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Tunable drug release profiles from salicylate-based poly(anhydride-ester) matrices using small molecule admixtures

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Abstract

Poly(anhydride-esters) with salicylic acid, a nonsteroidal anti-inflammatory drug, chemically incorporated into the polymer backbone provide high inherent drug loading. These poly(anhydride-esters) hydrolytically degrade to release salicylic acid over extended time periods (>30 days); however, an initial lag period of no salicylic acid release is observed. This lag period could be unfavorable in applications where immediate salicylic acid release is desired.

Poly(anhydride-esters) with short (2 days) and long (11 days) lag periods were admixed with various small molecules as a means to shorten or eliminate the lag period. Salicylic acid, larger salicylic acid prodrugs, and 1:1 combinations of the two were physically admixed, each at 1%, 5%, and 10% (w/w). All admixtures resulted in immediate salicylic acid release and a decrease in glass transition temperatures compared to polymer alone. By varying the amounts of salicylic acid and salicylic acid prodrugs incorporated into the polymer matrix, immediate and constant salicylic acid release profiles over varied time periods were achieved.

Keywords

Biodegradable; polymer; salicylic acid; salicylic acid prodrugs; drug delivery; sustained release; poly(anhydride-ester); timed release

Introduction

Salicylic acid (SA), the major metabolite of aspirin, has been used for centuries for its analgesic, anti-inflammatory, and antipyretic effects.¹ Recently, SA has been found to be beneficial for many other applications such as wound healing, diabetes, arthritis, and cancer treatment.^{2–6} The best results are obtained when SA is maintained at therapeutic levels at the desired area for as long as it is needed.⁷ Oral delivery of SA is systemic and potentially causes gastrointestinal problems, while not maintaining steady SA concentrations at the desired location.⁸ Localized delivery from polymers can help overcome undesired side effects and allow for higher localized SA levels than systemic delivery.^{9,10}

Previous attempts to control localized SA release have been through the physical mixture of SA into a biodegradable polymer matrix.^{11–15} This type of drug incorporation, however, generally results in a burst of SA,^{11–14} where large amounts of drug are released before the rate stabilizes.¹⁶ Burst profiles of drugs tend to be unpredictable¹⁶ and can lead to toxic

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concentrations of SA. Additionally, the maximum amount of drug loading is limited before it begins affecting the mechanical and degradation properties of the device.¹¹

Many drug-eluting polymer matrices exhibit a burst release without sustaining the drug concentration for the duration of complete polymer degradation.^{11–14} Wang et al. have demonstrated sustained release with minimal control over the degradation profile by altering polymer composition. Although the authors were able to obtain zero-order release, the amount of SA required to achieve this (40% in poly(lactide-*co*-glycolide) (PLGA)) significantly increased polymer degradation rates.¹⁵

To better control SA concentrations, salicylate-based poly(anhydride-esters) (SA-PAEs) were developed, in which SA is chemically incorporated into the polymer backbone via a biocompatible linker molecule. These polymers have been studied both *in vitro*^{17,18} and *in vivo*^{19,20} and have been found to be biocompatible and result in localized reduction of inflammation²¹ as they hydrolytically degrade to exhibit near zero-order SA release after an initial lag period, where minimal-to-no drug is measured. SA-PAEs are designed to fully degrade over a matter of days to many months.^{22,23} The chemical incorporation of SA enables inherent drug loading capacities up to 85% (w/w), with the ability to physically admix additional drug to obtain even higher loading.²⁴

The length of the lag period and the subsequent release rate is a direct function of the linker structure as shown for various polyanhydrides.^{23,25,26} The linkers herein were chosen based upon their chemical structures including linear (**1**) and branched (**2**) aliphatic linkers (Figure 1). Polymers with linear aliphatic linkers release SA at a faster rate with a shorter lag period than those comprising branched aliphatic linkers.²³

While the SA-PAE release rate can be easily changed for different applications via the linker molecule, the lag period is an important consideration. A lag period may be beneficial for applications, such as bone regeneration, where an initial inflammatory response is desired and localized, reduced inflammation is beneficial at a later time point.^{27,28} On the other hand, a lag period could be a disadvantage if SA was desired immediately following implantation, as for instances where inflammation is already present (e.g. arthritis and diabetes).

One method used to adjust the length of a lag period is admixing small molecules into the polymer matrix to act as channeling agents.²⁹ As these channeling agents are solubilized, pores are created in the disc surface, increasing water penetration and subsequent polymer degradation.³⁰ This effect has been observed using salt leaching techniques,³¹ as well as admixing molecules such as drugs^{15,32} or inert polymer precursors into the polymer matrix.^{33,34} For example, PLGA monomers (10% w/w) acting as channeling agents in drug-loaded PLGA discs resulted in the absence of a lag period in drug release.³⁴

To overcome the lag period exhibited by SA-PAEs, free SA and degradable polymer precursors, hereafter referred to as diacids (Figure 1), were physically admixed with SA-PAEs at different ratios and weight percentages, as described in Table 1. Two SA-PAEs were chosen, polymer **1** (comprised of a linear, aliphatic adipic linker) exhibiting a shorter lag period (approximately 2 days) and polymer **2** (comprised of a branched, aliphatic diethylmalonic linker) exhibiting a longer lag period (approximately 11 days). Polymers with admixed drug were compressed into discs, and drug release was monitored *in vitro* for 30 days. The admixture effects on drug release and thermal properties of the polymer matrices were determined.

Materials and methods

Materials

Acetic anhydride was purchased from Fisher (Fair Lawn, NJ). All other chemicals and reagents were purchased from Sigma-Aldrich (Milwaukee, WI) and used as received.

Polymer synthesis and characterization

SA-PAEs were synthesized according to previously described methods.^{23,35,36} In short, SA (2 equivalents (eqs)) were dissolved in tetrahydrofuran (THF) and pyridine (4 eqs). The acyl chloride (adipoyl chloride (**1**) or diethylmalonyl chloride (**2**), 1 eq) was dissolved in THF and added drop-wise forming a white suspension. The reaction mixture was stirred overnight, quenched over water, and acidified to pH 2 using concentrated hydrochloric acid. The formed precipitate was filtered, washed with water (3×250 mL), and dried *in vacuo* to yield diacid. The diacid was activated in an excess of acetic anhydride at room temperature, concentrated, and polymerized via melt-condensation polymerization at 180°C for 6 h at 160 r/min *in vacuo* to yield a tan powder. Polymer **1** had a weight average molecular weight (M_W) of 18,500 Da, a polydispersity index (PDI) of 1.3, and a glass transition temperature (T_g) of 42°C. Polymer **2** had a M_W of 15,600 Da, PDI of 1.7, and T_g of 88°C. Further chemical characterization of these polymers is discussed by Prudencio et al.²³

Disc preparation

SA, diacid **1**, and SA:diacid **1** (1:1 by weight) mixtures were separately mixed with polymer **1** at 1%, 5%, and 10% (w/w) (Table 1) and ground with mortar and pestle to achieve a homogenous mixture. SA, diacid **2**, and SA:diacid **2** (1:1 by weight) mixtures were also separately mixed with polymer **2** at 1%, 5%, and 10% (w/w) (Table 1) and ground with mortar and pestle to achieve a homogenous mixture. Polymer discs were prepared by pressing ground polymer mixtures (160 ± 5 mg) into 13 mm diameter $\times$ 1 ± 0.5 -mm-thick discs in an infrared pellet die (International Crystal Laboratories, Garfield, NJ) with a bench-top hydraulic press (Carver, Inc. Model M; Wabash, IN) at 10,000 lbf/in² for 5 min at room temperature. Polymer **1** and polymer **2** discs without admixtures were prepared as controls. All samples were prepared in triplicate to give a total of 30 discs for polymer **1** and 30 discs for polymer **2**.

Hydrolytic degradation

Each disc was placed in 20 mL Wheaton glass scintillation vials containing 10 mL of 0.1 M phosphate-buffered saline (PBS) at pH 7.4. Samples were incubated at 37°C with agitation at 60 r/min in a controlled environment incubator shaker (Excelsa E25; New Brunswick Scientific Co., Edison, NJ). All media were collected and replaced with fresh PBS (10 mL) at predesignated time points for 30 days. Spent media were analyzed by ultraviolet (UV) spectrophotometry using a Perkin Elmer Lambda XLS spectrophotometer (Perkin Elmer, Waltham, MA) to specifically monitor SA release. Measurements were obtained at $\lambda = 303$ nm, the maximum absorbance of SA that did not overlap with other polymer degradation products. Data were calculated against a calibration curve of absorbance values from standard solutions of known SA concentrations in PBS. All pH measurements were performed using an Accumet[®] AR15 pH meter (Fisher Scientific, Fair Lawn, NJ).

Influence of admixtures on glass transition temperature

Differential scanning calorimetry (DSC, TA Instruments Thermal Advantage Q200; New Castle, DE) was performed on all samples prior to degradation to monitor the T_g of all polymer systems as deformation after implantation may affect drug release *in vivo* due to the changes in surface area for these surface eroding polymers. Samples (3–8 mg) were

analyzed by heating under nitrogen gas. Data were collected at heating and cooling rates of 10°C/min from 221210°C to 200°C with a two-cycle minimum. TA Instruments Universal Analysis 2000 software, version 4.5A was used to analyze the data.

Results and discussion

Free SA and diacids were physically admixed into SA-PAE matrices with short and long lag periods to combine the immediate drug release commonly observed in physical mixtures¹⁶ with the zero-order characteristics of SA-PAEs. Addition of these molecules at all weight percentages increased SA release during the typical lag period of polymer alone while having little effect on the release rate at later times. The amount of SA released was dependent upon both the type of molecules admixed and the weight percentage within the matrix (Table 2).

In vitro SA release

In vitro drug release was measured by quantifying the SA concentrations in PBS over 30 days using UV spectrophotometry. The inflection points in the profiles for polymers **1** and **2** were used to define the lag periods and subsequent period of zero-order drug release. A short lag period of 2 days was observed for polymer **1** alone (Figure 2(a)) while polymer **2** alone (Figure 2(b)) displayed a longer lag period of 11 days. The pH of spent media was monitored through the lag periods with the greatest pH differential observed as 0.6, which should have negligible effects on polymer degradation rates. As shown in Figure 2, the lag period for polymer alone was overcome for both systems by all admixtures within the first 24 h where SA samples exhibited the highest SA concentration for their respective weight percentages, followed by the 1:1 mixture, and then diacid.

As expected, larger weight percentages of the SA-based additives resulted in higher SA concentrations over the initial time period. However, differences in weight percentage on early release were dependent on the admixed molecules. For polymer **1**, the incorporation of SA and 1:1 SA:diacid resulted in distinct differences in SA concentration as a function of weight percentage (Figure 3(a) and (b)), whereas the differences for the diacid incorporation were not as distinct (Figure 3(c)). After early stage release, all samples maintained near zero-order profiles of SA release (Figure 3(d)), with a post-lag period average of $2.06\% \pm 0.38\%$ and $2.33\% \pm 0.18\%$ released per day from polymer **1** alone and for polymer **1** admixtures, respectively.

The effect of the various small molecules on early SA release was much more defined for the polymer **2** system compared to that of the polymer **1** system. Changes in weight percentage had the greatest effect on SA-loaded samples and the least on diacid samples (Figure 4(a) to (c)) as determined by SA released during the lag period. In addition, each admixture sample exhibited distinct profiles of increased drug release. When SA was incorporated, SA release was increased for 4 days at all weight percentages, while 1:1 SA:diacid mixtures exhibited increased SA over 2 days, and the diacid samples exhibited slightly increased SA for less than a day before the rates decreased and stabilized. The differences in time frame were likely due to the additional hydrolysis steps needed to obtain SA from the diacid. After these initial periods, all admixtures maintained near zero-order profiles (Figure 4(d)), with a post-lag period average of $0.11\% \pm 0.03\%$ SA released per day from polymer **2** alone and $0.13\% \pm 0.04\%$ SA per day combined average for all polymer **2** admixtures.

All polymer **1** samples were compared to polymer **2** to ascertain admixture effects on initial SA release between the two systems. For example, on day 5, for 10% SA admixtures, polymers **1** and **2** had each released 13.71% and 14.69%, respectively, of SA (Figures 3(a)

and 4(a)). As SA weight percentage values decreased, a greater difference in amount of drug release was observed (10% SA < 5% < 1%). This was likely due to the hydrophobicity differences between the polymers (polymers **1** and **2** contact angle of 77° and 93°, respectively).²³ The diacid 10% admixture at day 5 was 7.81% and 0.65% SA release for polymers **1** and **2**, respectively. The difference in hydrophobicity of the diacids was likely the cause of these trends; diacid **2** comprised of the branched aliphatic linker and thus is more hydrophobic than the linear aliphatic linker in diacid **1**. The 1:1 10% admixture on day 5 for polymers **1** and **2** resulted in 10.86% and 7.90% of SA, respectively, showing an average of the other admixture types. Any admixture containing diacid exhibited significant differences at the same weight percentage between the polymer systems.

It is important to note that the samples in this study were compression-molded into discs. If these systems were formulated into fibers or microspheres, for example, the release profiles would likely differ as the geometry affects the erosion characteristics of the polyanhydride matrix.^{37,38} *In vivo* results may also differ as the degradation media do not contain enzymes or other proteins.

Admixture effect on glass transition temperature

The incorporation of small molecules into a polymer matrix often alters the thermal properties.³⁹ DSC measurements indicate a T_g of 42°C and 88°C for polymers **1** and **2**, respectively. A characteristic lowering of the polymers' T_g was noted as the weight percentage of the additive increased (Figure 5). This observation is consistent with previously reported results on diffusion-controlled drug release from polymers, where the admixed small molecules act as plasticizers.³⁹ This aspect constrains the maximum weight percent for some SA-PAEs as the device may not retain its shape *in vivo* if the T_g of a polymeric device is near or below physiological temperature (37°C). Deformation after implantation could alter the surface area, resulting in unpredictable drug release since these PAEs are primarily surface eroding.⁴⁰

Conclusion

As an anti-inflammatory drug, SA can be useful for the treatment of a wide range of diseases. Furthermore, localized, sustained release of SA can both minimize side effects and improve patient compliance. To develop a polymeric device that would ensure the desired amount of SA is being released at any given time, SA and diacids were used as channeling agents to alter the polymer release profiles and overcome the lag period. The duration as well as the amount of SA at early and late time points was easily controlled by adjusting multiple factors: polymer composition via the linker molecule, weight ratio of admixed molecules, and ratios of those molecules. With this ability to fine-tune the amount of SA present at various times over sustained periods, devices can be prepared that fit the specific needs of many different applications.

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Figure 1. Hydrolytic degradation scheme of polymers with adipic (**1**) and diethylmalonic (**2**) linkers that release SA and corresponding carboxylic acid.

Figure 2.

SA release profiles during the typical lag period of (a) 0–2 days for polymer 1 alone against 1%, 5%, and 10% (w/w) admixtures and (b) 0–11 days for polymer 2 alone against 1%, 5%, and 10% (w/w) admixtures.

Figure 3.

Cumulative release profiles of polymer 1 (circles) against 1% (light gray), 5% (medium gray), and 10% (black) (w/w) admixtures of (a) SA (squares), (b) SA:diacid combination (triangles), and (c) diacid (diamonds) over 30 days. (d) A comparison of the three different admixtures at the same weight percentage (10% w/w).

Figure 4.

Cumulative release profiles of polymer 2 (circles) against 1% (light gray), 5% (medium gray), and 10% (black) (w/w) admixtures of (a) SA (squares), (b) SA:diacid combination (triangles), and (c) diacid (diamonds) over 30 days. (d) A comparison of the three different admixtures at the same weight percentage (10% w/w).

Figure 5. Glass transition temperatures measured for polymers **1** (a) and **2** (b) systems. The highest point on the y -axis corresponds with the T_g of polymer alone.

Table 1

Representation of 1%, 5%, and 10% (w/w) admixtures used for various sample disc compositions comprising polymer **1** (R = adipic linker) and polymer **2** (R = diethylmalonic linker)

Polymer Alone	SA	Corresponding Diacid	SA : Diacid (1:1)
1,5, and 10 % (w/w)	1,5, and 10 % (w/w)	1,5, and 10 % (w/w)

Table 2

Theoretical drug loading for all samples

	None	SA	Diacid			SA:diacid (1:1)		
Polymer 1								
Admixture amount (%)	—	1	5	10	1	5	10	1
Drug loading (%)	72.2	72.5	73.6	75.0	72.2	72.2	72.2	72.9
Polymer 2								
Admixture amount (%)	—	1	5	10	1	5	10	1
Drug loading (%)	72.2	72.5	73.6	75.0	72.2	72.1	71.9	72.4
								72.9
								73.5