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A new bioerodible system for sustained local drug delivery based on hydrolytically activated *in situ* macromolecular association

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ABSTRACT

To prolong the duration of polymer erosion over existing approaches for sustained local drug delivery, we investigated a new bioerodible system based on hydrolytically activated *in situ* formation of interpolymer complexes in binary blends of high MW poly(vinyl methyl ether-co-maleic anhydride) (PVMMA) and poly(ethylene oxide) (PEO). In an aqueous environment of use, the hydrophobic PVMMA component of the blend undergoes hydrolysis converting the anhydride to free carboxylic acid groups which in turn form *in situ* intermolecular complexes with the PEO component of the blend. The formation of such hydrogen-bonded complexes with a condensed structure at the blend surface helps to retard the further progression of polymer erosion and drug release. The effects of PVMMA/PEO composition on blend morphology, polymer erosion and drug release were evaluated with the aid of fluorescence labeled PVMMA. The results show a decrease in miscibility in PVMMA/PEO blend with increasing PEO content. At low PEO contents (below 40%), the *in vitro* rate of release of a model drug metronidazole decreases with increasing PEO content, resulting in extended release duration over several days. On the other hand, excessive phase separation at PEO contents above 40% gives rise to higher rate and shorter duration of drug release.

1. Introduction

It has been widely accepted that sustained local drug delivery, particularly for antimicrobial agents, provides a better risk/benefit ratio than systemic therapy in relation to the reduction of side effects and enhancement of therapeutic efficacy, because an effective local concentration of antimicrobial agent can be established and maintained for a longer duration of treatment with minimum systemic drug load (Gooson et al., 1979). During the past decades, numerous types of local drug delivery systems employing various polymeric biomaterials have been investigated (Kanjickal et al., 2004; Jain et al., 2005). In particular, bioadhesive local drug delivery systems based on mucoadhesive materials have attracted significant attention because of their capability to extend the residence time at the site of administration (Chng et al., 1985; Longer et al., 1985; Smart, 1993). In this regard, a number of biodegradable polyanhydrides microspheres have been shown to exhibit high affinity towards the nasal and intestinal mucosa (Li et al., 2005; Jiang and Zhu, 2002). These polyanhydrides with anhydride bonds in the polymer backbone are well-known for their extremely hydrophobic nature and predominately surface erosion characteristics. In principle, such materials should be particularly suited for use as drug delivery implants when matching of the extent of polymer erosion with that of drug release is desired (Göpferich and Tessmar, 2002). Despite the wide interests in this type of polyanhydrides, poor mechanical properties primarily due to rapid degradation of hydrolytically labile anhydride linkages in the backbone have limited this class of polyanhydrides to only short-term drug delivery applications (Kumar et al., 2002; Domb et al., 1995).

On the other hand, another type of erodible polyanhydrides exists where the anhydride linkage exists as a cyclic side chain, not part of the polymer backbone. In this case, no reduction in polymer molecular weight is expected after the hydrolytic breakdown of the anhydride groups. From a stability point of view, this type of polyanhydrides would be more suited for applications where the polymer degradability is not essential. As a representative example, maleic anhydride copolymers have been employed in different fields of application ranging from anticorrosive coatings, conducting polymers, functional biomaterials, to targeted drug delivery (Zafar et al., 2004; Lee et al., 2004; Kesim et al., 2003; Kamada et al., 2003).

More recently, a maleic anhydride copolymer, poly(vinyl methyl ether-co-maleic anhydride) (PVMMA), has been finding increasing applications in the design and fabrication of bioadhesive dosage forms for oral and topical drug delivery including bioadhesive nanoparticles (Arbós et al., 2002; Irache et al., 2005), denture adhe-

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sives, transdermal patches and film-coatings (Sharma et al., 1999; McCarron et al., 2005; Luppi et al., 2003). Ordinarily, PVMMA in the anhydride form is hydrophobic but becomes surface erodible in an aqueous environment through the ionization of pendant carboxyl groups generated from the hydrolysis of side chain anhydrides. Since such ionization-induced polymer erosion process is quite rapid, the achievable drug release duration from PVMMA alone is relatively short (typically less than a day).

Chemical conversion of PVMMA into partial esters has been suggested as a means to decrease the erosion rate of the resulting polymer for controlled release drug delivery purpose (Heller et al., 1978). However, such chemical conversion inevitably generates new polymer entities which would not be readily acceptable for pharmaceutical and medical applications without lengthy toxicity testing. Furthermore, in structural terms, each of the five-member anhydride rings of PVMMA contributes two carbons in the backbone and confers rigidity to the polymer. In order to improve its flexibility to facilitate practical applications, much research has been focused on its chemical crosslinking via esterification of anhydride moieties with hydroxyl containing materials such as glycerin, PEG or other polyhydric alcohols (McCarron et al., 2005; Luppi et al., 2003). However, such reaction completely eliminates the hydrophobic characteristics of PVMMA, eventually yielding a hydrophilic gel formulation which does not provide any meaningful sustained release properties.

Recently, Heng and coworkers investigated the hydrogen bonding based complexation behavior between PVMMA and polyvinylpyrrolidone (PVP) and studied its effect on the release profiles of entrapped diclofenac sodium (Hao et al., 2004). However, both PVP and the PVMMA were separately dissolved in water before mixing these solutions in the desired proportion to form hydrogen bonded intermolecular complexes. In this case, the PVMMA component was converted to the hydrolyzed free acid form prior to mixing with the PVP solution. Presumably this was done to facilitate the strong interactions between the proton donating free acid groups and the carbonyl groups of PVP. In other recent studies, Jones et al. also investigated the physicochemical properties of gels composed of blends of hydrolyzed PVMMA in the free acid form and PVP (Jones et al., 2003, 2004). All these systems mentioned above provide a physical form that is convenient for application, but at the sacrifice of the inherent surface erosion characteristics of the hydrophobic PVMMA. Furthermore, it was reported by Heng and coworkers that the drug release from the intermolecular complexes with PVP is actually faster than that from the hydrolyzed PVMMA alone (Hao et al., 2004). This has been attributed to the high solubility of the PVP component and cited as the major reason for a lack of sustained release obtained from these systems. To be useful for local drug delivery applications (e.g. for periodontal or topical therapy), the duration of polymer erosion, which governs both the drug release duration and effective life time of the delivery device, should be at least several days up to a week or more to ensure circumvention of the device removal step. In addition, it is desirable that such bioerodible polymer system also exhibits sufficient bioadhesion that it can be retained at the delivery site for the duration of the therapy. So far, bioerodible polymers satisfying these criteria appear to be unavailable.

To overcome these drawbacks, we report here a novel preparation of bioerodible polymers based on binary blends of high MW poly(vinyl methyl ether-co-maleic anhydride) (PVMMA) and poly(ethylene oxide) (PEO) without first converting the anhydrides into free acids, in an effort to prolong the duration of PVMMA erosion and correspondingly achieve a sustained local drug release. To our best knowledge, this is the first time such a blend system based on PVMMA and PEO has been studied. In an aqueous environment of use, the PVMMA component of this blend undergoes hydrolysis converting the anhydride groups to free carboxylic acids which in turn form intermolecular complexes *in situ* with the PEO component. Such hydrolytically activated molecular association retains the hydrophobic nature of bulk PVMMA such that hydrogen bonded complexes occur only at the surface region of the blend as a result of hydrolytic activation triggered by the penetrating solvent (water) during drug release. The major advantage of the present system over existing approaches is that through the unique *in situ* interpolymer complexation process, the polymer erosion and drug release duration can be significantly extended by such PVMMA/PEO blends. In addition, the inherent bioadhesive nature of the hydrolyzed PVMMA as well as the PEO component in the blend should allow better adhesion and retention of the delivery system at the site of application. In the present study, we focus on the compatibility of such PVMMA/PEO binary blends and investigate their *in situ* complexation, *in vitro* erosion, and drug release properties using metronidazole as a model drug.

2. Materials and methods

2.1. Materials

Poly(vinylmethylether-co-maleic anhydride) (PVMMA, Gantrez® AN-169, Mw: 2,000,000) and poly(ethylene oxide) (PEO, POLYOX™ WSR-303, Mw: 7,000,000) were kindly donated by ISP (Mississauga, Ontario, Canada) and DOW Chemical Company (Midland, MI, USA), respectively. Fluoresceinamine isomer I (FA) and metronidazole were purchased from Sigma–Aldrich (Oakville, Ontario, Canada). Dimethyl sulphoxide (DMSO) and N,N-dimethylformamide (DMF) from Sigma–Aldrich were dried with calcium hydrate before use. All other chemicals were reagent grade obtained from commercial sources and used as received, unless otherwise noted.

2.2. Synthesis of FA labeled PVMMA

The introduction of a fluorescence label onto the PVMMA chain makes it feasible to study the polymer erosion process which would otherwise be intractable due to the lack of a detectable chromophore. In this study, the introduction of a fluorescent probe onto the PVMMA was achieved by a grafting reaction between the anhydride group on the PVMMA side chain and the amidocyanogen group on the FA molecule. In a typical reaction, 1.56 g PVMMA was first dissolved in 50 ml anhydrous DMSO in a 100 ml round-bottom flask followed by the dropwise addition of a FA solution prepared by dissolving 69.5 mg FA in 10 ml of anhydrous DMSO. The reaction was complete after 20 h at 35 °C under continuous stirring in a thermostated oil-bath.

After cooling to room temperature, the reaction mixture was dialyzed against an anhydrous DMSO medium in a dialysis tube (Mw cut off: 8000–10,000) for 3 days to remove un-reacted FA. Afterwards, the dialyzed reaction mixture was poured slowly into 4 L anhydrous ether under vigorous stirring, resulting in a fiber-like precipitate. The precipitated FA labeled PVMMA (FA-PVMMA) was washed repeatedly with ether until no fluorescence intensity could be detected in the extract. After collecting the washed precipitate by filtration and vacuum drying at room temperature, the FA-PVMMA product was stored in a desiccator prior to use.

2.3. Preparation of PVMMA/PEO composite films and model drug selection

FA-PVMMA, at 1% weight ratio, was first mixed with PVMMA. The mixture was then dissolved in acetone to form a 10 wt% solution. Separately, a 1% by weight PEO solution in acetone was prepared by heating to 60 °C under constant stirring for at least 3 h followed by cooling to room temperature. Subsequently, the

two polymer solutions were thoroughly mixed at different weight ratios of PVMMA/PEO: (a) 9.5/0.5; (b) 9/1; (c) 8/2; (d) 7/3; (e) 6/4; (f) 5/5; and (g) 4/6. For drug loaded films, model drug metronidazole was dissolved in the homogenous polymer blend solution to give a 10 wt% drug concentration. Film samples were prepared immediately afterwards by casting the polymer/drug solution onto PTFE dishes. The dishes were placed in a partially covered chamber to slow down the drying process and to prevent bubble formation in the resulting films. Acetone evaporation was initially carried out at room temperature for 2 days, the film samples were subsequently dried under vacuum for an additional 24 h. Metronidazole was selected as a model drug for this study because it is specifically active against anaerobic pathogens commonly associated with periodontitis (Addy et al., 1988). In addition, local delivery of antimicrobial drugs in the periodontal pocket is a recommended way of treating periodontal disease (Greenstein and Polson, 1998; Schwach-Abdellaoui et al., 2000).

Afterwards, disks of 1.75 cm in diameter were cut from the film samples with a punch and stored in a desiccator at room temperature prior to use. The disk samples selected for release testing weighed 80–90 mg with thicknesses ranged from 0.2 to 0.3 mm.

2.4. Morphology of PVMMA/PEO composite films

The morphology and micro-structure of composite films was observed using a polarizing interference microscope (Biolar PI, Poland) equipped with a Nikon D50 Digital SLR Camera at 10× magnification. For all observations, a flat piece was cut from the PVMMA/PEO blend film, placed between the slide and cover glass, and observed directly in the dry state using a birefringent prism. For the observation of cross-sections, samples were prepared by freeze-fracturing small film pieces in liquid nitrogen and placing samples sideways on the slide.

The phase separation behavior in the blend system was further investigated at ambient temperature using a confocal laser scanning microscope (ZEISS LSM 510, Germany) at 5× magnification. The light source used was a blue argon laser (λ_{ex} = 488 nm). The images were analyzed with ZEISS LSM 510 IMAGE BROWSER.

2.5. ATR-FTIR characterization of composite films

Fourier transform infrared (FTIR) spectra were recorded on a universal Attenuated Total Reflectance (ATR) Spectrum-one PerkinElmer spectrophotometer (PerkinElmer, CT, USA). All spectra were collected on the film samples at a resolution of 2 cm^{-1} and were repeated three times. A background spectrum without any sample was subtracted from all spectra. The spectra were recorded from 4000 to 650 cm^{-1}.

2.6. Polymer erosion and metronidazole release

The rates of polymer erosion and metronidazole release from PVMMA/PEO composite films were investigated on an ERWEKA USP DT600 dissolution apparatus (ERWEKA, Ontario, Canada) using a rotating disk sample holder as described previously (Xu and Lee, 1993; Gates et al., 1994). The release experiments were performed in 500 ml phosphate buffer saline solution (0.1 M, pH 8) at 37 ± 0.5 °C with a rotating speed of 60 rpm. The pH 8.0 buffer was selected as the *in vitro* release medium to simulate the gingival crevicular fluid (GCF) at the inflamed disease sites (Gates et al., 1994; Bickel et al., 1985). At a selected time interval, a 100 ml aliquot was removed and replaced with an equal volume of fresh dissolution medium. Metronidazole concentration in the aliquot was determined on a Cary 50 UV–vis spectrophotometer (Varian, Ontario, Canada) at 320 nm.

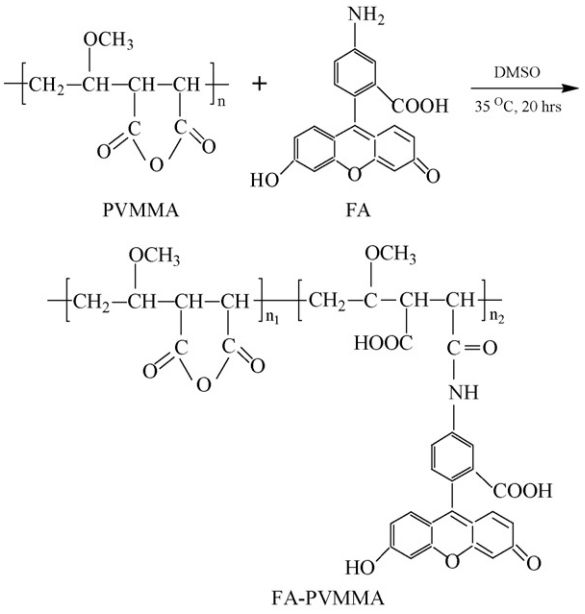

Fig. 1. Reaction scheme for the preparation of FA-PVMMA.

A Fluoromax-3® spectrofluorometer (Jobin Yvon Inc., Edison, NJ, USA) was employed in the determination of polymer erosion rate. With an excitation wavelength of 488 nm, a linear calibration curve relating the FA-PVMMA concentration to its fluorescence intensity in a dilute concentration range was established at an emission peak wavelength of 513 nm. Subsequently, the eroded PVMMA concentration in a given aliquot was calculated from the measured fluorescence intensity assuming that PVMMA erodes at the same rate as fluorescence labeled FA-PVMMA. All erosion and release experiments were carried out at least in duplicate and an average value was adopted for the final plots with error bars denoting the range of data.

3. Results and discussion

3.1. Characterization of FA-PVMMA

Being very reactive towards functional amines, maleic anhydride copolymers are useful for surface immobilization of bioactive molecules and preparation of fluorescent polymers (Ladaviere et al., 1999; Wang et al., 2002). In this work, fluoresceinamine (FA) was employed as the fluorescence probe for the preparation of FA labeled PVMMA. The attachment of FA to PVMMA was accomplished through the acylation of FA with the maleic anhydride moiety of PVMMA according to the reaction scheme of Fig. 1. In the present study, the molar percentage of the attached fluorescence probe FA is estimated to be around 10%. The resultant FA-PVMMA polymer emits strong yellow-green fluorescence.

As shown in Fig. 2A, the fluorescence spectrum of FA-PVMMA approaches that of FA, but with a slight upward shift of the peak emission wavelength from 510 nm of FA to 513 nm of FA-PVMMA, presumably due to the anchoring of fluorescence probe. The corresponding peak fluorescence intensity is found to increase with increasing solution concentration of FA-PVMMA (Fig. 2B). In fact, a good linear relationship between fluorescence intensity (I) and concentration (C, mg/ml) exists in a dilute concentration range from 0.000123 to 0.00246 mg/ml thus allowing the establishment of a calibration for determining the amount of polymer erosion (Fig. 2C).

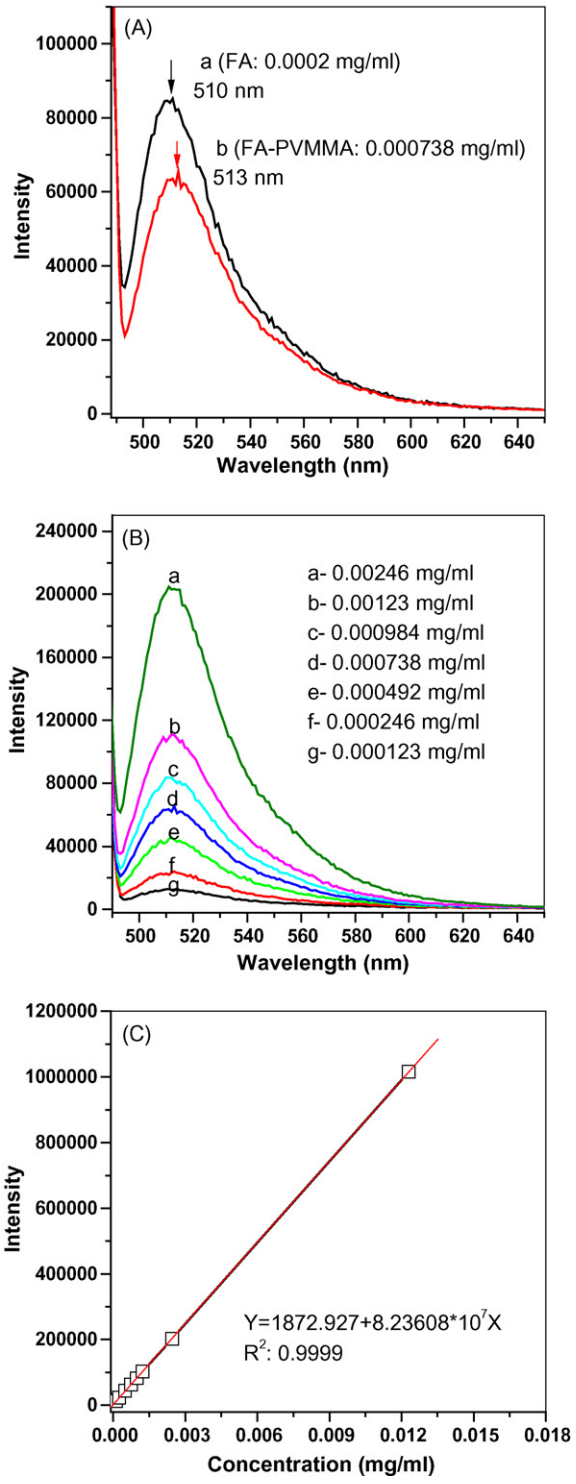

Fig. 2. Fluorescence emission spectra of (A) FA and FA-PVMMA in 0.1 M PBS (pH 8.0) and (B and C) linear relationship between the concentration and emission intensity (λ_{ex} = 488 nm).

3.2. Morphological characterization of PVMMA/PEO composite films

3.2.1. Polarizing interference microscope observation

Phase separation is an important phenomenon in polymer blends as it can significantly affect the resulting polymer erosion and drug release properties. In the present PVMMA/PEO blend system phase separation took place between amorphous PVMMA and semi-crystalline PEO. Because of the high molecular weight of PEO, adequate heating was necessary to obtain a homogeneous acetone solution prior to blending with the PVMMA solution in acetone. In preparing such polymer blends by the solvent method, it is important to use a common solvent or solvent mixture which can dissolve both the hydrophobic PVMMA and hydrophilic PEO components. During subsequent drying process, phase separation in a polymer blend can be induced either by cooling or by solvent evaporation (Petersson et al., 2005).

In the present system, the morphology and microstructure of the resulting composite film will be highly dependent on the phase separation kinetics in connection with the solvent evaporation process. A Biolar polarizing interference microscope was employed to investigate the morphology of such composite films. The method of differential interference has been recognized to be particularly suitable for the measurement of birefringence in fiber and film samples, especially for those samples containing minor heterogeneities. It is sometimes more preferable than the phase contrast method, since the differential interference method enables certain sample structures obscured or even invisible under phase contrast microscope to be observable under the polarizing interference microscope (Pluta, 1971). In this regard, this technique can provide a more comprehensive picture on the morphological changes occurring in the PVMMA/PEO blend system as a function of blend composition. As shown in Fig. 3a, the surface morphology of pure PVMMA film is generally smooth. However, upon addition of 10 wt% PEO the blend film becomes rough and uneven, exhibiting typical spinodal wrinkle morphology in Fig. 3b. As the PEO content is increased to 20 wt%, Fig. 3c shows clearly separated island-like domains, and the uneven surface is further divided into more separated regions at 30 wt% PEO content (Fig. 3d). When the PEO content is increased to between 40 and 60 wt%, PEO granular crystalline phases can be observed under the polarizing microscope as bright regions against a dark background of amorphous region with the size of the granular crystalline phase increasing with the PEO content (see Fig. 3e1, f1 and g1).

It is well known that the morphology of an immiscible polymer blend near the surface often differs from that in the bulk (Liu et al., 2005). In our PVMMA/PEO blend film samples, as a result of the rapid evaporation of acetone during the early stage of phase separation, fine crystalline granules of PEO appear on the surface while the dissolved PEO below the surface forms a less crystalline region in its blend with PVMMA. Fig. 3e2, f2 and g2 shows such typical PEO distribution across vertical sections of these film samples, where the enrichment of PEO components on the surface becomes more pronounced (brighter region) with increasing PEO content in the present PVMMA/PEO blend system.

3.2.2. Confocal laser scanning microscope observation

Polarizing light microscope method can provide certain information on the morphological and micro-structural changes in an immiscible system as shown in the previous section, but it will not be capable of distinguishing the two blend components when they are partially miscible in an amorphous region. On the other hand, confocal laser scanning microscope (CLSM) provides a unique tool that can directly reveal phase separation by mapping the spatial intensity and area of photoluminescence in a given film sample. From the photomicrographs of Fig. 4, it is seen that without any added PEO, the pure PVMMA sample exhibits uniform luminescence from the added trace of fluorescence probe, FA-PVMMA (Fig. 4a). However, in the blend samples, a visible separation is observed between the luminescent region which represents the PVMMA phase containing FA labeled PVMMA, and the darker region which represents the PEO phase. Such phase separation is seen to become more pronounced as the PEO content increases. At low PEO contents of 10% and 20% (Fig. 4b and c), randomly divided PEO

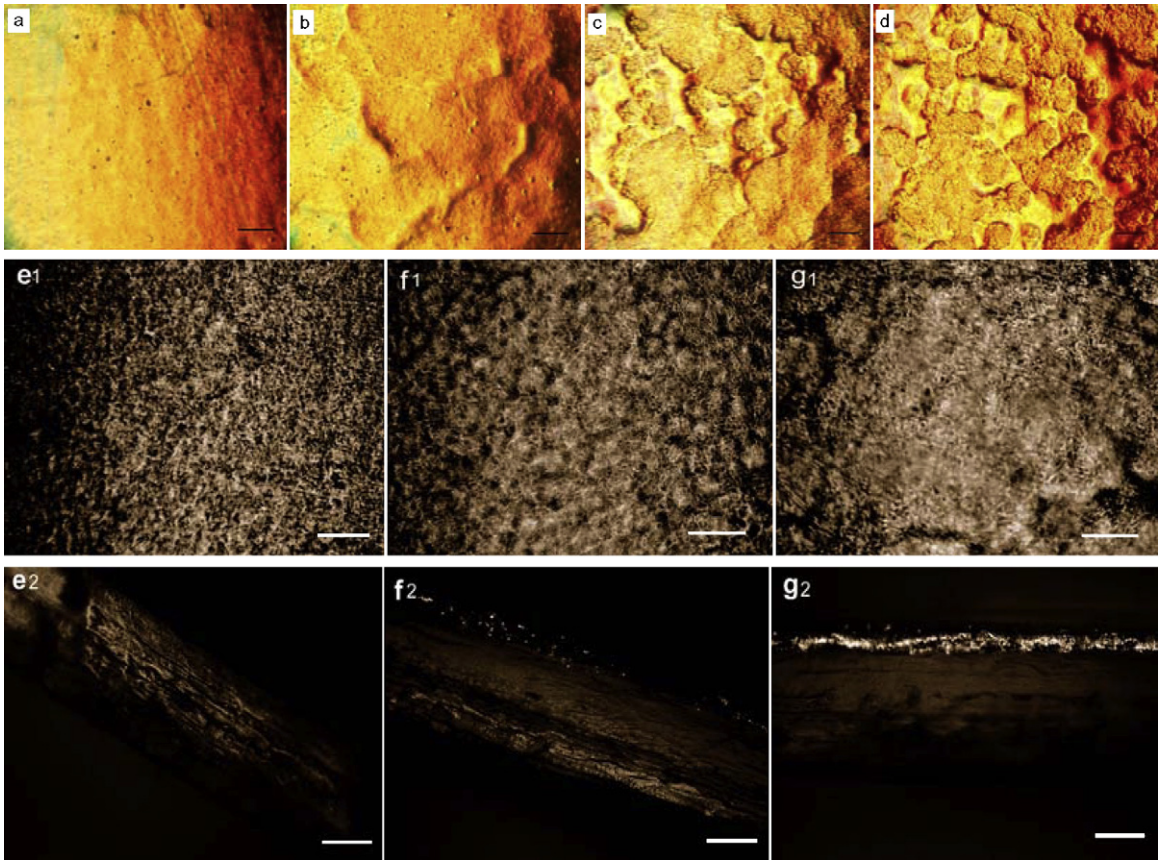

Fig. 3. Photomicrographs of PVMMA/PEO composite films with different PEO contents as seen through a polarizing interference microscope in uniform red-orange color differential field: (a) 0%; (b) 10%; (c) 20%; and (d) 30% of PEO. The surface and cross-section morphology of 40% PEO (e1, e2); 50% PEO f1, f2), and 60% PEO (g1, g2) were observed under polarizing field. Scale bar: 100 μm, 10× objective.

phases appear to be distributed within the PVMMA-rich phase; when the PEO content exceeds 30% (Fig. 4d–f), the PEO phases appear to evolve into particulate-like regions which then form aggregates and eventually become dominant phases at the highest PEO content of 60% (Fig. 4g).

Based on the microscopy results discussed above, it is clear that the present PVMMA/PEO composite system exhibits a heterogeneous structure. This is not surprising given the inherent hydrophobic nature of PVMMA and the hydrophilic properties of PEO.

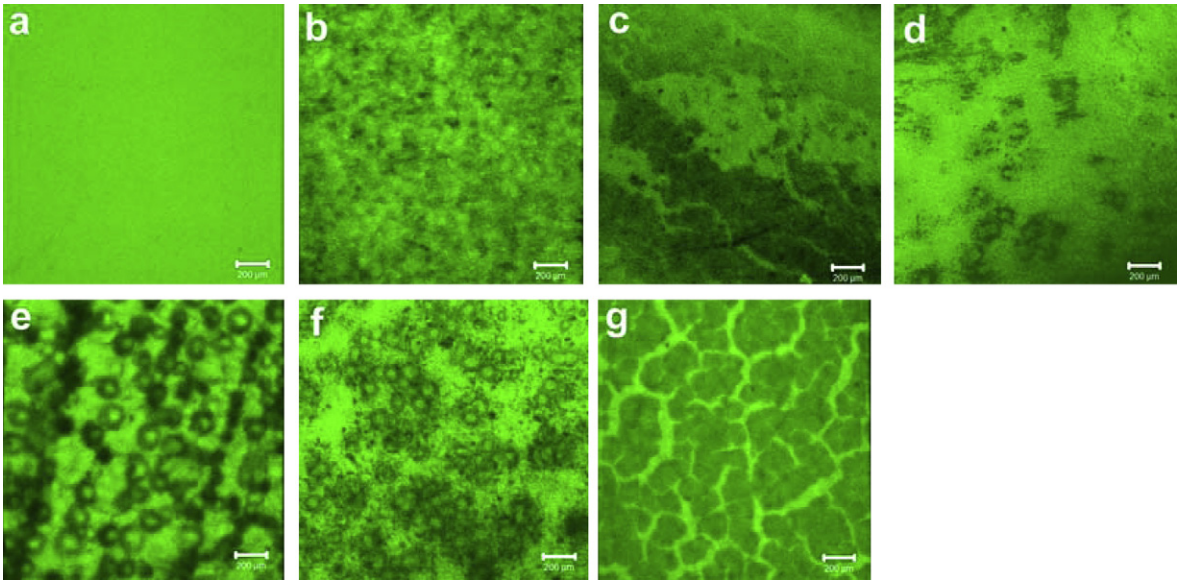

Fig. 4. Photomicrographs of PVMMA/PEO composite films with different PEO contents as seen through a Confocal Laser Scanning Microscope (ZEISS LSM 510): (a) 0%; (b) 10%; (c) 20%; (d) 30%; (e) 40%; (f) 50%; and (g) 60% of PEO. Excitation wavelength: 488 nm, scale bar: 200 μm, 10× objective.

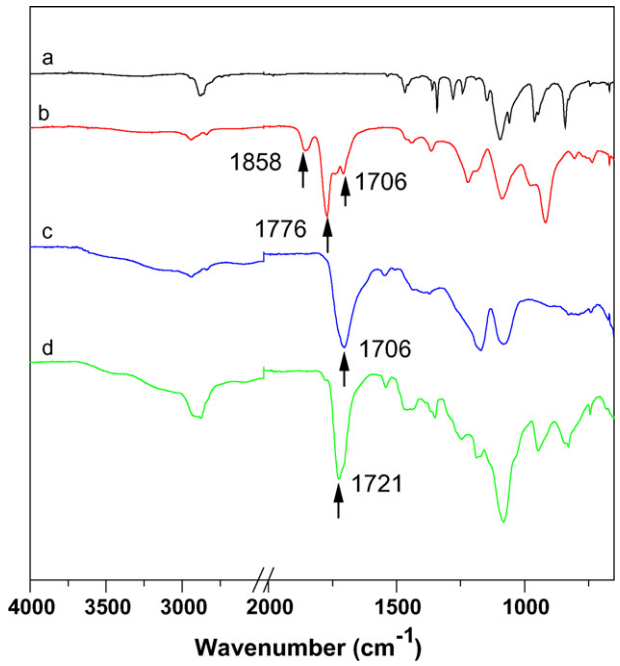

Fig. 5. The FTIR spectra of (a) pure PEO film; (b) pure PVMMA film before hydrolysis; (c) PVMMA film after hydrolysis; and (d) PVMMA/PEO composite film after hydrolysis.

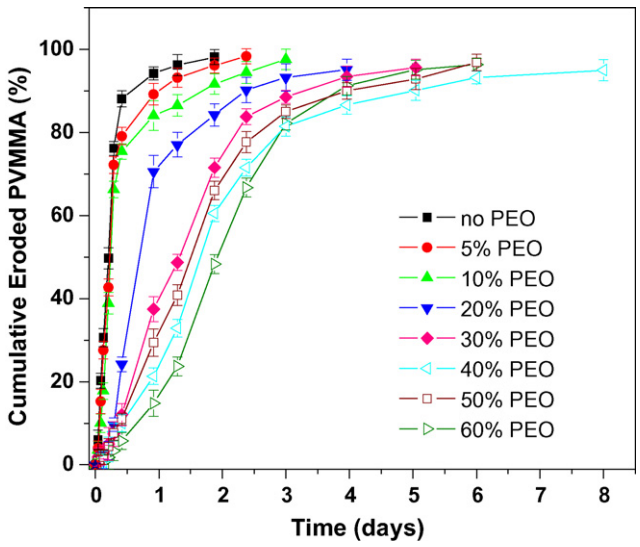

Fig. 6. *In vitro* PVMMA erosion behavior from PVMMA/PEO composite disks in 0.1 M phosphate buffer saline (pH 8.0) at 37 ± 0.5 °C: effect of PEO content; each point represents the average of two measurements with error bars denoting the range of data.

3.3. Erosion and drug release properties

The unique feature of the present system is that it is based on the *in situ* formation of interpolymer complexes in binary blends of PVMMA and PEO through hydrolytically activated molecular association in an aqueous environment of use. Unlike the conventional method of forming interpolymer complexes directly in solution, the present blend system is formed without first converting the anhydrides into free acids. Therefore the present blend system does not contain any interpolymer complexes initially. In an aqueous environment of use, the PVMMA component of the blend undergoes hydrolysis converting the anhydride groups to free carboxylic acids which in turn form *in situ* intermolecular complexes with the PEO component in the blend. Such hydrolytically activated molecular association retains the hydrophobic nature of the non-hydrolyzed PVMMA during water ingress such that hydrogen-bonded complexes form initially in the surface region of the blend as a result of hydrolytic activation triggered by the penetrating water during drug release. This molecular association process will be complete once the entire PVMMA bulk phase has been hydrolyzed by the penetrating aqueous medium. Further hydration of such intermolecular complexes would result in the eventual polymer erosion and exhaustion of drug release.

3.3.1. Characterization of hydrogen-bonding formation during the erosion of PVMMA/PEO blend

As is well known, hydrogen bonding between poly(carboxylic acid) and PEO results in the formation of interpolymer complexes (Jiang et al., 1999; Lutkenhaus et al., 2005). In our case, such hydrogen bonding only occurs once the PVMMA component in the PVMMA/PEO blend is hydrolyzed during the polymer erosion and drug release process, in which the hydrolyzed PVMMA serves as the proton-donating component, and PEO as the proton-accepting component. Such macromolecular interactions in the present PVMMA/PEO blend system have been characterized by FTIR and the resulting comparative FTIR spectra are shown in Fig. 5. Prior to hydrolysis, the characteristic anhydride doublet of PVMMA can be seen at 1776 and 1858 cm^{-1} and a trace carboxyl is evident by the presence of stretching band of acid dimmer carbonyl at 1706 cm^{-1}, which is likely coming from some limited hydrolysis in the starting material (Fig. 5b). Once the PVMMA component is fully hydrolyzed, the anhydride characteristic doublet disappears completely accompanied by a significant growth of the acid carbonyl stretching band at 1706 cm^{-1} (Fig. 5c). Here, an upward shift in the carbonyl stretching band from 1706 to 1721 cm^{-1} is evident in hydrolyzed PVMMA/PEO composite film (Fig. 5d). This reflects the formation of stronger intermolecular hydrogen bonding interactions between the acid O–H groups of hydrolyzed PVMMA and the ether oxygen groups of PEO thus liberating "free" C=O groups from the self-associated carboxylic acid groups in the fully hydrolyzed PVMMA. Similar upward shifts in carbonyl stretching band as a result of competing intermolecular hydrogen bonding have been reported in other miscible polymer blends (Lee et al., 1988; Xu and Lee, 1993). It is believed that such intermolecular hydrogen bonding developed during the *in situ* hydrolysis of the PVMMA component plays an important role in extending the erosion and drug release duration of the present PVMMA/PEO blend system.

3.3.2. Polymer erosion and drug release behavior

The erosion and drug release characteristics of the present PVMMA/PEO blend system were investigated using metronidazole, an anti-infective agent widely used in treating periodontal diseases, as a model drug. It has been shown previously that PVMMA and its partial ester derivatives typically undergo surface erosion giving rise to a near zero-order release of entrapped drug where the polymer erosion and drug release rates can be affected by the pH of the release medium (Heller and Trescony, 1979). In this case, the erosion rates of such carboxylic acid polymers will increase dramatically under basic pH conditions resulting in rapid drug release (Woodruff et al., 1972). For example, in periodontal applications, an elevated pH of the GCF at the inflamed disease site can lead to a faster polymer erosion and drug release than that observed in healthy animal models (Gates et al., 1994; Bickel et al., 1985). Therefore, as a more rigorous test, a pH 8.0 buffer was employed in the present study as the drug release medium. As shown in Fig. 6, the erosion of pure PVMMA in pH 8.0 buffer is quite rapid with the process completed within 1 day, whereas a pronounced retardation in polymer erosion up to 8 days can be achieved with increasing

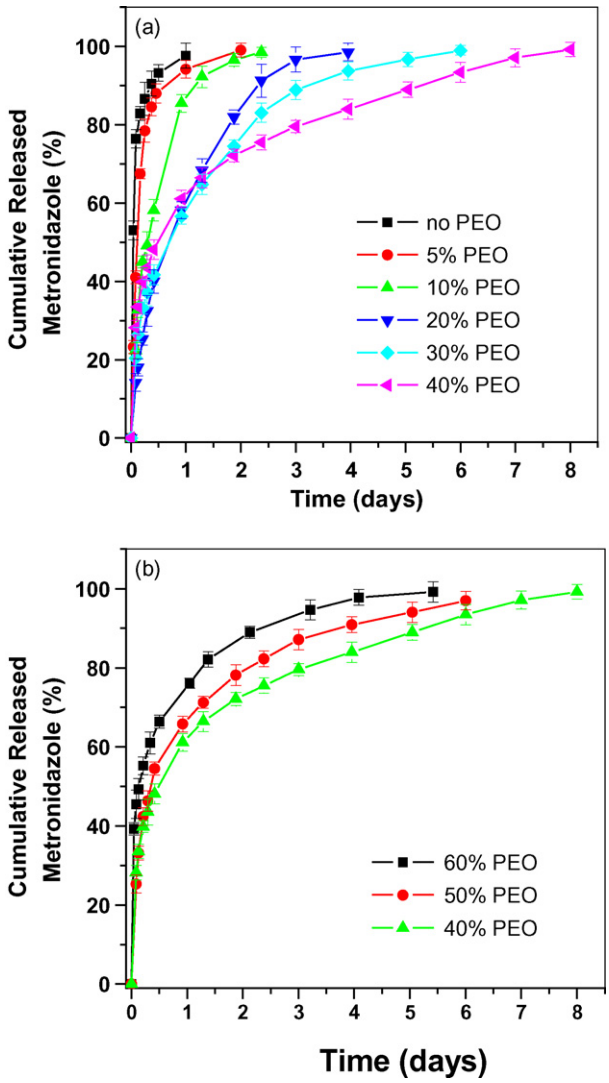

Fig. 7. *In vitro* release of metronidazole from PVMMA/PEO composite disks with PEO content of (a) 0–40% and (b) 40–60% in 0.1 M phosphate buffer saline (pH 8.0) at 37 ± 0.5 °C. Each point represents the average of two measurements with error bars denoting the range of data.

PEO content in the PVMMA/PEO blend. Similar trend is reflected in the corresponding metronidazole release profiles as shown in Fig. 7, where the metronidazole release from pure PVMMA is also completed well within 1 day and a pronounced retardation in metronidazole release is also associated with increasing PEO content. For example, a release duration of 2, 3, 4 or 6 days has been generated, respectively, with 5%, 10%, 20% or 30% PEO in the blend with an optimum release duration of 8 days achieved at 40% PEO (Fig. 7a). Upon further increase of the PEO content exceeding 40%, the corresponding metronidazole release duration actually decreases with increasing PEO content (Fig. 7b). This is most likely due to enhanced phase separation at higher concentrations of PEO in the blend which results in increasing contributions from diffusion through the more hydrophilic PEO region.

Schematic illustrations of the PVMMA hydrolysis and interpolymer complex formation between hydrolyzed PVMMA and PEO are presented in Figs. 8 and 9. During the early stage when the blend of PVMMA/PEO is in contact with an aqueous environment, the surface anhydride groups will be first hydrolyzed to free carboxylic acids. Subsequent formation of strong intermolecular hydrogen bonding between these pendent carboxylic acids and the ether oxygen groups of the PEO component results in the formation of

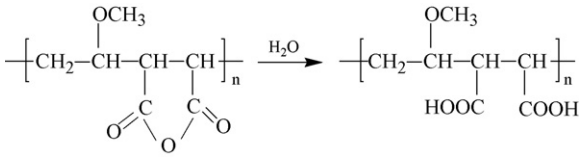

Fig. 8. Schematic illustration of the hydrolysis of the anhydride group in PVMMA.

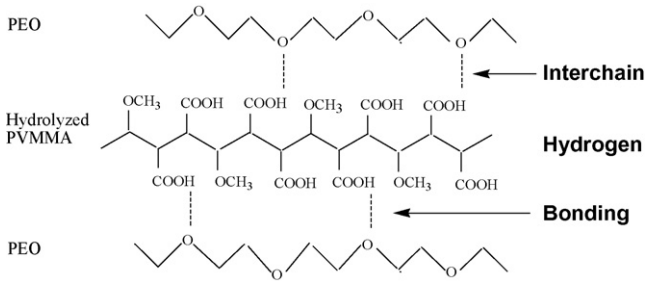

Fig. 9. Interchain hydrogen bonding between the carboxyl group of hydrolyzed PVMMA and the ether oxygen on PEO backbone.

an interpolymer complex layer which retards water penetration and drug release as well as the further ionization of these free carboxylic acid groups. The cooperativeness of such interactions between the hydrolyzed PVMMA and the PEO components further provides a stable ladder-like network structure in these interpolymer complexes. With the simultaneous formation of a large number of intermolecular hydrogen bonds between two polymers, the strength of such interactions can become very significant especially with high MW polymers as in the present case (Khutoryanskiy, 2007). Such long range attractive interactions will facilitate the formation of a condensed structure which serves as a barrier to retard water ingress and drug diffusion. This prevents immediate dissociation of the polymer complexes and thereby prolongs the resulting polymer erosion and drug release duration. Overall, the release kinetics of metronidazole from the present PVMMA/PEO blend system appears to be controlled by a combination of diffusion and erosion processes. The hydrolytically activated *in situ* polymer association behavior is believed to be the key factor in prolonging the duration of polymer erosion and drug release. With an increase in PEO content, the interpolymer interactions become stronger resulting in more extended polymer erosion and more pronounced sustained drug release behavior. This effect reaches a maximum extent at 40 wt% PEO in the blend system. On the other hand, as revealed in Figs. 3 and 4, the extent of phase separation increases with the addition of PEO. When the PEO content exceeds 40 wt%, larger aggregates of PEO components can form hydrophilic channels upon exposure to an aqueous medium, resulting in a correspondingly faster release of metronidazole from the PEO-rich region.

4. Conclusions

We have shown that the novel mechanism of hydrolytically activated *in situ* formation of interpolymer complexes in binary blends of high MW poly(vinyl methyl ether-co-maleic anhydride) (PVMMA) and poly(ethylene oxide) (PEO) can effectively extend the duration of polymer erosion and drug release to that suitable for applications in sustained local drug delivery. The formation of strong hydrogen-bonded complexes with a condensed structure at the blend surface during the *in situ* hydrolysis of the hydrophobic PVMMA component of the blend further retards the progression of polymer erosion and drug release. Although, the duration of such extended polymer erosion and drug release may be affected

to some extent by the MW of the blend components, the underlying mechanism describe here should remain the same. Based on the physicochemical data obtained here, there exists an optimum PEO content (40%) in the PVMMA/PEO blend for maximizing the sustained drug release duration. Beyond which, excessive phase separation in the PVMMA/PEO blend actually results in faster rate and shorter duration of drug release. Since the pH 8.0 buffer release medium employed in this study provides a more challenging dissolution condition for polycarboxylic acid based erodible polymers as compared with the normal dissolution medium at a neutral pH, the polymer erosion and drug release data presented here for the PVMMA/PEO blend system should provide a realistic, if not underestimated, measure of its utility. This new bioerodible system is therefore potentially useful for providing sustained drug delivery to various local diseased sites.

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