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Research Article

Development of a Layer-by-Layer Assembled Film on Hydrogel for Ocular Drug Delivery

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Hydrogel is a kind of attractive drug carriers because of its good biocompatibility and transparency. But traditional hydrogel showed some restrictions in its application in ocular drug delivery. A simple surface modification technique based on layer-by-layer (LbL) self-assembled multilayer for ocular drug delivery was developed in this work. Polycarboxymethyl-β-cyclodextrin (poly(CM-β-CD))/poly-l-lysine (PLL) multilayer film was designed and constructed for ocular drug delivery, since β-CD showed good drug delivery property. The properties such as the contact angle and transparency varied a little with the deposition of poly(CM-β-CD)/PLL multilayer. Orfloxacin and puerarin were loaded into multilayer during the self-assembly procedure by two methods, which were tracked by the largest drug absorbance of UV spectrum. The loaded drug amount by incorporating drugs into poly(CM-β-CD) solution was larger than that by incorporating drugs into PLL solution. The loaded drug in the multilayer could gradually be released from multilayer in some period either for orfloxacin or for puerarin. The drug release behavior was influenced by drug loading method and pH value of released medium. Moreover, the balanced released drug amount by incorporating drugs into poly(CM-β-CD) solution is much smaller than that by incorporating drugs into PLL solution.

1. Introduction

Poor ocular bioavailability and short action duration of eye drugs commonly trouble both patients and doctors. With the development of drug delivery system, the bioavailability is improved and the action duration is prolonged when ophthalmic drug is delivered by drug delivery system [1–4]. Therefore, the curative effects of ophthalmic drug would be enhanced. Hydrogel is a kind of attractive drug carriers because of its biocompatibility [5–7]. Moreover, hydrogel had good transparency, which made it have wide applications in ophthalmology [8–12]. However, traditional copolymer hydrogel as drug carrier had disadvantages of limited drug loading amount and burst release in our previous research work [13]. In order to solve this problem, we attempted to enhance the interaction between drug and hydrogel network by introduction of functional chitosan derivatives and water soluble graphene oxide [14, 15]. Though the method succeeded to a certain extent, it brought some new problems such as limited light transmittance. Therefore, some measures of hydrogel bulk design or hydrogel surface modification for ocular drug delivery are also needed.

Layer-by-layer (LbL) self-assembly technique is a simple and commonly used method to realize surface modification, which has attracted much attention because of its simplicity in procedure, wide choice of materials, and fine-tuning of the microstructure [16–21]. LbL assembled multilayer is fabricated by sequential adsorption of materials with complementary functional groups employing electrostatic interactions, hydrogen bonding, or covalent interactions [16–21]. The electrostatic interaction between cationic and anionic polyelectrolyte multilayer (PEM) is intensively used [19–21]. In our previous work, chitosan (CS)/hyaluronic acid (HA) multilayer is constructed on contact lenses using LbL technique to increase the hydrophilicity and reduce protein deposition as well as to deliver ophthalmic drug, but burst drug release within 2 hours still occurred [22]. Therefore, in

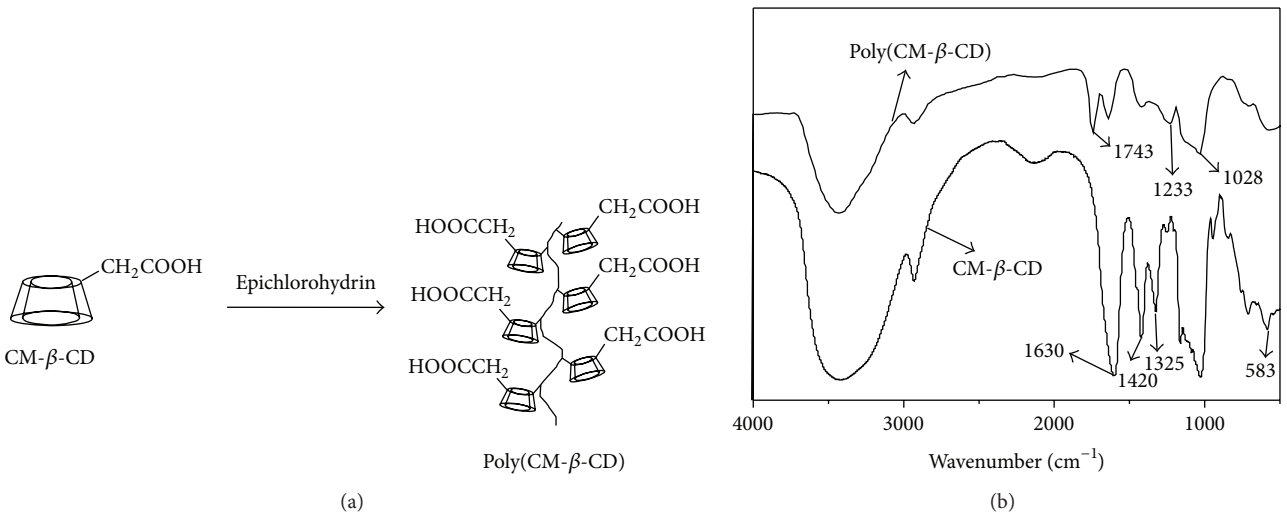

Figure 1: (a) Schematic illustration to show the synthesis of poly(CM-β-CD). (b) IR spectra of CM-β-CD and poly(CM-β-CD).

order to realize drug delivery, new PEMs are required to be designed for ocular drug delivery.

As far as we know, a group of cyclic oligosaccharides with a hydrophobic cavity can form inclusion complex with small molecules [23–25]. β-Cyclodextrin (β-CD) is one of cyclic oligosaccharides, which has exhibited good properties to control drug release [26–28]. Thus, β-CD has designed many kinds of carriers [26–28]. In order to satisfy the need of different kinds of drug carriers, many β-CD derivatives have been synthesized including carboxymethyl-β-cyclodextrin (CM-β-CD). Since β-CD has been proven to be a good material of drug carriers, a polyanion based on β-CD was designed and synthesized using CM-β-CD in the work. Moreover, poly-l-lysine (PLL) was chosen as a polycation due to its good biocompatibility and wide application in the field of drug delivery and tissue engineering. Furthermore, commonly used eye drugs, orfloxacin, and puerarin were loaded into PEMs during assembly procedure using different method. Finally, the drug release behaviors in different medium were investigated in detail.

Though LBL multilayers have been intensively studied, these researches focused on fundamental properties [29–32]. The investigations of their practical applications in many fields are also needed. The p(CM-β-CD)/PLL in this work was first designed and constructed, aiming at ocular drug delivery. The results of the research would help us to widen the application of multilayer.

2. Experimental

2.1. Materials. Hyaluronic acid (HA) and hydroxyethyl methacrylate (HEMA) were obtained from Shanghai Jingchun Industries Co. Ltd., China, and distilled under vacuum before use. Carboxymethyl-β-cyclodextrin (CM-β-CD) was obtained from Shandong Binzhou Zhiyuan Bio-Technology Co., Ltd.; epichlorohydrin, ammonium persulphate (APS), and N,N,N′,N′-tetramethylethylenediamine (TEMED) were obtained from Shanghai Chemical Industries Co. Ltd. (China). Poly-l-lysine (PLL) was obtained from Sigma. Orfloxacin and puerarin were purchased from Zhengzhou Andrew Biological Engineering Co., Ltd., China. All other reagents and solvents were of analytical grade and were used as received.

2.2. Preparation of Hydrogel. 2.7 mL of water was added into 5 mL HEMA, to which certain amounts of APS and TEMED with equal molar ratio were, respectively, added with final initiator concentration at 0.5%. 500 μL of the above mixture was injected into a circle model (200 μm thickness), which was then input into oven at 60°C. 1 h later, the formed hydrogel was obtained. The dried hydrogel was put in 20 mL epichlorohydrin solution, to which 2.8 mL 0.55 M sodium hydroxide was added. The hydrogel was transferred to 13.5 g/L HA solution, after the reaction had lasted for 5 h. HA was grafted onto hydrogel surface after the reaction had lasted another 10 h at 85°C. HA modified hydrogel was formed as a multilayer substrate.

2.3. Synthesis of Poly(CM-β-CD). 2 g CM-β-CD was dissolved in 10 mL 30% NaOH solution. The solution was heated to 40°C, to which 4 mL epichlorohydrin was slowly added. Further, the mixture was heated to 60°C. When the solution became viscous, another 36%–38% HCl was added to adjust the pH value of 7. The resultant mixture was sealed in a membrane with a cut-off molecular weight of 10 kDa and dialyzed in a large amount of triple-distilled water for 3 months. The white solid was obtained by freeze-drying and ground with KBr. Then they were made tablet and characterized by infrared spectroscopy (IR, Nicolet IS10).

2.4. Poly(CM-β-CD)/PLL Multilayer Deposition and Characterization. Two polyelectrolytes were dissolved in NaCl solution (0.15 M) with the final concentration of 1% (w/v). Self-assembled multilayer on hydrogel was performed manually. After swelling, hydrogel was gently rinsed with 0.15 M

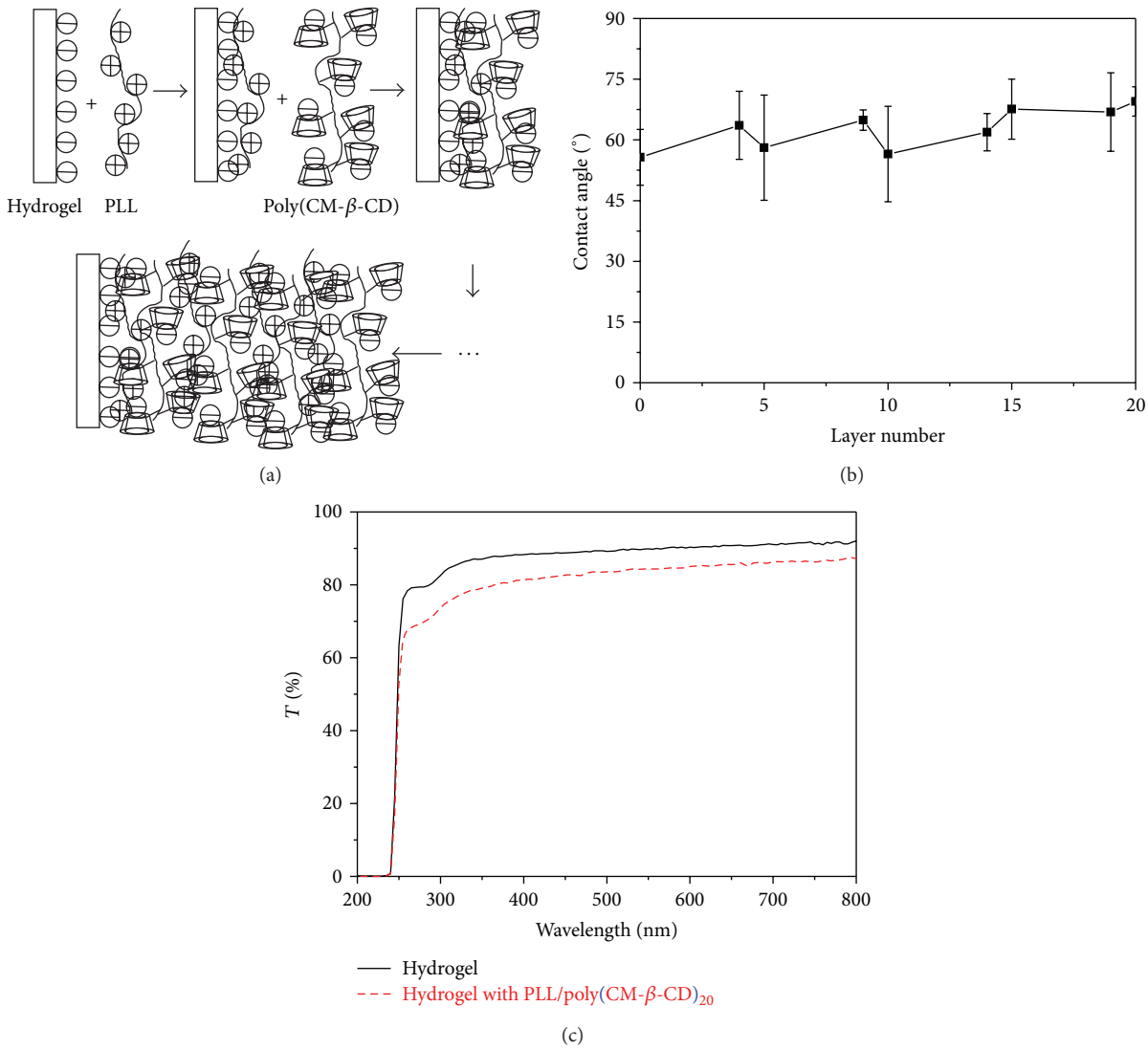

Figure 2: (a) Schematic illustration to show self-assembly process of poly(CM-β-CD)/PLL multilayer on hydrogel. (b) Contact angle of hydrogel with assembly of poly(CM-β-CD)/PLL multilayer. (c) Light transmittance of hydrogel and hydrogel with poly(CM-β-CD)/PLL$_{20}$ multilayer.

NaCl and immerged in PLL solution for 20 min. Hydrogel was then rinsed in 0.15 M NaCl solution and subsequently immerged in poly(CM-β-CD) solution for 20 min, followed by rinsing in 0.15 M NaCl solution again. After each step, the hydrogel was lightly blown to remove residual liquid. This procedure was repeated to assemble poly(CM-β-CD)/PLL multilayer on hydrogel. Poly(CM-β-CD)/PLL multilayer was characterized by UV spectroscopy (Cary 50) and contact angle measurement system (OCA35).

2.5. The Drug Assembling in Poly(CM-β-CD)/PLL Multilayer. Drug was loaded in poly(CM-β-CD)/PLL multilayer assembly procedure using orfloxacin and puerarin as model drugs. Drugs were introduced into poly(CM-β-CD) solution or PLL solution with final drug concentration at 1 mg/mL, respectively. 20 layers of poly(CM-β-CD)/PLL were built up on hydrogel using LBL technique as mentioned above. The assembly procedure was tracked by UV spectroscopy (Cary 50).

2.6. Drug Releasing Behavior. The hydrogels with drug were submerged in 4 mL medium. Every certain time, 2 mL released solution was moved and 2 mL fresh medium was added at the same time. The released solution was diluted to 4 mL. The absorbance of diluted drug solution at 285 nm for orfloxacin or 255 nm for puerarin was recorded by UV spectroscopy. The released drug concentration was obtained by referring to a calibration curve, which was constructed from known concentrations of drug solutions. Then the

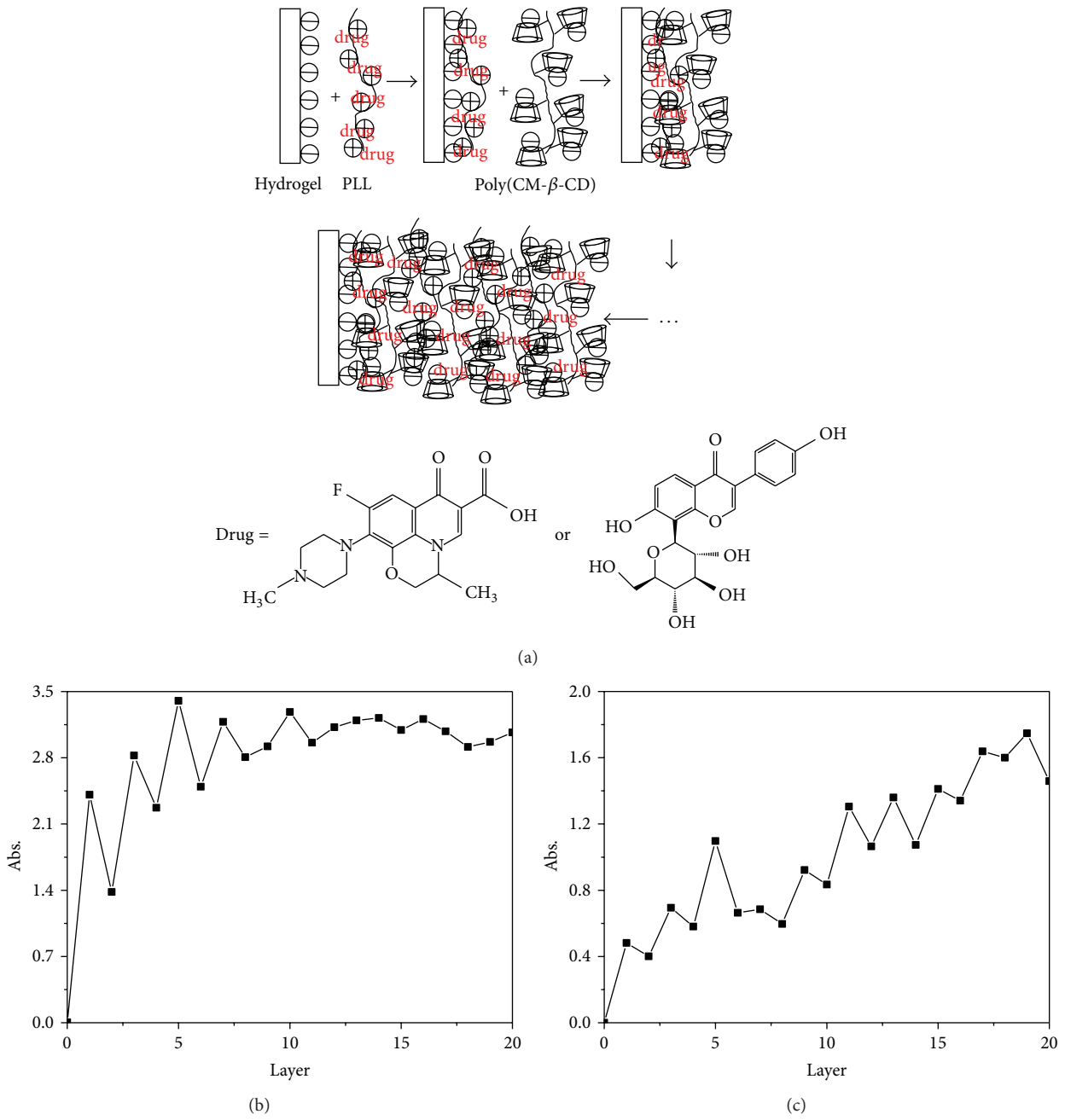

Figure 3: (a) Schematic illustration to show self-assembly process of poly(CM-β-CD)/PLL multilayer with drug by incorporating drug into PLL solution. (b) UV absorbance of hydrogel at 285 nm for orfloxacin as a function of layers. (c) UV absorbance of hydrogel at 255 nm for puerarin as a function of layers.

cumulative drug release amount was obtained according to drug concentration and volume.

2.7. Statistical Analysis. Data were analyzed using the t-test for differences. Results are reported as means ± standard deviation. The significant level was set at $P < 0.05$.

3. Result and Discussion

Poly(CM-β-CD) was obtained by epichlorohydrin cross-linking of –OH group as shown in Figure 1(a), which was characterized by IR spectrum in Figure 1(b). It is found that the peak of 1743 cm^{-1} belonging to ester and the peak of 1028 cm^{-1} belonging to ether emerged in the IR spectrum of poly(CM-β-CD), which indicated that CM-β-CD had been successfully cross-linked. At the same time, the peak of 1630 cm^{-1} belonging to –COOH group still existed in the spectrum of poly(CM-β-CD), which indicated that poly(CM-β-CD) was a polyanion.

Figure 2(a) showed multilayer self-assembled process on hydrogel with the alternate deposition of poly(CM-β-CD) and PLL by manual dip-coating. The electrostatic

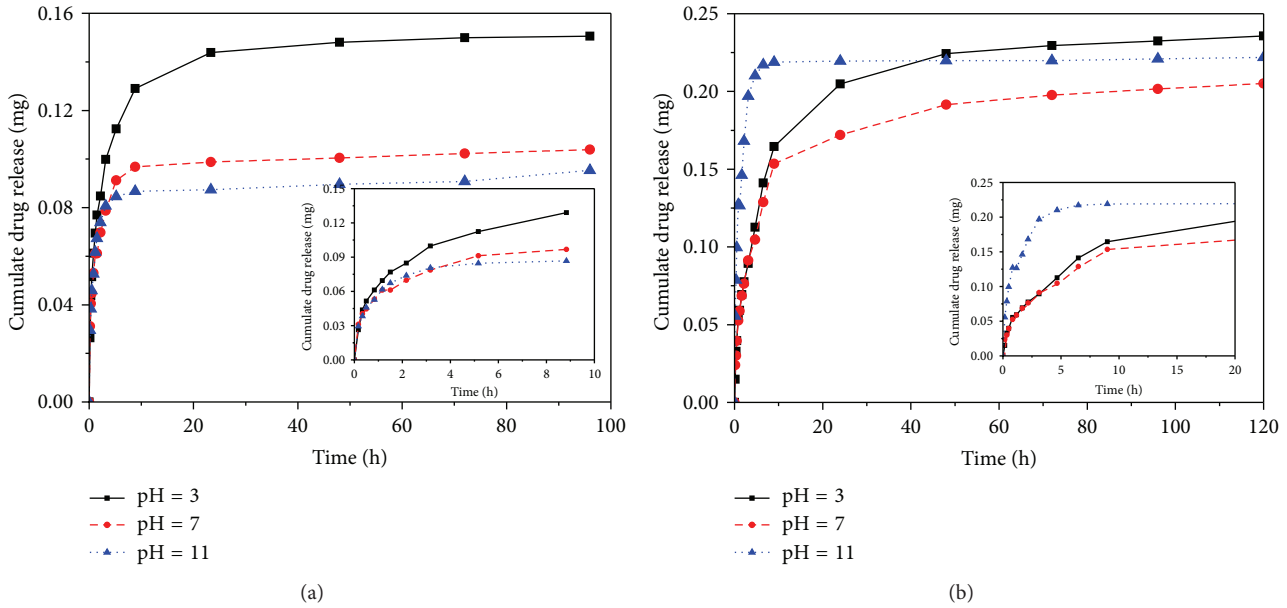

FIGURE 4: (a) The cumulate orfloxacin release from drug loaded poly(CM-β-CD)/PLL(drug)$_{20}$ multilayer in different medium at 37°C. (b) The cumulate puerarin release from drug loaded poly(CM-β-CD)/PLL(drug)$_{20}$ multilayer in different medium at 37°C.

interaction between these groups is the main driving force to form poly(CM-β-CD)/PLL multilayer on the hydrogel. Since hydrogel surface was modified by HA, it was negatively charged surface. Thus, positively charged PLL was anchored on the negatively charged hydrogel to form the first layer during the self-assembled process. The hydrophilicity of hydrogel was further investigated by contact angle measurements, as shown in Figure 2(b). The contact angle increased after two PLL layers and two poly(CM-β-CD) layers were assembled on the hydrogel and decreased little after another PLL layer was assembled. Subsequent assembling of PLL and poly(CM-β-CD) layers exhibited similar trends showing low and high contact angles until the layer number reached 14. Then the contact angle was not varied with assembled layers. However, all the variations showed no significant difference. Light transmittance of hydrogel was detected by UV spectrum in Figure 2(c). Although the transparence of copolymer hydrogel decreased after 20 poly(CM-β-CD)/PLL layers were assembled on the hydrogel, larger than 83% light could transmit the hydrogel when wavelength was larger than 350 nm, which means hydrogel had acceptable transparence in the visible region.

Drug was loaded into multilayer by two methods during the assembly procedure. Drugs were first incorporated in PLL assembly solution. As it is known to us, orfloxacin was an anion charged drug, which was bonded to polycation PLL by electrostatic attraction as well as intermolecular forces, while puerarin was a nonionic drug, which was bonded to polycation PLL by intermolecular forces, such as hydrogen bond between –OH group of puerarin and $-NH_2$ groups of PLL. In order to track the drug loading assembly procedure, the absorbance at 285 nm for orfloxacin or 255 nm for puerarin of hydrogel with different layers was recorded in Figures 3(b) and 3(c). When the first PLL layer was deposited on the hydrogel, the absorbance of hydrogel at 285 nm increased to 2.5 because of orfloxacin incorporation (Figure 3(b)). When the second poly(CM-β-CD) layer was deposited on the hydrogel, the absorbance of hydrogel at 285 nm decreased to 1.4 because of the mask of outer layer as well as diffusion of orfloxacin into the poly(CM-β-CD) assembly solution. Subsequent assembling of PLL and poly(CM-β-CD) layers exhibited similar trends showing high and low absorbance at 285 nm until the layer number reached 10. Then the absorbance of hydrogel at 285 nm stabilized to 2.8–3.0, perhaps because of saturated orfloxacin concentration in the multilayer of hydrogel. When the drug was puerarin, the variation of absorbance with assembled layer for puerarin showed similar trend to that for orfloxacin at initial 5-6 poly(CM-β-CD)/PLL layers (Figure 3(c)). Differently, this trend continued for puerarin until 20 layers were all assembled on the hydrogel. At the same time, the absorbance of hydrogel at 255 nm presented overall upward trend with the increase of assembled layer and reached 1.4–1.6. These results indicated that the saturated puerarin concentration in the multilayer of hydrogel was unreached.

The drug release behaviors of hydrogel with the above drug loaded multilayer in different medium were shown in Figure 4. At the initial 1 h, about 0.05 mg orfloxacin was released fast from drug loaded hydrogel (Figure 4(a)). Then orfloxacin release behavior at acid environment (pH = 3) was different from that at neutral environment (pH = 7) and alkaline environment (pH = 11). The orfloxacin was slowly released from hydrogel in the following 10 h at acid environment; the balanced cumulate orfloxacin release amount reached 0.15 mg. While the orfloxacin was slowly released from hydrogel in the following 10 h at neutral environment or alkaline environment, the balanced cumulate orfloxacin release amount reached 0.10 mg. Orfloxacin

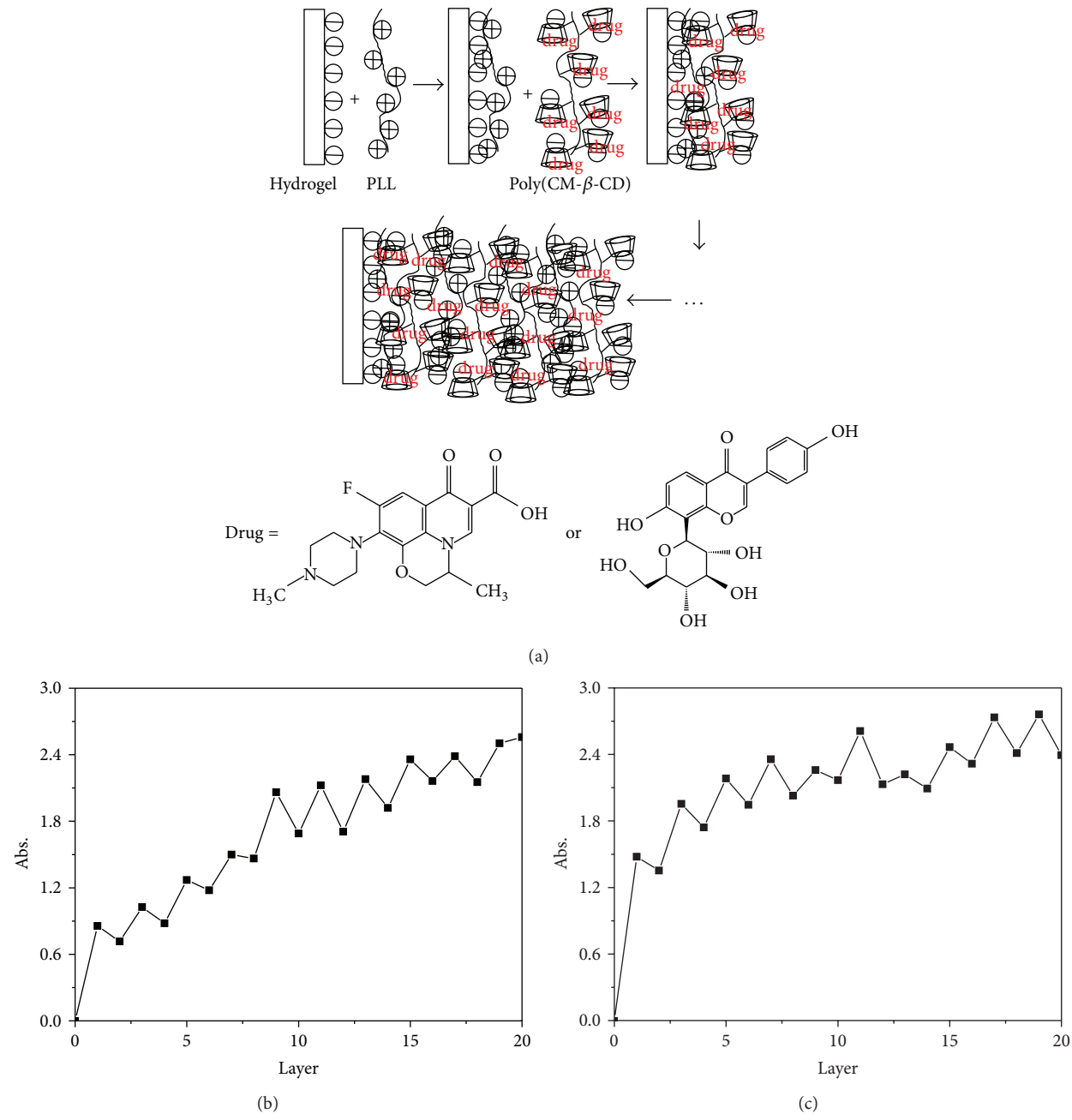

Figure 5: (a) Schematic illustration to show self-assembly process of poly(CM-β-CD)/PLL multilayer with drug by incorporating drug into poly(CM-β-CD) solution. (b) UV absorbance of hydrogel at 285 nm for orfloxacin as a function of layers. (c) UV absorbance of hydrogel at 255 nm for puerarin as a function of layers.

was nearly in neutral state at acid environment. Thus the interaction between orfloxacin and multilayer reduced at acid environment, which led to larger cumulate orfloxacin release amount. As for puerarin, the release behavior was different from that of orfloxacin (Figure 4(b)). Puerarin was gradually released from hydrogel in 20 h at neutral environment and alkaline environment after the initial burst release. The final cumulate puerarin release amount at neutral environment and alkaline environment reached 0.20 mg and 0.24 mg, respectively. However, puerarin was quickly released from hydrogel in the initial 1 h at acid environment. As discussed above, puerarin might be bonded to PLL by hydrogen bond, which would weaken in acid environment. Thus puerarin exhibited a burst release at acid environment.

Drugs were secondly incorporated in poly(CM-β-CD) assembly solution. Drugs were assembled into multilayer by the β-CD/drug inclusion complexes, which was also a noncovalent interaction of β-CD and drug molecules. The absorbance at 285 nm for orfloxacin or 255 nm for puerarin of hydrogel with different layers was recorded in

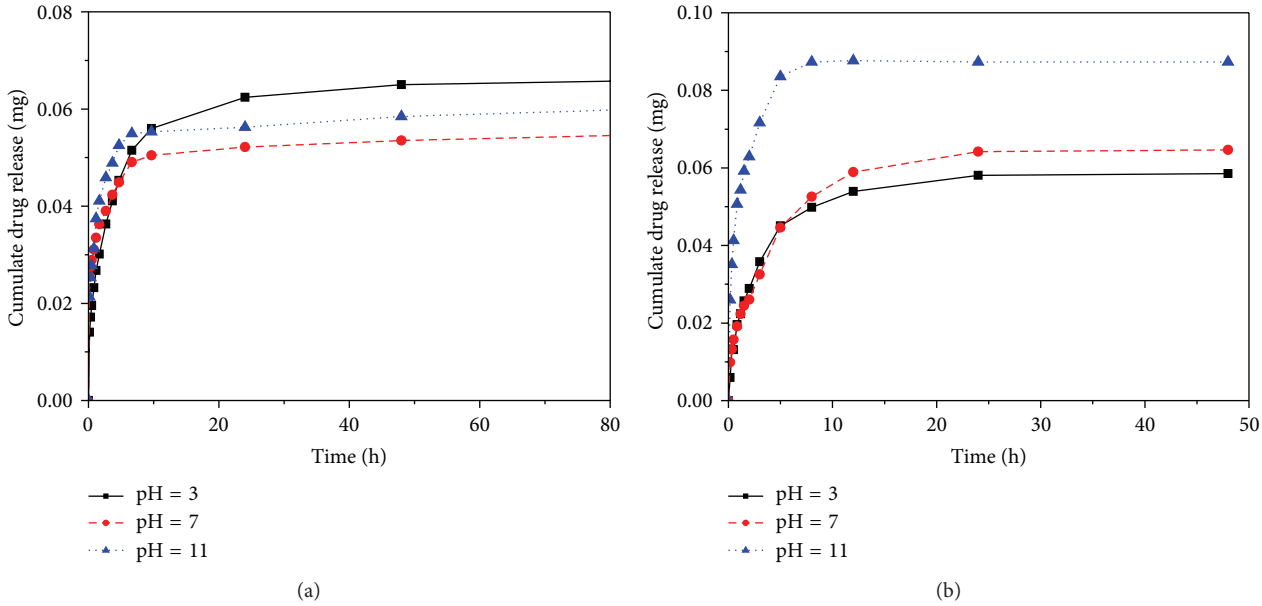

FIGURE 6: (a) The cumulate orfloxacin release from drug loaded poly(CM-β-CD)(drug)/PLL_{20} multilayer in different medium at 37°C. (b) The cumulate puerarin release from drug loaded poly(CM-β-CD)(drug)/PLL_{20} multilayer in different medium at 37°C.

Figures 5(b) and 5(c). The assembling of poly(CM-β-CD) and PLL layers exhibited similar trends showing relatively high and low absorbance at 285 nm (Figure 5(b)). The absorbance at 285 nm presented overall upward trend with the increase of assembled layer and reached about 2.4. The variation of absorbance with assembled layer for puerarin showed similar trend to that for orfloxacin and the balanced absorbance reached about 2.7 (Figure 5(c)). It was also found from Figures 3(c) and 5(c) that the global absorbance of puerarin loaded multilayer by incorporating puerarin in poly(CM-β-CD) solution was much larger than that by incorporating puerarin in PLL solution, which indicated that loaded puerarin amount in the multilayer from poly(CM-β-CD) solution was much larger than that from PLL solution. These results inferred that the interaction coming from β-CD/puerarin inclusion complexes was larger than the interaction of hydrogen bonds between PLL and puerarin.

The drug release behaviors of hydrogel with the above drug loaded multilayer in different medium were shown in Figure 6. Orfloxacin was gradually released from drug loaded hydrogel in 10 h at acid environment, neutral environment, or alkaline environment after first burst release (Figure 6(a)). But the balanced orfloxacin release amount only reached 0.06 mg. As for puerarin, the release behavior was similar to that of orfloxacin at acid environment or neutral environment and the balanced puerarin release amount only reached 0.06 mg (Figure 6(b)). The balanced puerarin release amount at acid environment reached 0.09 mg. Though the loaded puerarin amount in the multilayer through the second method was larger than that through the first method, the cumulate puerarin amount through the second method was much smaller than that through the first method, which indicated that many puerarin molecules stably existed in the multilayer due to relatively stable structure of β-CD/puerarin inclusion complexes. Therefore, we can conclude from these results that the drug loading and releasing behaviors can be adjusted by loading method, the structure of drug, and released environment.

4. Conclusion

A polyanion of poly(CM-β-CD) was successfully synthesized by epichlorohydrin cross-linking of CM-β-CD. The poly(CM-β-CD) and PLL were alternately deposited on the hydrogel by LBL self-assembly technique. With the deposition of poly(CM-β-CD)/PLL multilayer, the contact angle of hydrogel varied regularly and slightly. Larger than 83% light could transmit the hydrogel with poly(CM-β-CD)/PLL_{20} multilayer. Orfloxacin and puerarin could be gradually loaded into multilayer during the self-assembly procedure by incorporating drugs into PLL solution, which was tracked by the largest drug absorbance of UV spectrum. The loaded orfloxacin in the multilayer reached balance after 10 layers of polyelectrolyte were assembled on the hydrogel, while the loaded puerarin in the multilayer did not reach balance until 20 layers of polyelectrolyte were assembled on the hydrogel. The loaded drug could gradually be released from multilayer in 20 h either for orfloxacin or for puerarin. The pH of released medium influenced the drug release behavior. Orfloxacin and puerarin could also be gradually loaded into multilayer during the self-assembly procedure by incorporating drugs into poly(CM-β-CD) solution, and the loaded puerarin amount was larger than that by incorporating drugs into PLL solution. The loaded drug could gradually be released from multilayer in 10 h either. But the balanced released drug amount is much smaller than that by

incorporating drugs into PLL solution. Moreover, the pH of released medium also influenced the drug release behavior.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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