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Carbon nanotubes hybrid hydrogels for electrically tunable release of Curcumin

Giuseppe Cirillo[a,*], Manuela Curcio[a], Umile Gianfranco Spizzirri[a], Orazio Vittorio[b,c], Paola Tucci[a], Nevio Picci[a], Francesca Iemma[a], Silke Hampel[d], Fiore Pasquale Nicoletta[a]

[a] Department of Pharmacy Health and Nutritional Science, University of Calabria, Rende 87036, Italy
[b] Children's Cancer Institute Australia Randwick, NSW 2031, Australia
[c] ARC Centre of Excellence in Convergent Bio-Nano Science and Technology and Australian Centre for NanoMedicine, UNSW Sydney, NSW 2052, Australia
[d] Leibniz Institute of Solid State and Material Research Dresden, 01171 Dresden, Germany

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ABSTRACT

Electro-responsive hybrid hydrogels were synthesized by free radical polymerization using Gelatin-coated multi-walled carbon nanotubes as electro-conductive component, acrylamide and polyethylene glycol dimethacrylate as plasticizing and crosslinking monomer, respectively. Dynamic light scattering, Raman spectroscopy, scanning electron microscopy, resistivity measurement, cell viability assay, and evaluation of swelling degree upon application of an external voltage at 0, 12, 24, 36, and 48 V were performed as characterization tools. Composite materials were found to be highly versatile in modulating the drug delivery of neutral drugs (e.g. Curcumin) as a function of both nanotube content and voltage magnitude, with drug partition between carrier and releasing media being dependent on the balance between electrostatic attractive and repulsive forces and hydrogel swelling degree. Finally, suitable mathematical modelling were employed for the kinetic characterization of the release mechanism. The results allowed hypothesizing the use of hybrid for different therapeutic needs in wound healing treatment.

1. Introduction

The treatment of skin injuries often required either the development of a therapeutic protocol or the usage of a wound dressing with suitable and tunable properties [1,2]. The spontaneous tissue remodeling is a multifactorial process composed of different overlapped phases [3,4], with the involvement of inflammatory response and the production of high level of reactive oxygen and nitrogen species [5]. Additionally, the insurgence of bacterial infections may impede the healing process and lead to life threatening complications [6]. The evidence for the role of free radical species in the wound healing, suggested the use of exogenous antioxidants (e.g. coenzyme Q10 [7], vitamin C [8], β-carotene [9] and polyphenols [10,11]) as supporting skin defense mechanisms [12]. Among others, Curcumin (CUR), a naturally occurring o-methoxyphenol derivative found in the rhizome of *Curcuma longa* L., showed potential applications as co-adjuvant in wound healing treatments [3,13], due its well-known antioxidant, radical scavenger, antimicrobial and anti-inflammatory properties [14] resulting in favorable biological activity on different cellular pathways [15].

* Corresponding author.
E-mail address: giuseppe.cirillo@unical.it (G. Cirillo).

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CUR is poor water-soluble and shows a pronounced first-pass metabolism, thus resulting more active when topically administrated [16]. Several CUR formulations have been developed to improve its bioactivity, including polysaccharides sponges and foams [17,18], protein films [5], as well as polymeric bandages [19]. On the other hands, since high topical dosages may results in toxicity concerns, the development of a formulation ensuring a slow release of the bioactive molecule would be desirable [20].

Different wound dressing device have been proposed to address the key requirements of wound healing [21], namely protection from microorganism infection, gas exchange, exudate absorption, moist environment, and painless removal [22]. To this regard, polymeric hydrogels are emerging as valuable tools because of their high biocompatibility, water content, gas permeation and soft consistency [23]. Various natural (e.g. collagen, gelatin, silk, cellulose derivatives, chitin, chitosan, alginate, hyaluronic acid), or synthetic (e.g. poly(L-lactide), poly (vinyl alcohol), polyurethane, poly(ε-caprolactone), polyacrylates) polymers, as well as their blends, have been used as wound dressing materials [24–30].

The ability to entrap and release an active agent, together with the responsivity to an external modulating stimulus, further enhance the performances of hydrogels in wound dressing applications [31]. Among others, the electrical stimulus combines the possibility to control the drug release profile [32] with the ability to promote the tissue regeneration speed [33]. The first effect is obtained by finely tuning control parameters such as voltage intensity, pulse duration and shape, while the healing acceleration is related to the supplementation of natural bioelectric currents involved in the tissue regeneration processes [34]. For these reasons, the development of an electro-responsive hydrogel dressing device could be an appealing approach for wound healing application.

The literature is plenty of materials on the subject, with different polymers and synthetic approaches proposed, highlighting the importance of the incorporation of a conductive element (e.g. electroactive polymers or metal and carbon nanostructures in the hydrogel structure [35–39].

As far as the incorporation of carbon nanotubes (CNT) into hybrid hydrogel is concerned, electric field was employed for the fabrication of dual stimuli responsive Poly(N-isopropylacrylamide) hybrid hydrogel. It was found that the applied electrical energy triggered the shape-changing capability of the hydrogel by efficient conversion to heat [37]. In another approach, electro-sensitive drug delivery system was also successfully prepared by free radical polymerization of methacrylic acid in the presence of CNT, obtaining a pulsatile release behavior upon the on/off application of the external voltage [38].

It should be highlighted that the interactions between CNT hybrid hydrogels and drugs are strictly influenced by the electrical properties of both hybrid and drug counterparts, as proved in the evaluation of the release profile of tetracycline from CNT-doped polyvinyl alcohol hydrogels. In this case, indeed, electrical stimulation induced the charge–charge repulsion resulting in a consistent enhancement of the drug diffusion into the external media at pH 8.0 [39].

Similarly, in our previous work, we evaluated the influence of the drug charge on release/retention profiles by loading anionic (e.g. Diclofenac sodium salt) and cationic (e.g. Ciprofloxacin hydrochloride) drugs into CNT-hybrid hydrogel films. The hydrogels, prepared by free radical polymerization of acrylate monomers in the presence of Gelatin-coated CNT, were found to fast release the anionic drug upon application of an external 12 V voltage, while the cationic drug was retained in such conditions and fast released at 0 V [40].

Furthermore, the effect of the drug size (hydrodynamic diameter) on the release profiles of Ketoprofen and bovine serum albumin (BSA) was evaluated employing CNT-hybrid hydrogels as electro- and thermo- responsive carrier. For both therapeutics, enhanced releasing rates were recorded under thermal stimulation, while the application of the electric field resulted in a reduction of BSA and an enhancement of Ketoprofen release kinetics, as a consequence of the balance between diffusional constrains and electrostatic repulsive forces [41].

In this work, we explored the performance of CNT-doped acrylate hydrogels in wound healing treatments, to match the challenges of controlling the nonionic drug (e.g. CUR) release as a function of both the CNT amount and the strength of the applied external voltage. To the best of our knowledge, this is the first example of electro induced release of CUR, opening new opportunities for the topical administration of such bioactive molecule.

CNT hybrid films composed of Gel, AAm, and polyethylene glycol dimethacrylate (PEGDMA) were synthesized by grafting polymerization, varying the amount of CNT in the prepolymerization feed from 0.5 to 2.0% (by weight) to optimize the electric behavior and the drug to carrier interactions. The effect of different voltages (from 12 to 48 V) on release profile was investigated, and the application of two different mathematical models allowed the kinetic characterization of the release mechanism at the different experimental conditions.

2. Materials and methods

2.1. Synthesis of hybrid hydrogel

CNT were synthesized by aerosol assisted chemical vapour deposition according to our previous work [42], operating with an excitation frequency of 850 kHz. Ferrocene, cyclohexane and 100 sccm Ar were employed as metal–organic catalyst precursor, carbon source and carrier gas flow. After synthesis, CNT were purified by a thermal treatment at 450 °C in air for 1 h with hydrochloric acid to remove amorphous carbon and catalyst particles, respectively.

Hydrogel containing different amounts of CNT, H_{NTi} (i = 1, 2, 3), were prepared according to a previously developed polymerization procedure involving the preliminary dispersion of suitable CNT amount in a Gel water solution by a cup-horn high intensity ultrasonic homogenizer (SONOPULS) with a cylindrical tip (amplitude 70%, time 30 min) [43]. Defined amounts of AAm and PEGDMA were added to the solution, which was purged with gaseous nitrogen for 20 min before adding Ammonium persulfate (10% w/w). The polymerization mixture was placed between two 5.0 × 5.0 cm^2 glass plates, separated with a Teflon spacer