Materials Science and Engineering C 47 (2015) 313–324

Contents lists available at ScienceDirect

Materials Science and Engineering C

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

Multilayer encapsulated mesoporous silica nanospheres as an oral sustained drug delivery system for the poorly water-soluble drug felodipine

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ARTICLE INFO

Article history:
Received 24 March 2014
Received in revised form 27 September 2014
Accepted 21 October 2014
Available online 24 October 2014

Keywords:
Mesoporous silica nanospheres
Layer-by-layer
Sustained release
Poorly water-soluble drug
Felodipine

ABSTRACT

We used a combination of mesoporous silica nanospheres (MSN) and layer-by-layer (LBL) self-assembly technology to establish a new oral sustained drug delivery system for the poorly water-soluble drug felodipine. Firstly, the model drug was loaded into MSN, and then the loaded MSN were repeatedly encapsulated by chitosan (CHI) and acacia (ACA) via LBL self-assembly method. The structural features of the samples were studied using scanning electron microscopy (SEM), transmission electron microscopy (TEM) and nitrogen adsorption. The encapsulating process was monitored by zeta-potential and surface tension measurements. The physical state of the drug in the samples was characterized by differential scanning calorimetry (DSC) and X-ray diffractometry (XRD). The influence of the multilayer with different number of layers on the drug release rate was studied using thermal gravimetric analysis (TGA) and surface tension measurement. The swelling effect and the structure changes of the multilayer were investigated to explore the relationship between the drug release behavior and the state of the multilayer under different pH conditions. The stability and mucosa adhesive ability of the prepared nanoparticles were also explored. After multilayer coating, the drug release rate was effectively controlled. The differences in drug release behavior under different pH conditions could be attributed to the different states of the multilayer. And the nanoparticles possessed good stability and strong mucosa adhesive ability. We believe that this combination offers a simple strategy for regulating the release rate of poorly water-soluble drugs and extends the pharmaceutical applications of inorganic materials and polymers.

1. Introduction

It is commonly recognized that oral drug delivery is widely accepted and convenient administration route. For oral administration, a drug must first be dissolved in gastrointestinal fluids before adsorption. Since the dissolution is a rate-limiting step in drug absorption, poorly water-soluble drugs with low dissolution rate have low drug bioavailability [1,2]. Meanwhile, to achieve essential plasma drug concentration, the dosage must be raised. And the raised dosage will make the drug molecules easier to aggregate in gastrointestinal tract, which may also influence the drug dissolution. Nowadays, nearly 40% of commercially available drugs or new drug candidates under development are poorly water-soluble [3]. It is a great challenge for pharmaceutical researchers to improve the dissolution rate of poorly water-soluble drugs. Many strategies have been developed to solve this problem, such as nanotechnology and the use of solid dispersions, but the resulting formulations often suffer from poor stability.

In the past decade, silica-based mesoporous materials have attracted the attention of pharmaceutical researchers around the world. As we know, silica-based mesoporous materials have many unique properties, such as their non-toxic nature, large specific surface area and total pore volume, tunable pore size, as well as being chemically inert and having easily modified surface properties [4–9]. Various types of such materials have been developed into drug delivery systems [10,11]. It is generally considered that these materials are very promising to solve the problems mentioned above. When loaded using silica-based mesoporous materials, the drug molecules can be separated on the surface of these materials and so the intermolecular interactions of the crystal structure are prevented, which is the main reason why slow dissolution kinetics can be avoided [12–14]. In addition, the nanoscale drug particles in a higher free energy state are confined to the rigid porous structure, making the drug nanoparticles more stable [13]. Therefore, employing silica-based mesoporous materials as drug carriers will increase the dissolution rate and the stability of poorly water-soluble drugs. In addition, the increased delivery rate provides a foundation for further study and investigation of the application of poorly water-soluble drugs to provide controlled or sustained delivery.

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http://dx.doi.org/10.1016/j.msec.2014.10.067
0928-4931/

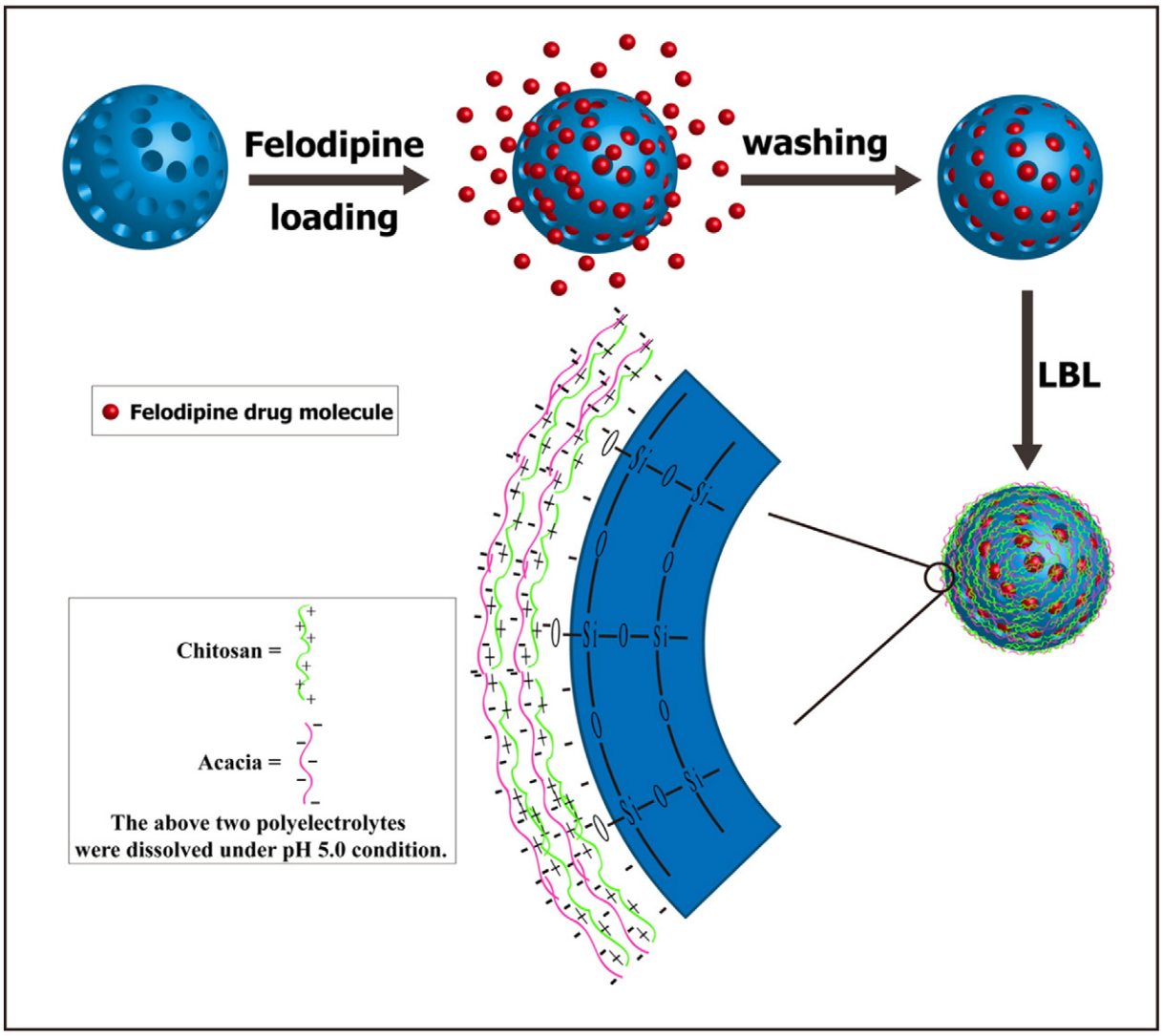

Fig. 1. Schematic representation of Fel loading into MSN and CHI/ACA multilayer encapsulation for drug release.

In order to improve patient compliance, drug efficacy and commercial value, it is better that the drug delivery rate is effectively controlled and, so, we focused on a recently developed nano/micro encapsulation technique, layer-by-layer (LBL) self-assembly technology. Using this technique, different particles may be repeatedly coated with oppositely charged polyelectrolytes. When placed in a polyelectrolyte solution with a relatively high concentration, charged particles can produce excess polyelectrolyte adsorption, which leads to surface charge neutralization and resaturation, and, eventually, charge reversal. The surface charge alternations will cause the positive and negative polyelectrolytes to assemble continuously, thereby resulting in the desired number of encapsulation layers [15]. By using such a simple procedure, drug crystals biological macromolecules and some drug/inorganic hybrids can be successfully encapsulated, resulting in desirable release features. Jasaswini Tripathy et al. have encapsulated bovine serum albumin (BSA) using sodium carboxymethyl cellulose (CMC) and poly(allylamine hydrochloride) (PAH) through LBL self-assembly. And the release profile showed a sustained release pattern up to 7 h [16]. When doxorubicin loaded porous $CaCO_3$ was coated by CHI/ALG multilayer, a sustained drug release pattern was also achieved [17]. Yufang Zhu et al. have encapsulated cytosine-phosphodiester-guanine olifodeoxynucleotide (CpG ODN) and enzyme degradable poly(L-lysine) (PLL) on funorescein loaded hollow mesoporous silica (HMS) through LBL technology, and an enzyme-triggered drug and gene codelivery system was achieved [18], while Yang et al. have used two polyelectrolytes pairs, PAH/PSS and ALG/CHI, to encapsulate drug-loaded mesoporous silica nanotubes, and obtained two different kinds of pH-controlled drug delivery systems [19].

As known, above the isoelectric point of SiOH (pH 2–3), the surface of mesoporous silica materials is negatively charged, which will favor the LBL self-assembly coating of polyelectrolytes [20]. CHI (pKa around 6.3 [21]) and acacia (ACA, negatively charged above pH 2.2 [22]), are natural macromolecular materials, and both exhibit good biocompatibility and are readily obtainable. Therefore, we chose this new polyelectrolyte pair to produce the LBL multilayer assembly. At pH 5.0, the positively charged CHI is well adsorbed on the negatively charged MSN, followed by the adsorption of the negatively charged ACA. Thus, polyelectrolyte multilayer can be easily coated on the surface of MSN and, so, we expected to be able to regulate the drug release rate by adjusting the number of layers.

Here, we have proposed a combination of silica-based mesoporous material, employed as drug carriers, and the polyelectrolyte multilayer film, coated by the LBL technique, to regulate the release rate of a poorly water-soluble drug and, eventually, obtain an oral sustained drug delivery system. Hence we synthesized mesoporous silica nanospheres