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Extrusion printed polymer structures: A facile and versatile approach to tailored drug delivery platforms

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ABSTRACT

A novel extrusion printing system was used to create drug delivery structures wherein dexamethasone-21-phosphate disodium salt (Dex21P) was encapsulated within a biodegradable polymer (PLGA) and water soluble poly(vinyl alcohol) (PVA) configurations. The ability to control the drug release profile through the spatial distribution of drug within the printed 3-dimensional structures is demonstrated. The fabricated configurations were characterised by optical microscopy and SEM to evaluate surface morphology. The results clearly demonstrate the successful encapsulation of dexamethasone within a laminated PLGA:PVA structure. The resulting drug release profiles from the structures show a two stage release profile with distinctly different release rates and minimal initial burst release observed. Dexamethasone release was monitored over a 4-month period. This approach clearly demonstrates that the extrusion printing technique provides a facile and versatile approach to fabrication of novel drug delivery platforms.

1. Introduction

Recent advances in the field of tissue engineering include the concept of tissue or organ printing (Fedorovich et al., 2008). This novel approach involves computer-aided deposition of cells and scaffolds to create complex 3-dimensional cell-laden structures (Fedorovich et al., 2008). This allows for accurate placement of cells, a clear advantage over traditional 3D constructs, which may have a complex geometry but lack a defined cell distribution. There are several techniques in use for computer-aided cell deposition such as laminated object manufacturing (LOM) (Ang et al., 2000), three-dimensional printing (3-DP) or ink-jet printing (Chang et al., 2011; Maier et al., 2011), selective laser sintering (SLS) (Mullen et al., 2010; Wiria et al., 2010), and fused deposition modelling (FDM) (Gu and Li, 2002; Too et al., 2002). Of these, printing offers a convenient non-contact method for deposition of biologically active macromolecules onto hydrogel scaffolds, dispensing cell dispersions onto/into scaffolds, as well as creating complex spatial patterns (Xu et al., 2005).

More recently researchers (Enayati et al., 2010; Sandler et al., 2011) have turned to printing technology in the quest to develop improved drug delivery platforms. Drug delivery implants are an attractive alternative for local delivery of drug in clinical applications with significant advantages over systemic delivery providing high therapeutic efficiency and low systemic toxicity. The quest for effective drug delivery systems, wherein the release profile can be modified, is ongoing. Drug delivery via biodegradable polymers benefits from both the protection of the encapsulated drug from hazardous conditions and the controlled release of the encapsulated drug, thereby reducing the administration frequency and improving patient compliance. Controlled release delivery is available for many routes of administration and offers many advantages (e.g., nano- and micro-particles, polymer scaffolds and porous mats) over immediate release delivery. These advantages include reduced dosing frequency, better therapeutic control, fewer side effects, and, consequently, these dosage forms are well accepted by patients. Advances in polymer material science, scaffold engineering design, manufacture, and nanotechnology have led the way to the introduction of several marketed controlled release products and several more are in pre-clinical and clinical development (Mansour et al., 2010).

Biodegradable polymers have received significant attention in the past few decades especially as host materials for controlled drug delivery systems (Lao et al., 2008; Lu and Chen, 2004) and have

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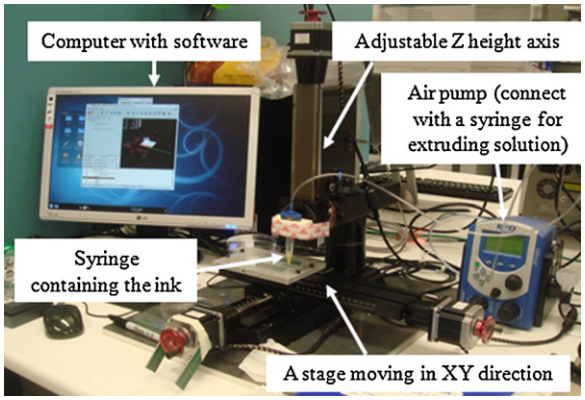

Fig. 1. The extrusion printing system (Mire et al., 2010).

been studied for use in treating disorders such as Alzheimer's (Gu et al., 2007) and Parkinson's (Kabanov and Gendelman, 2007) diseases as well as treating brain trauma (Emerich et al., 1999). These studies and others have highlighted the biocompatibility of such biodegradable polymers as poly(methylidene malonate) (Tamargo et al., 2002) and poly(ε-caprolactone) (Li et al., 2007). Among biodegradable polymers, poly(lactic-*co*-glycolic acid) (PLGA) has been widely studied (Dorta et al., 2002; Loo et al., 2004) and has been used to form solid scaffolds (Kim et al., 2010; Yoon et al., 2003), injectable implants (Choi et al., 2005; Wang et al., 2010) and encapsulated nanoparticles (Gomez-Graete et al., 2007; Liu et al., 2007), or microparticles (Galeska et al., 2005; Hickey et al., 2002; Jaraswekin et al., 2007; Zolnik and Burgess, 2008). The ability of such biodegradable polymers to be loaded with clinically relevant drugs has also been demonstrated (Manome et al., 2006). They can provide prolonged drug release (Yu et al., 2008) and the degradation products are ultimately metabolized or eliminated by the body (Jain, 2000; Vey et al., 2008). In addition PLGA has been investigated (Eroglu et al., 2001) as a suitable material to deliver the anti-inflammatory drug dexamethasone for the treatment of brain oedema. The polymer poly(vinyl alcohol) (PVA) has also been used extensively for drug deliver applications (Taepaiboon et al., 2006; Singh and Sharma, 2010).

Unfortunately one down side to polymer based drug delivery is the phenomenon of burst release encountered when the drug loaded polymer material comes in contact with fluid or tissue resulting in rapid release above therapeutic levels required. Burst release is due to a numerous factors such as the hydrophilic/hydrophobic properties of the drug and/or polymer as well as the polymer properties (e.g., molecular weight). A review by Huang and Brazel (2001) provides significant insight into the factors governing burst release. Researches have developed fabrication techniques to minimise this burst release, such as microencapsulation (Mao et al., 2008; Vey et al., 2008; Yu et al., 2008), freeze drying (Pignatello et al., 2007), wet-spinning (Liu et al., 2007), drop-casting (Rodrigues et al., 2009) and more recently printing (Boland et al., 2007; Radulescu et al., 2003; Roth et al., 2004; Rowe et al., 2002). Printing technology has been one of the more successful methods for achieving encapsulation and patterning at speed in recent years and it has attracted increasing interest as a tool for medical research (Derby, 2009). Extrusion printing is a simple and versatile approach that has been developed in our laboratories (Mire et al., 2010). The printing process fabricates structures by extruding or dispensing a liquid material onto or into a substrate with a prescribed pattern controlled via an appropriate software programme.

The drug dexamethasone (Dex) is synthetic glucocorticoid commonly used for the topical or systemic treatment of chronic inflammatory disorders, severe allergies and other diseases requiring anti-inflammatory and immunosuppressive effects (Radulescu et al., 2003). Dexamethasone 21-phosphate disodium (Dex21P) (structure I) is a salt form pro-drug which converts to dexamethasone rapidly in blood. In this study, a range of 3-dimensional (3D) biodegradable structures were fabricated from PLGA, PVA and Dex21P using the extrusion printing technique. The physical properties of these composites were evaluated and their drug delivery profiles obtained. Findings from this study are expected to contribute to the rational design of drug delivery system for providing sustained long-term drug release.

2. Methodology

2.1. Materials

The DL-lactic/glycolic copolymer (PLGA, 85:15 – inherent viscosity 0.7 dl/g) was purchased from Purac Asia Pacific, Singapore. Poly(vinyl alcohol) (PVA) with molecular weight 9000–10,000 (9k–10k: 80% hydrolyzed), 50,000–85,000 (50k–85k: 96% hydrolyzed) and 85,000–124,000 (84k–125k: 98–99% hydrolyzed) formulations were obtained from Aldrich, USA. Dexamethasone-21-phosphate disodium salt (Dex21P) was purchased from Sigma–Aldrich. Analytical grade dichloromethane (DCM) was obtained from Chem Supply Pty Ltd. Milli-Q water (18 MΩ cm^{-1}) was used in the preparation of aqueous solutions. Phosphate buffered saline solution (PBS, 10 mM, pH 7.4) was prepared from PBS tablets (Calbiochem, USA) and was used as the medium for the *in vitro* drug release study.

2.2. Extrusion printing

The extrusion printing system used in the present study was constructed in our laboratory at Intelligent Polymer Research Institute (IPRI), University of Wollongong, NSW, Australia (Mire et al., 2010). The syringe was connected to an air pressure line for dispensing the ink. The printing process fabricates structure by extruding or dispensing a liquid material onto a substrate with a prescribed pattern using an appropriate software programme. The syringe tip used in this work had an inner diameter of 100 μm. The extrusion printer set up used in this work is shown in Fig. 1.

2.3. Drug delivery scaffold design concept

Design of a controlled drug release device is an integral part of pharmaceutical research and development. In order to develop a superior platform for drug delivery systems, two types of drug encapsulation designs were attempted using extrusion printing technique. For the first technique, a solution of PVA:Dex21P was extrusion printed into square patterns on an evaporative cast PLGA film which was then rolled into a cylindrical scroll (Fig. 2). The second technique involved extrusion printing of a solution of PLGA upon which a solution of PVA:Dex21P was extrusion printed. A second layer of PLGA was printed to form a sandwich 1 layer configuration (Fig. 3). This process was repeated to form two and three layer structures. Based on the fabrication of these structures, extrusion printing technique is capable of offering new strategies for developing drug delivery device features for desired drug release profiles.

2.4. Methods

2.4.1. Preparation of PLGA drop cast film

The PLGA substrates were prepared by a simple solvent-casting technique. Briefly, PLGA solution (2%, w/v) was dissolved in DCM