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Tramadol loading, release and iontophoretic characteristics of ion-exchange fiber

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ABSTRACT

The objective of this study was to investigate the drug loading, release and iontophoretic characteristics of strong acidic ion-exchange fiber, using tramadol hydrochloride as a model drug. The complex of charged model drug and ion-exchange fiber was studied as a new approach to achieve controlled drug delivery. Structural characterization of the fiber was elucidated through different approaches including differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), scanning electron microscope (SEM) and infrared spectroscopy (IR). And the mechanism of drug binding into ion-exchange fibers was validated to be ion-exchange. The drug loading into and release from ion-exchange fiber were affected by the concentration, volume and valence of the counter-ions in the external solution. Iontophoresis could significantly increase the delivery rate and amount of transdermal drug, and the iontophoretic dose could be easily controlled by adjusting the current intensity and the amount of release medium. The tramadol could be steadily released both from the drug-loaded fiber and drug solution when applied the iontophoretic method, which was in disagreement with the previous publications. As a drug reservoir, ion-exchange fiber has good regularity of drug loading, release and iontophoretic characteristics.

1. Introduction

Ion-exchange fibers are receiving more attention recently for its ability as drug reservoir and to control the drug release behavior (Hanninen et al., 2007; Jaskari et al., 2000; Jaskari et al., 2001; Kankkunen et al., 2002a; Kankkunen et al., 2002b; Vuorio et al., 2004; Yao et al., 2008; Yu et al., 2006). Commonly, ion-exchange fibers consist of a hydrophobic framework, carrying a positive or negative electric fixed change, which is compensated by mobile counter-ions of opposite sign (Jaskari et al., 2001). Different from the conventional granular ion-exchange resins, ion-exchange fibers have non-cross-linked structure, leading to a more efficient ion-exchange process (rate and extent) and a higher loading capacity (Hanninen et al., 2003). Ionic drugs are bounded to the ion-exchange materials mainly by ion-exchange, which is a stoichiometric process with the equal molar amount of drug loaded onto the fiber to that of the counter-ions that leave the fiber, leading to an electroneutrality stable of the system (Jaskari et al., 2001). The obtained drug–fiber composite can be used to improve the stability of some unstable drug (Bouchard et al., 1958; Kankkunen et al., 2002a; Siegel et al., 1962), control the drug release rate and extent (Hanninen et al., 2003; Jaskari et al., 2000; Kankkunen et al., 2002b), and cover up unpleasant odors or bitter tastes (Anand et al., 2001; Bhise et al., 2008). In addition, ion-exchangers also have intrinsic pharmacological activities such as anti-hyperkalemia and anti-hypercholesterolemia (Iversen et al., 1995; Sterns et al., 2010). Ion-exchange fibers provide a new way for diversifying the drug dosage forms. As a drug carrier, they have great potential to be applied in many administration pathways, including oral administration (Atyabi et al., 1995; Bhise et al., 2008), transdermal drug delivery (Kankkunen et al., 2002a; Kankkunen et al., 2002b; Vuorio et al., 2004; Yu et al., 2006), intranasal administration (Illum, 1999; Mizushima et al., 1999), and ocular drug delivery (Jani and Hrria, 1990; Jungherr and Ottoboni, 1998). However, currently, ion-exchange fibers are still mainly used in the field of separation and purification of materials. There is still a long way to further realize their applications as drug carrier.

Iontophoresis is a process with the drugs ionized or polarized and directionally permeate through the skin under certain electric field, which will lead to an enhanced drug absorption (Xu et al., 1999). Iontophoresis transdermal drug delivery technology has existed for more than 200 years. It controls the transdermal drug flux by iontophoresis apparatus other than the skin, whose permeability changes with age and anatomical site. The topical drug delivery of iontophoresis also can prevent oral drug-induced adverse reactions by avoiding the contact with gastrointestinal

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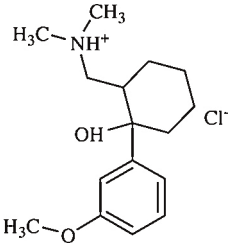
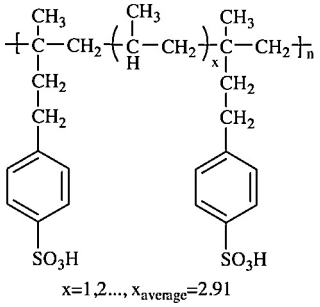
Table 1
Physicochemical properties of tramadol hydrochloride and structure of the fiber.

Tramadol hydrochloride					Structure of the fiber
M_w (g/mol)	pK_a	log P	Solubility	Structure	
299.84	9.61	2.32	Very soluble		

tract and directly deliver the drug into tissue or body fluid. The binding of charged drug molecules into the ion-exchangers has been proved to be a feasible method to stabilize active molecules before they are released when mobile ions are introduced into the system (Jaskari et al., 2000; Kankkunen et al., 2002a). In addition, the release rate of drug into the blood also can be controlled and reproduced. It has been reported that when combined with iontophoresis, ion-exchange fibers can significantly reduce the fluctuation of drug release and get a constant drug delivery (Kankkunen et al., 2002b; Yu et al., 2006). In this study, tramadol hydrochloride was used as a model drug to test the function and role of the fiber in the smooth drug delivery. Tramadol hydrochloride is a good candidate in the study of fiber on drug loading and iontophoretic delivery according to its positive charges when dissolved in water. Also, tramadol hydrochloride is an important centrally acting opioid analgesic used to treat moderate to moderately severe pain. However, the risk of toxicity due to sudden peaks in plasma level and abused/addiction potential due to overexposure is a worrying problem. It will bring great benefits if the controlled release of tramadol can be achieved. For a better understanding of the ion-exchange fiber, the preliminary study of their drug loading, structure characterization and release were conducted. The physicochemical properties of tramadol hydrochloride are presented in Table 1.

2. Materials and methods

2.1. Materials

Poly(propylene-g-styrene sulphonic acid) fiber (Strong acidic cation exchange fiber, hydrogen form, see the structure in Table 1) was purchased from Guilin Zhenghan Technology Development Co., Ltd. (Guangxi, China). Tramadol hydrochloride was from Wuhan Shuyuan Technology Co., Ltd. (Hubei, China). Methanol (HPLC grade), acetic acid, sodium acetate were obtained from Shandong Yuwang Chemical Industry Branch Co., Ltd. (Shandong, China). The other reagents are analytical grade and commercially available. Bi-distilled water was made in laboratory.

2.2. Drug loading

Ion-exchange fiber was treated with distilled water, 95% ethanol, 0.1 mol/L NaOH and 0.1 mol/L HCl consecutively in order to get the optimum effectiveness (Che et al., 2012b; Yao et al., 2008). The obtained fiber in hydrogen form can avoid tramadol precipitation during the loading process. Then the fiber was washed with sufficient distilled water to remove excess acid and dried at 40 °C.

The pre-treated ion-exchange fiber was immersed in tramadol solution of certain concentration under stirring for 24 at 25 °C. The amount of tramadol loaded onto the fiber was determined as the difference between the amount of tramadol in the initial loading solution and final solution using a UV-9100 spectrophotometer (Rayleigh Corporation, Beijing, China) under the wavelength of 271 nm.

2.3. Structure characterization of ion-exchange fiber

2.3.1. Differential scanning calorimetry (DSC)

The thermal behaviors of tramadol hydrochloride, ion-exchange fiber, tramadol hydrochloride–fiber physical mixture and tramadol-loaded fiber were measured by a Mettler DSC (Mettler-Toledo, Zurich, Switerland). Samples of 3 mg were weighted in a standard aluminum pan with a pinhole on the lid. The flow rate of purge gas (Dry nitrogen) was 40 mL/min. An empty pan of the same type was used as reference. Samples were heated from 20 °C to 250 °C with the heating rate of 5 °C/min.

2.3.2. Powder X-ray diffraction (PXRD)

A Rigaku D/Max 2500PC diffractometer (Rigaku Corporation, Tokyo, Japan) with Cu Kα radiation was used for X-ray diffraction measurements. The scattering angle was 3–50° 2θ in 0.02° steps of 0.15 s per step. The tube voltage and current were 50 kV and 300 mA, respectively. X-rays were monochromatized by a graphite monochromator. Tramadol hydrochloride, ion-exchange fiber, tramadol hydrochloride–fiber physical mixture and tramadol-loaded fiber were comminuted into powders and successively passed through an 80-mesh sieve prior to the test of X-ray diffraction.

2.3.3. Scanning electron microscopy (SEC)

The surface morphology of ion-exchange fiber and tramadol-loaded fiber were studied using a SURA 35 field emission scanning electron microscope (ZEISS, Germany, operated at 15.00 kV). The samples were gold-plated using double-sided adhesive tape prior to imaging.

2.3.4. Infrared spectra (IR)

Infrared spectra were obtained using a Bruker IFS 55 FTIR spectrometer (Billerica, USA). The spectra range was 4000–400 cm $^{-1}$. KBr compression method was used to prepare the samples. The infrared spectrum of tramadol hydrochloride, ion-exchange fiber, tramadol hydrochloride–fiber physical mixture and tramadol-loaded fiber were collected from OPUS 6.5 workstation.