Journal of Magnetism and Magnetic Materials 380 (2015) 285–294

Contents lists available at ScienceDirect

Journal of Magnetism and Magnetic Materials

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

Encapsulation of methotrexate loaded magnetic microcapsules for magnetic drug targeting and controlled drug release

Prabu Chakkarapani [a], Latha Subbiah [a,*], Selvamani Palanisamy [a], Arputha Bibiana [a], Fredrik Ahrentorp [b], Christian Jonasson [b], Christer Johansson [b]

[a] Department of Pharmaceutical Technology & Centre for Excellence in Nanobio Translational Research, Anna University, Bharathidasan Institute of Technology Campus, Tiruchirappalli 620024, Tamil Nadu, India
[b] Acreo Swedish ICT AB, Arvid Hedvalls backe 4, SE-411 33 Göteborg, Sweden

ARTICLE INFO

Article history:
Received 30 June 2014
Received in revised form
3 November 2014
Accepted 4 November 2014
Available online 25 November 2014

Keywords:
MMC
Methotrexate
Polyelectrolyte
Layer-by-layer
Rheumatoid arthritis

ABSTRACT

We report on the development and evaluation of methotrexate magnetic microcapsules (MMC) for targeted rheumatoid arthritis therapy. Methotrexate was loaded into $CaCO_3$-PSS (poly (sodium 4-styrenesulfonate)) doped microparticles that were coated successively with poly (allylamine hydrochloride) and poly (sodium 4-styrenesulfonate) by layer-by-layer technique. Ferrofluid was incorporated between the polyelectrolyte layers. $CaCO_3$-PSS core was etched by incubation with EDTA yielding spherical MMC. The MMC were evaluated for various physicochemical, pharmaceutical parameters and magnetic properties. Surface morphology, crystallinity, particle size, zeta potential, encapsulation efficiency, loading capacity, drug release pattern, release kinetics and AC susceptibility studies revealed spherical particles of ~3 μm size were obtained with a net zeta potential of +24.5 mV, 56% encapsulation and 18.6% drug loading capacity, 96% of cumulative drug release obeyed Hixson-Crowell model release kinetics. Drug excipient interaction, surface area, thermal and storage stability studies for the prepared MMC was also evaluated. The developed MMC offer a promising mode of targeted and sustained release drug delivery for rheumatoid arthritis therapy.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Drug delivery research aims to conveniently administer complex drugs to the target tissue in the biological system in a more stable and reproducible controlled way so that it would achieve higher activity at a minimal dose for prolonged period at the site devoid of side effects. Entrapment of a drug into a polymeric system may protect the drug from inactivation and help to retain its activity for prolonged durations, decrease its toxicity, dosing frequency and offers flexibility in administration. Hollow polymer capsules with definite structures and controlled properties have attracted much attention due to their potential applications in diverse areas, including artificial cells, biotechnology, drug delivery [1]. Several approaches have been established to fabricate capsules made of polymer, such as phase-separation, emulsion polymerization and layer-by-layer (LbL) templating technique [2,3]. The LbL templating technique is a highly versatile approach to prepare micro/nanometer sized capsules with tailored properties. The process involves the step-wise deposition of species onto a core, which is subsequently removed to generate free-standing capsules [4]. The sequential formation of these capsules is based on the facile selection of sacrificial templates [5–7] and assembly components [7–16]. Various active compounds can be sequestered in to the capsule shell [17,18] and/or interior [19,20] for drug delivery and various other applications. Generally biodegradable and bioabsorbable matrices are preferred so that they would degrade inside the body by hydrolysis or by enzymatic reactions.

Study of the control of microcapsule properties of varying shell composition and physicochemical parameters of the surrounding medium for encapsulation of substances and their controlled release was already published. However, many applications also require remote control over permeability of the microcapsule shell [21]. Introducing magnetic particles makes it possible to remotely control the permeability of their shells and for the shift of microcapsules to the target site [22].

Magnetic drug targeting is the pioneering concept proposed by Freeman et al. in 1960 [23]. This has become a very attractive field of research in which fine iron particles could be transported through the vascular system and concentrated at a particular point in the body with the aid of magnetic fields to achieve prolonged release with high, localized concentrations of drug by retention of the carriers in the region of interest [24].

* Corresponding author. Fax: +91 4312407333.
E-mail address: lathasuba2010@gmail.com (L. Subbiah).

http://dx.doi.org/10.1016/j.jmmm.2014.11.006
0304-8853/© 2014 Elsevier B.V. All rights reserved.

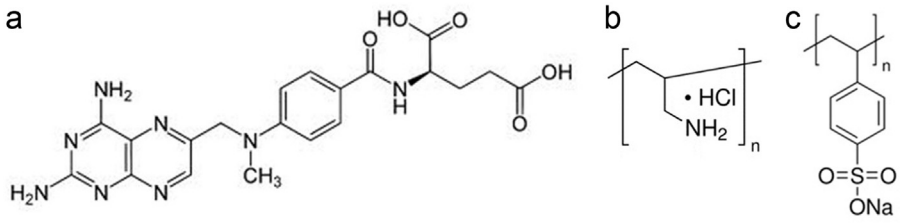

Fig. 1. (a) Structure of methotrexate. (b) Structure of poly (allylamine hydrochloride). (c) Structure of poly (sodium 4-styrenesulfonate).

Methotrexate (Fig. 1a) is a folic acid antagonist, an antiproliferative and immunosuppressive agent. It is the drug of choice in the treatment of the rheumatoid arthritis, an autoimmune disease. Methotrexate has an extensive toxicity range and adverse reactions that include gastrointestinal, hepatic, renal, pulmonary, and haematological disturbances that may also affect the central nervous system [25]. This lack of efficacy is due to the fact that large amounts of the administered methotrexate are rapidly eliminated by the kidneys, resulting in a short plasma half-life and low drug concentration in the targeted tissue [26].

Recently, $CaCO_3$-based colloidal templates have been shown to be promising for the synthesis of hollow polyelectrolyte capsules as $CaCO_3$ is nontoxic and the $CaCO_3$ core material can be easily removed by complexation with ethylene diamine tetra acetic acid (EDTA). Moreover, $CaCO_3$ particles are easy to synthesize and are easily filled with macromolecules up to a size of about 40 nm, owing to their high porosity [27].

Hence, to overcome these disadvantages and to improve the pharmacokinetic properties, methotrexate was encapsulated in porous calcium carbonate core which is a biocompatible and decomposable template over coated with biocompatible cationic polyelectrolyte poly (allylamine hydrochloride) (PAH) (Fig. 1b) and anionic polyelectrolyte poly (sodium 4-styrenesulfonate) (PSS) (Fig. 1c) alternatively [28,29]. Ferrofluid was ingrained between the multiple layers of polyelectrolytes. Consequently the calcium carbonate core was etched using EDTA yielded the methotrexate MMC The physicochemical, pharmaceutical and magnetic properties for the prepared MCs were evaluated and presented. The developed MMC would have a substantially prolonged half-life in the circulation could be magnetically targeted with improved efficacy and reduced adverse effects.

2. Experimental section

2.1. Materials

All chemicals were of analytical reagent grade and were used without any further purification. Methotrexate was a gift received from M/s. Madras Pharmaceuticals Pvt. Ltd, Chennai. Poly (allylamine hydrochloride) (PAH) Mw~58,000 and Poly (sodium 4-styrene sulfonate) (PSS) Mw~70,000 were supplied by Sigma Aldrich. All other chemicals were from Loba Chemie, Mumbai.

2.2. Preparation of methotrexate magnetic microcapsules

2.2.1. Preparation of $CaCO_3$-PSS microparticles

The $CaCO_3$-PSS microparticles were prepared by biomimetic mineralization method reported by Zheng Lu et al. [30] with slight modifications. Briefly, by rapidly mixing of (i) 0.2 M Na_2CO_3 in 100 mL water containing 400 mg of PSS with (ii) 0.2 M $CaCl_2$ in 100 mL water followed by stirring in a stirrer (Remi, 5MLH DX, India) for 30 min. $CaCO_3$-PSS microparticles were filtered out, repeatedly washed with water finally with acetone and dried in a vacuum oven (Bio Niik Innovation, India) for 1 h at 50 °C.

2.2.2. Drug loading on $CaCO_3$-PSS microparticles

Methotrexate was loaded to $CaCO_3$-PSS microparticles using solvent evaporation technique [31]. 200 mg of methotrexate was dissolved in 10 mL of alkali hydroxide solution. Drug solution was added to prepared microparticles of $CaCO_3$-PSS (400 mg) that was previously dispersed in absolute ethanol and kept under stirring (400 rpm) at room temperature for 12 h. Particles were collected by centrifugation (Eppendorf, 5430 R, India), and dried in a vacuum oven for 1 h at 50 °C.

2.2.3. Preparation of ferrofluid

Stable Fe_3O_4 ferrofluid was synthesized by co-precipitation method using Fe (II) and Fe (III) salts [32]. A solution of $FeCl_3.6H_2O$ and $FeCl_2.4H_2O$ in 2:1 ratio was then quickly charged and mixed together along with an excess amount of 3 M NaOH solution using a mechanical stirrer, under nitrogen atmosphere until the pH value reaches 11 and a black precipitate was obtained. Polyethylene glycol (1 g) was added to this and aged at 80 °C for 60 min and neutralized to pH 7.

2.2.4. Preparation of magnetic microcapsules

MMC were obtained after three steps viz., (i) Deposition of multiple layers of PAH/PSS alternatively onto the surface of drug loaded $CaCO_3$-PSS microparticles. (ii) Incorporation of ferrofluid between polyelectrolyte layers (iii) Etching of calcium carbonate core. The scheme of preparation was described in (Fig. 2).

The drug loaded $CaCO_3$-PSS microparticles were coated with cationic and anionic polyelectrolytes by layer-by-layer technique alternatively using PAH and PSS respectively. PAH/PSS polyelectrolyte solution (2 mg/mL) was prepared using 0.5 M NaCl and the pH of the solution was adjusted to 6.5. Each absorption cycle includes addition of $CaCO_3$-PSS microparticles (200 mg) to polyelectrolyte solution (5 mL) for 15 min, separation by centrifugation and washing with 0.001 M NaCl solution in sequence. We preferred to have a polycation as the outermost layer as the positive surface charge should enhance the cellular uptake of the capsules, considering that most cell types exhibit a negative surface charge. The multilayer build-up was followed by measuring the zeta potential of the particles after each adsorption step.

Ferrofluid 500 μL (1.2 mg/mL) was added to the coated $CaCO_3$-PSS microparticles (200 mg) and vortexed (Tarsons, Spinix MC-01, India) for 15 min, separation by centrifugation. The aforesaid assembly procedure was continued for more alternate layer of polyelectrolyte was deposited on the above product.

The drug-ferrofluid incorporated $CaCO_3$-PSS microparticles were incubated together with 0.2 M of EDTA solution maintained at pH 7.0 for 30 min in order to dissolve the $CaCO_3$-PSS core. Core etched MMC were collected by centrifugation, and dried in a vacuum oven for 1 h at 50 °C and stored for further studies [33].

2.3. Evaluation studies

Evaluation studies were carried out to determine the various physicochemical, pharmaceutical and magnetic properties either for the raw materials, intermediate products or for final products

Download English Version:

https://daneshyari.com/en/article/1798897

Download Persian Version:

https://daneshyari.com/article/1798897

Daneshyari.com