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Glucose-powered pulsatile release

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ABSTRACT

Pulsatile release is required for many drugs from hormones to vaccines, but automating this release typically requires elaborate pumping systems with electronic controls and transcutaneous catheters. This paper describes a materials-based approach to this functionality, using a combination of composite polymer membranes to provide discrete pulses of drug at preprogrammed intervals using only a static concentration of glucose in water. Drug is encapsulated in acid-sensitive polymer membranes. Enzymes which convert glucose to acid are immobilized in other polymer membranes, along with sacrificial acid scavengers. These membranes are stacked alternately into a polymer laminate and sealed around the bottom and edges. Glucose diffuses steadily into the top membrane and is converted to acid. This acid is consumed by the scavenger until the scavenger is exhausted, at which point it triggers the acid-sensitive drug membrane below. That membrane swells and delaminates from the stack, releasing its payload, and the process repeats, potentially with different drugs in each layer and different preprogrammed delay times between each dose. This paper provides the first experimental demonstration of such a system, characterizes its components, models the system computationally, and provides basic design rubrics for further development.

1. Introduction

Many chemicals, particularly pharmaceuticals, are best administered in discrete pulses. In some cases, this is due to chronobiological factors, where physiological response is different depending on the time of day, month, or year. For instance, timing the administration of cancer therapies to the patients' circadian rhythyms has been shown to improve outcomes (Lévi et al., 1997; Innominato et al., 2014). In other cases, the physiological response may change with duration of exposure, as demonstrated by the induction of tolerance to opiates (McKim, 2007) and nitrate (Abrams, 1988) therapies. Periodic challenges to the immune system are used both for induction of tolerance to allergens (Li et al., 2003) and for induction of sensitivity to pathogens (Centers for Disease Control and Prevention, 2009; Walters et al., 2015). For reproductive hormones, pulsatility is often a critical component of the signal (Brabant et al., 1992; Hayes and Crowley, 1998; Bhalla and Siegel, 2014), and the pulsatility of parathyroid hormones determines whether bone is remodeled or simply resorbed (Compston, 2007; Jeon et al., 2008). Where multiple chemicals are needed, their sequence of application may be critical, from angiogenesis (Richardson et al., 2001) to insect control (McCoy, 2009).

The simplest way to achieve pulsatile delivery is manual administration of individual pills or injections. Manual application is often problematic, however, for a variety of reasons ranging from simple forgetfulness to fear of needles (Hamilton, 1995; Nir et al., 2003) to limited access to healthcare providers. Automation of pulsatile delivery, on the other hand, typically requires pumps, power supplies, circuitry, central reservoirs, and chronic transcutaneous conduits.

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Materials-based approaches to pulsatile delivery have been limited largely to capsules which release at a predetermined time based on degradation or osmotic swelling of the capsule (Maroni et al., 2010; Tang et al., 2005; Thitinan and McConville, 2012). Several systems have demonstrated single delayed pulses with this approach, but none have demonstrated more than three discrete pulses from a single administration, as slight errors in timing control quickly lead to broadened, or overlapping pulses.

By linking the release of one pulse to the release of the next, this problem can be overcome as depicted in Fig. 1. Each dose of drug is embedded in a stimuli-sensitive depot membrane. These depot membranes are stacked between barrier membranes which each block the stimulant for a fixed period of time. Once a barrier membrane is exhausted, the stimulant triggers the release of drug dose from the underlying depot, then begins penetrating the next barrier. In this manner, multiple distinct pulses can be obtained from a single polymer chip. Each pulse may contain a different drug and may be separated from the previous pulse by a different, predetermined delay time. In its simplest form, soluble drug is layered between degradable polymer barriers. As each barrier erodes away, the underlying layer of drug is released and the next barrier starts to degrade (Fujioka et al., 1987; Jiang and Zhu, 2000; Jeon and Puleo, 2008; Liu et al., 2007).

Relying on polymer degradation for pulse timing is problematic, however, because it requires the polymer layer to be completely surface-eroding—*i.e.*, the polymer layer must get uniformly thinner while still completely protecting the depot until suddenly the entire layer disappears. Most degradable polymers are bulk-eroding, and doubling the delay time requires more than doubling the thickness of the barrier. Recently, this approach has been generalized using stimuli-sensitive hydrogel depots (Gandhi et al., 2015; Gandhi and Nuxoll, 2016). When exposed to acid, the hydrogel membranes swell with water, allowing the solid drug within to dissolve and release. The acid is blocked for a specific period of time by barrier membranes loaded with nanoparticulate zinc oxide, an acid scavenger. The delay time scales linearly with both the scavenger loading and the square of the barrier membrane thickness. Up to 10 discrete pulses have been demonstrated from these passive polymer chips, with no apparent limit on the maximum number of pulses (Gandhi et al., 2015).

For physiological applications, however, constant acid sources are unavailable except in the digestive tract, which has a relatively short residence time. Glucose, however, is distributed throughout the body via the bloodstream in a relatively tight, well-regulated concentration range of 70–140 mg/dL. This paper reports the creation of a polymer laminate which releases discrete pre-timed pulses of drug in response to a constant glucose source. Development and characterization of constituent materials are followed by construction and demonstration of prototype devices, then *in silico* investigation of key design parameters.

2. Materials and methods

2.1. Materials

Methyl methacrylate (MMA), 2-dimethylamino ethyl methacrylate (DMA), and divinyl benzene (DVB) were obtained from Sigma-Aldrich (Milwaukee, WI). Polymerization inhibitors in these monomers were removed by adsorption on alumina (Fisher Scientific, Pittsburgh, PA), the monomers were then refrigerated until used. 2,2′-Azobisisobutyronitrile (AIBN) powder and D-gluconic acid (51% aqueous solution) were obtained from Sigma-Aldrich (St. Louis, MO) and refrigerated until use. Zinc oxide (ZnO), citric acid, sodium hydroxide, and potassium chloride were obtained in crystalline powders from Sigma-Aldrich and used as received. Glucose oxidase (type X-S) and catalase were obtained from Sigma-Aldrich as lyophilized powders and stored at −18 °C until used. Monobasic potassium phosphate and sodium chloride were used as received from Research Products International (Mt. Prospects, IL). Poly (vinyl alcohol) (PVA, 99% hydrolyzed, MW∼133,000) was obtained from Polysciences (Warrington, PA) and used as received. Methylene blue (MB, Sigma-Aldrich) and methyl orange (MO, Alfa-Aesar, Wardhill, MA) were ground with a mortar and pestle then screened at 100 mesh before use.

2.2. Depot membranes

2.2.1. Depot membrane fabrication

Depot membranes were created by the copolymerization of methyl methacrylate (MMA) and dimethylamino ethyl methacrylate (DMA) in a 72:28 molar ratio of MMA:DMA with 0.1% w/w divinyl benzene (DVB) crosslinker. Poly(methyl methacrylate) (PMMA) is used in a wide range of commercial and industrial applications due to its excellent mechanical properties, including its glassy, hydrophobic nature, which makes it effectively impervious to water. Incorporation of an amine-containing comonomer, however, allows ionization of the polymer at low pH, making the polymer hydrophilic and prompting it to take up five times its own weight in water. Several amine comonomers have been investigated, with DMA providing the strongest swelling response to acidic (pH < 6) environments (Siegel and Firestone, 1988; Firestone and Siegel, 1991). By incorporating comonomers or cross-linking agents which can be cleaved hydrolytically or enzymatically, biodegradable pH-sensitive PMMA gels have also been produced (Halacheva et al., 2014).

Fabrication of the depot membranes adapted protocols used previously for acid-triggered BMPR systems (Gandhi et al., 2015). Poly(methyl methacrylate-co-dimethylamino ethyl methacrylate) (PMMA/DMA) membranes were synthesized by heating 6.315 mL MMA, 3.909 mL DMA, 10.5 μL DVB crosslinker, and 48.03 mg AIBN initiator to 70 °C with stirring until the solution reached a viscosity of approximately 65 cP. The solution was then chilled quickly to room temperature before adding the payload chemical to be released. This prepolymerization step reduces the effect of polymerization inhibition by payload chemicals such as methylene blue (MB) (Das and Mandal, 1982) as well as the effect of the negative volume of polymerization in a closed system. Methyl orange (MO) or MB powder were dispersed into the oligomer solution by stirring and sonication (Cole Parmer CPX750 with 3.2 mm microtip) at 300 W, 20 kHz for 1 min. The suspension was then poured between a pair of silanized glass plates with poly(tetrafluoroethylene) (PTFE) spacers to control the membrane thickness. The clamped plates were mounted vertically in a vacuum oven under nitrogen at 60 °C for 18 h, then removed. After cooling, the membranes were removed from the glass plates and stored under ambient conditions until used.

2.2.2. Depot membrane characterization

The swelling kinetics and equilibrium swelling ratio of the depot membranes were measured in sodium gluconate