European Journal of Pharmaceutics and Biopharmaceutics 127 (2018) 150–158

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Floating liquid crystalline molecularly imprinted polymer coated carbon nanotubes for levofloxacin delivery

Li-Ping Zhang, Xue-Xia Tan, Yan-Ping Huang*, Zhao-Sheng Liu*

Tianjin Key Laboratory on Technologies Enabling Development of Clinical Therapeutics and Diagnostics (Theranostics), School of Pharmacy, Tianjin Medical University, Tianjin 300070, China

ARTICLE INFO

Keywords:
Oral delivery
Liquid crystal elastomer
Molecularly imprinted polymer
Carbon naontube
Floating device
Levofloxacin

ABSTRACT

Liquid crystalline molecularly imprinted polymers (LC-MIPs) were low cross-linking MIPs (5–20 mol%) by introducing a LC monomer into the MIP polymerization system to keep the shape of the imprinted cavities due to additional interactions between the mesogenic groups. The multiwalled carbon nanotubes (MWCNTs) coated LC-MIP (MWCNT@LC-MIP) was the first fabricated as a novel floating interaction-controlled DDS. The synthesis was achieved by adding 9-vinylanthracene to obtain the high-density vinyl group functionalized MWCNTs firstly, and then polymerization of LC MIPs was performed on the surface of MWCNTs using a mixture of methacrylic acid, ethylene glycol dimethacrylate, and 4-methyl phenyl dicyclohexyl ethylene (LC monomer) with levofloxacin (LVF) as model template drug. Both template/functional monomer ratio and levels of crosslinker were optimized to obtain the best imprinting factor. Characterizations of polymer were investigated by the transmission electron microscope, nitrogen adsorption, thermogravimetric analysis, Fourier transform infrared spectra and floating behavior studies. The imprinting effect was confirmed by the adsorption isotherms, adsorption kinetics and effect of selectivity. *In vitro* release studies were examined by the LVF-loaded MWCNT@LC-MIP and the control samples, MWCNT@LC-NIP, MWCNT@MIP, MWCNT@NIP and the bare MWCNT using acetonitrile as the dissolute medium. The release profiles showed an obvious zero-order release of LVF from MWCNT@LC-MIP, which exhibited 3.8 μg/h of the release rate with duration of about 20 h. *In vivo* pharmacokinetic study displayed the relative bioavailability of the gastro-floating MWCNT@LC-MIP was 578.9%, whereas only 58.0% of MWCNT@MIP and 11.7% of the bared MWCNT. As a conclusion, MWCNT@LC-MIP showed potentials for oral administration by the innovative combination of floating and controlled release properties.

1. Introduction

Stomach specific drug delivery systems have been developed to remain the drug in the stomach to enhance the bioavailability of orally administered drugs, which is always limited by a short gastric emptying time [1–5]. Recently, floating drug delivery systems (FDDS) [6] emerged as efficient means for acid-soluble drugs, or drugs having a narrow absorption window in the upper part of the gastrointestinal tract (GIT) [7]. Several strategies have been invented to achieve the intragastric buoyancy such as the preparation low-density (< 1.004 g/cm^3, that of the gastric fluid) dry solid systems or with non-effervescent and effervescent systems, leading to decrease in density upon contact with gastric fluids based on swelling or CO_2 generation [8]. In addition, the newly emerging raft forming system [9] and polymeric nanofibers [10] can be used as an alternative approach for control release and bioavailability enhancement. The former involves not only the formulation of effervescent floating liquid, but also the gels formed in situ remained intact for more than 48 h. In contrast, the floating behavior of the carrier system can be controlled by a number of functional features from the latter. However, the methods for the preparation of floating drug delivery systems (FDDS) are often cumbersome and expensive.

Multiwalled carbon nanotubes (MWCNTs) are attractive in both *in vitro* and *vivo* drug delivery carriers to deliver many anticancer and non-anticancer drugs to improve the therapeutic efficacy because of high strength, large surface areas, lack of swelling and stability under acidic conditions [11,12]. However, it is believed that pristine CNTs have some cytotoxicity and cause inflammation to human organs [13,14]. On the contrary, functionalized CNTs exhibit less toxicity and can be excreted from the human body [15]. Up to now, many researches have displayed the efficacy of functionalized CNTs as drug delivery vehicles [16–20], which have been applied to the targeted delivery. Great drug

* Corresponding authors.
E-mail addresses: huangyanping@tmu.edu.cn (Y.-P. Huang), liuzhaosheng@tmu.edu.cn (Z.-S. Liu).

https://doi.org/10.1016/j.ejpb.2018.02.012
Received 12 August 2017; Received in revised form 7 December 2017; Accepted 7 February 2018
Available online 10 February 2018
0939-6411/

Table 1
Preparation protocol for MWCNT@LC-MIP imprinted polymers.[a]

Polymer	LVF (mmol)	MAA (mmol)	EDMA (mmol)	MPDE (mmol)	$CHCl_3$ (mL)	AIBN (mg)	IF
M1	0.4	1.6	6.40	4.80	8	10	2.50
M2	0.4	1.6	5.12	6.08	8	10	4.06
M3	0.4	1.6	4.48	6.72	8	10	2.27
M4	0.4	1.6	3.84	7.36	8	10	1.25
M5	0.4	1.6	2.56	8.64	8	10	1.16
M6	0.4	1.6	11.2	–	8	10	3.26
M7	0.53	1.6	5.12	6.08	8	10	3.84
M8	0.267	1.6	5.12	6.08	8	10	3.65
M9	0.2	1.6	5.12	6.08	8	10	3.51
M10	0.16	1.6	5.12	6.08	8	10	2.84
M11	0.133	1.6	5.12	6.08	8	10	2.59
M12	0.0667	1.6	5.12	6.08	8	10	2.60

[a] MWCNT: 80 mg, OD: 20–30 nm, Length: 0.5–2 μm.

release performance of functionalized CNTs DDS was observed compared with free drugs including small molecular weight drugs (dasatinib, paclitaxel or biotin) and macromolecules (proteins, pDNA or miRNA) [20–25].

Recently, molecularly imprinted polymers (MIPs) [26,27] characterized with the molecular recognition behavior for target molecule have served as the reinforcing shell in fabricating core-shell structural CNTs [28]. MIPs could provide an additional element for drug release control, and are representative of a class of the interaction-controlled drug delivery devices due to their reciprocal interaction with a desired drug stemming from their binding sites [29,30]. Liquid crystalline MIPs (LC-MIPs) are low cross-linking MIPs (5–20 mol%), which are sufficient to keep the shape of the imprinted cavities due to additional interactions between the mesogenic groups [31]. The LC-MIPs have much higher capacity compared with conventional MIPs due to higher accessibility to the sites. In addition, introduction of LC monomers could lead to the MIPs with deformation reversibly in response to various environmental factors (e.g., solvent, temperature as well as light irradiation) and a certain external stimulus (mechanical, electrical or magnetic field). Such LC networks in MIPs have already used successfully as catalysts [32], sensors [33], or as stationary phase for HPLC [34] and CEC [35,36]. Recently, LC-MIPs has been found to possess the floating behavior on the aqueous medium because of its solvent-responsive deformation, and first used as a FDDS for S-amlodipine delivery [37].

Integration of MIPs with MWCNTs has been achieved by surface imprinting method. In general, CNTs are used as support material and MIPs are prepared by “grafting to” or “grafting from” approach [38]. For example, the MIP coating grafted to the surface of MWCNTs is very thin (ca 15–20 nm), in which adsorption equilibrium would take less time to be achieved (within 35 min) due to the more accessible recognition sites to the template molecules. As a result, MWCNTs@MIPs possess excellent binding kinetics [39]. Up to date, many applications of CNT@MIPs have also been found in SPE [40], sensors [41] and drug delivery devices [42].

Here, we describe the first preparation of LC-MIP coated multiwalled CNTs (MWCNT@LC-MIP) as an oral FDDS using levofloxacin (LVF) as a model template. LVF is a third-generation broad spectrum fluoroquinolone antibiotic, mainly used for the treatment of respiratory tract, urinary tract, as well as soft tissue and skin infections. LVF was completely and rapidly absorbed after oral administration with short biological half-life, i.e., 1–2 h of peak plasma concentrations after oral dosing [43]. To reduce dose frequency and improve the bioavailability, many efforts were performed to formulate controlled release DDS for LVF. For local antibiotic delivery, lactose-modified commercial bone cement is regarded as a valuable approach in bone infections management [44]. LVF floating mini-tablets based on HPMC K100M [45], as well as size expanding gastro-retentive systems of LVF hemihydrate [46] were also prepared. In our experiment, MWCNT@LC-MIP against LVF was prepared using 4-methyl phenyl dicyclohexyl ethylene (MPDE) as a LC monomer. The floating property of MWCNT@LC-MIP was found and controlled release behaviors of elastomers were studied. *In vivo* studies showed that the floating MWCNT@LC-MIP had significantly higher bioavailability. Furthermore, we were interested in elucidating the effect of the new elastomer structure and adsorption property on drug delivery. In addition, due to their lower size, good permeability, higher surface volume ratio as well as enhanced drug loading ability, the enhanced drug loading ability of MWCNT@LC-MIP and better platforms for drug delivery than previously developed LC-MIP [37] was observed.

2. Experimental

2.1. Materials

Multiwalled carbon nanotubes (MWCNTs) were purchased from Dk Nano technology Co., Ltd (> 95.0%, Beijing, China). 9-Vinylanthracene (VA) and 2, 2-azobis (2-isobutyronitrile) (AIBN) was supplied by J&K Scientific Co., Ltd. (98.0%, Beijing, China). Methacrylic acid (MAA) was obtained from Beijing Donghuan Chemical Reagent (99.0%, Beijing, China). Ethylene glycol dimethacrylate (EDMA) was from Sigma (98.0% St. Louis, MO, USA). 4-Methyl phenyl dicyclohexyl ethylene (MPDE) was from Hebei Meixing Chemical Co., Ltd. (99.5%, Hebei, China). Levofloxacin (LVF), gatifloxacin (GTFX) and enrofloxacin (ENFX) were from Hubei Hengshuo Pharmaceutical Co., Ltd. (98.0%, Hubei, China). The commercial LVF sustained release tablets (No. H20060818) were purchased from Nanxin Pharmaceutical Co., Ltd. (Guangzhou, China). Other analytical reagents were from Tianjin Chemical Reagent Co., Ltd. (Tianjin, China).

2.2. Preparation of MWCNT@LC-MIP particles

MWCNTs (80 mg) were suspended in 20 mL chloroform, sonicating for 10 min. After 8 mg of VA was added, the resulting mixture was sonicated for 15 min and mixed for 2 h by magnetic stirrer. LVF, MAA, EDMA and MPDE were dissolved by chloroform, as shown in Table 1. The two solutions were mixed by ultrasonic cleaning machine after adding the initiator AIBN, and purged with N_2 for 10 min. Then, the pre-polymerization mixture was immersed in a water bath of 53 °C for 48 h. After reaction, the polymers were collected by centrifuge tube and washed with methanol-acetic acid mixture (9:1, v/v) repeatedly to remove LVF. The obtained MWCNT@LC-MIP was dried at ambient temperature, and then crushed with a pestle and mortar. Control non-imprinted MWCNT@LC-NIP without the imprinted molecule was synthesized in the identical manner.