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Chapter Title: 4. Tailoring thin films for implant specific applications

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Abstract: Research and development of polyester thin film implants can be tailored for controlled drug release, mechanical properties, and surface properties. The high number of parameters often makes the optimization process slow and laborious. By employing high-throughput drug release and gradient casting techniques, we show how these properties can be rapidly optimized. The employment of these techniques has yielded methods in which drug release can be tailored without the use of additives and how the choice of certain additives can change material properties while negligibly affecting drug release. Alternatively, plasma post-treatments may allow tailoring of thin film material properties though the judicious use of plasmas such as oxygen, argon, or combination thereof.

Key Words:
High-throughput screening, gradients, fluorescein, PLGA, polyester, plasma

INTRODUCTION

High throughput assessment of drug delivery

Hydrophobic drugs are prime candidates for encapsulation and controlled release in bioresorbable thin films. The common biodegradable matrices of polyesters and polyanhydrides offer an ideal environment for hydrophobic drugs to molecularly disperse with little phase separation. However, screening thin formulations is a tedious task--formulation parameters are diverse and often include thin film thickness, various grades and molecular weights of the polymer matrix, specific drug and its encapsulation percentage, additives to modulate drug release and material properties, etc. Optimizing several parameters can lead to several hundred formulations. Considering replicates and multiple sampling that comes with characterizing drug release kinetics, an efficient method must be found to characterize hundreds if not thousands of samples that can be generated per day.

When undergoing a high throughput screening of thousands of samples, a global perspective is often necessary that divides the standard operating procedures (SOPs) from formulation synthesis to data analysis. SOPs need to be designed for every stage of the drug release, with common SOPs covering the following drug release operations: 1) Synthesis of the encapsulated thin films 2) Characterization of thin film formulation constituents 2) Sampling and replacement of the release medium to prevent drug sink effects 3) Sample quantitation of drug, polymer, additive, or combination thereof 4) Data analysis and storage 5) Post-drug release polymer matrix characterization.

MATERIALS AND TECHNOLOGIES

Quantitation of release kinetics

Pertaining to sample quantitation, high performance liquid chromatography (HPLC) is the gold standard for drug quantitation, but is rather slow when considering the inherent sample preparation procedures (i.e. filtering and capping). Quantitation by microplate-based fluorescence spectroscopy is a faster methodology that avoids much of the laborious preparation HPLC SOPs, while maintaining similar levels of sensitivity. Microplates in plate readers shortens the instrument analysis time down to seconds per sample, and in our experience, speeds up analysis through automated Excel macros or algorithms. Several pharmacophores are readily fluorescent under certain conditions, including coumarins, nucleosides, dienones, and amido-pyridines [1, 2]. The downside of this approach is there are many more non-fluorescent pharmacophores than fluorescent ones. Two alternative strategies may be of benefit. First, most pharmacophores can be readily derivatized with a fluorophore such as dansyl chloride. The drawback of this approach is that the derivatized pharmacophore must have sufficiently different fluorescent properties from the reagent so separation or cleanup procedures are avoided. Fluorescent readings can then be rapidly recorded after the protocol.

Take for example the hydrophobic drug paclitaxel, a powerful drug employed in anti-tumour and heart disease therapies. Paclitaxel is not fluorescent, but fluorescent analogues exist towards various life science protocols where minute quantities suffice [3]. In the amounts required for encapsulation into thin films and subsequent drug release protocols, they are prohibitively expensive. The next best method is to employ a fluorescent economical mimic of the hydrophobic drug of interest to narrow down release formulations that fit the delivery profile so desired. Once the formulations are focused, the more laborious HPLC quantitation procedures can be verified with the original drug of interest.

Figure 1: Drug flux comparison of fluorescein diacetate (FDAc) and paclitaxel in PLGA 53/47 A) intrinsic viscosity (i.v.) of 0.2 ester terminated (Purac PDLG 5002) B) i.v. of 1.03 ester terminated (Purac PDLG 5010) C) PLGA 53/47 i.v. of 1.03 with 15% w/w 8kDa polyethylene glycol (PEG) D) with 25% w/w 8kDa PEG.

Figure 1 displays the end results for screening various hydrophobic fluorescent mimics against paclitaxel in a variety of thin film formulations[4]. Out of various fluorescent molecules that had similar log P values as paclitaxel, fluorescein diacetate (FDAc) was found to mimic paclitaxel drug release as long as additive ratios were kept low within a polyester PLGA matrix, as seen in **Figure 1**. Inclusion of large amounts of

polyethylene glycol (PEG) additive, a common plasticizer and drug release enhancer[5], caused phase partitioning within the PLGA matrix ultimately shifting the mechanism of release between FDAc and paclitaxel. As the ratio of PEG increased, drug release deviation did as well.

The encapsulation of fluorescein diacetate into drug release films has other advantages as well--by itself, FDAc isn't fluorescent and is only activated into fluorescein after base treatment or enzyme (esterase) activation[6]. Thus, FDAc will not photobleach (unlike fluorescein) and is a good candidate for investigations into photo-induced drug delivery[7]. FDAc is also colourless when mixed into thin film formulations, whereas fluorescein is a highly coloured greenish-orange dye and is easily discerned by the naked eye. In this regard, FDAc acts as a visual sensor towards thin film damage, especially for polymers that have a significant percentage of polyester backbone. For example, our laboratory once explored various polyamines as additives into PLGA films, but found the films quickly turning orange under dry storage conditions. Inherent amines (e.g. polyethylenimine) quickly catalyse the hydrolysis of the polyester backbone and fluorescein diacetate. Polyamine based additives where quickly abandoned as drug release modifiers (unpublished data).

Synthesis of thin film gradients

Thin films specified for medical applications often go through many rounds of optimization, considering a generic film constituent of one or more polymer matrices, encapsulated drugs(s), and the inclusion of modifying additives. Each formulation needs to be assessed empirically, often generating tens if not hundreds of films even when limiting the investigation to just a few parameters. We find the most important parameters to be the amount and method of encapsulated drug, and inclusion of modifying additive towards drug release, material properties, or both. This assumes that a formulation scientist can limit the matrix to a single commercially available (medical grade) polymer matrix and an agreed upon pharmaceutical suitable for the polymer matrix of choice.

To speed along product development, ideally one can make a single film that addresses the minimum and maximum variants under a single parameter. For example, specific rates of release are often sought from the surfaces of thin films (henceforth drug flux, with typical units of $\mu g\ cm^{-2}\ d^{-1}$), based on known clearance rates, therapeutic levels desired, or tissue absorption characteristics. Thus, by synthesizing a horizontal gradient of drug concentrations within a *single* thin film, various rates of drug flux could be assessed. Simple techniques exist for gradient casting thin films by knife casting (as seen in **Figure 2**) or through film extrusion. Knife casting is a simple and inexpensive procedure, but suffers from residual solvent encapsulation. This is a problem only when direct in vivo investigations are planned. Modern R&D extruders have the capability of using only 2 g of polymer towards filament or film extrusion, with

no solvent required (e.g. Xplore® twin screw compounder from Xplore Instruments, Netherlands). Both methods have the advantage of minimal materials needed, manpower, and faster return of results.

Figure 2: (A) Scheme of a theoretical gradient of two constituents of solution A and solution B. Solution A flows into solution B as both valves are opened. A gradient mixture of B to A is then flowed onto a glass plate for knife casting.

In our experience, drug flux based on polymer additive concentration or polymer matrix blending tends to yield more worthwhile information (in terms of drug flux) while exploring levels of drug encapsulation within the thin films is one of the last parameters that should be assessed. In the sections that follow, we will describe how the combination of high-throughput quantitation and gradient film casting were employed to assess and predict drug flux, material properties, and phase separation.

CHALLENGES AND EXAMPLES

Tailoring drug delivery without additives through polyester acidic end-groups

Depending on the medical application, tailoring the drug flux from a resorbable thin film is a first priority and is dependent on the therapeutic of choice and the pathology under treatment. Additives are the most common method for modifying drug flux from biodegradable thin films. Polyethylene glycol (PEG) is a common additive employed in various thin film formulations. PEG is known to increase drug flux as it readily dissolves in both organic and aqueous solvents, increasing matrix water penetration or because it acts as a solubility enhancer towards sparingly soluble drugs[5, 8]. However the addition of PEG or other additives often has far reaching effects on more than drug flux--it can act as a plasticizer, induce phase separation, alter surface wetting, or combination thereof[5, 9]. To avoid these detrimental shifts in material properties, the modulation of drug flux without additives has been attempted with varying success by blending of molecular weight, polymer blends, or inclusion of various functional groups[10-16]. We have found acidic end-groups particularly adept at tuning drug release from polyester matrices[11, 17].

Figure 3. Drug flux of fluorescein diacetate (FDAc; z axis) with respect to time (x axis) and A) gradient casted P02E, B) gradient casted P02A, C) fixed casted P02A, D) Gradient composition of P02E/P103E, 2.5% w/w FDAc/P103E E) Gradient composition of P02A/P103E, 2.5% w/w FDAc/P103E F) Fixed composition of P02A/P103E, 10% w/w FDAc/P103E. **P103E**: PLGA 53/47 i.v. of 1.03 ester terminated (Purac PDLG 5010), **P02E**: PLGA 53/47 i.v. of 0.2 ester terminated (Purac PDLG 5002). **P02A**: PLGA 53/47 i.v. of 0.2 acid terminated (Purac PDLG 5002A).

Figure 3 displays the typical results obtained with the high-throughput assessment methods as described above. Thin films (ca. 20 µm thick) of medical grade PLGA 53/47 obtained from Purac (Netherlands) were synthesized through gradient knife casting. **Figure 3A-C** shows the drug flux of FDAc with respect to composition (ester or acid terminal end-groups) and time. Various compositions are present at different lengths of the gradient casted film (**Figure** 3D & 3E). **Figure 3A** displays a relatively flat drug flux with little to no dependence on the amount of the ester terminated P02E over 30 d. This is in sharp contrast to the acid terminated P02A composition, where a high Pearson R correlation (> 0.9) was assessed between drug flux and the concentration the acidic groups. Most useful for the formulation scientist was the wide range of total drug release that could be selected. For example, at day 20 the compositions in **Figure 3B** could be predicted to give a total drug release of 40-90%. FDAc flux of 1-2, 2-6, and 5-30 µg cm^{-2} d^{-1}, were observed in the formulations observed in **Figure 3A, 3B, and 3C,** respectively.

It should be noted that these investigational studies encapsulated a relatively small amount of drug (2.5% w/w FDAc/P103E) to limit drug release from diffusion or burst release based processes. As one increases the FDAc concentration 5-fold, higher linear correlations of drug flux are observed, as seen in **Figure 3C**. This results from the balance of burst release and polymer degradation within the thin film. Burst release allows fast drug flux at the start of the medium incubation by diffusion while polymer degradation processes only allow high drug flux after an initial incubation period. The encapsulation of the terminal acidic groups catalyses polyester hydrolysis and shortens the incubation period where degraded oligomer fragments become soluble in aqueous mediums[18, 19].

The corresponding surface compositions of Total PLGA, PLGA ratio, and FDAc concentration are given in **Figure 3D, 3E,** and **3F**. This data is easily generated through NMR and GPC instruments equipped with appropriate autosamplers. It should be noted that gradient casting gives many formulations for assessment, but the technique does have its drawback. Most notable is the large variance in Total PLGA across the films in gradient casted films (**Figure 3D**) compared to fixed formulations (**Figure 3F**). This is caused by changes in viscosity during gradient casting. Variations in viscosity lead to disparities in film thickness and constituent surface concentrations. Another drawback is the additional analysis required--a fixed formulation requires minimal characterization of the constituents, but gradient casting requires a dedicated approach (NMR or GPC). However, this analysis can be subject to the film surpassing certain milestone requirements before the labour is invested. If the films don't display the required drug flux--they can be discarded and the R&D can quickly move on to the next phase.

Tailoring material properties through oligomer additives while maintaining drug flux

The previous section focused on altering drug flux while minimizing changes in material properties and the use of additives. In this section, we focus on the challenge of shifting material properties, such as modulus, while minimizing changes in drug flux. Polyethylene glycol (PEG) and its more hydrophobic variant polypropylene glycol (PPG) are found to affect both drug flux and modulus in concentration dependent ways. PEG, which is amphiphilic, has a small shift in drug flux with 15% w/w additive concentration in PLGA 53/47. However, much more PPG is required in order to observe a significant increase in drug flux--ca. 25% w/w as shown in **Figure 4A**. Below the stated w/w ratios, little to no changes in drug flux are observed within the 30 days measurement window. The modulus has a drastic change within these stated w/w ratios however. Mechanical properties of PEG and PPG additives in PLGA 53/47 are assessed according to ASTM standard D882 from 0-15% w/w additive/PLGA. PEG additives of 2,4, and 8 kDa decrease the neat PLGA 53/47 sample modulus from ca. 13 MPa to less than

0.05 MPa at 15% w/w additive as displayed in **Figure 4B.** Elongation was only slightly affected with changes of 50% or less. PPG 4000 has the opposite effect--the modulus was seen to linearly increase the PLGA 53/47 thin films to ca. 19 MPa at 15% w/w PPG additive but elongation was decreased by more than 10 times--the films effectively became more brittle. It should be noted that the modulus characterized in these studies was from dry thin films and the mechanical properties will dramatically shift in wet conditions--for example the wet modulus of neat PLGA 53/47 samples decreases to ca. 3.7 MPa in phosphate buffered saline at 37°C[11]. Thus the PEG & PPG containing films will have completely different properties in wet environments.

Figure 4. A) FDAc flux from PLGA 53/47 i.v. of 1.03 ester terminated (Purac PDLG 5010) with a range of PEG 4000 and PPG 4000 additives. B) Modulus of PLGA 53/47 i.v. of 1.03 ester terminated thin films with 5, 10, and 15% PEG and PPG additives. Some data points have been redrawn from[9].

An example of how oligomer additives can achieve controlled drug flux

Films loaded with anti-cancer drugs may find their applications in managing localized tumour while avoiding the route of systemic administration. Oftentimes, such an approach is ideal for tumours that have been excised for biopsy, and a film can be locally implanted as a device, to release drugs to the surrounding tissues. For example, a drug such as Vemurafenib (VF) can be loaded into biodegradable PLGA film using the gradient casting solvent evaporation method as outlined above. To accelerate the release of this hydrophobic drug from the film, polyethylene glycol (PEG) was introduced to the PLGA solution to act as a plasticizer. Similarly, a film applicator was used to cast the film under atmospheric conditions. These films were left to dry in a vacuum oven for up to a week.

These films were subsequently investigated for the release profile of the VF drug. For this study, the drug-loaded films were punched-out into 6mm diameter discs. The discs were placed individually into wells of a 96 well plate and immersed in 200 µl of Phosphate Buffer Saline (PBS) of pH 7.4 at 37°C. The medium was removed at predetermined time points and replaced, maintaining sink conditions throughout. The withdrawn medium was filtered through a 0.2 µm PTFE syringe filter directly into HPLC vials and immediately capped. VF was quantified with an Agilent Series 1100 HPLC (Santa Clara, CA) equipped with a UV/vis detector, autosampler, and column heater set to 35 °C. A ZORBAX Eclipse XDB-C18 (5 µm) column of acetonitrile/water 60/40 (vol.%) served as the mobile buffer, eluting the Vemurafenib peak at 5.4 min at a flow rate 1.0 ml min^{-1}, with the UV/vis detector recording at 227 nm. The results showed that VF can be released in a controlled linear fashion **Figure 5A**, whereby the release each day was rather consistent at ~0.5ug per day **Figure 5B**. Such a release profile was made possible because of

209 the introduction of an additive, i.e. PEG, into an otherwise hydrophobic PLGA film, which generally
210 inhibits the release of a hydrophobic drug. This shows the key contribution of another polymer in creating
211 a blend to achieve a profile that is ideal for a particular application. The continuous release of drugs will
212 be useful to locally deliver drugs to surrounding tissues and to inhibit the growth of local tumours in
213 cancer therapy.
214
215

Figure 5. A) Cumulative release of VF from PEG-PLGA polymer blend films. Linear release, from *in vitro* studies, was obtained for up to a week. B) Release of VF per day from the blended films, giving a release amount of approximately 0.5 µg/day.

216

FUTURE TRENDS

Tailoring surface properties, drug flux, and mechanical properties through plasma post-treatments

The formulations described above necessitate designing and manufacturing myriad formulations to optimize drug flux and material properties. The properties are generally fixed and can't be changed once the synthesized films are prepared, or so the conventional thinking goes. If a post-treatment method were developed, a fixed manufactured film could be optimized after it has been manufactured. Treatment of PLGA 53/47 thin films with oxygen and argon plasma has recently been shown to have this unique post-treatment flexibility. **Figure 6** displays how contact angle, surface roughness, and drug flux could be shifted with specific treatments of RF vacuum plasma[20]. A brief 1 min treatment is all that is required to change the surface energy by using a 1:1 argon:oxygen plasma. Longer treatments won't necessarily change the contact angle more, but more intense treatments of 5 min or longer display the ability to etch the PLGA 53/47 surface in the tens of nanometers, as seen in **Figure 6A**. Surprisingly, little effect on the PLGA molar mass is seen, as the etching process is believed to degrade the polyesters chains through a terminal end-group induced thermal oxidative pathway. Drug flux of plasma treated PLGA thin films is found to increase up to 65% versus that of the untreated PLGA control under the 1:1 argon:oxygen plasma. However, pure argon plasma initially increases drug flux, but higher flow intensities subsequently decrease the drug elution almost to that of the untreated PLGA control as displayed in **Figure 6B**. This is likely due to radical induced polymer chain crosslinking. Plasma post-treatment can be also utilized to tune the mechanical properties of polyester films as well. Savoji et al. has shown that fiber mats synthesized from poly(ethylene terephthalate) gave a substantial reduction in Young's modulus within 5 min of oxygen plasma treatment with no apparent damage to the nanofibers[21].

Plasma based post-treatment processing of thin films is still in its infancy as high-throughput and scaled up manufacturing is relatively difficult for the current generation of vacuum based radiofrequency plasma instruments. However, as atmospheric pressure based plasma instruments become cheaper and simpler to operate, more laboratory and commercial application will ensue.

Figure 6. Plasma post-treatment of PLGA 53/47. A) Contact angle (left y-axis) and surface roughness (right y axis), plotted against treatment time of 1:1 argon:oxygen RF vacuum plasma. B) Drug flux plotted against argon plasma flow rate (top x-axis) or treatment time of 1:1 argon:oxygen RF vacuum plasma (bottom x-axis). Data points have been redrawn from[20].

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