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Bulk Manufacture of Complex Geometry Millirod Implants and Their Degradation and Drug Delivery Characteristics

Melissa Slagle and Iris V. Rivero
Iowa State University, Ames, IA, USA
rivero@iastate.edu, maslagle@iastate.edu

Abstract
This study evaluated the impact of manufacturing process modifications aimed at the bulk manufacture of curcumin implants for diabetic neuropathy pain relief. Poly (caprolactone) (PCL) and curcumin were blended using cryomilling as an alternative to the solvent mixing method which has higher manufacturing and time delay costs. X-ray diffraction (XRD) was used to characterize the resulting mixture to determine the efficacy of cryomilling as an option for blending curcumin and PCL powders. By adopting compression molding as a manufacturing method we were able to create implant molds featuring threaded geometry on the millirod surface. Implants were subsequently evaluated *in vitro* for 30 days. Curcumin loaded millirod implants with a complex threaded surface geometry were found to have a higher, but not significant, percent mass loss after degradation and average daily curcumin release than the cylindrical implants. It can be concluded that the utilization of cryomilling for the creation of curcumin loaded implants in bulk is an easier to manipulate and more cost effective method of combining PCL and curcumin without sacrificing implant effectiveness.

Keywords: implants, controlled drug release, surface geometry, curcumin, bulk manufacture

1 Introduction

Type 2 diabetes is the most prevalent form of diabetes in the United States affecting 9.3% of the total population (Center for Disease Control and Prevention, 2014). This form of diabetes is more commonly associated with obesity or lack of physical activity resulting in reduced insulin production and sensitivity (Rydén *et al*., 2007). In addition, type 2 diabetics may also suffer from additional painful or debilitating conditions as a result of diabetes related complications. These can include blindness, amputations, kidney problems, and neuropathy (Center for Disease Control and Prevention, 2014). Of these adverse diabetic complications, 50% of diabetics experience neuropathy in some form, which often manifests in foot and leg pain (Boulton *et al*., 2005; Dyck *et al*., 1993). A particular form of this

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condition, painful diabetic neuropathy (PDN), remains difficult to treat, as a 50% reduction in pain is considered a successful treatment (Huizinga & Peltier, 2007). Current solutions for PDN treatment include the use of cyclic antidepressants or antiepileptic drugs, both of which have negative side effects that may include dizziness, blurred vision, or weight gain (Huizinga & Peltier, 2007).

Curcumin is a natural anti-inflammatory agent found naturally occurring in the spice turmeric. Many studies have been done to evaluate the impact of curcumin on various diseases including several different types of cancer (Bansal *et al*., 2011a; Bansal *et al*., 2014), asthma (Ammar *et al*., 2011), cardiovascular disease (Bronte *et al*., 2013), and diabetes (Chuengsamarn *et al*., 2012; Maradana *et al*., 2013; Weisberg *et al*., 2008; Zhang *et al*., 2013). Despite the positive effects curcumin exerts as an anti-inflammatory agent, it has been shown that curcumin has poor bioavailability when taken orally (Prasad *et al*., 2014). One option to overcome this challenge is through encapsulation of curcumin within a polymer matrix. This type of drug delivery is most notably used for effective birth control through subcutaneous implantation that provides protection for 3 years (Stoddard *et al*., 2011). This type of solution is ideal for treatment applications that require sustained treatment over a long period of time. As PDN is a chronic disease currently without a cure, an implantable drug delivery device would provide an alternative method of pain management without jeopardizing patient quality of life.

Previous literature has developed cylindrical millirods impregnated with curcumin as a potential chemopreventive solution (Bansal *et al.*, 2011a; Bansal *el al*., 2011b; Bansal *et al*., 2011c; Gupta *et al*., 2012). Implants were manufactured using the solvent mixing method to create a curcumin polymer matrix. After removal of the solvents overnight, the molten curcumin and polymer was extruded through silastic tubing and cooled prior to removal from the tube. Based on the findings from Bansal et al. (2011c) it was confirmed that an increase in implant surface area via changes in the diameter created an increase in drug release rate of curcumin. This study also found that daily drug increases with proportional increase in drug loadings less than or equal to 10%. With that knowledge, we wanted to test the effects of a drastic change in implant geometry on the degradation and drug release rate of curcumin. However, in order to achieve this geometry an alternative method of manufacturing was needed. Through the use of a custom compression mold we developed a threaded cylindrical implant to compare against a traditional cylindrical implant. With the drastic increase in surface area it is expected that the threaded geometry implants will have an increased drug release rate. This experiment also looks to evaluate an alternative to solvent mixing of curcumin and polymers. Additionally, to minimize the effect of drug loading on daily average drug release, a drug loading percentage greater than 10% was selected. This proof of concept experiment for the threaded implant design will also be evaluated for future manufacturing scaling up of implants.

2 Materials and Methods

2.1 Materials

Poly (caprolactone) 50,000 molecular weight was purchased from (Capa 6506, Perstorp, Sweden). Phosphate-buffered saline powder (pH 7.4) and bovine calf serum (BCS) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Additional BCS was purchased from Hyclone (Logan, UT, USA). Curcumin (98% pure) was purchased from Acros Organics (Morris Plains, NJ, USA). No further analysis was done on any of the received materials.