



## Novel gradient casting method provides high-throughput assessment of blended polyester poly(lactic-co-glycolic acid) thin films for parameter optimization

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### ABSTRACT

Pure polymer films cannot meet the diverse range of controlled release and material properties demanded for the fabrication of medical implants or other devices. Additives are added to modulate and optimize thin films for the desired qualities. To characterize the property trends that depend on additive concentration, an assay was designed which involved casting a single polyester poly(lactic-co-glycolic acid) (PLGA) film that blends a linear gradient of any PLGA-soluble additive desired. Four gradient PLGA films were produced by blending polyethylene glycol or the more hydrophobic polypropylene glycol. The films were made using a custom glass gradient maker in conjunction with a 180 cm film applicator. These films were characterized in terms of thickness, percent additive, total polymer (PLGA + additive), and controlled drug release using drug-like fluorescent molecules such as coumarin 6 (COU) or fluorescein diacetate (FDAC). Material properties of elongation and modulus were also accessed. Linear gradients of additives were readily generated, with phase separation being the limiting factor. Additive concentration had a Pearson's correlation factor ( $R$ ) of  $>0.93$  with respect to the per cent total release after 30 days for all gradients characterized. Release of COU had a near zero-order release over the same time period, suggesting that coumarin analogs may be suitable for use in PLGA/polyethylene glycol or PLGA/polypropylene glycol matrices, with each having unique material properties while allowing tuneable drug release. The gradient casting method described has considerable potential in offering higher throughput for optimizing film or coating material properties for medical implants or other devices.

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### 1. Introduction

When engineering polymeric thin films for medical devices, the research and design (R&D) team must optimize numerous parameters. It is rare for a pure polymer to meet all the considerations required for the function of a device.

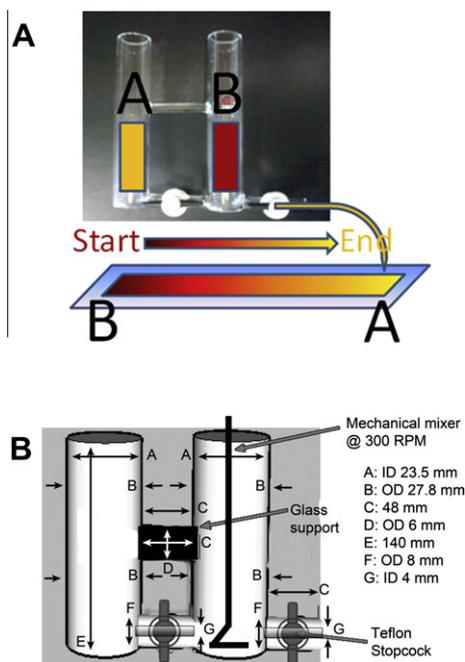
To develop the thin films for a specific application, the neat polymer must have various additives incorporated into polymer solutions or melts to meet the final design specifications [1]. These additives are used to modify properties such as controlled drug release [2], surface tension [3], mechanical properties [4,5], adhesion [6], etc. These modifications need to be assessed empirically, hence significant resources in labour and materials are often needed. Complicating the assessment is the influence of the parameters on one another. One additive included to improve a specific property may be deleterious to other functions. For example, adding

porogens (pore-forming additives) in thin films increases surface area and diffusional drug release as desired. However, the inclusion may drastically change the mechanical properties to an extent where the thin film is no longer suitable for the intended purpose.

At present, optimizing a film with permutations of several additives is a considerable undertaking which may hinder progress in the R&D process. To address this problem, we have successfully developed a novel procedure of thin film casting that produces additive gradients from 0% to 50%. As displayed in Fig. 1, the design of the custom gradient caster allows up to 100 ml of mixed solution to be cast in one session. The casting allows an ascending polymer ratio vs. length, with maximum lengths of 180 cm possible. The method was designed to provide enough material for analysis using the multiple procedures required for characterization, including mechanical testing, controlled drug release, proton nuclear magnetic resonance ( $^1\text{H}$  NMR) analysis, thickness measurements, etc. The advantages of this technique include lower material investment, labour efficiency, and a higher rate of throughput. Moreover, trends dependent on additive concentration in material and film properties are quickly identified.

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**Fig. 1.** (A) Diagram of gradient casting. As the two stopcocks are opened in the gradient caster, solution B immediately flows out and solution A is mixed in increasing concentrations in chamber B. (B) Dimensions of gradient caster. ID: inner diameter. OD: outer diameter. All glassware was constructed from laboratory-grade borosilicate glass.

When thin films of fixed additive amounts are synthesized, it is unlikely that the initial preparation will match the sought material parameters. This will necessitate another round of film casting, synthesis, or both. In the system described here, additive concentration will be dependent on the length for gradient cast films; one simply has to return to the original film and sample from a different section along the gradient.

Our process is a straightforward approach that provides greater film area than other recently published gradient methods based on controlled evaporative spin coating or surface-plasma-generated methods [7,8]. It has similarities in design and features to the methodology utilized in casting gradient polyacrylamide gels for protein characterization [9]. In the present study it was employed to cast thin films of polyester poly(lactic-co-glycolic acid) (PLGA).

Polyesters are a well-known biodegradable polymers employed in thin film drug delivery systems [10]. Commercially available polyesters consist of polycaprolactone (PCL), polylactic acid (PLLA) and the more common PLGA. They have been used in various applications such as the controlled delivery of drugs [11], antibiotics [12], and vaccines [13], and also tissue engineering [14] and bone defect healing [15]. PLGA has found favour due to its biodegradability, biocompatibility and approval for parenteral use by regulatory authorities around the world. Numerous active pharmaceutical drugs such as growth factors, antibiotics and anti-cancer drugs have been incorporated into PLGA-based platforms with considerable therapeutic effect [16,17].

Polyester/hydrophobic drug formulations utilize a number of methods and additives to modulate their release, including particulate leaching [18,19], matrix foaming [20], and additive incorporation such as polyethylene glycol (PEG) and polypropylene glycol (PPG). Etanidazole pressed discs-PEG [21], stent coatings [22], and spray-dried films [23] have all utilized low-molecular-weight PEG (2–4 kDa) to modify drug release or acted as a versatile plasticizer for PLGA [22,24]. Incorporation of PEG or PPG into similar block copolymer polyesters can also affect mechanical or release properties, respectively [25,26].

The effect on mechanical properties by the incorporation of PEG into PLGA thin films has been seen to be detrimental when mixed in high concentrations, limiting its use as a drug release modulator [2].

As a first application of our gradient knife-casting method, we hypothesized that the more hydrophobic cousin of PEG, PPG, would retain such material properties as high modulus, elongation, and low amounts of phase separation when incorporated into PLGA, yet allow an increase in overall drug release due to its water miscibility. Herein we incorporated 4000 Da PEG (PEG 4 K), 4000 Da PPG (PPG 4 K) into thin films of PLGA 53/47 with an intrinsic viscosity of  $1.03 \text{ dl g}^{-1}$ , with a molecular weight of  $\sim 100 \text{ kDa}$  (PLGA 100 K), through gradient films. Fluorescein diacetate (FDAC) and coumarin-6 (COU) were used as model drugs for controlled release. We have previously published how FDAC can be used as a high-throughput screen for paclitaxel release in PLGA thin films, and is therefore a good rationale for choice in this study [27].

## 2. Materials and methods

### 2.1. Materials

PLGA 53/47 (with intrinsic viscosity of  $1.03 \text{ dl g}^{-1}$  was purchased from Purac, the Netherlands. HPLC-grade dichloromethane (DCM) and acetonitrile was purchased from Tedia, USA. Deuterated chloroform ( $\text{CDCl}_3 + 0.03\% \text{ v/v TMS D99.8\%} + \text{silver foil}$ ) was purchased from Cambridge Isotope Laboratories, Andover, USA. Polyethylene glycol and polypropylene glycol of molecular weight of  $4000 \text{ g mol}^{-1}$ , and polysorbate 80 (Tween 80) were purchased from Sigma-Aldrich, Singapore. Rhodamine 6 g, COU and FDAC were purchased from TCI Japan, Singapore. All other polar solvents used were of high-performance liquid chromatography (HPLC) grade and purchased from Sigma-Aldrich, Singapore. All chemicals and materials were used as received.

### 2.2. Gradient casting thin films

Gradient films were produced using the gradient caster in Fig. 1. Initially 20 ml of the more viscous solution (15% PLGA (w/v DCM)) was poured into Chamber B, and the additive in Chamber A, i.e. 20 ml 15% PEG 4000 (w/v DCM). Each well contained 65 mg (in 20 ml) of FDAC or COU for later release studies. The gradient maker was tilted at a 10% incline for faster flow rate and fixed to the film applicator with flow rate adjusted by the Teflon stopcock. Gradient mixing was initiated after a few seconds ( $\sim 5\text{--}10 \text{ cm}$ ) of knife casting pure PLGA/drug film – in this amount of time, the viscous solution was allowed to fill the entire 8 cm width of the knife caster. The chamber A valve was then opened to begin mixing with chamber B. Chamber B mixing was performed using a battery-operated “milk frother” (Ikea, Singapore) modified for overhead mixing and taped into place. Gradient solutions were poured (rate of  $\sim 20 \text{ ml min}^{-1}$ ) directly into the film applicator within a fume extractor hood. Film applicator height was set at  $500 \mu\text{m}$  and the flowing viscous gradients were directly cast onto  $50 \mu\text{m}$  polyethylene terephthalate sheets at  $20 \text{ mm s}^{-1}$ , room temperature (RT), employing a S125 knife caster, capable of 180 cm length films (MTL Systems Pte Ltd, Singapore). DCM was evaporated at RT for 24 h in a fume hood, followed by vacuum oven ( $<10 \text{ Torr}$ ) at  $55 \text{ }^\circ\text{C}$  for 48 h. Punchouts of 6 mm diameter (using a simple paper punch) were taken every 5 or 10 cm for characterization.

### 2.3. PLGA 100 K, PEG 4 K, and PPG 4 K quantification by $^1\text{H NMR}$

Dried (6 mm diameter  $\times$  3 pieces) punch-outs were dissolved in  $1050 \pm 10 \mu\text{g}$  ( $700 \mu\text{l}$ ) of  $\text{CDCl}_3$ , vortexed, and centrifuged at 10,000 rpm for 5 min prior to transferring the supernatant into

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