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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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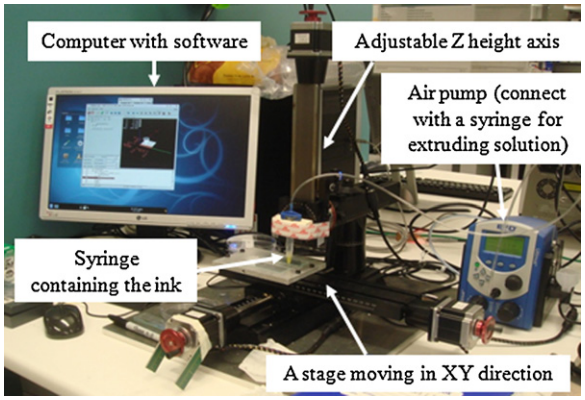

Fig. 1. The extrusion printing system (Mire et al., 2010).

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

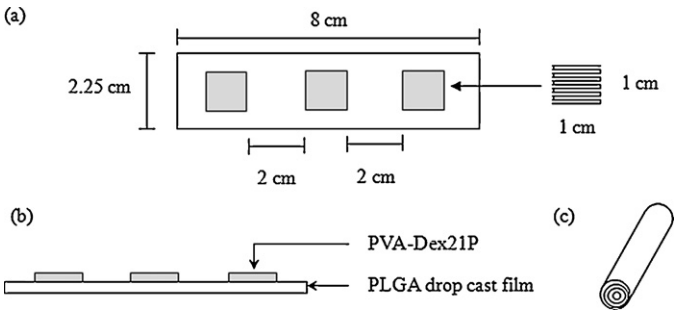

Fig. 2. Schematic representation of the printed PVA–Dex21P on the PLGA drop cast film: (a) top view, (b) side view and (c) scroll configuration.

(30 mL) and poured into a Teflon mould (10 cm × 10 cm × 0.5 cm). It was allowed to dry overnight at room temperature before being removed from the mould and cut into 3 rectangular strips (2.25 cm × 8 cm). These films were then kept in desiccators to remove any residual solvent before use. The thickness of the PLGA films was measured using a Mitoyo micrometer.

2.4.2. Preparation of ink solution

A 50 mg mL^{-1} (0.096 M) of Dex21P was prepared in Milli-Q water. A 20% (w/v) of PVA solution was dissolved in Milli-Q water and the solution stirred at 90 °C for 3 h. The printing solution was prepared by mixing PVA and Dex21P solutions at a ratio 7:3 (Dex21P concentration in the composite was 0.029 M) and then stirred at room temperature in order to produce a homogenous solution. This printing solution will hereafter be referred to as the "ink". Where the PLGA was printed the "ink" was prepared in the solvent dichloromethane (DCM). Viscosity measurements were performed using a Brookfield viscometer.

2.4.3. Design and fabrication of drug encapsulation

2.4.3.1. Structure A: drug encapsulation by rolled and sealed PLGA film. The printed pattern was designed using EMC^2 software (LinuxCNC) as simple tracks (Fig. 2a and b). The PLGA film was divided into three squares of printed area, each square was 1 cm × 1 cm and printed 2.0 cm apart with the first square 0.5 cm from the leading edge of the PLGA film.

An ink solution was prepared by mixing 20% (w/v) PVA and Dex21P solutions at a volume ratio 7:3. In this case, three different PVA molecular weights (9k–10k, 50k–85k and 85k–124k) were chosen. The PVA:Dex21P ink was extrusion printed onto drop cast PLGA film. The gas pressure used for extruding the ink solution was 0, 10 and 15 psi for PVA molecular weight 9k–10k, 50k–85k and 85k–124k, respectively.

After printing, each drug-loaded PLGA film was rolled into a scroll configuration (Fig. 2c) before sealing with a small amount of DCM placed along the leading edge and at each end to seal the structure. Drug-loaded films were then vacuum dried in a desiccator for 1 h. This pattern was designed for the purpose of encapsulating the drug into a PLGA reservoir.

2.4.3.2. Structure B: drug encapsulation by printing PLGA solution on top and bottom of printed Dex21P layer. A PVA–Dex21P printed layer sandwiched between printed PLGA layers was constructed by continuously printing PLGA layers to form a film (Fig. 3). The printed square size of PLGA film and PVA–Dex21P layer were 1.5 cm × 1.5 cm and 1.0 cm × 1.0 cm, respectively. The printed pattern and schematic representation of PVA–Dex21P sandwiched between PLGA layers are shown in Fig. 3.

The printing process fabricates structure by extruding PLGA solution onto the glass slide with a pattern controlled via the use of EMC^2 software. This printing process was repeated 5 times in order to produce a film of appropriate thickness. Following this, the PVA:Dex21P ink was extruded onto the PLGA film. The PVA:Dex21P layer was allowed to dry at room temperature for 10 min before printing another 5 layers of PLGA solution over the top. A pressure of 0.5 psi was applied to extrude the PLGA solution through the tip orifice (100 μm i.d.) to form a continuous film. This gas pressure was necessary to prevent clogging of the tip orifice due to a quickly evaporating solvent. A pressure of 3.5 psi was used to extrude the PVA:Dex21P ink through the 100 μm i.d. needle and onto the PLGA film. A pressure of 3.5 psi was chosen as this produced a discrete PVA:Dex21P line. This process forms a sandwich structure in 1 layer system as shown in Fig. 3c. This layering procedure was repeated to prepare the 2 and 3 layer structure (Fig. 3d and e). All films were then vacuum dried in desiccators for 1 hr before removing from the glass slide to form a free standing structure (Fig. 3f).

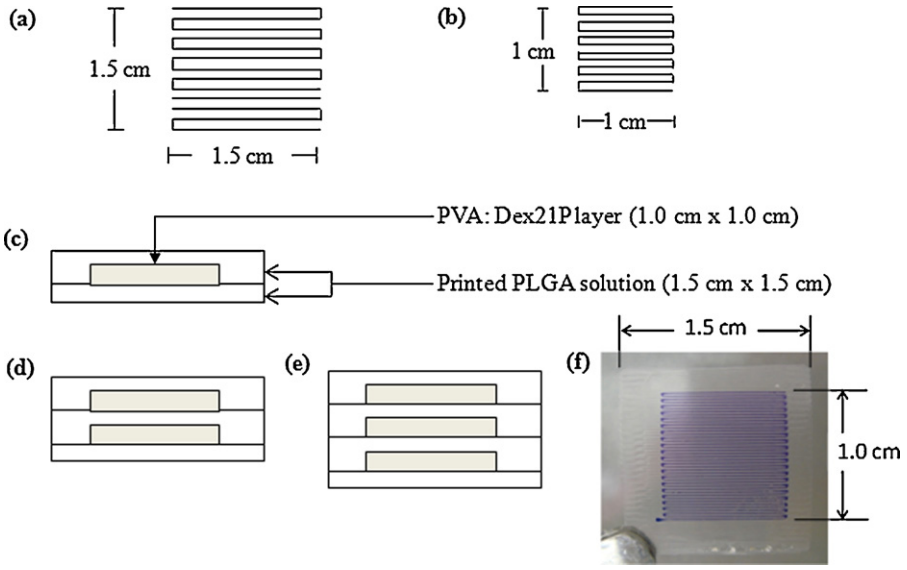

Fig. 3. The printed pattern of (a) PLGA solution and (b) PVA–Dex21P ink. The schematic representation (side view) of PVA–Dex21P sandwiched between PLGA layers (c) 1 layer system, (d) 2 layers system, and (e) 3 layers system. The digital image of a 1 layer structure (f) shows the printed PVA:Dex21P line (containing a small amount of violet dye for visualization) between PLGA layers.

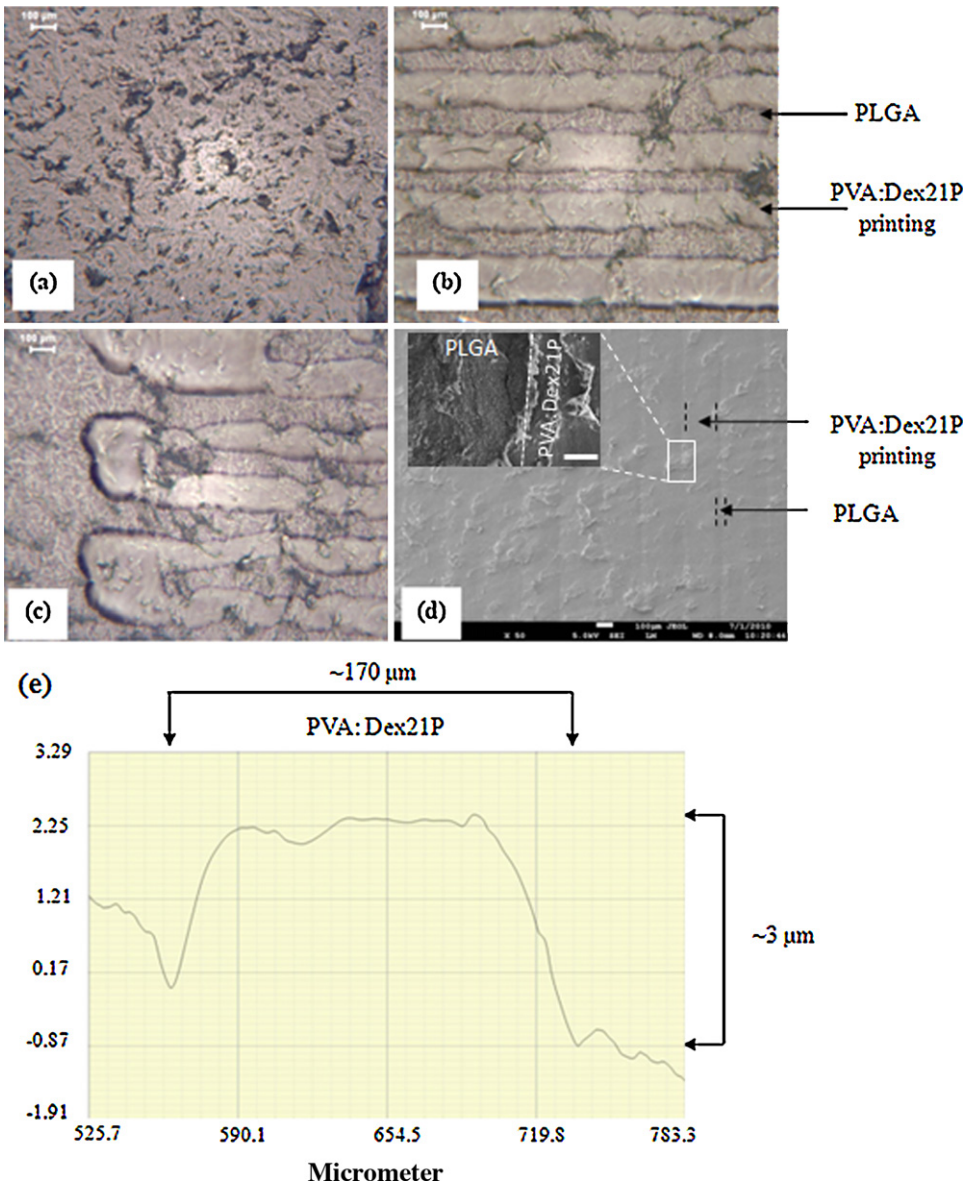

Fig. 4. Structure A: optical images of PLGA 85:15 (a) before and (b and c) after printing PVA:Dex21P onto the surface; (d) SEM image of printed PVA:Dex21P on PLGA substrate; (e) profilogram of printed line. The inset in (d) shows a SEM image of the PLGA surface exhibiting pores, scale bar is 10 µm.

2.4.4. Morphology characterisation

Morphological analysis was performed using scanning electron microscopy (SEM) (JEOL JSM7500FA, JEOL TOKYO), optical microscope (Leica DMEP). SEM samples were sputter-coated with a thin (10 nm) layer of platinum to eliminate sample charging. The thickness of the printed line was evaluated using a profilometer (Veeco Dektak 150). Cross sections were obtained by cutting the printed structures with a razor blade in order to observe the internal structure.

2.4.5. Weight measurements

Weight measurements of the printed structures A and B were performed in triplicate in PBS at 37 °C. Three separate samples from each structure was placed in PBS and weighed at selected time intervals. The weight change was calculated using Eq. (1):

$$\Delta W = \frac{W_t}{W_0} \quad (1)$$

where ΔW is the weight change, W_t is the weight at time t and W_0 is the initial weight of the sample.

2.4.6. In vitro drug release

All *in vitro* drug deliver studies were performed in a static bath with out shaking. The drug-loaded structures were placed in 1.5 mL of phosphate buffer saline (PBS) solution (10 mM, pH 7.4) in glass vials and sealed air tight to avoid evaporation and incubated at 37 °C in a water batch. At appropriate time intervals, all of the PBS solution was removed and replaced with equal volume of fresh PBS solution. The amounts of Dex21P in the PBS (released from the printed drug-loaded structures) were determined by UV–vis spectrophotometer (Shimadzu UV-1601) at 242 nm (λ_{max} of Dex21P). The release data was obtained from 3 separate printed structures to provide triplicate release profiles. UV–vis analysis of solutions of PVA and PLGA indicated there was no interference with the Dex21P 242 nm absorbance peak.

The experimental results were fitted to the following exponential Eq. (2) proposed by Ritger and Peppas (1987a):

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

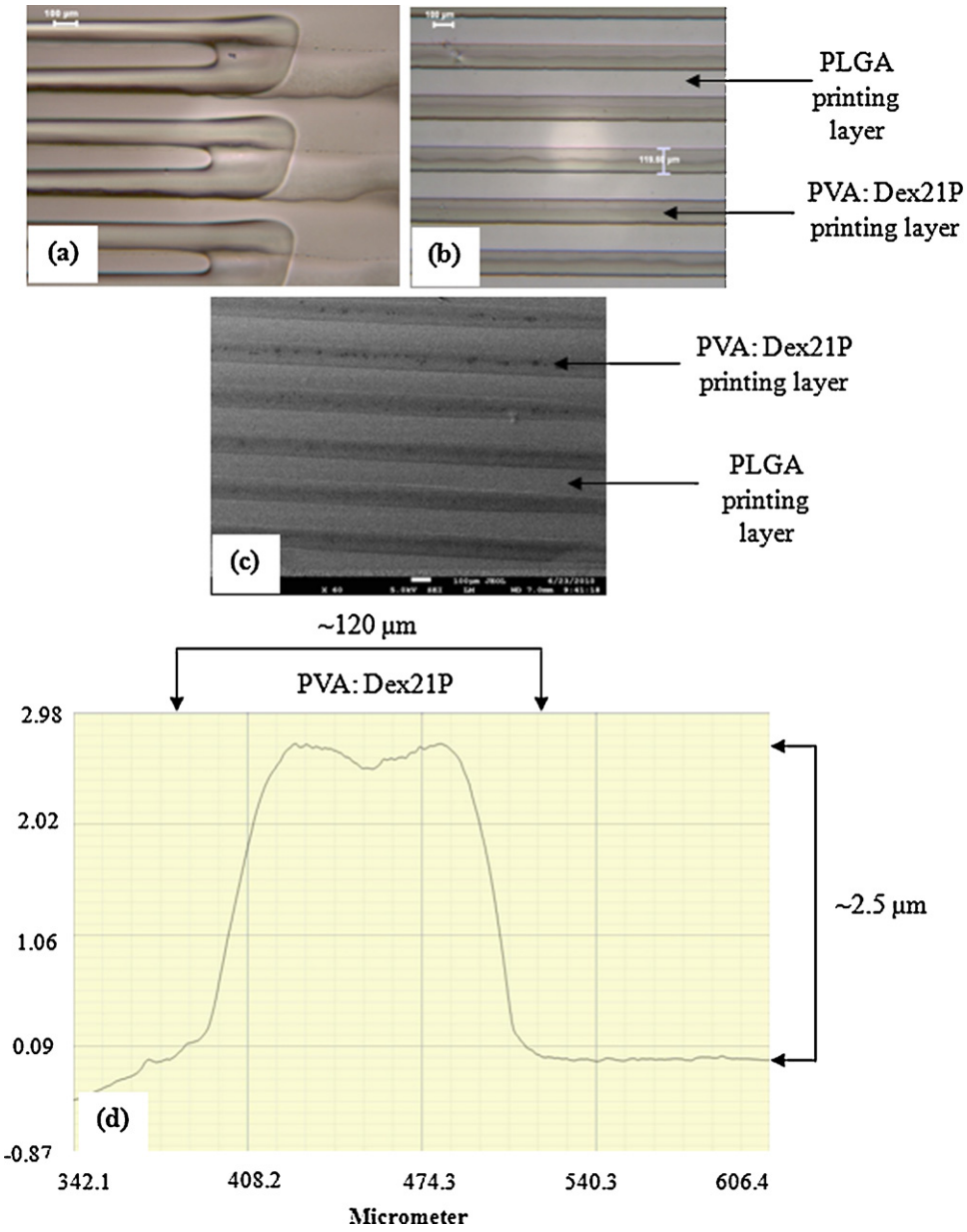

Fig. 5. Structure B: optical images of printed both of PVA:Dex21P and PLGA solution (a) at ledge end and (b) centre of printing area; (c) SEM image of printed solution in one-layer system and (d) profilogram of printed line.

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released at infinity, k is a dissolution rate constant and n is the diffusional exponent characteristic of the release mechanism. The values of n were obtained by regression analysis. In the case of drug release from a swellable structure containing hydrophilic polymers, the exponent n of Fickian diffusion is defined by $n = 0.45$, whereas anomalous (non-Fickian) transport is $0.45 < n < 0.89$ and Case-II transport is indicated by $n = 0.89$ (Ritger and Peppas, 1987b).

3. Results and discussion

To demonstrate the versatility of the approach, PVA containing the Dex21P drug was printed onto a biodegradable PLGA platform. This platform was prepared either by drop casting PLGA (structure A) or extrusion printing PLGA (structure B). The drop cast PLGA substrate had an average thickness of 70 µm. Due to the procedure used for fabrication of the PLGA platform in structure B, the film thickness of the PLGA layers could not be determined using the profilometer. However, the thicknesses of the PLGA–PVA:Dex21P composites (structure B) are presented in Table 1.

3.1. Properties of PLGA and PVA:Dex21P ink and printability

For successful extrusion printing, the viscosity of the ink formulation is critically important. The viscosity of PVA solutions, of varying molecular weight, containing 30% (w/w) Dex21P was determined (Table 2). All fall within the range suitable for extrusion printing and also these PVA solutions (containing 50 mg mL^{-1}

Table 1
Thickness of printed structure determined from profilometry data.

Printed film	Thickness (µm)
One-layer system	50
Two-layer system	65
Three-layer system	80

Table 2
Properties of the ink solution. Viscosities were measured using a Brookfield viscometer at room temperature. The gas pressure is the pressure required to successfully extrude the solution from the printer tip.

PVA:Dex21P solution (three different PVA molecules weights)	Viscosities (cP)	Gas pressure (psi) required for extruding
9k–10k	16.4	0
50k–85k	419.7	10
85k–124k	861.0	15

Dex21P) were used to construct structure A (Fig. 2). For the 9k–10k molecular weight PVA no gas pressure was required for extrusion, for higher molecular weights gas pressure was required.

For the preparation of structure B (Fig. 3) a PVA molecular weight of 50k–85k was chosen to mix with Dex21P at volume ratio 7:3. This molecular weigh and ratio was chosen due to the viscosity properties facilitating successful printing as well as incorporation of therapeutic levels of Dex21P. PVA is a water soluble polymer and was used in this study to facilitate the partitioning of the Dex21P from the PLGA layers utilizing the solvent/non-solvent effect (PLGA is dissolved in DCM whilst PVA is dissolved in water). For the formation of this structure the PLGA layer is also extrusion printed, therefore the viscosity of 2% (w/v) PLGA was also determined along with the 20% (w/v) PVA:Dex21P ink to be 9.1 cP and 419.7 cP, respectively. Whilst the printing patterns of the PLGA solution and PVA:Dex21P ink, used to fabricate structure B, was the same (continuous track as show in Fig. 3a and b) different solution viscosities produced different printed morphologies. The 2% PLGA solution has lower viscosity, resulting in the printed tracks merging together when extruded from the syringe. This resulted in the formation of a PLGA film. Digital images of printed drug sandwiched between polymer layers is shown in Fig. 4. Whilst the PLGA tracks merged to form a continuous film the PVA:Dex21P tracks remained as discrete components.

3.2. Characterisation

3.2.1. Morphology

The morphology of prepared materials was investigated by both optical and scanning electron microscopy (SEM). The quality of the PVA:Dex21P printing onto cast PLGA substrate (structure A) is shown in Fig. 4. Optical and SEM images of the printing, PVA:Dex21P and PLGA solution (structure B) is shown in Fig. 5. The optical and SEM images revealed discrete continuous tracks of printed ink solution. Due to the dissimilar solvents used (water for PVA and DCM for PLGA) there appears to be no diffusion between of the two deposited material. For structure A the height and the width of the printed line ranged between 3–6 μm and 160–180 μm with an average height of 4.2 μm and width of 171.5 μm. For structure B the height and the width of the printed line ranged between 2–4 μm and 115–129 μm with an average height of 2.5 μm and width of 120 μm.

The SEM cross-section image of the printed structure B one-layer system (Fig. 6) shows encapsulation of PVA:Dex21P between the PLGA layers (indicated by the dashed white lines). The sharp and well-defined boundary between the two materials is due to the dissimilar solvents used which prevent diffusion and mixing of the two materials. The PLGA layers show internal nano-pores in the PLGA layers whilst the PVA:Dex21P shows no pores, in addition the surface of structure B also show no visible pores. The thickness, as determined with a micrometer, of the printed structure fabricated by extrusion printing is shown in Table 1. As one would expect the thickness increased with increasing number of layers printed.

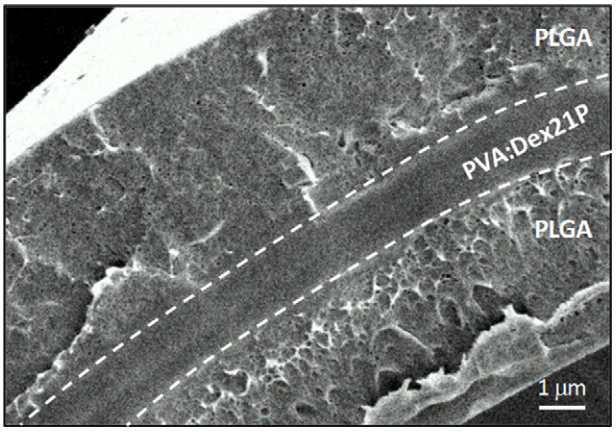

Fig. 6. The SEM cross-section image of printed one-layer system (structure B) obtained by extrusion printing. The individual layers are labelled with the PVA:Dex21P layer highlighted by the dash lines.

The surface morphology of printed structure B was analysed by SEM (Fig. 7). Prior to *in vitro* drug release studies the structure showed a featureless surface morphology with some slight undulations in the bottom right of Fig. 7a possibly associated with the underlying printed PVA:Dex21P. After 2 weeks *in vitro* the surface morphology has changed to show separation of the printed PVA:Dex21P tracks and the

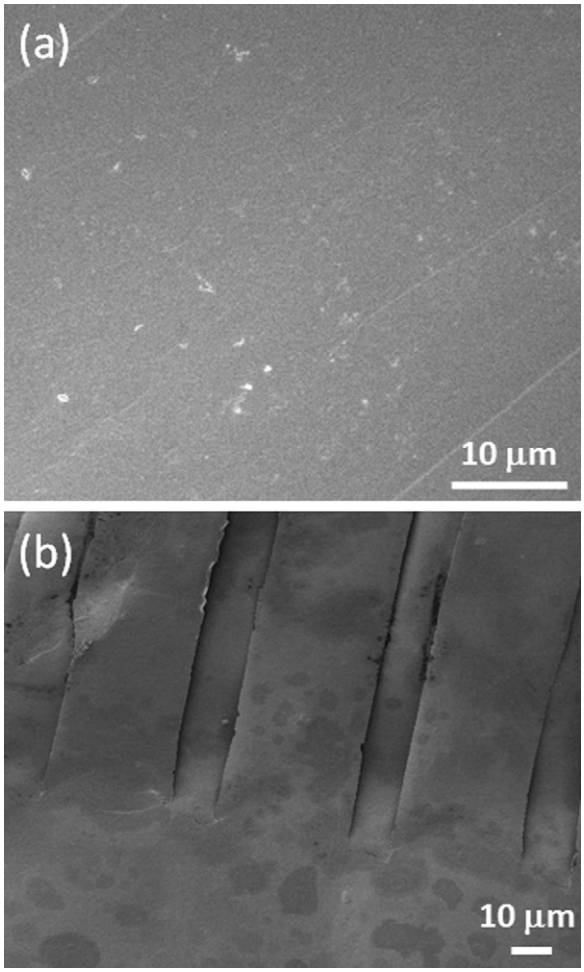

Fig. 7. SEM images of structure B surface morphology (a) before *in vitro* drug delivery and (b) after 2 weeks *in vitro* in PBS (pH 7.4).

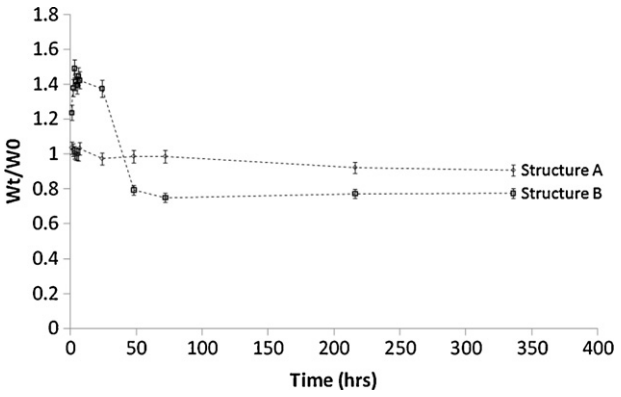

Fig. 8. Weight loss measurements recorded from the printed structures incubated in PBS (pH 7.4) at 37°C. Each data point was obtained from averaging the weight loss of triplicate samples with the errors representing one standard deviation about the mean.

PLGA layer (Fig. 7b). Upon further investigation this separation is confined to the top layer of the three-layer print structures, with the remaining internal layers appearing to be intact.

3.2.2. Weight loss measurements

Weight loss of each structure was monitored *in vitro* by placing triplicate sample of structure A and B in PBS and weighing the samples at various time intervals. The samples were removed from the PBS and surface bound liquid was removed by wicking using a tissue cloth. Removal of any surface bound PBS ensured that the weight variations observed can only be attributed to changes in the polymeric structures.

Weight loss measurements were performed over a 2-week period in order to investigate the initial stage of *in vitro* drug release. Weight loss measurements (Fig. 8) show considerable variation between structures A and B. Structure A shows no significant weight change over the time investigated which is not surprising as it has been shown that weigh loss due to degradation is not observed for 85:15 PLGA until at least 8 weeks *in vitro* (Husmann et al., 2002). Whilst dexamethasone release has been shown to occur from structure A (see Section 3.3) the weight change associated with this release in not sufficient to be detected. The weight loss profile for structure B shows an initial increase in weight possibly the result of the infiltration of water through the PLGA layers and subsequently interacting with the PVA:Dex21P layer. The interaction of water with PVA is well documented (Hodge et al., 1996). Water acts as a plasticiser for PVA resulting in degradable and several hours later the weight starts to decrease possibly associated with the slow dissolution of the PVA:Dex21P layer. The weight loss data in Fig. 8 demonstrates that the fabrication method clearly influences the way in which the polymer components interact with the *in vitro* media.

3.3. In vitro drug release

An encapsulated drug may be released in three ways: (i) drug transport through the polymer phase, (ii) drug transport through water-filled pores, and (iii) due to dissolution of the polymer encapsulating the drug (which does not require drug transport) (Fredenberg et al., 2011). Drug transport through water-filled pores is the most common way, as the encapsulated drug is usually a hydrophilic molecule, and drug release usually starts before the onset of any significant polymer erosion. The transport takes place either by diffusion (driven by the concentration gradient) or convection (driven by a force such as osmotic pressure). Pore formation

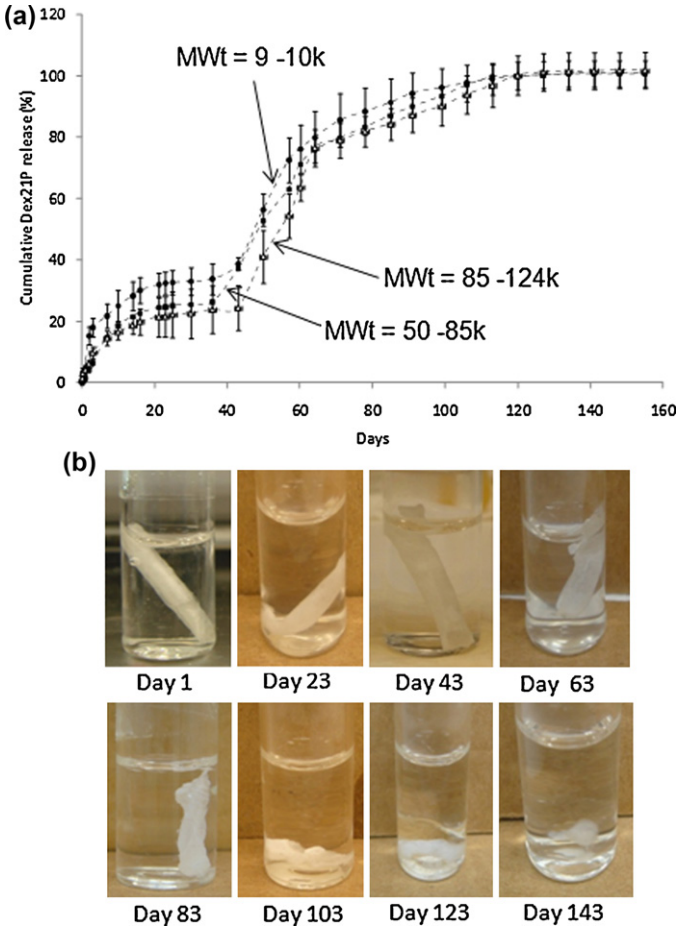

Fig. 9. (a) The drug release profiles, loaded with different PVA molecular weight and (b) digital images of PLGA reservoir at different times.

and pore closure are two very important processes. Pore formation is influenced by the rate of water absorption and the rate of degradation/erosion (Matsumoto et al., 2005; Mochizuki et al., 2008). Due to the auto-catalytic nature of degradation, the rate of pore formation, and thus drug diffusion, may not be homogeneous throughout the polymer matrix. Similarly, the rate of the other process, pore closure, may be heterogeneous throughout the polymer matrix.

3.3.1. Structure A

The drug loadings onto the PLGA substrate (structure A) were approximately 650 μg, 550 μg and 660 μg for a mixed solution with PVA formulations 9k–10k, 50k–85k and 85k–124k, respectively.

The Dex21P release from the printed structures was studied and the results are presented in Fig. 9a. All of the PVA formulations investigated (9k–10k, 50k–85k and 85k–124k) exhibited a similar release profile, with an initial burst release within the first 24 h, followed by a lag phase and sudden release of Dex21P, then continuous release of a small dosage. Release of a drug molecule from polymer may combine diffusion and dissolution process, so the release profiles often present several phases depending on which process predominates (Park et al., 1998). In the initial phase the main driving force for drug release is either transport through the PLGA or through the pores in the PLGA layer (Fig. 4d, inset) as at this stage the PLGA has not significantly eroded. A sudden increase in Dex21P release is observed at approximately day 40 which is attributed to the collapse of the structure. This collapse facilitates the influx of PBS that in turn removes any Dex21P that was trapped with the scroll and/or interacts with the PVA:Dex21P component thus releasing more Dex21P over the next 10–15 days. The method

Table 3
Dexamethasone release kinetics parameters obtained from *in vitro* release data and Eq. (1).

Structure A		
PVA molecular weight	Diffusional exponent (n)	Correlation coefficient (r^2)
9–10k	0.560	0.960
50–85k	0.610	0.956
85–124k	0.561	0.960
Structure B		
Configuration	Diffusional exponent (n)	Correlation coefficient (r^2)
1 Layer	0.644	0.983
2 Layer	0.689	0.988
3 Layer	0.749	0.982

of fabrication for structure A involves the flat PLGA–PVA:Dex21P structure being rolled and sealed into a scroll configuration (Fig. 2c). This configuration may give rise to ingress of the PBS through any region of the scroll that was not adequately sealed resulting in increased drug dissolution out of the structure.

The 9k–10k, 50k–85k and 85k–124k PVA:Dex21P formulations demonstrated an initial burst release of approximately 30%, 20% and 19%, respectively. The observed decrease in the initial burst with increase in polymer molecular weight may be a result of decreased diffusion pathway in the higher molecular weight PVA (Yu et al., 2008). The second phase began after a lag time of approximately 20 days. This delay reflected the time necessary for PLGA hydrolysis to sufficiently erode to allow dissolution of the remaining PVA and release the entrapped drug (Vey et al., 2008). Sample collapse on day 43, resulted in an increase in the Dex21P release profile from approximately 40–80% by day 63 and then slowly increased to 100% within 155 days. The slower release at the later stage was due to the gradual depletion of Dex21P in the polymer phase (Gomez-Graete et al., 2007).

In order to evaluate the release mechanism the Dex dissolution data up to 60% was taken and a linear fit was generated by a double logarithmic plot. The diffusional exponent (n), and correlation coefficient (r^2) are shown in Table 3. The results for all structures show anomalous (non-Fickian) drug release, indicating that the drug release is controlled by more than one process.

Images in Fig. 9b present the morphology of the PLGA:PVA–Dex scaffolds containing the 50–85k molecular weight PVA as a function of incubation time in PBS. The PLGA reservoirs were dimensionally stable for 40 days of incubation in PBS before starting to lose integrity and finally collapsing on day 43. All of the PLGA:PVA–Dex scaffolds showed the same morphological breakdown regardless of the PVA molecular weight. The breakdown of the scroll structure is significantly different to that of structure B below (Fig. 10c). This variation in morphological breakdown could be attributed to the accelerated catalytic degradation of the PLGA due to the scroll configuration trapping the acidic degradation products therefore accelerating the degradation process as reported by Park (1995).

3.3.2. Structure B

The amount of drug loading sandwiched between PLGA layer (structure B) was approximately 100 μg, 200 μg and 300 μg for one, two and three layer system (Fig. 3c–e), respectively. The release profiles of Dex21P from different layer scaffolds fabricated by the printing method are presented in Fig. 10(a). The profiles differ considerably for structure A profiles, with the profiles for structure B indicating better encapsulation. The result showed that when the film thickness increases (Table 1), the percentage release within the 105 days decreased from 92% to 76% and 55% for one, two and three layer systems, respectively. The maximum release rate was observed in one layer system where approximately 40% Dex21P

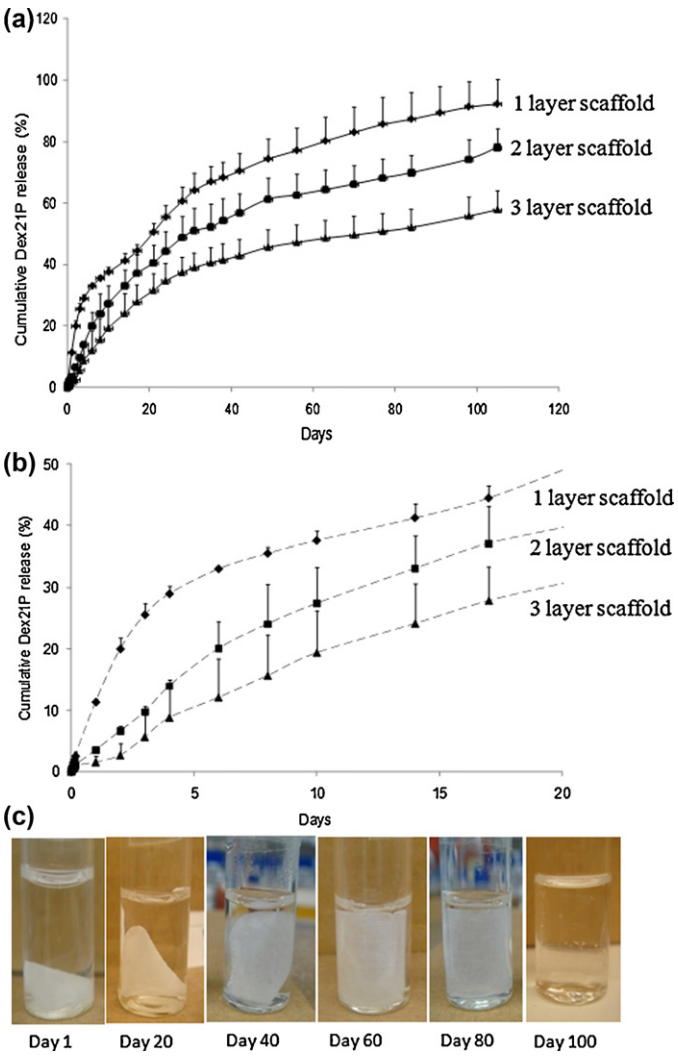

Fig. 10. The drug release profiles from (a) different layer system and (b) digital images of printed scaffolds at different times.

was released in the first 14 days and progressively to 92% in 105 days. Two and three layer system was much slower than one layer system due to thickness of printed film. For two layer system, 31% Dex21P was released in the first 14 days and increased to 76% in the day 105. The release percentage of three-layer system was 22% in the first 14 days and progressed to 55% in the day 105. The release profiles for the first 20 days profiles indicate the release of the drug from a polymer based structures involves absorption of water into the polymer matrix and subsequent diffusion of the drugs via the nano-pores (Fig. 6) as determined by Fick's Law (Fredenberg et al., 2011). For release times longer than 20 days the release process is considered to be a combination of diffusion and dissolution of the printed structure.

The release mechanism was investigated using the same approach as that used for structure A. The diffusional exponent (n), and correlation coefficient (r^2) shown in Table 3 indicate anomalous (non-Fickian) drug release, suggesting that the drug release is controlled by more than one process.

However, increasing the number of printed layers resulted in increasing the thickness of the printed film effectively reducing the initial burst release (Fig. 10a and b). This is attributed to the increase volume of PLGA the Dex21P has to diffuse through. Unlike the release profile shown for structure A (Fig. 9a) there is no

significant second release phase observed for structure B indicating the erosion of structure B to be more uniform than structure A.

Fig. 10c presents the morphology of the printed PLGA–PVA:Dex21P structures as a function of incubation time in PBS. The films were transparent and dimensionally stable for a few days, after that they started to become opaque and continuously changed colour to white due to the degradation process.

4. Conclusions

Extrusion printing provides a facile and versatile approach to the fabrication of tailored drug delivery platforms. Two types of drug encapsulation designs (rolled and sealed as well as layer-by-layer) were successfully fabricated using printing technology. The continuous release of the anti-inflammatory Dex21P over a 4-month period *in vitro* was shown for structures constructed by a rolling and sealing method (structure A). The layer-by-layer approach (structure B) whereby the drug is sandwiched between printed polymer layers, demonstrated improved encapsulation resulting in long-term release profile (>100 day). When the amount of PLGA is increased in structure B the release rate is decreased, thus allowing for prolonged drug release with control over the profile attained.

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