedicine, environmental health and quality control due to its simple production and low cost [16].

The use of nanomaterials in biosensor applications has become very common in recent years. They are widely preferred because of their high surface area, high activity, high catalytic effects, surface reactions, and high bio-detection [17]. Various nanomaterials such as plasmonic nanoparticles, quantum dots and other nanoparticles are used in paper-based immunochromatographic assays [18]. Particularly, AuNPs are widely used nanomaterials in LFA technology due to their high biocompatibility and high optical properties. However, in the case of the determination of analytes with low detection limits, their low sensitivity is thought to hinder future applications. Recently, iridium oxide nanoparticles (IrO_2NPs) have emerged as remarkable metal oxides that are widely used in electrocatalytic [19,20] and antitumor applications [21,22] due to their considerable large surface area, high chemical stability, high catalytic properties as well as corrosion resistance [23]. Besides, IrO_2NPs have been also used as an alternative to AuNPs in LFA to detect human immunoglobulin. The features of this nanomaterial, such as its unique sharp dark blue color, as well as its biocompatibility with antibodies and its advantage in conjugation thanks to its large surface area [24] have increased the reason to choose these nanoparticles [25–30].

In this study, considering all these advantages of IrO_2NPs, we developed a cost-effective, fast and robust biosensor for PTH determination. The optimization of each LFA component was conducted. The assay was created by determining the optimum quantity of BSA (1%, 3% and %5) and Tween-20 (0.01%, 0.025%, 0.050%, 0.075%, and 0.100%) in the optimization of the membrane, conjugate pad and sample pad. To find the optimum condition, the flow rate of iridium oxide nanoparticles on the membrane surface was taken into consideration. Then, qualitative and quantitative determination of PTH was performed in the LFA under the optimum conditions. LOD and LOQ values for PTH determination were calculated as 3.92 ng/mL and 11.88 ng/mL, respectively. This study is the first work to develop an

LFA for the determination of PTH using IrO_2NPs.

MATERIALS AND METHODS

Materials and Equipment

The sample pad (CFSP001700), glass fiber (GFCP000800), test membrane (HF090MC100), and adsorbent pad (CFSP001700) used in the LFA design were purchased from Millipore. K_2IrCl_6 (450162) used for IrO_2NPs synthesis was obtained from Sigma Aldrich. PTH hormone (P7036) was purchased from Sigma-Aldrich, polyclonal parathyroid hormone antibody (ab40630), polyclonal goat antibody (ab6702), and monoclonal parathyroid hormone antibody (ab154792) were purchased from Abcam.

Field Emission Scanning Electron Microscope (ZEISS GeminiSEM 500) with the Scanning transmission electron microscopy (STEM) detector was performed for the characterization of IrO_2NPs. Spectroscopic measurements were carried out with an Ultraviolet, Visible and Near Infrared Spectrometer (Shimadzu UV-3600 Plus). Spraying of test and control lines on the membrane surface was achieved with the Linomat 5 (CAMAG) device. Signal intensities on the test and control lines were measured with a colorimetric reader (Qiagen LR3).

Synthesis, Characterization, and Functionalization of Iridium Oxide Nanoparticles

For the synthesis of IrO_2NPs, all glass materials and magnetic stirrer were cleaned with HNO_3/HCl=1:3 (v/v), pure water, and dried in an oven to prevent pollution that could disrupt particle formation and size distribution. IrO_2NPs synthesis was carried out according to the Harriman and Thomas [30] method. For this, 30 mg K_2IrCl_6 was added to the aqueous solution (50 mL) of 3.80 mM sodium citrate sesquihydrate. The pH of the resulting solution (brown color) was adjusted to 7.5 using NaOH and boiled under reflux with constant stirring. This process was continued until the color of the brown solution changed to light blue. The pH of the solution, which was left to cool at room temperature, was adjusted to 7.5. Then, after boiling under reflux in the presence of oxygen gas for 2 hours, the process was completed when the solution turned dark blue (Figure 1) [24,30]. The solution was stored at 4°C, wrapped in aluminium foil.

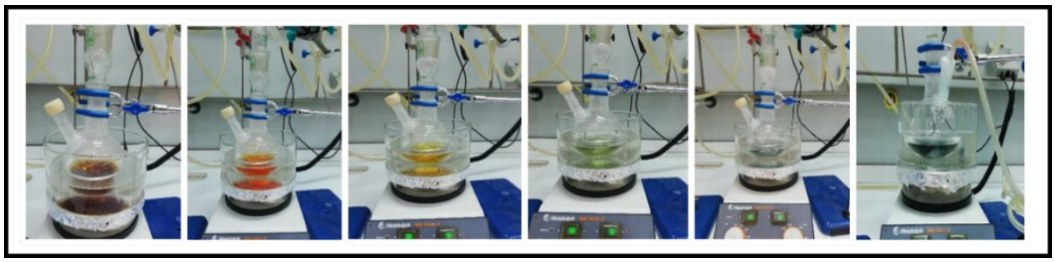

Figure 1
Synthesis of IrO_2NPs.

STEM images for the characterization of the IrO_2NPs were taken by FESEM. In the functionalization step of IrO_2NPs surfaces with antibodies, 100 µL of anti-PTH antibody (250 µg/mL) from goat was added to 1.5 mL of IrO_2NP solution and mixed at 650 rpm for 2 hours at room temperature. For the functionalization step of IrO_2NPs surfaces with antibodies, 100 µL of anti-PTH antibody (250 µg/mL) from goat was mixed with 1.5 mL of IrO_2NP solution at 650 rpm for 2 hours at room temperature. After the resulting mixture was centrifuged at 35000 rpm at 4°C for 2.5 hours, the resulting precipitate added 0.5 mL of borate containing 10% sucrose and 25% BSA. The buffer was obtained according to the literature [24].

Optimization of LFA

Washing of Sample Pad, Test Membrane and Conjugate pad

Both sides of the sample pads were washed with pure water, phosphate buffer solution (PBS), PBS + Tween 20 (PBST) and immunobuffer (PBST + BSA-bovine serum albumin) solutions, respectively. The washed pads were dried in an oven at 37 ºC for 2 hours. The test membrane was washed with immunobuffer solution and dried in an oven at 37 ºC for 2 hours. The glass-fiber (conjugate pad) was also washed with immunobuffer solution and dried in the same conditions for 1 hour. Then, it was dipped into IrO_2NPs/antibody. Then, it was dried under a vacuum at 30 ºC for 1 hour.

Design of LFA

For the design of LFA, the adhesive tapes on the backing card were opened and the adsorbent pad was placed at the bottom, a part of the sample pad (~2 mm) was assembled onto the upper part of the membrane, overlapping the conjugate pad. The kits were cut to 5 mm thick with a guillotine and made ready for the experiments (Figure 2).

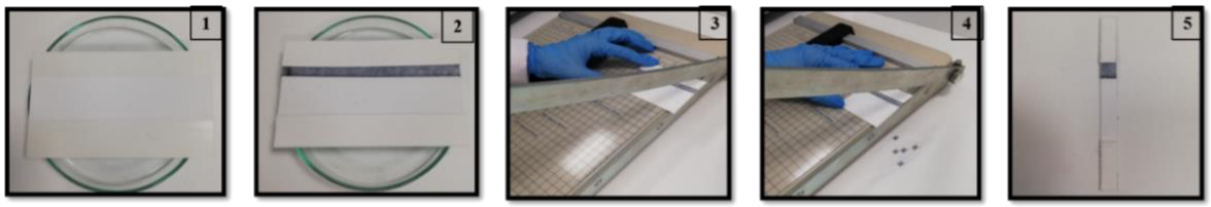

Figure 2
Preparation and cutting steps of LFA.

RESULT AND DISCUSSION

Characterization of Iridium Oxide Nanoparticles

The unique characteristic shapes of IrO_2NPs, whose STEM images were taken at 125KX and 500KX magnification, were presented in Figure 3.a-a'. Figure 3b shows the size distribution graph for IrO_2NPs, in which sizes of the nanoparticles ranged between 10-23 nm and the average nanoparticle size was found around 17.5 nm.

The image of the aqueous solution of IrO_2NPs obtained in dark blue color is shown in Figure 3c. Optical characterization of this solution was performed by UV-Vis spectrometer, and the obtained spectrum showed a maximum absorbance at 585 in agreement with the literature [24,31].

Effect of Washing on Optimization of Membrane and Glass Fiber

To examine the flow of the analyte solution and IrO_2NPs in the conjugate pad on LFA platforms, the performances of the LFA obtained by washing the surface of the membrane and the glass fiber with immunobuffer were investigated. For this purpose, different amounts of BSA and Tween-20 were added to the immunobuffer solution. For the optimum ratio of BSA and Tween-20, 0.01%, 0.025%, 0.050%, 0.075% and 0.100% Tween-20 were added to 1%, 3% and 5% BSA solutions.

The flow of IrO_2NPs on the membrane surface was investigated by using the membranes washed with immunobuffer solutions including 1%, 3% and 5% BSA and Tween-20 in different amounts. To this aim, the time was recorded to see the point where the nanoparticles reached on the membrane surface. First, the movement within 3 seconds, secondly the time taken to reach the midpoint of the membrane and then the adsorbent pad, respectively (Figures S1, S2 and S3). The particularly important and decisive points here are (i) no neither too fast nor too slow nanoparticle flow on the membrane surface (ii) no accumulation of particles on the membrane surface, (iii) and the homogeneous flow of nanoparticles on the membrane surface. In the performed experimental study, the optimum condition was obtained with 3% BSA and 0.050% Tween-20 including solution.

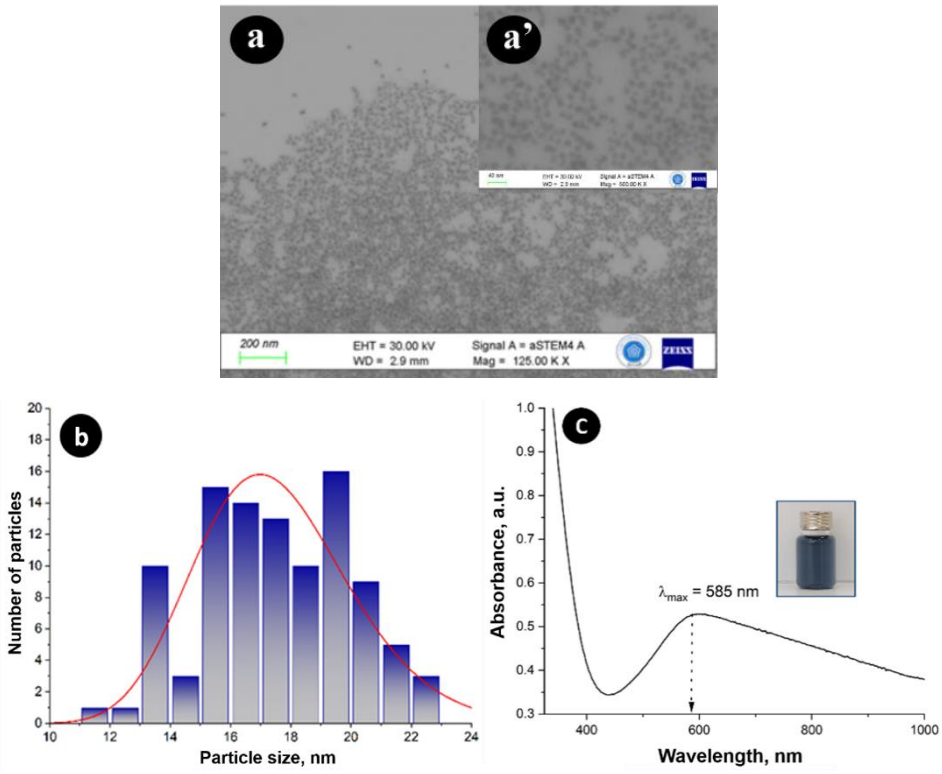

Figure 3
*STEM images of IrO_2NPs at **(a)** 125KX, **(a')** 500KX magnifications, **(b)** Size distribution graph of IrO_2NPs, **(c)** UV-Vis spectrum and the image of IrO_2NPs dispersion.*

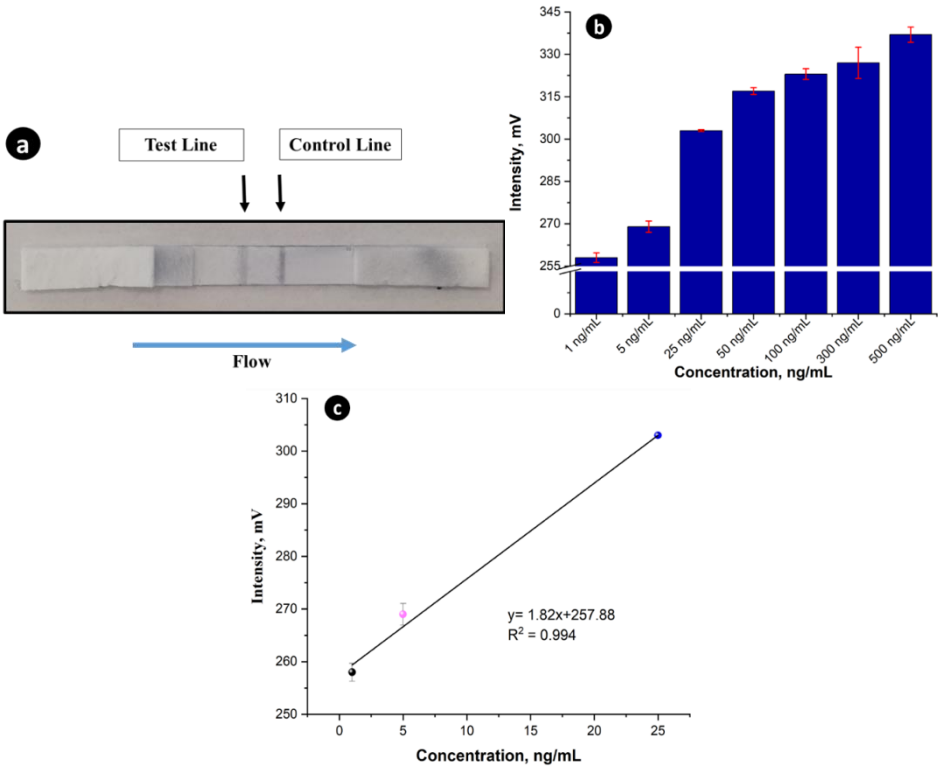

Figure 4
***(a)** The qualitative LFA test **(b)** Signal intensity obtained for various concentrations of PTH between 1-500 ng/mL, **(c)** The linear curve for the change of intensity of the signal obtained against PTH concentration.*

For the quantitative determination of PTH, PTH solution at different concentrations (0-500 ng/mL) was transferred to the sample pad of LFA. The intensity values of the test lines obtained in these experiments at different concentrations were determined with a colorimetric reader and they are presented as a graph shown in Figure 4.b. Using the linear range (see Figure 4.c) of the graph in which the intensity values on the test line were plotted against different concentration values, the LOD and LOQ values were determined to be 3.92 and 11.88 ng/mL, respectively.

CONCLUSION

In this study, an IrO_2NPs-based LFA was designed for the qualitative and quantitative detection of PTH. As the result of quantitative analysis, LOD and LOQ values were calculated as 3.92 ng/mL and 11.88 ng/mL, respectively. Although there are many LFAs for hormone detection in the literature, an LFA for the determination of PTH was obtained for the first time using IrO_2NPs in this study. Unlike the nanoparticles (AuNPs) commonly used in the literature, this study shows that IrO_2NP will pave the way for its use as an alternative in different studies. Since the use of nanoparticles in LFAs is very important, especially in terms of selectivity, alternative nanoparticles increase the effectiveness of these systems. For this reason, the combination of existing nanoparticles and the hybrid systems they create have recently attracted the attention of researchers. We believe that using hybrid structures of IrO_2NPs with different nanoparticles in future studies will lead to new, more sensitive, and selective LFA studies.

Ethical Statement

This study is an original research article designed and developed by the authors.

Author Contributions

Research Design (CRediT 1): E.G. (%30) – H.B. (%30) – E.Z. (%40)
Data Collection (CRediT 2): E.G. (%60) – H.B. (%20) – E.Z. (%20)
Research - Data Analysis – Validation (CRediT 3-4-6-11): E.G. (%60) – H.B. (%20) – E.Z. (%20)
Writing the Article (CRediT 12-13): E.G. (%45) – H.B. (%20) – E.Z. (%35)
Revision and Improvement of the Text (CRediT 14): E.G. (%45) – H.B. (%20) – E.Z. (%35)

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Sustainable Development Goals (SDG)

Sustainable Development Goals: Not supported.

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