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Carbon nanotubes buckypapers for potential transdermal drug delivery

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ABSTRACT

Drug loaded buckypapers based on different types of carbon nanotubes (CNTs) were prepared and characterized in order to evaluate their potentialities for the design of novel transdermal drug delivery systems. Lab-synthesized CNTs as well as commercial samples were employed. Clonidine hydrochloride was used as model drug, and the influence of composition of the drug loaded buckypapers and processing variables on *in vitro* release profiles was investigated. To examine the influence of the drug nature the evaluation was further extended to buckypapers prepared with flurbiprofen and one type of CNTs, their selection being based on the results obtained with the former drug. Scanning electronic microscopy images indicated that the model drugs were finely dispersed on the CNTs. Differential scanning calorimetry, and X-ray diffraction pointed to an amorphous state of both drugs in the buckypapers. A higher degree of CNT–drug superficial interactions resulted in a slower release of the drug. These interactions were in turn affected by the type of CNTs employed (single wall or multiwall CNTs), their functionalization with hydroxyl or carboxyl groups, the chemical structure of the drug, and the CNT:drug mass ratio. Furthermore, the application of a second layer of drug free CNTs on the loaded buckypaper, led to decelerate the drug release and to reduce the burst effect.

1. Introduction

Carbon nanotubes (CNTs) have potentialities for novel applications in nanomedicine as biocompatible and supportive substrates, as well as pharmaceutical excipients for creating versatile drug delivery systems [1–4]. In recent years there has been a growing interest in nanopharmaceutical products based on CNTs [4–7]. Several studies have been devoted to examine systems for injecting modified CNTs vectors that subsequently reach the target cell and deliver their therapeutical load. The delivery usually requires the nanostructure to enter the cell by an endocytosis-independent, "needle-like" penetration mechanism [8]. Different diseases have been addressed, being cancer and chronic infections representative examples [2–6].

However, only a few recent publications have focused on CNTs for transdermal drug delivery applications. In these systems, CNTs are not directly incorporated inside the organism, but are applied outside the stratum corneum of the skin and only the active pharmaceutical ingredient is intended to cross the body barriers. Usually, the CNTs employed are dispersed in various polymers [9–13]. Some other more sophisticated proposals include programmable transdermal devices based on aligned CNT–epoxy resin composites for nicotine delivery, which involve a complex sequence of processing steps [14,15]. Also, single wall CNTs-povidone iodine bandages have been reported for wound healing, which showed a slow release of the antiseptic from the composite with local action [16]. In this scenario, and taking into account that CNTs can be arranged in macroscopic thin films (buckypapers) [17,18], systems based on CNTs buckypapers may be conceived. To the best of our knowledge, this kind of systems has not been earlier investigated for transdermal drug release, at least in the open scientific literature. Furthermore, the electrical conductivity of CNTs could facilitate the design of electromodulated transdermal systems [10,12,13,15,19]. For these systems, the absence of added polymers appears to be advantageous since the electrical conductivity of thin films based on CNTs has been reportedly found to decrease for increasing proportions of various polymers used as dispersants [20]. Additionally, the intrinsic antimicrobial activity of CNTs [21] would contribute to the development of transdermal patches within the microbiological limits for non-sterile pharmaceutical products.

In the present work, drug loaded CNTs buckypapers were prepared and characterized in order to examine their potentialities as platforms for the design of novel transdermal drug delivery systems. For this purpose, different types of CNTs and clonidine hydrochloride (CHC) as model drug, were used. The influence of formulation and processing variables on *in vitro* release profiles was investigated. In order to explore the effect of the drug characteristics, the evaluation was further extended to buckypapers prepared with flurbiprofen (FB) and one

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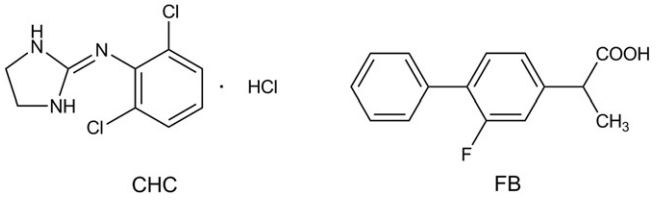

Fig. 1. Chemical structures of clonidine hydrochloride (CHC) and flurbiprofen (FB).

type of CNTs, selected accounting for the results obtained with CHC. The representative model drugs were chosen because they are currently used in conventional dermal patches and differ in their acid–base characteristics. Clonidine is a basic drug, whereas FB is of acidic nature (Fig. 1). Oral administration of the antihypertensive drug CHC might result in some adverse effects, including dry mouth, drowsiness, dizziness, constipation, and sedation. Flurbiprofen, a nonsteroidal anti-inflammatory agent, could cause gastrointestinal discomfort [22,23]. Both drugs are relatively small molecules with short half-lives. As a result of these characteristics the transdermal route appears as a suitable alternative for both drugs.

2. Experimental

2.1. Materials

Commercial and lab-synthesized carbon nanotubes (CNTs) were used for the preparation of the buckypapers. The former were purchased from Timesnano (Chengdu Organic Chemicals Co. Ltd./Chinese Academy of Sciences) and included CNTs with different features: single wall CNTs (SWCNTs) and multi wall CNTs (MWCNTs), functionalized either with hydroxyl (—OH) or carboxyl groups (—COOH). Their main characteristics, provided by the supplier, are presented in Table 1.

Besides, aligned MWCNTs arrays were lab-synthesized by the floating catalyst chemical vapor deposition process under flowing Ar/H_2 and pre-established conditions. Analytical grade iron(II) phthalocyanine ($C_{32}H_{16}N_8Fe$) was used as precursor. Experiments were carried out at reaction temperatures of 880 °C. A total gas flow rate of 30 ml min^{-1}, H_2 concentration of 50% v/v, and total reaction time of 1 h, were employed. Oxidation was then performed by exposing the synthesized CNTs to an O_2 atmosphere (O_2 molar fraction of 0.10) at 375 °C for 90 min, using the same set-up employed for the synthesis. The oxidized CNTs were subsequently subjected to acid treatment, to remove oxide nanoparticles. This treatment consisted in contacting the oxidized sample with HCl aqueous solution (50 wt.%), and gently mixing at room temperature. Afterwards, the CNTs were rinsed repeatedly with distilled water until neutral pH was achieved. CNTs were dispersed in ethanol and the dilute dispersion was ultrasonicated at room temperature for 120 min. Finally, ethanol was evaporated up to constant weight. The obtained MWCNTs functionalized with carboxyl groups had a ≈ 10 μm length, and inner and outer average diameters of 15 and 28 nm, respectively. More details on the synthesis and oxidation protocols, as well as on their characteristics may be found elsewhere [24,25].

On the other hand, the model drugs used, CHC (USP) and FB (USP), were generously donated by Laboratorios Casasco SAIC (Buenos Aires, Argentina) and Laboratorios Gador SA (Buenos Aires, Argentina), respectively. All the other reagents used were of analytical grade.

Table 1
Characteristics of the commercial CNTs employed.

Type	OD[a] (nm)	Length[a] (μm)	Functional group content[a] (w/w%)	Manufacturer code[a]
SWCNTs (—OH)	1–2	≈30	3.96	SH080509
SWCNTs (—COOH)	1–2	≈30	2.73	SC080524
MWCNTs (—OH)	20–30	≈30	1.76	MH5080222
MWCNTs (—COOH)	10–20	≈30	2.00	MC3080425

[a] Information provided by the supplier.

2.2. Preparation of drug-loaded CNTs and derived buckypapers

The commercial and lab-synthesized CNTs were sonicated with 10 mL of CHC or FB ethanol solutions. 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%, and the effective processing time was 20 min. On/off pulse cycles were set at 1 s and temperature was kept at 25 °C. Each mixture was 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. The CNTs dispersed in hexane were filtered through a 0.22 μm, 47 mm Nylon membrane (GE Osmonics/MSI). In the case of bilayered buckypapers, the CNTs hexane suspension prepared as described before but without drug addition, was filtered above the first layer of the drug loaded CNTs through the Nylon membrane. The buckypapers were dried in an oven at 60 °C for 2 h. All the experimental conditions used are listed in Table 2.

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

Scanning electronic microscopy (SEM) of gold metallized buckypapers 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×.

Measurements by differential scanning calorimetry (DSC) were performed in a SDT Q600 (TA Instruments) thermal analyzer. Experiments were carried out using 4–6 mg of samples in open aluminum oxide crucibles. The samples were heated from room temperature to 1000 °C at a heating rate of 15 °C min^{-1}. During the heating ramp a nitrogen flow (100% v/v, 100 mL min^{-1}) was used as purge gas. Once the temperature attained 1000 °C, a mixture of 50% air/50% nitrogen was introduced, keeping constant the total gas flow rate (100 mL min^{-1}). Raw data was processed with the Universal Analysis 2000 software, version 4.2E, build 4.2.0.38 (TA Instruments).

The samples were also characterized by X-ray powder diffraction (XRD) using a Siemens D5000 diffractometer with Cu Kα radiation ($\lambda = 1.54056$ Å), equipped with a curved graphite crystal monochromator. The scanning angle was in the range 5–60° of 2θ (steps of 0.05°). The counting time was 2.0 s $step^{-1}$.

FT-IR analysis was performed using a Nicolet 8700 spectrophotometer (Thermo Electron Scientific Instruments LLC) employing the KBr disk method; the spectral range measured was 4000–400 cm^{-1} and 256 scans were taken with a resolution of 4 cm^{-1}.

Drug loading efficiency was determined by immersing the drug loaded buckypapers in 100 mL phosphate buffer pH 5.0 for CHC, and in pH 7.0 for FB. Every day, the flasks containing the buckypapers and the buffers were agitated for 23 h by mechanical means and then sonicated in an ultrasonic bath for 1 h, in order to achieve the maximum attainable desorption of the drug. Samples were taken every 24 h until constant concentration values were obtained. The samples were filtered and quantified by UV spectroscopy at 220 nm for CHC and at 247 nm for FB (Shimadzu UV-Mini 1240). Experiments were carried out in triplicate and efficiency was calculated as the mean percentage of drug recovered with respect to the drug initially incorporated into the CNTs.

2.4. In vitro drug release experiments

A 0.22 μm, 47 mm Nylon membrane was mounted on a Franz diffusion cell [11]. The drug loaded buckypaper also supported on other Nylon membrane was placed above the first membrane with the CNTs facing downwards. The system was covered with a plastic disk in order to