Electrospun fibers of layered double hydroxide/biopolymer nanocomposites as effective drug delivery systems

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ABSTRACT

Ibuprofen intercalated layered double hydroxide (LDH-IBU)/polycaprolactone (PCL) and LDH-IBU/poly(lactic acid) (PLA) nanocomposite fibers are electrospun based on a combination of LDH-IBU with two kinds of biopolymers (i.e., PCL and PLA), to act as effective drug delivery systems. Ibuprofen (IBU) is chosen as a model drug, which is intercalated in MgAl-LDH by coprecipitation. Poly(oxyethylene-oxypropylene-oxyethylene) (Pluronic) is also added into PLA-based fibers as hydrophilicity enhancer and release modulator. LDH-IBU nanoparticles are uniformly dispersed throughout the nanocomposite fibers, as evidenced by transmission electron microscopy (TEM) observations. In vitro drug release studies show that initial IBU liberation from LDH-IBU/PCL composite fibers is remarkably slower than that from IBU/PCL fibers due to the sustained release property of LDH-IBU and heterogeneous nucleation effect of LDH-IBU on PCL chain segments. Surprisingly, the initial IBU release from LDH-IBU/PLA and LDH-IBU/PLA/Pluronic composite fibers is faster than that from the corresponding IBU/PLA and IBU/PLA/Pluronic fibers. This effect can be attributed to the strong interaction between alkyl groups in IBU molecules and methyl substituent groups of PLA as well as the hydrophilicity of LDH-IBU, which lead to an easier diffusion of water with a faster release of IBU from LDH-IBU/PLA and LDH-IBU/PLA/Pluronic composite fibers.

1. Introduction

Electrospinning is a versatile technique for fabricating polymer fibers with diameters in the range of nanometers to a few microns [1]. These fibers possess high surface area to volume ratio, high porosity and other outstanding properties making them excellent candidates for filtration, catalysis, sensors as well as in biomedical applications [2–4]. Drug delivery systems based on electrospun nanofibers have attracted increasing interests in pharmaceutical field since Kenawy et al. first examined the release properties of tetracycline hydrochloride from polylactide (PLA) and poly(--vinyl acetate) fibrous mats [5]. Their studies indicated that the release kinetics of the fiber mat was highly influenced by the state of the drug and the structure of the polymer that forms the fiber. In general, semi-crystalline polymers showed a higher extent of burst due to two reasons: the instantaneous release of the drug deposited at the fiber surface, followed by the sustained release of the drug from the fiber bulk due to limited water uptake in the semi-crystalline regions. Natu et al. reported electrospun bicomponent fibers of two semi-crystalline polymers, poly(--caprolactone) and poly(--oxyethylene--oxypropylene) for controlled drug release applications [6]. The release kinetics and regression analysis results implied a three-stage release mechanism: the first stage was dissolution of the crystalline drug that was not totally encapsulated in the fibers, followed by erosion (for bicomponent fibers) or drug desorption and subsequent diffusion through water-filled pores of PCL fibers, while the last stage was controlled by polymer degradation. The release profiles of entrapped drugs can be finely tuned by controlling the crystallinity, glass transition temperature (Tg) of the polymer, hydrophilicity or hydrophobicity of the drug, as well as the binding affinity between the drug and polymer matrix [7–9]. In addition, these systems may offer site-specific delivery of drugs to the body, which may be a promising approach in wound healing or surgical implant.

Recently, biodegradable and biocompatible polymers have received significant attention because they are environmentally friendly and extensively used in biomedical applications, e.g. aliphatic polyesters such as PLA, polycaprolactone (PCL), as well as chitosan and cellulose [10–12]. Nevertheless, a possible drawback of electrospun nanofibers for drug delivery is the rapid release of...
drugs, generally due to the methods of coating/embedding drugs onto or within nanofibers [13,14]. Coaxial electrospinning approaches, which allow the formation of core-shell nanofibers, can effectively weaken the initial burst release of drugs to achieve sustained release profiles [15,16]. However, substantial optimization of the electrospinning conditions is essentially required for coaxial electrospinning. Therefore, the development of new delivery systems allowing for effective loading and sustained release of drugs still remains a great challenge.

Nanomaterials with sophisticated structures have attracted much attention due to their sustained release properties as drug delivery vehicles [17,18]. With the general formulation of \( \text{M}^{2+}\text{Al}^{3+}(\text{OH})_{2}\text{L}^2\), layered double hydroxides (LDHs) are a large class of host–guest layered inorganic materials consisting of positively charged brucite-like layers and exchangeable interlayer anions. Arising from the anisotropic accommodation of the guest molecules, an interesting and constrained environment is constructed between the LDH interlayer space, which is essential for building well-crystallized hybrid assemblies and allowing new properties in some cases [19,20]. Several synthesis methods, including direct ion-exchange, coprecipitation, and reconstruction of calcined LDHs, have been usually employed in the preparation of LDHs [21–23]. Given the ease of preparation, low cost, good biocompatibility, low cytotoxicity, and full protection for the loaded drugs (to prolong drug activity and enhance the loading efficiency and release modulator [31]). The morphology and structure of the electrospun fibers are thoroughly characterized. In vitro drug release studies show that initial liberation of IBU from LDH-IBU/PCL composite fibers is remarkably slower than that from PCL fibers. To our surprise, the opposite phenomena are observed in PLA and PLGA/Pluronic systems. Initial IBU release from both LDH-IBU/PLA and LDH-IBU/PLA/Pluronic composite fibers is faster than that from the corresponding IBU/PLA and IBU/PLA/Pluronic fibers. The possible reasons for this phenomenon are discussed, including drug state, hydrophilicity of drugs, fiber crystallinity and drug–polymer interactions.

2. Experimental section

2.1. Materials

Poly(lactide) (PLA, 2002D) was supplied by Nature Works. Polycaprolactone (PCL, Mn = 80,000) and poly(oxyethylene-b-oxypropylene-b-oxyethylene) (Pluronic, Mn = 5,600) were purchased from Sigma–Aldrich. Ibuprofen (IBU) was supplied by Zhejiang Juhuan Pharmacy. All other reagents were purchased from Sinopharm Chemical Reagent Co. Ltd. and used as received.

2.2. Synthesis of ibuprofen intercalated MgAl-LDH

Ibuprofen intercalated MgAl-LDH (LDH-IBU) was prepared by coprecipitation according to the procedure described in previous studies [22,24]. 10 mL of mixed salt solution containing MgCl2 (2.0 mmol) and AlCl3 (1.0 mmol) was quickly added (within 5 s) into 40 mL of mixed basic solution containing 0.15 M NaOH and 0.03 M IBU with vigorous stirring, followed by 20 min stirring in the reactor isolated from air. The resultant suspension was separated by centrifugation and washed twice with deionized water and then manually dispersed in 40 mL of deionized water. This aqueous suspension was transferred into a 50 mL stainless steel autoclave with a Teflon lining and hydrothermally treated at 100 °C for 16 h, followed by subsequent cooling in air. LDH-IBU particles were then collected via high speed centrifugation and dried in the vacuum oven.

2.3. Electrospinning

Mixed solvent of tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) (v/v = 3/1) was used to prepare the electrospinning solutions. The electrospinning solution was fed at a speed of 1.0 mL h⁻¹ with a distance of 20 cm between tip of the needle and the collector. A fixed electrical potential of 16 kV was employed to charge the steel capillary. All fibers were deposited on the aluminum foil during electrospinning, forming fiber mats which can be peeled off for subsequent drug release experiments and characterizations. Electrospun fibers of neat PCL, 2 wt% IBU/PCL, and 5 wt% LDH-IBU/PCL were fabricated from their respective solutions containing 22% (w/v) solid content. Likewise, PLA, 2 wt% IBU/PLA and 5 wt% LDH-IBU/PLA fibers were also obtained in similar procedures using solutions with solid content of 12% (w/v). In order to investigate the hydrophilicity enhancement of Pluronic on PLA fibers, three different compositions of PLA and Pluronic mixtures (i.e., 90/10, 85/15, 75/25, w/w) were also electrospun from their respective
solutions with 12% (w/v) solid content, forming PLA/Pluronic fibers, 2 wt% IBU/PLA/Pluronic fibers and 5 wt% LDH-IBU/PLA/Pluronic composite fibers.

2.4. Characterization

X-ray diffraction (XRD) patterns of LDH nanoparticles and the electrospun fibers were conducted from 2θ = 2° to 70° on an X’Pert Pro X-ray diffractometer with Cu Kα radiation (λ = 0.1542 nm) under a voltage of 40 kV and a current of 40 mA. Fourier transform infrared (FTIR) spectra were obtained in the range of 4000–400 cm\(^{-1}\) with a 4 cm\(^{-1}\) spectral resolution on a Nicolet Nexus 470 spectrometer equipped with a DTGS detector by signal-averaging 64 scans using the KBr pellet technique. Particle size and morphology of LDH-IBU were examined with a Jeol JEM 2100 transmission electron microscope (TEM). Thermogravimetric analysis (Pyris 1 TGA) was performed under nitrogen flow from 100 to 800 °C at a heating rate of 20 °C min\(^{-1}\).

Intercalated ibuprofen content was determined with a Perkin-Elmer Lambda 35 UV–vis absorption spectrophotometer by dissolving a known amount of LDH-IBU in 0.1 M HCl solution, followed by successive dilution with phosphate buffer saline (PBS) at pH = 7.0. The absorbance of the solution was measured at \(\lambda_{\text{max}} = 221\) nm and IBU content was determined from a set of calibration points.

The morphology and fiber diameters of the electrospun fibers were investigated using scanning electron microscope (SEM). The dispersion of LDH-IBU in the composite fibers was characterized using TEM. TEM specimens were prepared by directly collecting the electrospun nanofibers onto copper grids during the membrane fabrication. Static contact angles were measured using a commercial drop shape analysis system (Data Physics SCA20, Germany).

2.5. In vitro ibuprofen cumulative release studies

IBU release from LDH-IBU was performed by dispersing 25 mg LDH-IBU nanoparticles in 50 mL PBS at pH = 7.0 with magnetic stirring at 37 °C. At selected time intervals, 3 mL solution was taken out and centrifuged to remove LDH-IBU nanoparticles. The clear supernatant was diluted and measured for IBU concentrations at 221 nm using UV–vis spectrophotometer.

To obtain the drug release profiles from the electrospun nanofiber samples, both IBU/polymer and LDH-IBU/polymer composite fibrous mats were accurately weighed to ensure the absolute amount of IBU is comparable. The samples were then placed in different vials containing 50 mL PBS with magnetic stirring. Similarly, at selected time intervals, 3 mL solution was taken out for UV–vis measurements. All the drug release studies were carried out in triplicate.

3. Results and discussion

3.1. Structure and morphology of IBU intercalated LDH nanocrystals

Highly crystalline and monodisperse LDH-IBU nanocrystals were prepared by a fast coprecipitation method and subsequent hydrothermal treatment. From the XRD pattern of LDH-IBU (black curve in Fig. A.1(a)), it can be seen that LDH-IBU is well crystallized, as indicated by the sharp (003) and (006) basal reflections as well as (110) reflection peaks. The basal spacing of LDH-IBU is 2.10 nm, which is close to those previously reported for IBU intercalated MgAl-LDH [25]. Correspondingly, LDH layer thickness is 0.48 nm, suggesting an increase of 1.62 nm in basal spacing for LDH-IBU. As ibuprofen molecule has a length of about 1.0 nm, we propose that IBU ions are inclinedly accommodated in the interlayer region of LDH forming a bilayer arrangement as shown in Fig. A.1(b). FTIR spectrum (red curve in Fig. A.1(a)) also confirms the formation of IBU intercalated LDH hybrid. Two characteristic peaks arising from anti-symmetric (1552 cm\(^{-1}\)) and symmetric (1396 cm\(^{-1}\)) stretching of RCOO\(^-\) in ibuprofen are observed, corroborating the presence of intercalated IBU in its anionic form [26].

The LDH-IBU nanohybrid particles consist of thin hexagonal platelets with an average size of ca. 180 nm, as observed by TEM.
Fig. 3. SEM images of electrospun fibers of (a) neat PCL, (b) 2 wt% IBU/PCL, (c) 5 wt% LDH-IBU/PCL, (d) neat PLA, (e) 2 wt% IBU/PLA and (f) 5 wt% LDH-IBU/PLA.

Fig. 4. Low and high magnification TEM images of (a and b) 5 wt% LDH-IBU/PCL composite fibers; (c and d) 5 wt% LDH-IBU/PLA composite fibers.
This result is further confirmed by tapping-mode AFM image of LDH-IBU nanosheets (Fig. 2(a)) on mica, which shows that their lateral size is about 180 nm. The corresponding AFM height profile measurement, by scanning along the marked white line in Fig. 2(a), indicates that the height of the nanosheets is about 10 nm (Fig. 2(b)). Since the basal spacing of LDH-IBU is 2.10 nm as determined by XRD (black curve in Fig. A.1(a)), it can be deduced that LDH-IBU nanosheets are stacked up with 4–5 units of the lamellar structure (see Fig. A.1(b)).

**3.2. Electrospun LDH-IBU/biopolymer nanocomposite fibers**

The morphology and fiber diameters of electrospun PCL and PLA fibers were investigated by SEM, as shown in Fig. 3. Neat PCL and PLA fibers without beads are obtained with an average diameter of about 2.0 µm (Fig. 3(a) and (d)). From Fig. 3(b), (c), (e) and (f), it can be seen that there is no significant change in fiber diameters after the addition of IBU or LDH-IBU into both PCL and PLA solutions. Electrospun fibers from different compositions of PLA and Pluronic mixture (90/10, 85/15, 75/25, w/w) were also obtained. As shown in Fig. A.3, the electrospinnability is substantially enhanced by adding Pluronic, which is used as polymer surfactant in the electrospinning process as well as hydrophilicity enhancer and release modulator for PLA matrix.

TEM observations show that LDH-IBU nanoparticles are uniformly dispersed in PCL, PLA and PLA/Pluronic matrices, compared to previous studies [29,30], even at a high loading level of 5 wt% LDH-IBU (see Fig. 4 and Fig. A.4). The highly uniform dispersion of LDH-IBU in polymer fibers can be attributed to its minute size. In addition, IBU can be treated as an organic surfactant, which is also beneficial for the compatibility between LDH particles and polymer matrix. Therefore, the tough issue of LDH nanoparticle agglomeration usually observed in polymer fiber matrices is easily solved here, which may have diverse applications with special emphasis in the biomedical fields, such as drug delivery, wound healing and surgical implant.

XRD data in Fig. 5 provide useful information about the dispersion state of the nanohybrid in polymer matrices. Neat PCL shows well developed crystalline structure with two main peaks at 2θ = 21.6° and 23.9° respectively (Fig. 5(a)); while PLA is almost completely amorphous, exhibiting only a broad halo at 2θ = 15° (Fig. 5(b)). Despite of the crystalline nature of IBU, no characteristic peak of IBU is observed for both IBU/PCL and IBU/PLA fibers, indicating a homogeneous dispersion of IBU molecules in both polymer matrices. Nevertheless, XRD patterns of PCL and PLA nanocomposites containing 5 wt% LDH-IBU show different reflection peaks. For LDH/PCL/PLA nanocomposite fibers, only typical reflection peaks of crystalline PCL and an inconspicuous hump of LDH-IBU at 2θ = 3.0° (basal spacing: 2.88 nm) can be observed in Fig. 5(a). The swelling of the basal spacing of LDH-IBU is attributed to the intercalation of PCL chains into the regularly stacked LDH-IBU lamellar structure, leading to the formation of intercalated or even exfoliated nanostructure within the matrix. In contrast, basal peaks of the inorganic component are clearly seen in XRD patterns of LDH-IBU/PLA (Fig. 5(b)) and LDH-IBU/PLA/Pluronic (Fig. A.5) nanocomposite fibers. The presence of diffraction peaks of LDH-IBU indicates the inorganic lamellae were neither exfoliated nor intercalated by PLA chains in PLA and PLA/Pluronic systems.

The thermal stability of the electrospun fibers is evaluated by TGA (Fig. A.6). It can be seen that the onset temperature of degradation (T onset) of IBU/polymer fibers has no obvious change compared to their corresponding neat polymer fibers. This can be attributed to the low loading level of IBU. However, the T onset of all the three kinds of LDH-IBU/polymer composite fibers decreases by about 80 °C compared to neat PCL, PLA and PLA/Pluronic fibers respectively. This indicates that adding LDH-IBU into PCL and PLA matrix does not improve the thermal stability of the matrix, which is similar to the case of loading 5 wt% polylactide with carboxyl end group (PLA-COOH) modified LDH into poly(ε-lactide) matrix in previous studies [11]. Nevertheless, it indirectly proves the successful introduction of LDH-IBU into electrospun fibers in our present study.

**3.3. Release of ibuprofen from LDH-IBU/biopolymer nanocomposite fibers**

The drug release profile for LDH-IBU is presented in Fig. A.7. Initially, high drug release rate is observed which reaches a plateau
after 30 min, with more than 90% of the total amount of IBU being released. Sustained release effect of LDH-IBU is not as good as expected, which can be attributed to its nanoscale size.

IBU release profiles from electrospun fibers are shown in Fig. 6. As can be seen, drug release from PCL-based fibers is completely faster than that from PLA-based fibers. Approximately 70% and 40% of IBU were released from IBU/PCL and LDH-IBU/PCL fibers within the first 2 h respectively; while less than 10% of the total amount of drug was discharged from both IBU/PLA and LDH-IBU/PLA fibers within the same time period. It is known that both PCL and PLA are hydrophobic aliphatic polyesters, with their water contact angle values of about 140° (Fig. 7(a) and (b)). However, PCL is linear polyester with a very low T_g (about -60 °C), while PLA has many substituent groups, with much higher T_g value (about 60 °C). According to Wu et al., for polymers with T_g lower than body temperature, the diffusion of the water uptake and the releasing drug will be greatly increased[32]. Therefore, the extremely slow IBU release from PLA fibers can be attributed to poor chain flexibility of PLA, leading to high T_g as well as restricting the chain mobility and water diffusion.

To modulate the release rate of IBU from PLA-based fibers, Pluronic was introduced into PLA fibers with different PLA/Pluronic ratios. As a result, IBU release rates from both IBU/PLA/Pluronic and LDH-IBU/PLA/Pluronic fibers are dramatically accelerated, with more than 80% of IBU being released by just replacing 25% of PLA with Pluronic, as shown in Fig. 8. This phenomenon can be attributed to the hydrophilicity of Pluronic, which changes the water contact angle from 140° for PLA fibers to 0° for PLA/Pluronic fibers (Fig. 7(b) and (c)). As hydrophilicity enhancer and release modulator, the introduction of Pluronic can sharply increase the uptake of water molecules into PLA fibers which make IBU molecules to escape more easily. Moreover, both the presence of the surfactant, in our case is Pluronic, and the uptake of water molecules may also result in a plasticization effect which synergistically accelerates IBU release rate, according to previous studies[32,33].

The influence of LDH-IBU on drug release rate was also carefully studied. As seen in Fig. 6, the initial release rate of IBU from LDH-IBU/PCL composite fibers is much slower than that from IBU/PCL fibers. However, an opposite phenomenon is observed in both PLA and PLA/Pluronic systems. There are several main factors which may affect drug release rate from electrospun fibers, such as drug state, hydrophilicity of drugs, fiber crystallinity and drug–polymer interactions. For drug state, we can conclude that IBU molecules are uniformly dispersed in both polymer matrices, as evidenced by XRD data. However, the distribution state of LDH-IBU in PCL and PLA matrices is totally different.

For PCL system, LDH-IBU platelets are intercalated or even exfoliated and randomly dispersed throughout the matrix, forming intercalated/exfoliated nanocomposites (see Figs. 4(a), (b) and 5(a)). Based on our previous study, LDH nanoparticles have a heterogeneous nucleation effect on PCL chain segments, which can induce the LDH-IBU platelets being wrapped up in the crystalline regions of PCL (as shown in Fig. 9), thus restricting molecular movements of water and IBU molecules[34]. Schematic representation of the possible drug release process from LDH-IBU/PCL fibers

![Fig. 6. In vitro release of IBU from PCL-based fibers and PLA-based fibers. Each value is the mean ± S.D. n = 3.](image6)

![Fig. 8. In vitro release of IBU from PLA/Pluronic-based fibers. Each value is the mean ± S.D. n = 3.](image8)

![Fig. 7. Static contact angles with the values of 140° for (a) PCL fibers and (b) PLA fibers; 0° for (c) (75/25, w/w) PLA/Pluronic fibers.](image7)
in Fig. 9 illustrates that the amorphous regions of LDH-IBU/PCL fibers are first swollen by PBS solution, followed by ionic exchange and IBU release. Therefore, more time is needed for IBU to escape from LDH-IBU/PCL exchange and IBU release. Moreover, after an initial burst release from both IBU/PCL and LDH-IBU/PCL fibers, there is almost no IBU release during the following 12 h, as shown in Fig. 6. The rest drugs are likely to be encapsulated in the crystalline regions and can only be released by polymer degradation [6].

For PLA system, LDH-IBU nanoparticles are also uniformly dispersed throughout PLA matrix (see Fig. 4(c) and (d)). However, they are neither intercalated nor exfoliated by PLA chains (from the XRD pattern in Fig. 5(b)) compared to the case in PCL system (Fig. 5(a)). Lamellar structure of LDH-IBU leads to less interaction with the crystalline regions and can only be released by polymer degradation [6].

In summary, we have successfully fabricated LDH-IBU containing biopolymer composite fibers via electrospinning for efficient drug loading and release. LDH-IBU nanoparticles are uniformly dispersed throughout the matrices without any aggregation. Pluronic, as a hydrophilic polymer, is also successfully incorporated into drug loading and release. LDH-IBU nanoparticles are uniformly dispersed throughout PLA matrix (see Fig. 4(c) and (d)). However, they are neither intercalated nor exfoliated by PLA chains (from the XRD pattern in Fig. 5(b)) compared to the case in PCL system (Fig. 5(a)). Lamellar structure of LDH-IBU leads to less interaction with the crystalline regions and can only be released by polymer degradation [6].

4. Conclusions

In summary, we have successfully fabricated LDH-IBU containing biopolymer composite fibers via electrospinning for efficient drug loading and release. LDH-IBU nanoparticles are uniformly dispersed throughout the matrices without any aggregation. Pluronic, as a hydrophilic polymer, is also successfully incorporated into PLA fibers to enhance hydrophilicity of PLA and modulate the drug release rate. In short, a new drug delivery system is developed which has potential applications in the biomedical fields, such as drug delivery, wound healing and surgical implant. Through in vitro drug release tests, it is found that incorporation of LDH-IBU significantly prolongs the release rate of IBU from LDH-IBU/PCL fibers, which remarkably weakens the initial burst release problem in conventional electrospun polymer fiber-based delivery systems. Surprisingly, the release characteristic is opposite in the two PLA-based systems. The possible strong interaction between IBU and PLA side groups as well as the hydrophilicity of LDH-IBU lead to slower release of IBU from IBU/PLA and IBU/PLA/Pluronic fibers than that from LDH-IBU/PLA and LDH-IBU/PLA/Pluronic composite fibers. Therefore, the release rate is mainly affected by drug–polymer interactions, fiber crystallinity, hydrophilicity of drugs, as well as drug state in the fiber matrix.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.matchemphys.2012.03.041.

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