Carbon-based nanomaterials for skin-related applications

Nanomateriales de carbono para aplicaciones relacionadas con la piel

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Abstract

Skin is the largest organ of the body and the first protective barrier to the environment, playing a crucial role in covering other organs and also as a health state indicator. In this review, we describe the benefits of using carbon-based nanomaterials (CBN) for skin-related applications, focusing on carbon nanotubes (CNT) and graphene derivatives. Tactile, temperature and humidity sensors containing these nanomaterials, as well as advanced devices for health monitoring are discussed. Furthermore, the biodegradation and the biomedical applications, such as skin cancer treatment, of carbon nanomaterials-based hybrids are summarized over the manuscript.

1. Introduction

Human skin is the largest sensory organ of the body. It is one of the best indicators of health condition and it acts as an environmental barrier to protect other organs. Human skin consists of epidermal, dermal, and subcutaneous layers, all connected by a complex vascular nervous network [1]. In addition, skin has a well-developed stroma, which has neurosensory properties where receptors sense touch, pain, and heat stimuli [2,3].

The unique structural dimensions and excellent physicochemical properties of carbon-based nanomaterials (CBN), including fullerenes, carbon nanotubes (CNT), graphene and its derivatives, nanodiamonds and carbon dots, make them extremely interesting materials [4]. These extraordinary properties (i.e. electrical, mechanical, thermal, catalytic, and electrochemical properties) encourage the use of CBN in diverse areas, including biomedical engineering [5]. Because of their abundance and low production cost, CBN have been considered for replacing other conventional materials, such as the Si-based ones, in order to develop novel smart devices with high-temperature stability, high electrical conductivity or enhanced mechanical properties, among others. In parallel, the great development of soft materials has enabled a precise modulation of 3D scaffolds' properties so they are quite similar to those of the mimicked organ of interest, including skin [6].

In such context, the so-called "skin-inspired electronics" [7] and more precisely, stretchable electronic skin (e-skin), has attracted a high degree of interest due to its ability to detect subtle stimuli changes, and undoubtedly, CBN play a crucial role on the design of such cutting-edge devices. In particular, e-skins based on graphene derivatives have experienced a huge progress in the last few years with the development of advanced tactile [8,9], temperature [10], or humidity [11] sensors, and also regarding multimodal e-skin [12] or health-care monitoring [13]. Considering the high number of articles published in the skin-related field using CNT and graphene derivatives, in this review we will mainly focus on both kinds of CBN.

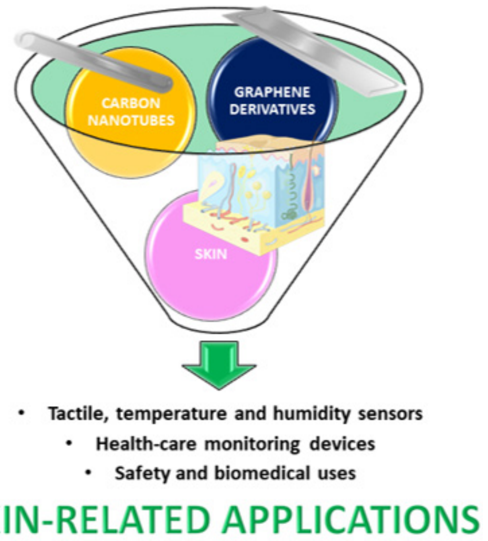

Figure 1. Carbon nanotubes and graphene derivatives for skin-related applications.

2. Tactile, temperature and humidity sensors

Since the moment a prosthetic hand with tactile feedback was reported by Clippinger *et al*. in 1974, [14] multiple investigations have been carried out to study the enormous application of tactile bionics [15,16]. The piezoelectric property of some anisotropic materials is known to convert mechanical forces into electrical charges due to the occurrence of electrical dipole moments. Due to the excellent electrical conductivity and good flexibility properties of CNT and/or graphene-related materials, a tiny stress deformation applied on these sensors can lead to a dramatic change of resistance. Thus, this ability has been used for the generation of multiple bioinspired tactile sensors based on carbon-related materials, that are able to undertake similar tasks to that of human skin, namely the sensing of external stimuli such as pressure, strain and torsion [17–19]. Lipomi *et al*. [20] developed a skin-like pressure and strain sensor based on transparent elastic films of CNT. Another example is the work reported by Lou *et al*., [21] who manufactured an ultra-sensitive and rapid response speed graphene pressure sensor with a highly reproducible electrical response to repetitive 100,000 loading-unloading cycles of 500 Pa. CNT and reduced graphene oxide (rGO) were also used together to manufacture composite nanofibers for ultraflexible, optically transparent and piezoresisitive pressure sensor arrays [22]. The device could be attached on the surface of human skin or other soft movable scaffolds to precisely monitor the pressure distribution, showing a negligible crosstalk thanks to the 1 mm spacing between sensor arrays.

Regarding the mimicking of the temperature-sensing ability in skin to help maintaining the thermal equilibrium between human body and ambient environments, multiple temperature sensors containing CBN have been developed [9,18,23–25]. Temperature-dependent resistance variations can be measured through the temperature coefficient of resistance (TCR = $(\Delta R/R)/\Delta T$) [9,26]; the temperature dependence of sensitive rubbers, for instance, depends on the concentration and type of filler: CNT-filled rubber displays decreasing resistance with increasing temperature, while graphene–filled rubber displays the opposite trend. However, by co-dispersing both CNT and graphene in an elastomer matrix, the temperature sensitivity of the composite resistivity can be eliminated [27].

which usually display a negative temperature coefficient. An interesting example could be the work reported by Ko and co-workers [30], who designed a human-skin-inspired temperature sensor based on rGO sheets. They confirmed a typical negative temperature coefficient behavior with a high TCR of 2.93 %/ºC, that could be attributed to the changes of contact resistance among the rGO sheets by thermomechanical changes. In this case, the sensor also had the capacity to detect the temporal response to cycling temperature variations.

Monitoring the water concentration coming from the human body or its surroundings is convenient for personalized healthcare. In such direction, pressure, temperature or humidity sensors containing CBN, that can be wearable or adhesive to human skin, have been developed [31,32]. The advantages in this case over other materials are more notable, since commercially available porous ceramics for humidity sensing are normally stiff and fragile [33]. In the case of humidity sensors, graphene derivatives are the most promising candidates due to its hygroscopic characteristic and large specific surface area. Typically, the performance mechanism of graphene-based humidity sensors is ascribed to the influence of vapor molecules on the charge carrier density of the nanomaterial, resulting in the resistance variation of the graphene sheets.

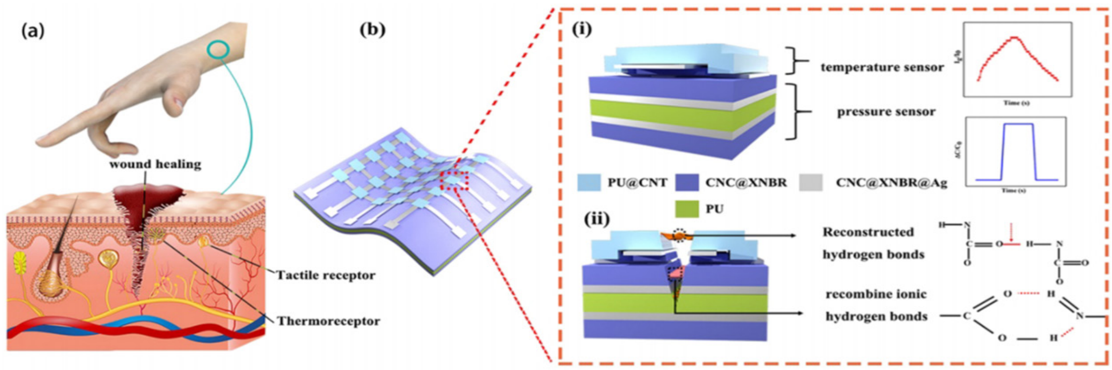

Figure 2. (a) Scheme of the human tactile receptors and temperature receptors with self-healing properties. (b) Scheme of the developed self-healable bifunctional e-skin. Adapted with permission from [28]. Copyright 2020 American Chemical Society.

Shen and co-workers [28] have recently reported a bifunctional self-healing e-skin with stacked integrated capacitive pressure and resistive temperature sensors based on polyurethane and multiwalled CNT (Figure 2). As a semiconductor, CNT with negative temperature coefficients stimulate electrons to enter the conduction band with increasing temperature, resulting in a resistance decrease. Even microfluidic sensors using CNT [24] or graphene derivatives [29] have been manufactured for sensing temperature and/or pressure. Graphene has ultrahigh thermal conductivity and unique sensitivity to temperature changes. Moreover, it shows a lower convective heat-transfer coefficient compared to metals and CNT, resulting in a higher final temperatures and faster heating rates. Because of these features, in the last few years, graphene has been extensively applied in flexible and stretchable temperature sensors,

In the case of rGO, the resistance of the nanomaterial can be increased, since water molecules can be adsorbed at the residual functional groups of the surface. In general, humidity can create distance changes between adjacent graphene oxide (GO) layers in a reversible way. The main problem regarding these systems is the generation of sufficiently flexible and stretchable devices keeping a high sensitivity. In this context, a sensing graphene/polypyrrole material was created by Wu and co-workers [32], reaching response and recovery times of approximately 15 s and 20 s, respectively, and a high humidity sensitivity. In another work, a humidity sensor based on rGO and polyurethane has been recently reported [34]. Here, the authors highlighted the maintenance of the sensitivity under high stretching state of 60% strain after 10,000 stretching cycles. An interesting example is the work developed by Sreeprasad *et al*. [35], who used graphene quantum dots and demonstrated a high humidity sensitivity by a mechanism governed by those graphene quantum dots, selectively interfaced with polyelectrolyte microfibers forming an electrically percolating-network.

Nevertheless, physiologically skin-to-skin contact induces a simultaneous temperature and humidity variation, and moreover, a tactile stimulus occurs on human skin at the same time. This means that e-skin should be designed to sense multiple stimuli in order to really mimic human skin, which is known as "multimodal e-skin". Park *et al*. [30] developed microstructured ferroelectric skins containing different concentrations of rGO that could detect and discriminate between multiple spatiotemporal tactile stimuli. The authors demonstrated the applicability of these sensors by the simultaneous monitoring of pulse pressure and temperature of artery vessels. Shortly after, a stretchable and multimodal "all graphene" electronic skin was reported [36]. Humidity, thermal and pressure functional sensors were included in that matrix and were judiciously integrated into a layer-by-layer geometry through a simple lamination process. Concerning CNT, a highly sensitive and multimodal skin sensor which was capable of simultaneously detecting tactile and biological stimuli was developed [37]. In this case, a wearable and multimodal skin sensor using CNT fabrics was capable of sensing external stimuli such as tactile, temperature, humidity at the same time, and even discern input signals derived from versatile chemical fluids with different dipole moments.

It is important to highlight the opportunity offered by printing techniques, perfect tools to generate a variety of solution-based materials on polymeric substrates over big areas for multifunctional electronics [38,39].

3. Health-care monitoring devices

The increasing necessity for patient-friendly therapies together with the rise in medical costs arising from the population aging and an increment in chronic diseases, have sparked the development of skin-mountable therapeutics and drug delivery systems that are more efficient and easier to use than conventional techniques [1]. These devices provide point-of-care services at home, thereby potentially reducing primary care patient load. Salvatore and co-workers [40] thoroughly reviewed in 2017 the concept of "lab-on-skin" to describe a variety of electronic devices with physical properties similar to those of skin and that are able to provide accurate, non-invasive, long-term and continuous health monitoring.

Stretchable CNT strain sensors for human-motion detection were reported in 2011 [41]. The authors assembled the CNT sensors on stockings, bandages and gloves in order to obtain devices able to detect movement, typing, breathing and even speech. Continuing with CNTs, Tai *et al*. [42] developed a flexible pressure sensing film based on single wall CNT and polydimethylsiloxane spheres for human pulse signals monitoring.

Graphene derivatives have been also used for health monitoring machines. In that sense, the work carried out by Coleman and co-workers is very well known [43]. The authors published a simple method to infuse liquid-exfoliated graphene into natural rubber, obtaining strain sensors that can effectively monitor joint and muscle motion besides breathing and pulse. In a more recent work, Park and co-workers [44] have reported a smart bandage consisting of MXene-functionalized porous graphene scaffold. Thanks to the synergistic effect between graphene and MXene, the hybrid scaffold displayed high conductivity and improved electrochemistry with a fast heterogeneous electron transfer rate. These features led to the application of the final bandage for chronic wound care management, since it was able to sense uric acid, pH and temperature at the wound site. Regarding drug-delivery, a graphene-based electrochemical device with thermoresponsive microneedles for diabetes monitoring and therapy was reported [45]. The patch could be thermally activated to deliver Metformin transcutaneously, reducing blood glucose level in diabetic mice.

Perspiration from the skin gives helpful information including pH and chemical composition such as metallic ions, glucose, urea, volatile organic compounds, and so on [46], which can facilitate a prompt diagnosis of health state. In that context, interesting studies have been published. In 2013, Liao *et al*. [47] reported improved glucose sensors based on organic electrochemical transistors by incorporating graphene derivatives, achieving higher sensitivities and extending the detection limits due to the enhancement of the charge transfer and the surface to volume ratio of the gate electrode. Moreover, the authors found a negligible effect caused by uric acid an dL-ascorbic acid was observed when incorporating chitosan or Nafion. More recently, a wearable electrochemical glucose sensor was reported by Xuan *et al*. [48], based on a rGO electrode in which GO catalyzes the oxidation of glucose to glucarolactone and H_2O_2 by a redox reaction.

Despite the fact that some characteristics, such as the ability to shapely adapt to the rough surface of the skin, normally through van der Waals forces (tattoo-like) [49], still need to be improved in terms of thickness and modulus, the ongoing research on this kind of adherent skin-electronic devices has been highly improved in the last years [50,51], and they could map pressure, temperature or humidity distributions on the skin with high fidelity, being imperceptible by the customer and allowing even the long-term track diseases.

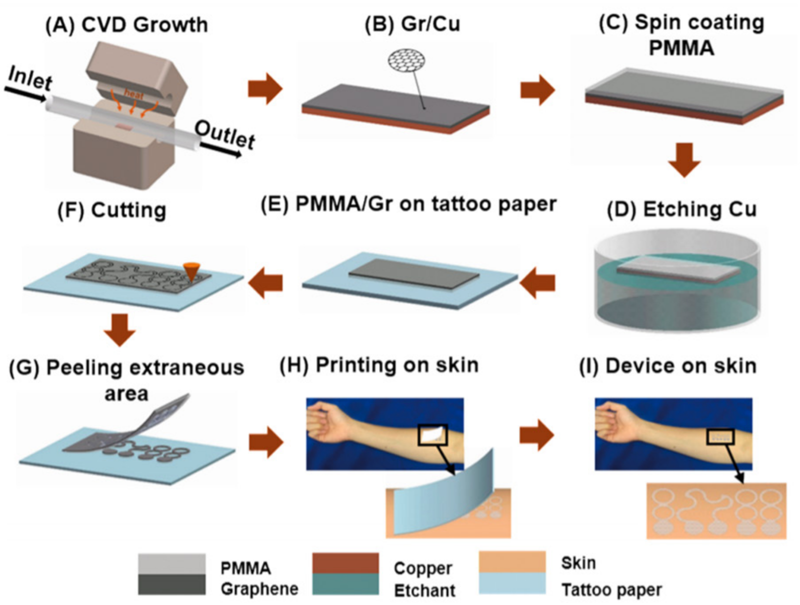

Figure 3. Fabrication process of a graphene electronic tattoo. Adapted with permission from [49]. Copyright 2017 American Chemical Society.

4. Safety and biomedical use of CBN

CBN have been described as excellent candidates with multiple applications in several sectors of society. In fact, the increasing exploitation of these nanomaterials has led to many comprehensive evaluations of their impacts on human health and environment [52–54]. In order to be aware of the possible risks on health of CBN, several works and reviews have been reported over the last few years concerning their biocompatibility and their biodegradation abilities [53,55]. Macrophages and multiple types of microbes including bacteria and fungi have the ability to degrade CNTs and graphene derivatives [56,57]. Additionally, enzymatic catalysis has been demonstrated to cause the biodegradation of single-walled CNT and other graphene-related materials using human enzymes such as eosinophil peroxidase or myeloperoxidase [58,59]. The physicochemical features of the nanomaterials play a key role on the biodegradation ability of CBN: a dispersibility-dependent biodegradation effect was found by Kurapati *et al*. [60], and chemical functionalization of the materials can enhance their degradation extent [61].

Furthermore, given the chemical nature of CBN, their dermal effects have to be taken into account: skin irritation could be considered as an important outcome after cutaneous exposure, and skin sensitization cannot be excluded in light of the tendency of CBN to interact with proteins [53]. Only a few studies reported the toxicological data and de differential effects of this kind of nanomaterials, and most of them are carried out *in vitro* on skin keratinocytes and/or fibroblasts [62]. Moreover, the conclusion about the cytotoxicity of these materials varies from one work to another, depending basically on the physicochemical properties of each specific nanomaterial such as the shape, the dimensions or the oxidative state: few-layer graphene containing almost no functional groups showed, for instance, a lower cytotoxic effect compared to GO [63]. Palmer *et al*. [64] have recently demonstrated that multi-walled CNT with a high level of carboxylation displayed increased cytotoxicity in keratinocytes compared to the multi-walled CNT with intermediate levels of carboxylation. The concentrations used for the experiments are also a key parameter regarding cytotoxicity. Tubaro and co-workers have demonstrated how keratinocytes are capable of selectively sensing low amount of graphene derivatives (concentrations up to 1 µg/mL), showing no reduction of cell viability [65]. However, adverse effects such as dermatitis or increase on protein expression due to cutaneous contact with CBN have been reported [66,67]. Due to the relevance of this topic, Fusco *et al*. [68] studied the potential of differently prepared graphene derivatives causing skin irritation using a non-animal test, SkinEthic™ Reconstructed human Epidermis. The authors concluded that graphene-based materials prepared with non-irritant exfoliation agents do not induce skin irritation after a single acute exposure.

Biomedical applications of CBN such as CNT and graphene derivatives, have been extensively studied [69,70]. Cancer therapy is maybe the most investigated area in that sense, since these nanomaterials present special physicochemical properties to load drugs on their surfaces and target them to the site of interest [71–73], as well as the possibility of using phototherapies [74]. Additionally, CNT have been demonstrated to improve transdermal drug delivery [75] and they have been also used for skin cancer diagnosis and its treatment [76,77]. Not only CNT, but of course functional GO, for instance, have been used as a plasmid-based Stat3 siRNA carrier inhibiting mouse malignant melanoma growth *in vivo* [78]. A different example could be a hybrid material based on GO and hyaluronic acid that has been used for the photothermal ablation therapy of skin cancer [79].

5. Conclusions

Skin is the outermost shell of the body and, because of its interfaces with the environment, skin plays a key role in protecting other organs and as a health state indicator. In this review, we introduced the use and the role of CBN for skin-related applications, focusing on CNT and graphene derivatives. Not only tactile, temperature and humidity sensors, but also devices for health monitoring and carbon nanomaterials-based hybrids for skin cancer, have been summarized across this review.

Although research on adherent skin-electronic devices has been highly improved in the last years, some features such as the capacity to shapely adapt to the rough surface of the skin still need to be improved in terms of thickness and elastic modulus to be able to map signal distributions on the skin with high fidelity, being imperceptible by the customer and allowing even the long-term track of diseases.

Despite the facts that the use of CBN for skin diseases is increasing, and also given that they have revealed to be biodegradable, the great hope raised by the inclusion of CBN in complex biological systems such as real skin constructs, remains a challenge. Therefore, this review shows that these are still emerging research areas with scientific and technical challenges requiring extensive work.

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