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Controlled release from bioerodible polymers: effect of drug type and polymer composition

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Abstract

The effect of the chemical nature of the drug on matrix degradation and drug release behavior of degradable polymers was studied, using lidocaine as a model drug in base and salt forms. We show in this study that the drug in the base form has a substantial effect on the release characteristics, through an accelerating effect on matrix degradation. Study of drug release from PdlLGA shows that lidocaine salt follows a three-phase release pattern, in contrast to the biphasic release of the lidobase. However, PlLA shows a different drug release pattern, with only a single diffusion phase exhibited for both lidobase and lidosalt. We also demonstrate that the crystallinity of matrix plays an important role on drug release profiles: a crystalline matrix (PlLA IV=2.04) releases the drug at a much slower rate compared to its amorphous counterpart of similar molecular weight (PdlLA IV=2.4). The details of the study of different factors influencing the drug release may have important implications for the control of delivery of potent drugs in various therapeutic windows.

Keywords: Bioerodible polymer; Effect of drug; Lidocaine; Diffusion control; Degradation control; Biphasic and triphasic

1. Introduction

Drug delivery devices using biodegradable polymers use mostly diffusion for drug release. Drugs have been formulated in two basic designs: reservoirs and matrices [1–4]. Poly(lactide-co-glycolide) (PLGA) is among the few synthetic polymers approved for human clinical trials. For acidic drugs, one can expect faster hydrolysis of ester bonds because of acid catalysis. In contrast, conflicting results have been reported as to how the properties of the basic drugs contained in the matrix affect their own release. Drug release can be accelerated: basic drugs catalyze the matrix degradation and in the process accelerate their own rate of release due to a bulk erosion of the matrix [5], or drug release can be suppressed. Basic drugs can neutralize the polymer terminal carboxyl residues, so that the autocatalytic effect of acidic chain ends on polymer degradation is minimized, thereby resulting in

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a less-hydrated matrix and consequent diminished rate of the drug diffusion [6–9].

The effects of crystallinity [8,9] and composition [5,6,10] of the polymer on the matrix degradation and drug release pattern have also been reported. In the case of crystallinity, there are conflicting reports about its effect: some report an increase in rate [9,11,12], while others report a rate reduction [13].

In summary, the literature reflects contradictions about the effects of the chemical nature of the drug and of matrix crystallinity; in addition, comparison has not been made at comparable M_w and copolymer composition. We attempt in this study to report on some of the above aspects, and try to reconcile some of the reported contradictions.

Lidocaine (a Na^+ blocker and class IB antiarrhythmic) was selected as a model drug. Both the base and salt (lidocaine hydrochloride) forms were used to study the effect of base and salt forms on the matrix degradation as well as water absorption. In vitro studies were carried out for drug release as well as matrix degradation, using buffer of pH 7.4 as the release medium. The systems have been characterized with respect to weight loss, water uptake, morphological changes, change of average molecular weight (M_w), in order to explain the kinetics of drug release and the possible pathways of matrix degradation.

2. Materials and methods

2.1. Materials

The drugs, lidocaine ($C_{14}H_{22}N_2O$, henceforth referred to as lidobase) and lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot H_2O$, HCl; henceforth referred to as lidosalt) were purchased from Sigma-Aldrich Pte, Singapore. Polylactides and the polyglycolides were purchased from Purac Far East Pte., Singapore. Table 1 summarizes details of the polymers used in this study. Molecular weights (M_w) for all the polymers in the granule and film form were determined prior to immersion, using Size Exclusion Chromatography (SEC). The numbers following the description of copolymers represent the molar ratio of monomers. Thus, PDLLGA 53/47 is a random copolymer of 53% D- and L-lactides with 47% of glycolide. For the sake of convenience, PdlLGA 53/47 0.84, PLGA 80/20 4.8, and PdlLA 2.4 would be referred to in the manuscript here onwards, as PdlLGA, PLGA, and PdlLA, respectively.

Table 1
Details of the polymers used in this study

Polymer	Intrinsic viscosity (dl/g)[a]	Average molecular weight (M_w; kDa)[b]
PdlLGA 53/47	0.84	40
PLGA 80/20	4.8	910
PdlLA	2.4	313
PlLA	2.04	300
PlLA	4.37	810

[a] Supplier data.
[b] Determined by SEC.

2.2. Preparation of polymer films

Polymer solutions were prepared by dissolving the materials in dichloromethane at room temperature. The solution of the drug in the same solvent was added to the polymer solution and the mixture homogenized by stirring for hours under magnetic stirring. The resulting solution was subsequently sonicated for 30 min to achieve complete homogenization. The wet film was allowed to dry under ambient conditions for 24 h, following which, the drying was continued in a vacuum oven at 30 °C, for 3 weeks. Almost complete removal of solvent is achieved under these conditions (residual solvent less than 0.3% as determined by thermogravimetry). Samples of 40×25 mm dimension and thickness 25±5 μm was cut from the dry film to be subjected to in vitro degradation and subsequent characterization.

2.3. Degradation study

All films were put into glass vials (of 60-ml capacity each) and completely submerged in 50 ml of buffer solution (pH 7.4). The individual vials with the films and buffer solution, were capped and placed in an incubator, maintained at 37±0.1 °C. Films were removed at regular intervals, rinsed with distilled water to remove deposited salts from buffer, if any, on the film surface, and characterized