Recycled Low Density Polyethylene for Non-Invasive Glucose Monitoring. A Proposal for Plastic Recycling that Adds Technological Value

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ABSTRACT

In this work we present a successful strategy to convert recycled LDPE films, which usually end up in landfills or leak into the environment, in an advanced biomedical product. More specifically, LDPE films for food packaging have been treated with atmosphere corona discharge plasma for electrochemical detection of glucose. Enzyme-functionalized sensors manufactured using such recycled material, which acts as a mediator capable of electro-communicating with the glucose oxidase (GOx) enzyme, are able to detect glucose concentrations in sweat that are fully compatible with the levels of such bioanalyte in both healthy and diabetic patients. Covalent immobilization of the GOx enzyme on the plasma treated LDPE films has been successfully performed using the carbodiimide method, as proved by X-ray photoelectron spectroscopy. Then, the electronic communication between the deeply buried active site of the GOx and the reactive excited species formed at the surface of the plasma-treated LDPE has been demonstrated by linear sweep voltammetry. Finally, cyclic voltammetry in artificial sweat has been used to show that the LDPE-functionalized sensor has a linear response in the concentration of range of 50 μM to 1 mM with a limit of detection of 375 $\mu A \cdot \mu M^{-1} \cdot cm^{-2}$. Comparison of the performance of sensors prepared using recycled (*i.e.* with additives) and pristine (*i.e.* without additives) LDPE indicates that the utilization of the former does not require any pre-treatment to eliminate additives. The present strategy demonstrates a facile approach for recycling LDPE waste into a high value-added product, which will potentially pave the way for the treatment of plastic waste in the future. Non-invasive glucose sensors based on recycled LDPE may play a crucial role for monitoring diabetes in underdeveloped regions.

INTRODUCTION

Plastic waste in environment is considered to be a big problem due to its very low biodegradability and presence in large quantities. Therefore, recycling plastic waste has become a social demand. Recycled plastic is usually "*down-cycled*" into lower-quality and lower-value products, such as carpet fiber or car parts. This creates a problem of sustainability since the energy and water consumptions sometimes do not justify the recycling process.[1] Unfortunately, in practice the vast majority of used plastic is not recycled, ending up in landfills. This is usually the case of low-density polyethylene (LDPE), which is a flexible plastic used for shrink wrap, bags, flexible films and toothpaste tubes. These elements cannot be recycled in the same facilities as curbside recycling (*i.e.* they clog up sorting machines) and most of them end up in landfills or leak into the environment.[2] This work presents a new development to transform LDPE films into a higher-value biomedical product. More specifically, we propose a strategy to transform used LDPE films into low-cost and easy production non-invasive sensors for monitoring diabetes.

Diabetes is a chronic disease that affects the way the body treats glucose in the blood. In type 1 diabetes, the pancreas cannot produce insulin, a hormone that allows the body's cells convert glucose into energy, while in type 2 diabetes the pancreas does not produce enough insulin or body's cells do not use insulin properly (*i.e.* known as insulin resistance). Many diabetic people do not experience any particular symptom until the glucose level gets too low (hypoglycaemia) or too high (hyperglycemia). Severe hyperglycemia can cause significant damage, including cardiac or vascular event, such as myocardial infarction or stroke, kidney problems that may require dialysis, eye problems that may lead to blindness, problems with circulation and scarring that can lead to amputation, etc.

To avoid the complications of diabetes, the glucose level must be accurately controlled using sensitive and selective glucose sensors. At present time, most of the biosensors market corresponds to glucose sensors. Although glucose can be monitored using a wide number of methods, as for example spectroscopic (e.g. fluorescence, IR and Raman), iontophoresis and sonoforesis,[3,4] electrochemical sensors are among the most successful not only from an academic perspective but also from a commercial point of view. An analysis of excellent scientific reviews reporting electrochemical glucose sensing points out that non-invasive sensors with measurements based on the evaluation of sweat, saliva and/or tears are very attractive from the user's point of view, whereas the collection of blood samples by venipuncture or finger pricking causes reluctance among patients.[5-7]

Enzymatic and non-enzymatic electrodes for glucose monitoring are fabricated using outstanding materials with excellent electrochemical properties, as for example graphene,[8-10] carbon nanotubes,[11-13] conducting polymers,[14-16] and both metallic and metallic oxide nanoparticles.[17-19] Considering all such achievements, Nery and co-workers[20] published a critical review entitled with a fascinating question: "Electrochemical Glucose Sensing: Is There Still Room for Improvement?". With an increasing number of people suffering from diabetes, these authors demanded a joint effort of governments and societies, including the research community, to control and reduce the increase in the prevalence of this disease. Among others proposals, they emphasized the social interest in the development of novel less expensive platforms for non-invasive glucose monitoring and low-cost diagnostics.

We recently reported on the application of corona discharge plasma (CD-plasma) as a very simple and effective technology for the transformations of cheap commodity plastics, which are insulating and electrochemical inert low-cost materials, into electro-

catalysts and electrochemical mediators for sensors.[21-23] Plasma exposure promoted the formation of a large variety of reactive excited species at the surface of the fresh plastic, converting it in an electro-catalyst able to induce the oxidation of some neurotransmitters, as for example dopamine,[21] and in a mediator capable of electro-communicating with enzymes dropped on it, as for example glucose oxidase (GOx).[23] To expand the utility and applicability of this technology, here, for the first time, we go one step further by manufacturing a low-cost non-invasive sensor for monitoring glucose in sweat. For this purpose, the following two approaches have been used. Firstly, recycled plastic films, used in supermarkets for food packaging, have been transformed into electrochemical mediators using a controlled plasma treatment. The recycled plastic was labelled as LDPE by the manufacturer, even though probably it contained other undefined compounds (e.g. antioxidants, plasticizers, slip agents, biocides, antifogs and/or antiblocks). Secondly, the enzyme GOx has been covalently tethered to such recycled mediators (rather than physically adsorbed by simple dropping), as currently done in commercial sensors. GOx-based sensors prepared using recycled LDPE (hereafter RPE) have been compared with controls manufactured using virgin (*i.e.* without additives) LDPE (named VPE) under the same experimental conditions. Our study offers an effective method for the easy production of non-invasive glucose sensors recycled LDPE. The low cost of these sensors is useful not only from a circular economy perspective but also represents an attractive opportunity to control diabetes in patients from underdeveloped regions.

RESULTS AND DISCUSSION

As is illustrated in Scheme 1, the fabrication process can be summarized in four steps. Firstly (a), both the RPE films and VPE (supplied as pellets) were dissolved in

dichlorobenzene (5 mg/mL). After this (b), 2 µL of the resulting solutions were deposited onto bare glass carbon electrodes and allowed to dry at room temperature. Thirdly (c), a CD-plasma was applied to the surface of RPE- and VPE-modified electrodes during 1 min in ambient atmosphere, and using a voltage of 45000 V at a frequency of 4.5 Hz. Figure S1 shows a scanning electron microscopy (SEM) micrograph of RPE after plasma treatment. Finally (d), RPE and VPE plasma-treated electrodes were functionalized by immobilizing GOx on their surfaces.
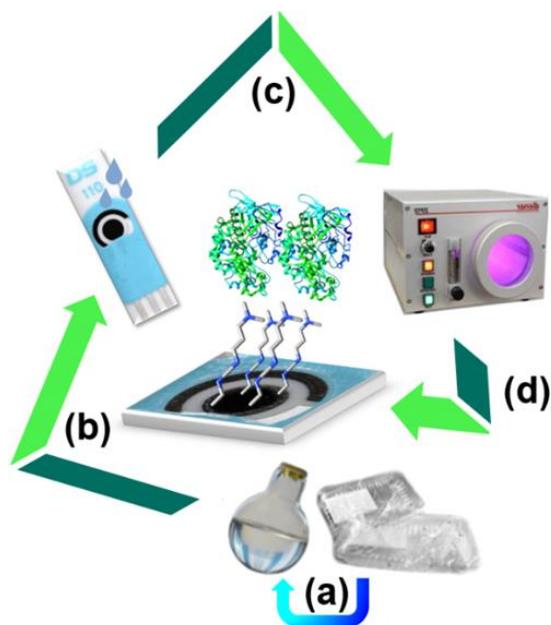
Scheme 1. Sketch describing the fabrication process of the RPE-based sensor: a) recycled plastic dissolution; b) deposition of the dissolved plastic on the electrode; c) atmospheric plasma treatment; and d) immobilization of the enzyme on the plasma-treated electrode.

Covalent immobilization of GOx onto the surface of RPE or VPE films was performed using the carbodiimide method (Figure 1). It is worth mentioning that, although GOx can also be immobilized using the glutaraldehyde crosslinking method, in a recent study it was found that sensors prepared using the carbodiimide method exhibit higher sensitivity and lower limit of detection than those obtained using

glutaraldehyde one.[24] Carbodiimides are able to activate –COOH functions, making them reactive towards nucleophilic groups such as the ε-NH$_2$ group from lysine. Previous X-ray photoelectron spectroscopy (XPS) studies on VPE films indicated that plasma treatment induces the formation of C_{sp2}–O bonds of carboxylic groups, as revealed the main bands appeared in the C 1s and O 1s spectra.[21] Accordingly, plasma treatment should be considered the pre-activation step of the recycled or virgin LDPE surface (Figure 1a). After this, in the activation step (Figure 1b), the plasma treated electrode was introduced into a buffered solution with the coupling agent, which was 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide. The central carbon atom of the carbodiimide is electron-poor and, therefore, susceptible to nucleophilic attack by –COOH groups from the plasma treated RPE or VPE surface, forming amine-reactive *O*-acylisourea. Finally, in the last step (Figure 1c), such intermediate directly undergoes nucleophilic attack from added GOx amino groups for covalent coupling. Experimental details about the immobilization of the enzyme on the RPE and VPE electrodes are provided in the ESI.
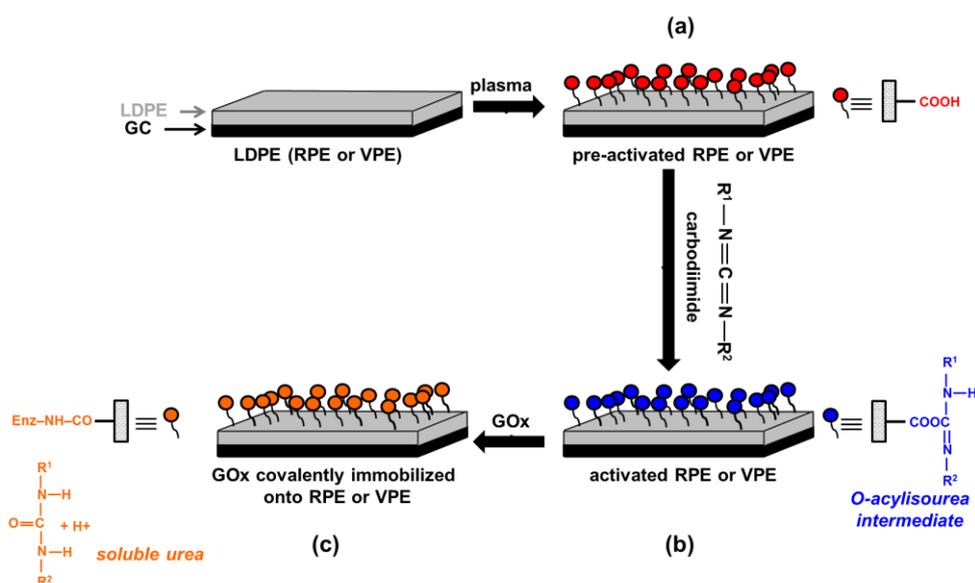

Figure 1. Scheme of (a) pre-activation, (b) activation and (c) steps for the covalent immobilization of GOx onto PT-LPDE/GC electrodes.

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The success of the carbodiimide method for the covalent immobilization of peptides and proteins, including GOx, on surfaces was previously reported.[25-28] As anticipated, XPS experiments confirmed the covalent immobilization of the GOx enzyme on the plasma treated LDPE films. Table 1 provides the atomic composition found for untreated VPE, plasma treated VPE and plasma treated VPE with the immobilized enzyme. In brief, the composition of VPE is fully consistent with those reported for naturally aged LDPE (*i.e.* LPDE stored at atmospheric conditions is slowly attacked by the oxygen and the temperature cycles from summer to winter or vice-versa), considering that samples were purchase some years ago.[29] Besides, the C / O and C / N ratios are 3.5 and 154.4, respectively, the low content of N 1s being attributed to N_2 molecules adsorbed from the atmosphere. After plasma treatment, the C / O and C / N ratios (Table 1) decrease to 2.2 and 3.5, respectively. These observations indicate that plasma functionalization provokes the formation of very reactive excited species, as discussed in previous work.[21] Finally, after GOx immobilization, the content of N 1s increases drastically and C / N ratio decreases from 35.3 to 6.0, which is consistent with the contribution of the amide bond, N–C=O, from the enzyme.[25-28]
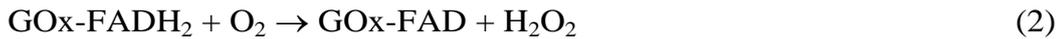
Cyclic voltammograms for RPE- and VPE-functionalized electrodes, recorded in phosphate buffered saline (PBS) solution at pH= 5.5 (the pH of human sweat being comprised between 4.0 and 6.8[30,31]) without glucose (Figure 2a), show an oxidation peak at 0.07 V. This corresponds to the oxidation of the complex formed by the GOx enzyme and the flavin adenine dinucleotide (FAD) cofactor GOx-$FADH_2$ into GOx-FAD, which occurs through the following process:

$$GOx\text{-}FADH_2 \rightarrow GOx\text{-}FAD + 2H^+ + 2e^- \text{ (at the sensor)} \qquad (1)$$

Table 1. Atomic percent composition (C 1s, O 1s and N 1s) and both C / O and C / N ratios found by XPS for untreated VPE, plasma treated (pre-activated) VPE, and plasma treated VPE and RPE with GOx covalently immobilized on the surface.

	C 1s	O 1s	N 1s	C / O	C / N
VPE					
Untreated	77.2	22.3	0.5	3.5	154.4
Plasma treated	67.1	31.0	1.9	2.2	35.3
Plasma treated + GOx	61.7	28.1	10.2	2.2	6.0
RPE					
Plasma treated + GOx	53.3	38.3	8.4	1.4	6.3

The detection of this oxidation process evidences that the covalent immobilization by means of the carbodiimide method facilitates the electronic communication between the deeply buried active site of the GOx and the network of reactive excited species formed at the surface of the plasma-treated plastic. However, this process is more detectable for the VPE-functionalized sensor than for the RFE-functionalized one. This has been attributed to the amount of immobilized GOx that is lower for RPE than for VPE, as proved by the decreasing of the current density of the linear sweep voltammetry (LSV) reported in Figure 2b. Besides, the reduction peak observed at ~0.63 V in Figure 2a corresponds to the reduction of O_2 with formation of H_2O_2, which is catalysed by GOx-FADH$_2$:[32,33]

$$GOx\text{-}FADH_2 + O_2 \rightarrow GOx\text{-}FAD + H_2O_2 \tag{2}$$
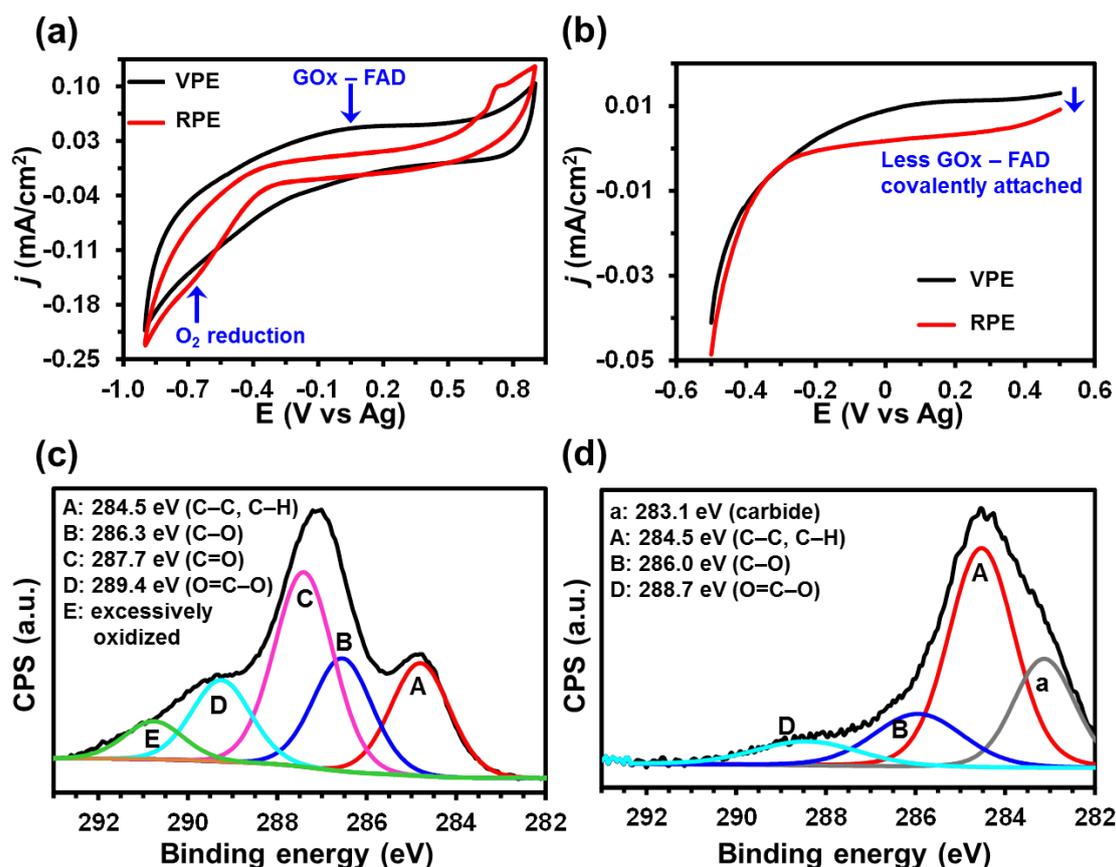
Figure 2. (a) Cyclic and (b) linear sweep voltammograms obtained for RPE- and VPE-functionalized electrodes in PBS solution without glucose (Scan rate: 35 and 5 mV/s for (a) and (b), respectively). C 1s high-resolution XPS spectra for (c)VPE- and (d) RPE-modified electrodes.

The atomic composition of plasma treated RPE is different than that of VPE due to the utilization of additives. The XPS spectra of RPE- and VPE-modified samples indicate that the content of oxygen is significantly higher for the former than for the latter (Table 1), the C / O ratios being 1.4 and 2.2, respectively. Moreover, comparison of the high resolution C 1s spectra (Figure 2c-d) shows the formation of different species for plasma treated RPE and VPE. In particular, a significant content of carbides (Table S1), which probably are due to the interaction of excited carbon atoms with the Si from the substrate, is detected in the modified RPE. Instead, this functional group is absent in the plasma treated

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VPE (Figure 2c). Also, the amount of O–C=O groups, which is involved in the GOx immobilization reaction (Table S2), and the N 1s content is significantly higher in VPE than in RPE (Table 1), explaining the easier detection of the GOx-FAD complex by the former functionalized sensor. Consistently, the N 1s atomic perfect composition reflects that the amount of GOx immobilized on RPE is lower than on VPE (Table 1).

Figure S2a-b compares the linear sweep voltammograms between -0.50 and 0.50 V recorded for VPE- and RPE-functionalized electrodes, respectively, in PBS with different glucose concentrations. In both cases the current density at the end potential decreases with increasing glucose concentration. Figure 3 represents the variation of the current density at 0.50 V for glucose concentrations ranging between 50 μM and 1 mM normalized with respect to current density in absence of glucose (j_g/j_0) for the VPE- and RPE-functionalized electrodes. The j_g/j_0 value experiences a linear reduction for the two sensors, which is maintained until the concentration of glucose reaches a value of 200 and 400 μM for the VPE- and RFE-functionalized electrode, respectively. After these threshold values, the j_g/j_0 ratio continues to decrease linearly with the glucose concentration although with a different slope (*i.e.* an inflection point appears). Differences between the two sensors have been attributed to the fact that the amount of immobilized enzyme is lower in the latter than in the former, as discussed above. More specifically, the change in the slope has been interpreted as follows. The glass carbon electrode participates in the detection process of the first tract of the profile (before the inflection point). Therefore, the contribution of H_2O_2 molecules capable of reaching the carbon of the glass by diffusion and oxidizing to O_2 plays an important role in that section of the profile. Instead, the second tract of the curve

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(after the inflection point) is dominated by the action of the immobilized GOx and its electro-communication through the mediator. As the amount of immobilized enzyme is lower for RPE than for VPE, the interval of glucose concentration associated to the first tract is wider for the former than for the latter. However, the behaviour of the two sensors is very similar, as evidenced by the almost parallel slopes of the two profiles. On the other hand, although control experiments were conducted using untreated RPE (both functionalized and non-functionalized), the electrochemical response was null (not shown) since LDPE is not an electrochemically active material.
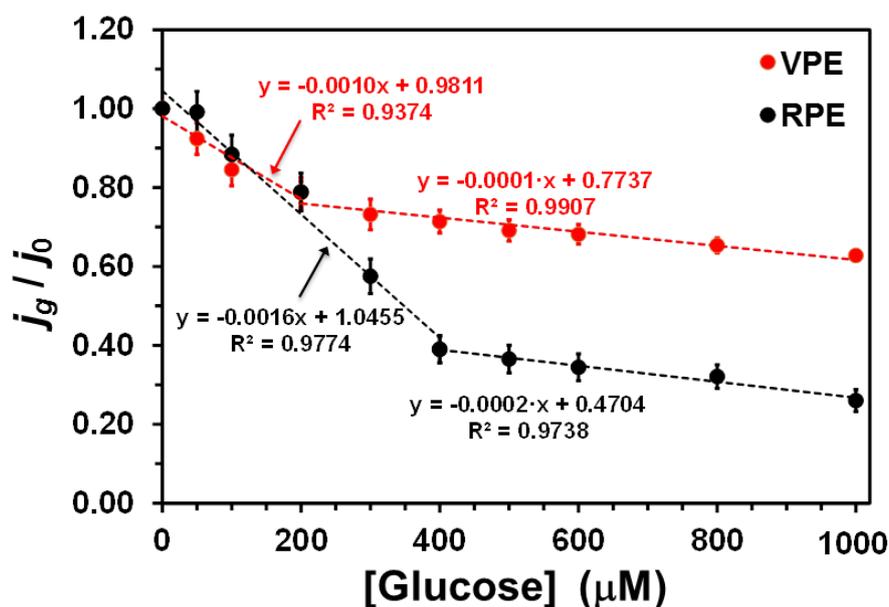

Figure 3. Variation of the current density at 0.50 V as determined by LSV in PBS with different glucose concentrations (j_g) relative to the current intensity without glucose (j_0) for VPE- and RPE-functionalized electrodes (Scan rate: 5 mV/s). Averages correspond to five independent replicas, while error bars indicate the standard deviations

The different behaviour of VPE- and RPE-functionalized electrodes at low glucose concentrations has been attributed to the fact that, in the latter, the tethered enzyme is not covering the whole electrode surface and, therefore, the

amount of H_2O_2 in the surrounding environment is not high enough to provide clear and systematic differences between j_g and j_0 until the glucose concentration is 400 μM. Instead, in the VPE-functionalized sensor, the j_g/j_0 ratio stabilizes at a glucose concentration of 200 μM only. These results have been attributed to the fact that the amount of O–C=O groups (necessary for GOx immobilization, as shown in Figure 1) are less abundant in RPE than in VPE, as demonstrated by XPS.

After demonstrating that the RPE can be used to manufacture glucose sensors similar to those prepared with VPE, the performance of the RPE-functionalized sensor was evaluated using a synthetic fluid that mimics biological sweat. More specifically, artificial sweat with a pH of 6.5 (adjusted by adding ammonia) and containing 0.5% sodium chloride, 0.1% lactic acid, and 0.1% urea (percentages expressed in mass) was prepared according to the British Standard (BS EN1811-1999).[34] Figure 4a displays representative cyclic voltammograms for RPE-functionalized electrodes recorded between –0.90 and 0.90 V in artificial sweat containing different glucose concentrations (0 μM – 1 mM). The current density at the reversal potential decreases drastically with the addition of a small amount of glucose, while such effect is much more moderate, but progressive and sustained, when the glucose concentration increases from 50 μM to 1 mM. The drastic glucose effect has been attributed to the presence of redox species in the artificial sweat (*i.e.* lactate and urea), which produces interferences with the detection at potential values higher than –0.10 V.[35-39] This oxidation current in artificial sweat is demonstrated in the inset of Figure 4a, which compares the voltammograms recorded in PBS and in synthetic fluid without glucose.
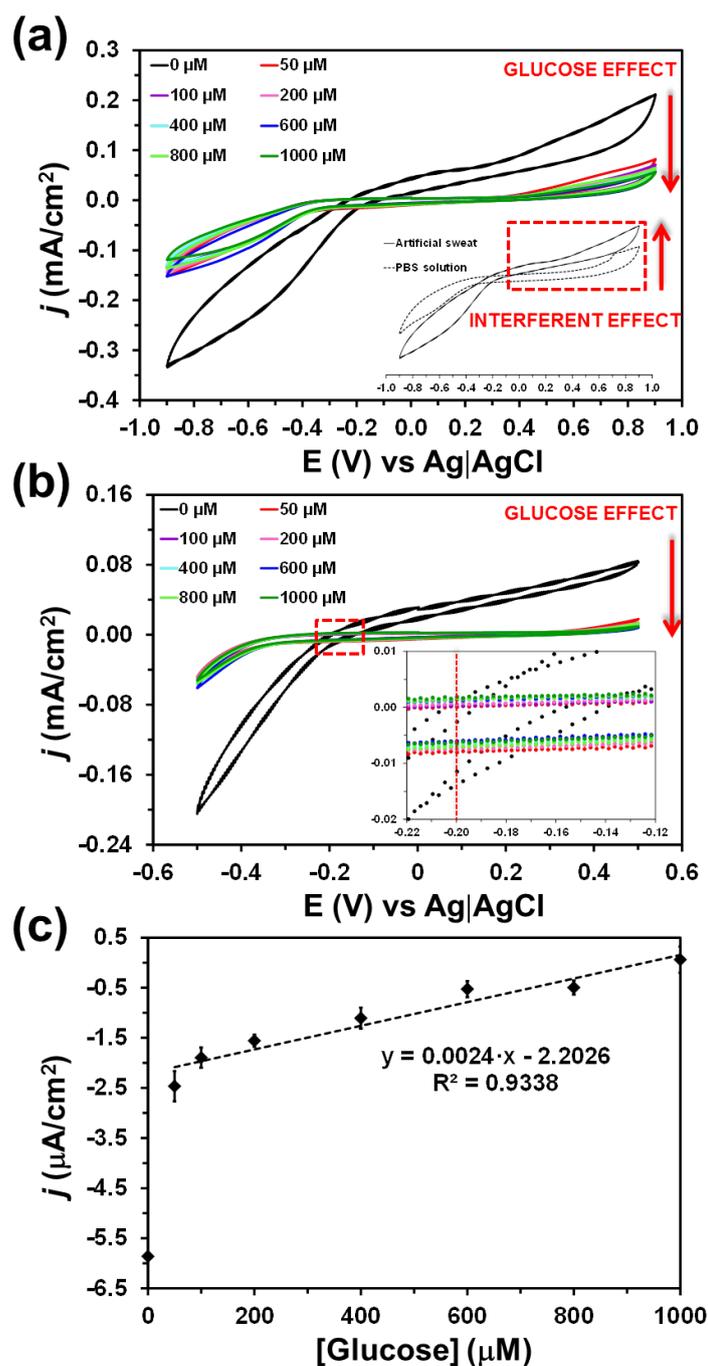
Figure 4. Cyclic voltammograms for RPE-functionalized electrodes recorded at 37 ℃ in synthetic sweat using different glucose concentrations. Voltammograms were recorded using the following interval potentials: (a) –0.90 to 0.90 V; and (b) –0.50 to 0.50 V. In all cases the scan rate was of 35 mV/s. The inset in (a) compares the blank (without glucose) in synthetic sweat and PBS, showing the effect of the interferents. The inset in (b) corresponds to the magnification in the –0.22 V to –0.12 V intervals. (c) Calibration curve of the proposed RPE-functionalized glucose sensor in synthetic sweat.

In order to avoid the interferent effect, different potential intervals were examined. Figure 4b displays the cyclic voltammograms recorded between -0.50 and 0.50 V, in which the interferent phenomenon is not detected while the glucose effect is maintained. This is clearly displayed in the magnification of the inset, which shows that current density increases with the concentration of glucose. The calibration curve in artificial sweat for the proposed RPE-functionalized sensor was determined using the current density at –0.20 V, in which the effect of the interferents can be neglected.

Figure 4c evidences that the voltammetric response is linear for the 50 μM – 1 mM glucose concentrations interval. The limit of detection (LOD) evaluated as $3 \cdot \sigma / m$, where σ is the standard deviation of the blank and m is calibration sensitivity (*i.e.* the slope of the linear plot) is 375 $\mu A \cdot \mu M^{-1} \cdot cm^{-2}$, while R^2 is 0.924. These values are fully compatible with glucose concentration in sweat, which ranges from 60 to 110 μM for healthy patients, the upper limit increasing to 1 mM in diabetic patients.[40] Furthermore, additional assays showed that RPE sensors can be re-utilized without loss of properties by at least three times.

The effective recycling of flexible LDPE is a pending challenge for the plastics recycling sector. The main advantages of the strategy presented in this work are the low-cost of the proposed glucose sensor, which is due to the absence of expensive and sophisticated materials as mediators (*e.g.* gold nanoparticles, carbon nanotubes and graphene), the simplicity of the production process and the transformation of a commodity plastic used for packaging in a high-value biomedical product, that is not accessible to many diabetic patients from underdeveloped regions. It is thus proved that the developed non-invasive glucose sensors shows a great potential to both decrease the impact of plastics in

the environment and produce a high-value biomedical product for disfavoured societies.

CONCLUSIONS

In summary, in this work we propose the use of recycled polyethylene, which, within the current framework of circular economy that demands a second life plastic waste, becomes an interesting alternative to produce electrochemical sensors with an extremely low cost and easy production. The re-utilization of LDPE from packaging is based on the application of plasma-treatment, the resulting electrochemically active material can be easily functionalized with GOx. Using cyclic voltammetry in artificial sweat, the RPE-functionalized sensor showed a linear response in the concentration of range of 50 µM to 1 mM with a LOD of 375 $\mu A \cdot \mu M^{-1} \cdot cm^{-2}$. The innovative development of non-invasive electrochemical sensors from plastic waste not only brings benefits to the end users from less favoured societies, but also is a caring effort to add an element of technological value. Thus, RPE-functionalized sensors exceed the traditional models used for recycling plastics, which are based on applications with smaller, or at most equal, technological value.

SUPPORTING INFORMATION

Materials and experimental procedures, atomic concentrations of functional groups derived from the C 1s and O 1s XPS spectra, linear sweep voltammograms from solutions without and with different glucose concentrations.

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TOC

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An approach for converting recycled low density polyethylene into an electrochemical mediator for non-invasive and low-cost biosensors, which are able to monitor glucose in sweat, is presented.