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Development and *in vitro* evaluation of potential electromodulated transdermal drug delivery systems based on carbon nanotube buckypapers

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ABSTRACT

Buckypapers based on different types of carbon nanotubes with and without the addition of four model drugs, two of basic nature (clonidine hydrochloride, selegiline hydrochloride) and the others of acidic character (flurbiprofen, ketorolac tromethamine) were prepared and characterized. The influence of the conditions employed in the preparation of the buckypapers (dispersion time and solvents used in the preparation, as well as the type of carbon nanotubes used and the characteristics of the drug involved) on their conductivity was especially examined. The *in vitro* performance of the drug loaded buckypapers as passive and active transdermal drug release systems, the latter being modulated by means of the application of electric voltages, was studied. Passive drug loaded buckypapers presented characteristic release profiles, also depending on the drug used, which indicate differences in the drug-carbon nanotubes non-covalent interactions. Application of electrical biases of appropriate polarities enabled the modulation of the drug release profiles in any desired direction. Different mathematical models were fitted to passive and electromodulated experimental release data for the four model drugs. Among these models, the most appropriate for data description was a two-compartment pseudo-second-order one.

1. Introduction

Potential use of carbon nanotubes (CNTs) for creating innovative drug delivery systems has been a growing research field in recent years, with some promising results. Most of the reported work has been devoted to the use of CNTs as nanovectors injected by the parenteral route for the delivery of anticancer drugs, antimicrobials, anti-inflammatories, antihypertensives, and antioxidants [1]. Instead, only few publications have focused on the transdermal route, although it is considered to be a feasible way for drug administration using CNTs [2]. In transdermal delivery, the CNTs are intended to remain in the surface of the stratum corneum and release the drug that crosses the skin barriers to reach the bloodstream. Generally a variety of polymers have been used to disperse the CNTs and to form thin films [3–7].

There are a number of benefits of the use of CNTs in transdermal applications. They exhibit transdermal penetration enhancement effects of drugs [2,8] and due to the CNTs inherent antimicrobial activity [9], they would also help to maintain the patches within the microbiological limits for non-sterile pharmaceutical products. Another important advantage is the straightforward interfacing of CNTs buckypapers with programmable electronic devices in order to create responsive drug delivery systems [10–11]. In this sense, systems based only on CNTs have been reported to increase the electrical conductivity compared to CNTs-polymers films [12].

Perhaps, other current CNTs research application areas such as Li ion batteries [13,14], biosensors [15,16], and even flexible carbon nanotube electronic devices [17–19] would converge in the future in the assembly of integrated devices based mainly on CNTs acting as responsive drug delivery systems. These devices would detect the levels of specific endogenous substances, and applying control logic they would use the drug loaded CNTs buckypapers as actuators to deliver appropriate amounts of drug to the patient, in order to fulfill the treatment requirements [10,20].

Recently, we have shown the feasibility of using only CNTs arranged in buckypapers, without the addition of polymers for passive transdermal delivery of flurbiprofen and clonidine HCl [21]. We also identified different factors that influenced the release profiles such as the type of carbon nanotubes (SWCNTs vs MWCNTs), their functionalization with

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hydroxyl or carboxyl groups, the drug: CNTs mass ratio, the type of arrangement of the CNTs in the buckypapers (monolayer vs bilayer) as well as the chemical structure of the drug.

The aim of the present work is to further characterize drug loaded CNTs buckypapers and to study, *in vitro*, their performance as active transdermal drug release systems, modulated by means of the application of electric voltages. For this purpose, four different model drugs, two of basic nature (clonidine hydrochloride, CHC, and selegiline hydrochloride, SHC) and other two of acidic character (flurbiprofen, FB, and ketorolac tromethamine, KT) were used.

2. Experimental

2.1. Materials

CNTs were purchased from Timesnano (Chengdu Organic Chemicals Co. Ltd./Chinese Academy of Sciences). They included single wall CNTs (SWCNTs) and multi wall CNTs (MWCNTs), functionalized either with hydroxyl (−OH) or carboxyl groups (−COOH). Characteristics of the CNTs used are described in a previous publication [21]. The model drugs used (CHC, SHC, FB, and KT) were generous donations from Laboratorios Casasco SAIC (Buenos Aires, Argentina), IVAX Argentina, Teva Group member (Buenos Aires, Argentina), Laboratorios Gador S.A (Buenos Aires, Argentina), and Laboratorios Richet SA (Buenos Aires, Argentina), respectively. The CHC and SHC are basic drugs, whereas FB and KT are of acidic nature; their chemical structures are presented in Fig. 1. The drugs complied with USP specifications and all the other reagents used were of analytical grade.

2.2. Dispersion of the CNTs

In order to ensure a thorough dispersion of the CNTs, the optimal sonication time was determined by monitoring the leveling of the UV–vis absorption intensity at 660 nm and the disappearance of visible aggregates [22]. A VCX 750 (20 Khz, 750 W) Sonics Vibracell ultrasonic processor equipped with a 3 mm tip diameter probe was employed. Power output was set at 20%. A mass of 1.6 mg of CNTs was dispersed in 10 mL ethanol.

2.3. Preparation of drug-loaded CNTs and derived buckypapers

For preparation of the buckypapers, the same ultrasonic processor and settings mentioned above were used. The buckypapers prepared with SWCNTs (−COOH) are designated as samples 1–4, and 8–13. Likewise, those obtained by using SWCNTs (−OH), MWCNTs (−OH), MWCNTs (−COOH) are denoted as 5, 6, and 7, respectively. An amount of 1.6 mg of CNTs was sonicated with 10 mL ethanol (samples 1–7, 8 and 9), 10 mL hexane (sample 8) or 10 mL of 0.064 mg mL^{-1} ethanol solutions of CHC, SHC, FB or KT (samples 10–13 respectively). The effective processing time was 5 min (sample 1), 10 min (sample 2), 20 min (samples 3, 5–13) or 30 min (sample 4). On/off pulse cycles were set at 1 s and temperature was kept at 25 °C. Samples 1–8 were filtered through a 0.22 μm nominal pore size, 47 mm diameter Nylon membrane (GE Osmonics/MSI). Samples 9–13 were then dried in an oven at 60 °C overnight and re-suspended in hexane with the assistance of a 40 Khz, 80 W ultrasonic bath Test Lab TB02 for 30 min and filtered through the Nylon membrane. Finally, all the buckypapers were dried in an oven at 60 °C for 2 h. For samples 9–13, the drug: CNTs mass ratio was 0.4. Information regarding the preparation of the buckypapers is detailed in Table 1.

2.4. Characterization of the drug-loaded CNTs and of the derived buckypapers

2.4.1. Raman spectroscopy

Raman spectra were measured for the detection of drug-CNTs associations using a confocal microscope (Olympus BX41) coupled to a high resolution spectrometer (Jobin Yvon XY-800) equipped with a liquid-nitrogen-cooled back-illuminated CCD detector. The excitation was provided by an Nd-YAG laser ($\lambda_{exc} = 532.5$ nm) with a power of 16 mW and an objective of 20×. Data was acquired during 8 s and 5 spectra were averaged.

2.4.2. Scanning electronic microscopy

Scanning electronic microscopy (SEM) of gold metallized buckypapers (both unloaded and loaded with drugs) was performed in a Zeiss DSM 982 Gemini microscope (Carl Zeiss) equipped with a field emission gun (FEG) and an in-lens secondary electrons detector (SE). Acceleration voltages were 3 or 5 kV. Magnification ranges applied were between 200× and 100,000×.

2.4.3. Electrical properties

Measurements of the electrical properties of the buckypapers supported on the Nylon membranes were carried out in air atmosphere using the standard four-point method [23], varying the DC current intensity between 0 and 2.5 mA. The conductivities were determined by recording electrical voltages at fixed current intensities with a 15 s interval until the system reached steady state. The electrical contacts were made with silver paste. Simultaneously, the temperature of the buckypapers was measured with a copper-constantan (T-type) thermocouple [23]. Six replicates of each experiment were performed.

2.4.4. Drug loading efficiency

Drug loading efficiency was determined by means of an exhaustive extraction method as described previously [21] and UV spectroscopy quantification was performed at 220 nm for CHC, 206 nm for SHC,

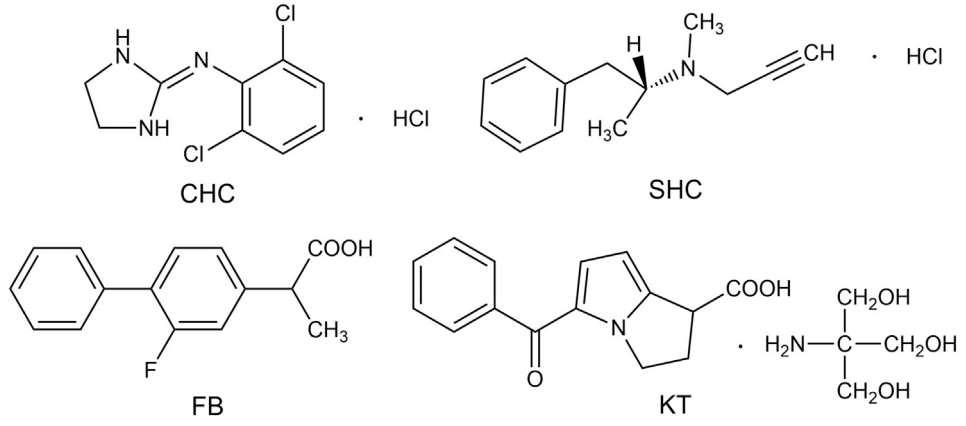

Fig. 1. Chemical structures of clonidine hydrochloride (CHC), selegiline hydrochloride (SHC), flurbiprofen (FB), and ketorolac tromethamine (KT).