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European Journal of Pharmaceutics and Biopharmaceutics 66 (2007) 48–54
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Encapsulation of ketoprofen for controlled drug release

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Received 17 March 2006; accepted in revised form 20 September 2006
Available online 1 October 2006

Abstract

Ketoprofen particles were encapsulated with polyions and gelatin to control the release of the drug in aqueous solutions. Charged linear polyions and gelatin were alternatively deposited on 6 μm drug microcrystals through layer-by-layer (LbL) assembly. Sequential layers of poly(dimethyldiallyl ammonium chloride) (PDDA) and poly(styrenesulfonate) (PSS) were followed by adsorption of two to six gelatin/PSS bilayers with corresponding capsule wall thicknesses ranging from 41 to 111 nm. The release of Ketoprofen from the coated microparticles was measured in aqueous solutions of pH 1.4, 4.1, and 7.4. The release rate has changed at these different pH values. At pH 7.4 the release rate of Ketoprofen from the encapsulated particles was less by 107 times compared to uncoated Ketoprofen. The results provide a method of achieving prolonged drug release through self-assembly of polymeric shells on drug crystals.

Keywords: Ketoprofen; Encapsulation; Controlled release

1. Introduction

A trend in NSAID development has been to improve therapeutic efficacy and reduce the severity of upper GI side effects through altering dosage forms of NSAIDs by modifying release of the formulations to optimize drug delivery. These formulations are designed to increase patient compliance through a prolonged effect and reduce adverse effects through lowered-peak plasma concentrations. Indeed, enteric coated (EC) and sustained release (SR) formulations of several NSAIDs have resulted in a reduction in endoscopic findings in the stomach and duodenal bulb as these formulations are intended to release NSAIDs in the intestine [1–3].

In this work the chemical principles for a new type of polymer micro-vehicle for sustained drug release were investigated. A large number of biopharmaceutical issues still need to be resolved before the method can be used clinically. Important issues include the biocompatibility and biodegradability of the nanocapsules, cytotoxicity tests, optimization of release in different parts of the gastrointestinal tract, targeting of the capsules, and the possibility of turning drug release on or off by an external influence. In this study gelatins were used because they are biocompatible, but other materials, such as different polysaccharides, specifically synthesized polypeptides, and DNA, could be used to produce more specialized capsules. Previously, it has been demonstrated that it is possible to assemble an outermost microshell layer of antigen and antibody and that such shells can be used for targeted drug delivery [4]. The use of magnetic nanoparticles on the outer shell allows focused targeting to specific areas for localized action and provides a means by which the capsules can be opened with a high-gradient localized magnetic field [5].

Microencapsulation of drug microparticles is a useful technique for prolonging release. Polymer-based and liposome-based systems have been used for drug encapsulation, mostly as unordered drug/polymer conjugates [6–8].

Layer-by-layer (LbL) self-assembly technique based on alternate adsorption of oppositely charged components

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doi:10.1016/j.ejpb.2006.09.010

was developed in the 1990s to coat nanometer-thick films on any surface [9–14]. The film thickness could be controlled within an accuracy of a few nanometers. LbL assembly has been applied to produce nanoshells on micro/nanotemplates such as cells [4], fluorescein, and ibuprofen microparticles [15,16]. Charged materials, including linear polyelectrolytes, enzymes, antibodies, and inorganic nanoparticles, are used in the microencapsulation process [4,15–18]. For controlled release systems, micron-scale cores of material are encapsulated with an outer shell. The core must be insoluble under some condition, such as low pH, and soluble under the conditions at which controlled release is to take place. The release rate generally depends on the thickness of the encapsulating shell and the material used in the coating. Thicker shells lead to longer release times.

Encapsulation of ibuprofen also resulted in prolonged release at different pH values [16]. The ibuprofen dissolution time from capsules with walls built from 15 bilayers of chitosan/dextran was 40 s at pH 7.4, compared to 10 s with no coating. Therefore, prolongation of the release was minimal.

To determine whether encapsulation by LbL assembly can substantially increase the drug release time, the technique was used to assemble polypeptides and polyions on microcrystals of ketoprofen. Ketoprofen is a nonsteroidal anti-inflammatory drug that relieves the pain, tenderness, inflammation (swelling), and stiffness caused by arthritis [19]. Frequent dosing of Ketoprofen is required for therapeutic maintenance because of its fairly fast elimination from the body [20,21]; it usually is taken three or four times a day for arthritis or every 6–8 h as needed for pain. Exposure of the stomach to high levels of ketoprofen can cause gastric damage such as ulceration or bleeding [22]. To improve this disadvantage, sustained release or enteric-coating dosage forms have been developed, resulting in less frequent dosing and less gastrointestinal disturbance [23].

Ketoprofen release from the LbL assembly was measured under three physiological pH conditions, pH 1.4 (stomach), pH 4.1, and pH 7.4 (blood). By optimization of microcapsule wall thickness and composition, ketoprofen release time was controlled in simulated physiological environment.

2. Materials and methodology

2.1. Reagents and materials

Ketoprofen (MW: 254.29) was obtained from APM Company (Sult, Jordan) and finely ground by using a mortar and a pestle (before coating). Cationic poly(dimethyldiallyl ammonium chloride) (PDDA, MW 200,000, Aldrich), poly(ethyleneimine) (PEI, MW 50,000, Aldrich), and anionic sodium poly(styrenesulfonate) (PSS, MW 70,000, Aldrich) were selected for the LbL assembly. A positively charged polypeptide, gelatin type A (MW 50,000–100,000), was obtained from Sigma Chemical Co., St. Louis, USA. Solutions of 3 mg/ml PSS, 2 mg/ml PDDA, and 2 mg/ml gelatin type A were prepared in 20 mM acetic buffer at pH 4. Aqueous 0.1 M NaCl was added to increase thickness of adsorbed polyion layers. A phosphate buffer solution of pH 7.4 was prepared according to USP 24.

The size of most of Ketoprofen microcrystals observed under a microscope was ~6 μm. Ketoprofen is practically insoluble in water at 20 °C. Consequently, Ketoprofen particles were dispersed in water at 20 °C to prevent the drug crystals from dissolving and losing their original shapes during the coating procedure.

2.2. Instrumentation

Instrumental techniques used to study and characterize ketoprofen particles and LbL assembly included a 9-MHz quartz crystal microbalance (QCM, USI-Systems, Japan), a Zeta-Plus photon correlation and microelectrophoresis instrument (Brookhaven Instruments), a UV–visible spectrophotometer (Milton Roy Company, USA), a USP paddle dissolution apparatus (Hanson Research Corporation, Chats Worth, California USA), and an Eppendorf 5804R centrifuge.

2.3. Experiment protocol

Prior to polyion multilayer formation on ketoprofen crystals at pH 4, the coating procedure was elaborated on the gold-electrode resonators of a 9-MHz quartz crystal microbalance. The resonators were immersed in a polyion solution for 15 min, removed, and dried. The added mass and the coating thickness (ΔL) were calculated from the frequency shift (ΔF), according to the Sauerbrey equation, using a special scaling [25,26]. For the instrument used in this study, the calibration was ΔL (nm) = 0.017 ΔF (Hz). Several coating configurations were studied initially to determine the most appropriate conditions for the drug-release application. These optimized assembly conditions were applied to the LbL shell assembly on microcrystals.

After each polyion coating, the zeta-potential of the capsules was calculated as the average of 10 measurements with a Zeta-Plus photon correlation spectroscopy and microelectrophoresis instrument. All measurements were performed in air-equilibrated 1 mM KCl solution.

The coating procedure was carried out as follows: a negatively charged PSS solution was added to 200 mg of the ketoprofen particles in pH 4 acetic acid solution (saturated with ketoprofen) and kept for 30 min, which was sufficient time to ensure that all crystals were coated. A pH of 4 was used because the low solubility of ketoprofen at this pH [24] ensured that the particle shapes and sizes were not altered. Negative polyions were used as the first layer because the electric potential measurements showed that the surface of ketoprofen is positively charged at this pH.

The chemical name for ketoprofen is 2-(3-benzoylphenyl)-propionic acid. Its empirical formula is $C_{12}H_{12}O_2$, with a

molecular weight of 254.29. Ketoprofen is a white or off-white, odorless, nonhygroscopic, fine to granular powder, melting at about 95 °C. It is freely soluble in ethanol, chloroform, acetone, ether, and soluble in benzene and strong alkali, but practically insoluble in water at 20 °C, and at low pH [24]. Zeta-potential measurements demonstrated that the surface charge of a ketoprofen particle was positive at pH 4. Referring to the chemical structure of ketoprofen (Fig. 1) we believe that due to the high electron-withdrawing abilities of the oxygen atoms in the two aromatic structures of the compound, and because of their high electronegativities, this will create a high positively charged center around the carbon–carbonyl from one side and the carbon–carbonyl atom from the other acidic side. In addition to that we believe that the two aromatic structures of the compound and their highly conjugated abilities through the entire molecule, this might increase the probability of creating positive charges to the drug particles.

The coated ketoprofen microcrystals were separated from the polyion solution by 5 min centrifugation in an Eppendorf 5804R centrifuge at 1000*g*. Recovered microcrystals were washed twice with acetic acid solution saturated with ketoprofen before further assembly. The procedure was then repeated with polycation PDDA, a second PSS layer, and a second PDDA layer to form a $(PSS/PDDA)_2$ precursor layer. This layer of strongly charged polyions forms a stable foundation for further coating. Next, four layers of (PSS/gelatin) were deposited by the same method. Negatively charged PSS was chosen for this step because, with an isoelectric point near pH 8, gelatin is positively charged at pH 4. Gelatin layers strongly decrease the drug release and are biocompatible. The coated particles were removed from the solvent and air dried on a filter paper before performing dissolution test. This capsule wall composition was the most effective for ketoprofen because capsules composed of other linear polyions, such as poly(ethyleneimine), chitosan, and poly(allylamine), were found to have high permeability.

Gelatin is insoluble in ethanol, and to calculate its encapsulation rate, 20 mg of encapsulated ketoprofen particles, which were prepared by the usual LbL technique as before, was gently stirred into 100 ml ethanol and left to settle freely for 10 min. Samples from the supernatant solution were withdrawn and analyzed through a calibration curve of ketoprofen. The absorbancies of triplicate samples were taken and through the calibration curve a recovery of about 1.25% of ketoprofen was noted. Therefore encapsulation rate can be assumed to be more than 98% which is quite high.

Drug release before and after encapsulation was monitored with a UV–visible spectrometer. The release of ketoprofen from the capsules was conducted in a quartz cuvette by monitoring UV absorbance at 256 nm. The peak UV absorbance remains the same at different pHs used in this study. As ketoprofen has low solubility at low pHs, and to ensure sink conditions for different samples, concentrations of ketoprofen in the dissolution media were kept below 2 mg%. Recording time intervals varied from seconds to hours for different samples. All release studies were performed at room temperature (~25 °C). After encapsulation the microcrystals were kept in a saturated ketoprofen solution. Before each release study, the capsules were rinsed in water for 10 s.

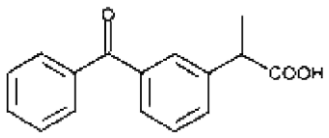

Fig. 1. The molecular structure of ketoprofen.

The dissolution rates of the coated ketoprofen particles, commercially available ketoprofen tablets (Profenid 100 mg film-coated tablets, Aventis) and ketoprofen controlled release tablets (Profenid SR 200 mg, Aventis) were measured using Method 2 of the United States Pharmacopeia (USP 24) [27]. The paddles were rotated at 50 rpm and 5 mL samples were withdrawn from the dissolution medium at regular intervals and extending as long as 8 h. Samples taken were compensated with the same amount of the dissolution media, taken at the same temperature from a control vessel of the dissolution apparatus. Initial concentration levels which were below 30 s were extrapolated. For each test, 5 mg of the dried coated particles was placed in 500 ml of either 0.1 M aqueous hydrochloric acid solution or 0.2 M aqueous acetate buffer (pH 4.1). The medium was degassed and kept at 37 °C. The concentration of ketoprofen in solution was calculated from the UV absorbance of withdrawn samples. The pH 7.4 solution was a phosphate buffer prepared according to USP as all other buffers in the work.

3. Results and discussion

In the first stage, PEI, PDDA, PSS, and gelatin were assembled onto quartz crystal microbalance electrodes. Assembly of $(PDDA/PSS)_2(PSS/gelatin)_4$ multilayers was monitored by QCM frequency shift measurements (Fig. 2). Additional NaCl was added to the solution because the film thickness of each polyion layer varies with the ionic strength of the solutions [10], with higher ionic strength solution generating thicker polyion films. As shown in Fig. 1, 0.1 M NaCl in acetic acid buffer provided a 2-nm thick PDDA/PSS bilayer. Assembly steps for gelatin were easily monitored with QCM frequency shifts because the film thickness sharply increased. The averaged frequency shift for each gelatin layer was 479 Hz, which corresponds to a thickness (ΔL) of ~8 nm. This thickness indicates that each polypeptide layer included more than one gelatin monolayer. This feature probably led to the drastically decreasing permeability of the capsule walls. The PSS layers were much thinner than the gelatin layers, having a thickness of ~0.8 nm. Finally, the total thickness of the 11-layer coating composed of $[PDDA + (PSS/PDDA) + (PSS/gelatin)_4]$ was ~38 nm.

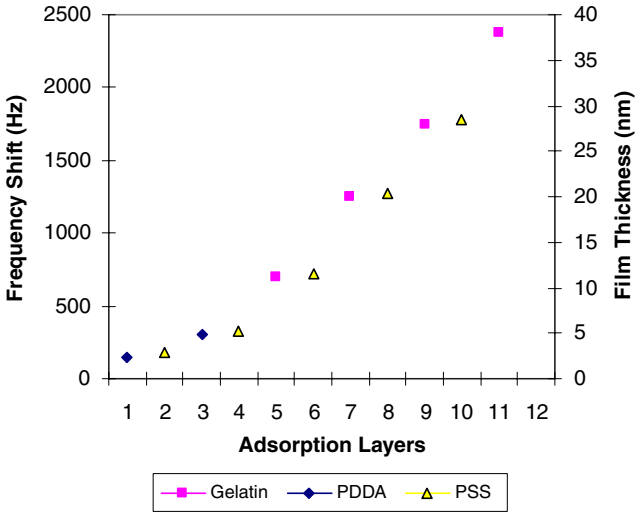

Fig. 2. Frequency shift and film thickness of each assembly layer for PDDA + (PSS/PDDA) + $(PSS/gelatin)_4$ adsorption on QCM electrodes. The first three-layer precursor [PDDA + (PSS/PDDA)] is ~4 nm thick. The averaged frequency shift of every gelatin layer is 479 Hz, corresponding to a thickness of 8 nm.

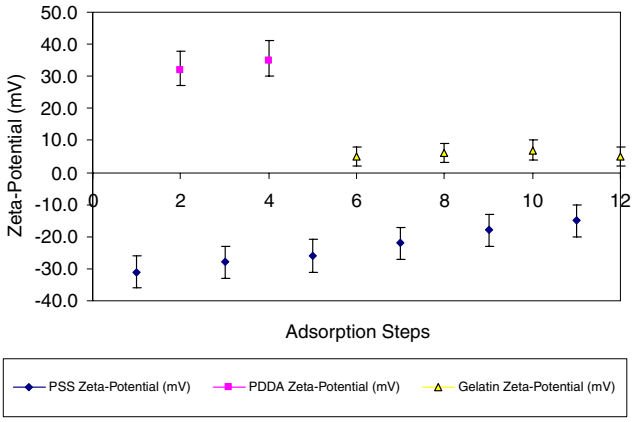

Fig. 3. Zeta-potential of the coated ketoprofen microcrystals versus the number of adsorption steps for shell compositions of $(PSS/PDDA)_2$ + $(PSS/gelatin)_4$.

The QCM assembly data were used as a guide for selection of polyion capsule formation conditions (i.e. the component concentration, solution pH, and deposition time) on the particles. It was difficult to directly measure shell thickness on particles, but in a previous study it was found that the layer thickness coated on QCM electrodes was half the shell thickness on microtemplates [15,17,28]. The QCM measurements indicated that a single gelatin layer coated on drug microcrystals was ~16 nm thick, taking into account the doubling of the layer thickness for a swollen polyion multilayer compared with dry multilayer [12]. The nano-shell thickness ranged from 41 to 111 nm for two to six gelatin/PSS bilayers, as estimated from QCM data. The corresponding swollen wall thickness was 122 nm for a two-block shell with the composition [(PDDA/PSS) + $(PSS/gelatin)_6$]. Therefore, the polymer wall/ketoprofen core mass ratio is 0.20.

Ketoprofen is available in the market by prescription as 25, 50, 75, 100, 150, and 200 mg capsules. Some of its brand names in the USA are Orudis and Oruvail. Orudis capsules contain 25, 50, or 75 mg of ketoprofen. While, each Oruvail 100, 150, or 200 mg capsule contains ketoprofen in the form of hundreds of coated pellets. In this work, and upon addition of gelatin layers, particles have increased in their size and this was checked with microscope after addition of every layer and after measuring charges by QCM. This would tell that the addition of gelatin has been done physically.

Surface electrical potentials (zeta-potential) for the encapsulated ketoprofen particles at each step of the alternate adsorption process are shown in Fig. 3. The uncoated drug is positively charged with potential +51 mV. The first PSS layer converted it to negative −31 mV. The first PDDA coating gave positive charge at +32 mV. The gelatin layers tended to have zeta-potentials with lower magnitudes, averaging +5 mV. The surface potential of the PSS layers slightly decreased with each application from −28 mV after the first layer to −15 mV at the 11th layer. Probably, in some regions PSS did not completely overcome the more bulky gelatin layer. This decline could limit total thickness of the shell after another five to six bilayers of gelatin/PSS. The alternating surface charge of coated drug particles was strong evidence that the layer-by-layer assembly of the oppositely charged components was successful.

The amount of drug released from microcapsules with different numbers of gelatin layers was quantified (minimum of 95% of the sample tested for dissolution by measuring the absorbance of the solution containing the microencapsulated particles. These data are shown as a function of time in Fig. 4. At pH 1.4 (close to stomach pH), the half-release times ($t_{1/2}$) were 0.30, 0.60, and 0.80 h for two-, four-, and six-layer gelatin coatings, respectively. The $t_{1/2}$ of the unmodified drug particles was ~0.15 h. After encapsulation, the $t_{1/2}$ was two, four, and 5.33 times longer compared to the uncoated ketoprofen particles. The total release times were 1.8, 3.2, and 6.4 h for two, four, and six gelatin bilayers, respectively. The four- and six-layer coatings are thick enough to provide slow release in a gastric environment (pH 1.4). Ketoprofen coated with four to ten PSS/PDDA bilayers did not demonstrate a significant increase in release time.

At pH 7.4, the half-release times were 0.006, 0.03, and 0.25 h for two, four, and six layers of gelatin, respectively (Fig. 5). The half-release time for unmodified ketoprofen particles was estimated to be 0.0005 h (1.8 s). The total release times were 0.05, 0.32, and 0.75 h for two, four, and six gelatin layers, respectively. The uncoated ketoprofen particles dissolved in 0.007 h (25 s). Thus, the release time was 7, 46, and 107 times longer after encapsulation with two, four, and six layers, respectively.

At pH 7.4, the drug half-release time ratio of the six-layer coating/zero-layer coating was much higher

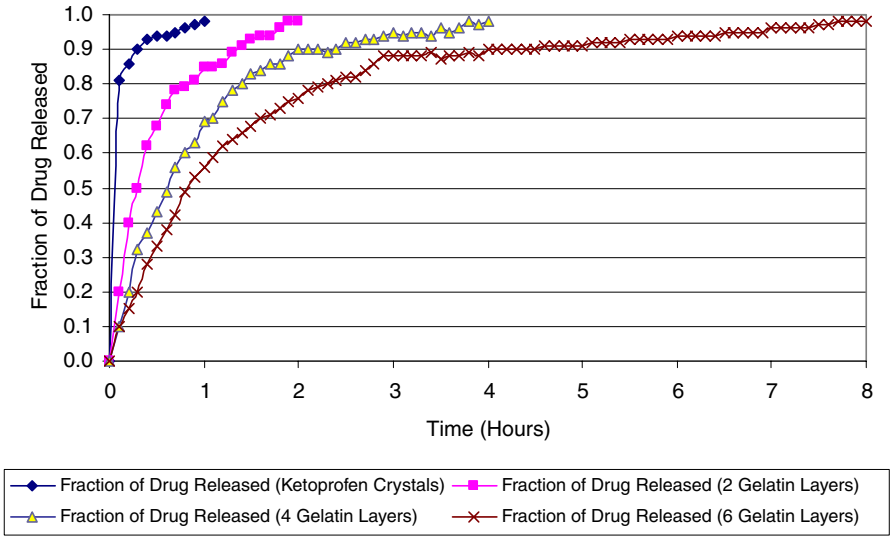

Fig. 4. Release profiles of ketoprofen before and after encapsulation at pH 1.4.

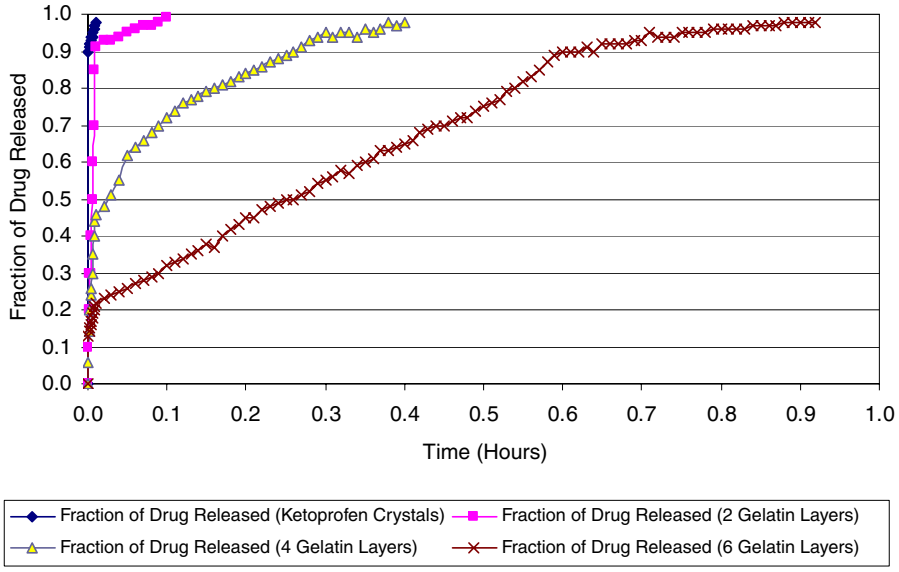

Fig. 5. Release profiles of ketoprofen before and after encapsulation at pH 7.4.

compared to that at pH 1.4. At pH 7.4 the release appears to occur in three stages (Fig. 5); an initial burst occurs for the first few seconds, followed by a slow release that is linear in time. In the final stage, release slows exponentially, tending asymptotically to the saturation concentration (total dissolution) of the drug.

Drug release in the pH 1.4 solution did not exhibit a linear region. The total release time for the six-layer coating was twice that of the four-layer coating. Additionally, the initial burst for the six-layer capsules lasted for a shorter amount of time than that for the thinner coatings, and the slow release part of the curve was nearly linear in time (Fig. 4). Because the half-release time of the six-layer microcapsules was much longer than that for the uncoated particles, it should be possible to use the encapsulation to design controlled-release microdevices.

Dissolution profiles (Fig. 6) show that LbL coating of ketoprofen particles with anionic PSS and cationic PDDA, followed by adsorption of gelatin, significantly slowed the dissolution rate of the drug in physiologically relevant media. The shell architecture is $(PSS/PDDA)_2 + (PSS/gelatin)_4$. At pH 1.4 and 4.1, respectively, as would be encountered by the drug in the gastrointestinal tract of humans, the release of the drug from the coated particles was three and two times slower than from the film-coated particles. At pH 4.1 the dissolution time of film-coated drug was 1.9 h (114 min) compared to 3.5 h for the coated drug. At pH 1.4, similar to the pH of the stomach, the coated drug dissolved within 5 h. The release of drug from the coated particles (Fig. 6) was also 2.5 times as slow as that from a ketoprofen tablet (Profenid 100 mg film-coated tablets, Aventis) and not significantly different from that of

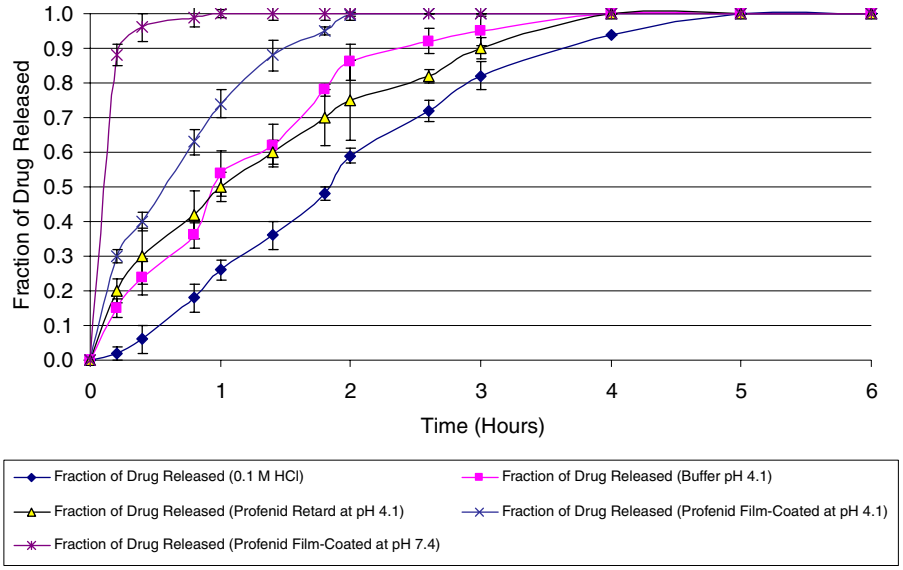

Fig. 6. Dissolution profiles of $(PSS/PDDA)_2 + (PSS/gelatin)_4$ coated ketoprofen microparticles compared to film-coated ketoprofen tablets and sustained released ketoprofen commercially available tablets in physiologically relevant media.

commercially available controlled release tablets (Profenid SR 200 mg). However, LbL-coated microparticles are much smaller. To elucidate the difference between the SR, LbL and the film-coated ketoprofen at pH 4.1, ANOVA test was performed. The test indicated that they are significantly different with actual p value equal to 0.007. Further analysis to find the differing group indicated that while Profenid film-coated are significantly different from both Profenid Retard ($p = 0.015$) and the gelatin microencapsulated ketoprofen ($p = 0.0012$), the latter two did not show significant difference from each other ($p \leqslant 0.05$).

An important aspect of the current study is the use of gelatin for capsule formation. In previous work [10,16] it was not possible to substantially increase the release time of ibuprofen using dextran sulfate/chitosan capsules. In another study [15], a fluorescent compound coated with poly(allylamine)/poly(styrenesulfonate)$_{4-8}$ capsules resulted in small increases in release time compared with bare fluorescein dye microcrystals. Ai et al. [28] tried to encapsulate Furosemide microcrystals with polyions to control the release of the drug in aqueous solutions through LbL assembly. The release rate of furosemide from the encapsulated particles was reduced compared to uncoated furosemide.

Klitzing and Mohwald [29] found that rhodamine diffusion through $(PSS/PAH)_8$ multilayers was much slower when the layers were deposited in the presence of 1 M NaCl than it was when they were deposited in pure water which is a strongly charged polyion. Klitzing and Mohwald results were similar to the finding of this work. In this work, gelatin A was used. It is a weak polybase with isoelectric point around pH 8; therefore it has a small positive charge at pH 7.4. Nevertheless the multilayer capsule is stable and even less permeable at this pH than at a pH of 1.4, where both PSS and gelatin are strongly charged. Gelatin B has an isoelectric point of 5 therefore it was not used in this work.

In comparison with other traditional methods of drug delivery, the method described here has the following advantages: (i) the wall thickness and diameter of the microcapsule can be varied with a precision; (ii) the capsule wall architecture can be designed in a wide variety of ways and can include polymers, lipids, enzymes, DNA and inorganic nanoparticles [5,15–17,26,30,31]; (iii) attachment of antibodies or antigens will allow targeting of capsules [4]. Typically a polymer:drug mass ratio of 10:1 is used in the preparation of a polymer-based drug-delivery system [8,32], and in this work a 0.20 was obtained.

4. Conclusion

Sustained drug release was achieved by 6-μm ketoprofen particles micro-encapsulated with 41–111 nm thick gelatin/polyanion multilayer shells. This shell composition was a substantial improvement over shells constructed from poly(allylamine) or chitosan, and provided up to 107 times slower release time, when compared with dissolution of conventional ketoprofen particles.

Acknowledgement

The authors gratefully acknowledge the support from the Deanship of Scientific Research and Higher education at Philadelphia University of Jordan, without which this work could not be done.

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