Structured Drug-eluting Bioresorbable Films: Microstructure and Release Profile

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ABSTRACT: Bioresorbable drug-eluting films can be used in many biomedical applications. Examples for such applications include biodegradable medical support devices which combine mechanical support with drug release and antibiotic-eluting film coatings for prevention of bacterial infections associated with orthopedic implants or during gingival healing. In the current study, bioresorbable drug-loaded polymer films are prepared by solution processing. Two film structures are studied: A polymer film with large drug crystals located on its surface (A-type) and a polymer film with small drug particles and crystals distributed within the bulk (B-type). The basic mode of drug dispersion/location in the film (A or B-type) is found to be determined mainly by the process of film formation and depends mainly on the solvent evaporation rate, whereas the drug’s hydrophilicity has a minor effect on this structuring process. Most release profiles from A-type films exhibit a burst effect of approximately 30% and a second release stage that occurs at an approximately constant rate and is determined mainly by the polymer weight loss rate. An extremely high burst release is exhibited only by a very hydrophilic drug. The matrix (monolithic) nature of the B-type film enables release profiles that are determined mainly by the host polymer’s degradation profile, with a very low burst effect in most of the studied systems. In addition to the drug location/dispersion in the film, the host polymer and drug type also strongly affect the drug’s release profile from the film. It has been demonstrated that appropriate selection of the process parameters and film components (polymer and drug) can yield film structures with desirable drug release behaviors. This can lead

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Los Angeles, London, New Delhi and Singapore
to the engineering of new bioresorbable drug-eluting film-based implants for various applications.

**KEY WORDS:** bioresorbable films, controlled drug delivery, dexamethasone, gentamicin, metronidazole, cortisone.

**INTRODUCTION**

Bioresorbable drug-eluting films can be used as basic elements in various biomedical implants. Poly(α-hydroxy acid) films loaded with water-soluble and water-insoluble drugs have been developed and studied for various applications [1–8]. For example, tetracycline was released from PLLA barrier films and the system was studied for potential use in periodontal therapy [1], gentamicin was released from poly(α-hydroxy acid) films for potential use in local treatment of bone infection [2,3], dexamethasone (DM) was released from various poly(α-hydroxy acid) films used as basic elements in tracheal films [4,5], and sirolimus was released from a bi-layer PLLA-PLGA film in order to simulate its release from a stent [6]. Bioactive agents with a relatively high molecular weight, such as albumin and the malaria vaccine (synthetic polypeptide), were released from PLGA films [7]. New combinations of materials, other than the traditional poly(α-hydroxy acid), were tried as host polymers [8–12] in order to exhibit appropriate mechanical properties with the desired release profile from polymeric bioresorbable films. For example, a combination of alginate and polyethylene glycol and a graft copolymer of vinyl alcohol and lactic/glycolic acid were tried in paclitaxel eluting films for stent applications [8,9] and segmented poly(ether-ester-amide) films and cross-linked gelatin films were loaded with bioactive agents, such as metronidazole for dental applications [10,11].

Solution casting of polymers is a well-known method for preparing polymer films. In order to incorporate drugs by this method, the polymer is dissolved in a solvent and mixed with the drug prior to casting. The solvent is then evaporated and the polymer/drug film is created. A method for controlling drug location/dispersion within the film has been reported earlier [4,5,13,14]. This method is briefly described in this paragraph. Bioresorbable polymeric films containing drugs were prepared using the solution casting technique, accompanied by a post-preparation isothermal heat treatment. In this process, the solvent evaporation rate determines the kinetics of drug and polymer solidification and thus the drug dispersion/location within the film. Solubility effects in the starting solution also contribute to the post-casting diffusion processes, and occur concomitantly to the drying step. In general, two types of polymer/drug
film structures were created and studied: a polymer film with large drug crystals located on the film surface (A-type), and a polymer film with small drug particles and crystals distributed within the bulk (B-type). The morphology and formation process of these structured films have been studied extensively and a detailed model describing the structuring of these films is described elsewhere [4].

However, the promising technique for controlling the drug location/dispersion in the film raised the need to investigate structured films loaded with various hydrophilic and hydrophobic drugs and to elucidate the effect of drug type and polymer type on the film microstructure and on the drug release profile. Four types of drugs were chosen in the current study: dexamethasone (DM, hydrophobic), cortisone (CO, hydrophobic), gentamicin sulfate (GS, hydrophilic), and metronidazole (ME, partially hydrophilic). These drugs were incorporated into various poly(α-hydroxy acids) and the resulting polymer/drug films were studied.

Dexamethasone is a steroid anti-inflammatory drug. It has been incorporated into bioresorbable systems for several uses: DM-containing systems were developed and studied for intraocular application in the treatment of inflammation following cataract surgery [14,15], DM-containing microspheres and tablets were investigated for treatment of inflammatory bowel disease [16,17]. Local DM release was also used for vascular applications. For example, microspheres and nanoparticles were used for local delivery of DM to the arterial wall in order to reduce neointimal formation after balloon angioplasty [18,19]. DM was also released from an intravascular eluting stent in order to prevent restenosis [20]. The authors have previously prepared poly(α-hydroxy acid) solution cast films loaded with DM using their structuring technique in order to control the drug location/dispersion in the film. The mechanical properties of the films and the expandable bioresorbable tracheal stents developed from the films have been studied [5]. Dexamethasone was incorporated into the film-based stent to permit its controlled local release. In addition to its anti-inflammatory activity, DM has been demonstrated to inhibit the fibrotic response and the authors thought that the addition of this drug may help prevent proliferative reactions, such as induced airway stenosis. Cortisone (CO) is also a steroid anti-inflammatory drug. DM and CO are both hydrophobic.

Gentamicin sulfate (GS) is a water soluble antibiotic drug used to treat bacterial infections, especially Gram-negative ones. GS molecules react with the bacterial ribosomes and consequently interfere with protein synthesis. GS was incorporated in poly(methyl methacrylate) (PMMA) to form GS-containing PalacosTM PMMA bone cement [21,22]. GS was also incorporated into fracture fixation devices for the
prevention of bacterial infections associated with orthopedic implants. For example, researchers have coated metal implants, such as plates and wires with a polymer/gentamicin layer, using the dipping technique [23–25]. The obtained release profile demonstrated that most of the drug was released within several hours after exposure to an aqueous environment. Melt processing techniques, such as compression molding and extrusion, were used to develop bioresorbable implants loaded with gentamicin to serve as an additional part of the fracture fixation device. Cylinders, films, and disks were developed and studied [26–28]. Based on the polymer/drug film structuring technique, gentamicin-loaded bioresorbable films were prepared that can be ‘bound’ to orthopedic implants (by slightly dissolving their surface before attaching them to the implant surface) and prevent bacterial infections by controlled release of gentamicin for at least one month. It is expected that these systems will provide desired drug delivery profiles and will not require an additional implant.

Metronidazole is a partially hydrophilic drug, which effectively inhibits anaerobic microorganisms and protozoan infections [29,30]. This drug is used for the treatment of many infections, including periodontal and vaginal infections [31–33]. This drug was incorporated in drug delivery systems for various applications, such as tablets for treatment of peptic ulcers [34], microspheres for the treatment of diseases associated with the colon and the gastric mucosa [35], mucoadhesive gel and tablets for the treatment of periodontal diseases [36,37], alginate gel beads for gastric applications [38], and films for the treatment of periodontal pockets [32].

The aim of the present study was to examine polymer/drug films based on amorphous and semicrystalline poly(α-hydroxy acids) and to determine the effects of drug type, film type, and polymer weight loss kinetics on the film structure (drug location/dispersion in the film) and on the resulting drug release profile from the film.

**EXPERIMENTAL DETAILS**

**Materials**

*Bioresorbable polymers*

Two types of poly(L-lactic acid) were used:

1. Poly(L-lactic acid), Resomer L210, Inherent viscosity (I.V.) = 3.9 dL/g in CHCl₃ at 30°C, M.W. ≈ 450,000 Da, Boehringer Ingelheim, Germany. This polymer will herewith be designated PLLA.
2. Poly(L-lactic acid), Medisorb 100 L, I.V. = 1.6 dL/g in CHCl₃ at 30°C, M.W. = ~200,000 Da, Alkermes, USA. This relatively low molecular weight polymer will herewith be designated PLLA(L).

Two types of 75/25 poly(DL-lactide-co-glycolide) were used:

1. 75/25 poly(DL-lactic-co-glycolic acid), A123-12, I.V. = 0.65 dL/g in CHCl₃ at 30°C, M.W. = 97,100 Da, Absorbable Polymer Technologies Inc., USA. This polymer will herewith be designated 75/25 PDLGA.

2. 5/25 poly(DL-lactic-co-glycolic acid), A123-03, I.V. = 0.24 dL/g in CHCl₃ at 30°C, M.W. = 23,800 Da, Absorbable Polymer Technologies Inc., USA. This relatively low molecular weight polymer will herewith be designated 75/25 PDLGA(L).

50/50 Poly(DL-lactic-co-glycolic acid), I.V. = 0.60 dL/g in CHCl₃ at 30°C, M.W. = ~80,000 Da, Birmingham Polymers, USA. This polymer will herewith be designated 50/50 PDLGA.

Poly(DL-lactic acid), I.V. = 1.07 dL/g in CHCl₃ at 30°C, M.W. = ~93,000 Da, Birmingham Polymers, USA. This polymer will herewith be designated PDLLA.

The inherent viscosity, initial molecular weight, and approximate degradation time of all polymers used in this study are presented in Table 1.

**Drugs:**

Dexamethasone (DM) USP, 9α-fluoro-162-methylprednisolone, Sigma D-9184.

Gentamicin sulfate (GS), (cell-culture tested), 590 μg gentamicin base per mg, Sigma G-1264.

Cortisone (CO), 17α,21-dihydroxy-4-pregnene-3,11,20-trione, Sigma C-2755.

**Table 1. Properties of the bioresorbable polymers used in this study.**

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Inherent viscosity* (dL/g)</th>
<th>Initial molecular weight (Da)</th>
<th>Approximate degradation time (months) in water [40]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLLA</td>
<td>3.90</td>
<td>450,000</td>
<td>&gt;24</td>
</tr>
<tr>
<td>PLLA(L)</td>
<td>1.60</td>
<td>200,000</td>
<td>&gt;24</td>
</tr>
<tr>
<td>75/25 PDLGA</td>
<td>0.65</td>
<td>97,100</td>
<td>4–5</td>
</tr>
<tr>
<td>75/25 PDLGA(L)</td>
<td>0.24</td>
<td>23,800</td>
<td>N/A</td>
</tr>
<tr>
<td>50/50 PDLGA</td>
<td>0.60</td>
<td>80,000</td>
<td>2–3</td>
</tr>
</tbody>
</table>

*The inherent viscosity values were measured by the manufacturers.
Metronidazole (ME), 2-Methyl-5-nitroimidazole-1-ethanol, Sigma M-3761.

The molecular weight and water solubility of all drugs used in this study are presented in Table 2.

**Film preparation**

Polymer films (0.12–0.15 mm thick) consisting of poly(α-hydroxy acid) and drug were prepared by a three-step solution processing method:

Step 1. Components were mixed in a solvent at room temperature until polymer dissolution. A constant quantity of 1 g polymer and 0.1 g drug (10% w/w) were chosen for all experiments. Both a diluted and a concentrated solution were prepared for each polymer/drug system. Chloroform was used as a solvent for all polymer/drug systems, except those containing ME, in which methylene chloride was used.

**Dilute solutions**

Dilute solutions were prepared by using relatively large volumes of solvent (polymer concentration: 0.01 g/mL, drug concentration: 0.6 mg/mL). Both the polymer and the drug were totally dissolved.

**Concentrated solutions**

Concentrated solutions were prepared by using relatively small volumes of solvent (polymer concentration: 0.05 g/mL, drug concentration: 3.0 mg/mL). In these solutions the polymer was totally dissolved, whereas the drug powder was only broken into small particles (aggregates), which yielded an opaque solution.

Step 2. Solution casting into a Petri dish and solvent drying under atmospheric pressure at room temperature. Two solvent evaporation rates were used. They could not be measured precisely

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**Table 2. Properties of the drugs used in this study**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular weight (g/mole)</th>
<th>Solubility in H₂O (mg/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (DM)</td>
<td>392.46</td>
<td>25</td>
</tr>
<tr>
<td>Cortisone (CO)</td>
<td>360.44</td>
<td>28</td>
</tr>
<tr>
<td>Gentamicin sulfate (GS)</td>
<td>477.6</td>
<td>5000</td>
</tr>
<tr>
<td>Metronidazole (ME)</td>
<td>171.15</td>
<td>1000</td>
</tr>
</tbody>
</table>

*The data were taken from the Merck index.*
but were evaluated as a relatively slow rate of 2–5 mL/h and a relatively fast rate of 10–20 mL/h. In order to get slow evaporation the Petri dish was covered with aluminum foil and in order to get slow evaporation rate the Petri dish was not covered.

**Step 3. Isothermal heat treatment at a temperature higher than the glass transition temperature of the polymer for at least 1 h in a vacuum oven.** This heat treatment enabled disposal of residual solvent.

**Morphological characterization**

Polarized light microscopy (LM) was performed using an Olympus BHS compound microscope or a Leica microscope (transmission mode).

**In vitro weight loss studies**

The polymer films (weight range 0.2–0.3 g) were weighed and then immersed in sterile water (50 mL, in a Petri dish) at 37°C in order to determine their weight loss profiles. Samples (also those broken into small pieces) were removed every week, dried in a vacuum oven, and weighed. If samples started to break down into small pieces due to degradation, the pieces were first collected. The weight loss was calculated as:

\[
\text{Weight loss (\%)} = 100 \times \frac{w_0 - w_f}{w_0},
\]

where \(w_0\) and \(w_f\) are the weights of the dried films before and after exposure to water, respectively. Five samples were tested for each point. The mean values and standard deviations are presented in the graphs.

**In vitro drug release study**

Polymer/drug films (0.08–0.1 g) were immersed in sterile water (only polymer/GS films were immersed in PBS) at 37°C in order to determine the kinetics of drug release from the films. Samples, 1.5 mL, were collected every week and replaced with a fresh medium of sterile water. The drug content in each sample was measured. DX500 Dionex High Performance Liquid Chromatography (HPLC) was used to measure DM and CO contents and an AD-20 Ultraviolet detector was used to monitor absorbance of DM at 254 nm and CO at 245 nm. The GS concentration was measured by spectrophotometry after derivatization.
with o-phthalaldehyde using Sampath and Robinson’s procedure [39], as follows: O-phthalaldehyde reagent was prepared by adding 2.5 g o-phthalaldehyde, 62.5 mL methanol, and 3 mL 2-hydroxyethylmercaptan to 560 mL 0.04 M sodium borate in distilled water. Two-hundred microliters gentamicin solution, 200 µL isopropanol (to prevent sedimentation), and 200 µL o-phthalaldehyde reagent were reacted for 45 min at room temperature. The absorbance, which corresponds to the gentamicin concentration, was then measured at 333 nm. ME contents were measured directly at 320 nm, without using any specific reaction. The GS and ME measurements were performed using a UV/vis scanning spectrophotometer (Anthos, Zenyth 200rt). At least three samples were examined for each film type. The mean values and standard deviations are presented in the graphs.

RESULTS AND DISCUSSION

The morphology of polymer/drug films

Polymer drug films were prepared by solution casting. In this process, the solvent evaporation rate strongly affects the kinetics of drug and polymer crystallization, and thus the mode of drug dispersion in the polymer [4]. Two types of film structures were created for most polymer/drug films in this study:

(a) A polymer film with large crystalline drug particles located on its surface, as presented in Figure 1(a) for PLLA films loaded with DM. This structure was derived from a dilute solution of both polymer and drug and was obtained using the slow solvent evaporation rate which enables prior drug nucleation and growth on the polymer solution surface. This skin formation is accompanied by a later polymer core formation/solidification. This structure was named the ‘A-type’.

(b) A polymer film with small drug particles and crystals distributed within the bulk, as presented in Figure 1(b) for PLLA films loaded with DM. This structure was derived from a concentrated solution and was obtained using the fast solvent evaporation rate and resulted from drug nucleation and segregation within a dense polymer solution. Solidification of drug and polymer occurred concomitantly. This structure was named the ‘B-type’. It has been noted earlier that in semi-crystalline based films, such as PLLA/DM, the drug is located in amorphous domains of a semi-crystalline matrix, around the spherulites [4].
The concept of ‘film structuring’ was investigated and it was found that A-type and B-type DM loaded films can be developed for both types of polymers, i.e., amorphous and semi-crystalline. Amorphous A-type films based on PDLLA and 50/50 PDLGA are presented (as examples) in Figure 1(c) and (e) and B-type films based on PDLLA and 50/50 PDLGA are presented (as examples) in Figure 1(d) and (f). In these films large rectangular DM crystals are located on the film surface of the A-type films, whereas small DM particles and crystals are spread within the bulk of the B-type films. Thus, it is demonstrated that the host polymer type affects the film morphology but has almost no effect on the drug.

**Figure 1.** Polarized light micrographs of various polymer/DM films. ((a) and (b) are taken from an earlier publication by the authors [5] and (c) and (d) from [4]).
location/dispersion within the polymeric film. The latter is determined mainly by the kinetics of film formation [4].

Three additional drugs were used in order to study the effect of the drug on the film structure: cortisone (CO) – a water insoluble drug, gentamicin sulfate (GS) – a water soluble drug, and metronidazole (ME) – a partially water soluble drug. Both A and B-type structures were created for these polymer/drug films. The film structures (based on PLLA) are presented in Figure 2. ME, similar to DM, also created large rectangular crystals on the surface of the film when a slow solvent evaporation rate was used to create the A-type film (Figure 2(a)). In contradistinction, when a fast evaporation rate was used most of the

Figure 2. Light micrographs of various PLLA/drug films.
ME was spread in particles and small crystals within the film, but some of the drug was located on the surface (Figure 2(b)). Large drug crystals on the surface of the polymeric films were also observed when CO was used. However, they were arranged in star-like structures (Figure 2(c)) rather than in rectangular structures, as with DM and ME. PLLA/GS films also created an A-type structure when a slow solvent evaporation rate was used. However, in this case it is difficult to see the drug particles, probably because of the irregularity of the host polymer (Figure 2(e)). B-type films were also created for PLLA/CO and PLLA/GS systems when a high solvent evaporation rate was used (Figure 2(d) and (f)). While observing the film morphologies it was noticed that part of the drug particles in B-type films loaded with ME and GS are located on the surface of the film. This was probably due to the hydrophilic nature of the drug. Although a concentrated solution and fast solvent evaporation rate were used, some of the drug molecules are not ‘trapped’ in the viscous crystallizing medium and tend to diffuse out to the surface because of their hydrophilic nature (the polymer solution is hydrophobic). In conclusion, the basic mode of drug dispersion/location in the film (A or B-type) is determined mainly by the film formation process and depends mainly on the solvent evaporation rate. The drug’s hydrophilicity has some effect on this structuring process.

**In vitro Drug Release from Bioresorbable Polymer/Drug Films**

In the current study, the effect of film structure (drug location/dispersion), drug type, polymer type and initial molecular weight on the drug release profile was examined. Five host polymers of various chain (chemical) structures were chosen for this study. Their inherent viscosities, initial molecular weights (evaluated by the manufacturers), and approximate total degradation times are presented in Table 1. PLLAs are the only semicrystalline polymers used in this study. 50/50 PDLGA and 75/25 PDLGA are amorphous. The neat films were exposed to aqueous medium and their weight loss was measured at weekly intervals. The weight loss profiles are presented in Figure 3. The weight of the polymers that degrade relatively fast could not be measured adequately for long periods of time and in these cases the weight loss study was performed only for a few weeks.

Both PLLAs degrade slowly. The relatively high M.W. PLLA showed almost no weight loss for 28 weeks in aqueous medium and the relatively low M.W. PLLA lost only 7% of its initial weight after 20 weeks of incubation. Both 75/25 PDLGA and 50/50 PDLGA contain glycolic acid in addition to lactic acid monomers. Lactic acid degrades slower than
glycolic acid due to the additional CH₃ group which makes it more hydrophobic and also provides steric hindrance to water attack on ester bonds. Both PDLGAs therefore degraded much faster than PLLA and practically could not be handled after several weeks of degradation. The low M.W. 75/25 PDLGA exhibited the fastest weight loss profile.

Effect of Drug Location/Dispersion in the Film

The cumulative release profiles of DM from both A-type and B-type PLLA films are presented in Figure 4(a). Both PLLA based films exhibited an almost linear release profile, i.e., constant release rate (slope). Such systems are desirable for many controlled release applications. The A-type film contains large DM crystals on the polymer film surface (Figure 1(a)). The A-type film therefore exhibited a ‘burst effect’, as expected, i.e., ≈30% of the drug was released during the first week of immersion in an aqueous medium. In contradistinction, most of the DM in the B-type film is located within the polymer film (Figure 1(b)) and only a small portion is located on the surface. The B-type PLLA/DM film therefore did not exhibit a burst effect, and its relatively slow rate of release results from the low rate of degradation and weight loss (Figure 3). It is clear that in this system degradation of the matrix polymer is essential in order to enable water penetration into the film and DM release from the film. Surprisingly, only 30% of the DM was released from the A-type PLLA/DM film during the first 3 days of degradation. This release behavior probably results from DM’s very hydrophobic nature (water solubility of 25 mg/100 mL, Table 2). Furthermore, PLLA contains ester groups and each DM molecule

Figure 3. Polymer weight loss of various films as a function of degradation time: x – 50/50 PDLGA, ▲ – PLLA, ○ – PLLA(L), ■ – 75/25 PDLGA, Δ – 75/25 PDLGA(L).
contains two carbonyl and three hydroxyl groups. Relatively strong specific interactions, namely hydrogen bonds, may have formed between the carbonyl oxygen atoms in the PLLA chains and the hydroxyl hydrogen atoms in DM. Such interactions may prevent intensive release of DM to the aqueous medium. Degradation of the polymer must occur in order to enable further release of drug located in the film. The fact that the constant DM release rate from the B-type PLLA/DM film is very similar to that from the A-type film supports the latter suggestion.

The 75/25 PDLGA film is amorphous and degrades relatively fast (Figure 3). The release profiles of DM from A and B-type 75/25 PDLGA films are presented in Figure 4(b). Unexpectedly, the DM release profile from the 75/25 PDLGA (A-type) film is similar to the release profile from the 75/25 PDLGA (B-type). A difference was observed mainly during the first 4 weeks of the study, and in both cases most of the drug was released after 20 weeks. This phenomenon is attributed to the relatively high rate of matrix polymer degradation and weight loss.

The cumulative release profiles of GS from PLLA and 75/25 PDLGA films are presented in Figure 4(c) and (d). The effect of drug location/
dispersion in the film is similar to that observed for DM loaded films. However, since GS is a very hydrophilic drug (water solubility of 5000 mg/100 mL, Table 2), it tends to diffuse from the host polymer and the release rates of GS from the PLLA films (Figure 4(c)) are therefore higher than those of DM (Figure 4(a)). When a host polymer which degrades very rapidly (such as 75/25 PDLGA) is used, a very high undesired burst release of hydrophilic drugs is obtained (Figure 4(d)). Drug location/dispersion in the polymeric film thus has a dominant effect on the release profile of the drug from the film when the degradation rate of the host polymer is slow. When the host polymer exhibits a fast degradation rate, a weight loss of several weeks probably enables some porosity which accelerates the diffusion of the drug molecules and the drug location/dispersion in the film therefore has a minor effect on the drug release profile.

Effect of Drug Type

The effect of the drug on its release profile from 75/25 PDLGA films is presented in Figure 5. A-type films loaded with DM, CO, and ME exhibited very similar release profiles, with a burst release of 30% followed by a moderate drug release (Figure 5(a)), as expected for A-type films with drug located on the surface of the film. Only GS-loaded films released most of the drug during the first day, due to the hydrophilic nature of the drug molecules. B-type films loaded with DM and CO exhibited a very low burst release followed by a relatively slow release at constant rate during weeks 2–20 (Figure 5(b)). B-type films loaded with ME also exhibited a relatively low burst release, but continued to release the ME molecules at a relatively high rate during the first 4 weeks of release. ME is partially water soluble (water solubility of

![Figure 5](image-url)
1000 mg/100 mL, Table 2) and therefore diffuses out of the bioresorbable films faster than the hydrophobic DM and CO (water solubility of 25 and 28 mg/100 mL, respectively). The relatively high rate of ME release from the B-type films may also result from the film structure, i.e., in these films some of the drug particles are located on the surface of the film (Figure 2(b)). B-type 75/25 PDLGA/GS films released 65% of the drug during the first day of release and a second phase of release started after 4 weeks (Figure 5(b)). The high burst release results from the hydrophilic nature of the drug and the second phase of release probably results from intensive degradation of the host polymer (8% weight loss after 4 weeks), which enables further diffusion of the remaining drug molecules. It can be concluded that the drug’s hydrophilicity has a major effect on its release rate, in addition to the drug location/dispersion in the film.

Effect of the Host Polymer and its Initial Molecular Weight

A series of three polymers: 50/50 PDLGA, 75/25 PDLGA, and PLLA, were used to elucidate the effect of the host polymer on the release profile. The DM release profiles from the B-type films (Figure 6(a)) indicate that the weight loss rate of the matrix polymer (Figure 3) has a significant effect on the rate of drug release. This behavior is expected, since most of the drug is located within the polymeric film, and supports the conclusion that degradation processes play a major role in these controlled release systems and that release does not occur solely by simple diffusion. Actually, these B-type films are monolithic (matrix) systems based on bioresorbable polymers. When monolithic systems are based on non-resorbable polymers, the release rate will usually decrease with time. In this research, the systems are based on bioresorbable matrix polymers. Degradation processes and the resulting increase in the system’s porosity therefore enable more effective diffusion of drug molecules from the film, which in most cases give rise to release profiles that are closer to a straight line (constant release rates).

All release profiles of the hydrophobic DM from A-type films exhibit a burst effect of ≈30% during the first 3 days (Figure 6(b)), indicating that 30% of the drug is probably located on the surface of the film but is not bound. The second release phase from the A-type film occurs at an approximately constant rate, which depends on the rate of polymer degradation. This phenomenon supports the suggestion that part of the drug may be physically bound to the polymer molecules within the film via hydrogen bonds. In contradistinction, the release profiles of the hydrophilic GS from A-type films based on PDLGAs exhibit a high burst effect of at least 65% (Figure 6(c)). Only PLLA/GS films showed a more
Figure 6. Effect of the host polymer type on the cumulative drug release from A-type and B-type polymer/drug films: (a) B-type polymer/DM films, (b) A-type polymer/DM films, and (c) A-type polymer/GS films. The host polymer is indicated.
moderate release profile. It is therefore suggested that if controlled release of water soluble drugs, for example GS, is desired, they should be loaded only onto films based on polymers with a slow rate of degradation (preferably B-type films).

The effect of the initial molecular weight of the host polymer on the release profile of GS from 75/25 PDLGA and PLLA films is presented in Figure 7. When 75/25 PDLGA was used as a host polymer, a higher initial molecular weight resulted in a lower burst release from the B-type film (Figure 7(b)), but did not affect the release profile of GS from the A-type film (Figure 7(a)). When PLLA was used as a host polymer, a higher initial molecular weight resulted in a lower burst release and a moderate release profile (Figure 7(c) and (d)). As expected, this trend is more significant for B-type films than for A-type films. Films based on higher molecular weight polymers exhibited lower burst effects due to a greater amount of hydroxyl and carboxylic edge groups, which make the polymer more hydrophobic. Furthermore, a higher molecular weight results in a higher glass transition temperature, which facilitates slower drug release from the polymer. A relatively high

\[\text{Figure 7. Effect of the host polymer's initial molecular weight on the cumulative release from polymer/GS films: (a) A-type 75/25 PDGLA/GS films, (b) B-type 75/25 PDGLA/GS films, (c) A-type PLLA/GS films, and (d) B-type PLLA/GS films. \(\square\) – Low M.W. host polymer, \(\blacktriangle\) – Relatively high M.W. host polymer.}\]
initial molecular weight is thus favorable when bioresorbable films are loaded with hydrophilic drugs which tend to diffuse out easily from the host film. It is more effective in B-type films and when the host polymer is more hydrophobic.

Finally, the results demonstrate that in addition to the drug location/dispersion in the film, the host polymer and drug type also strongly affect the drug’s release profile from the film. The ability to control the drug release profile by choosing the right process parameters and polymer type makes it possible to fit the release profile to the application. For example, if relatively high release rate is needed, a system based on polymer with fast degradation rate should be chosen and A-type film should be considered when burst release is needed. In contradiction, when relatively low release rate is needed, a system based on polymer with slow degradation rate should be chosen and B-type film should be considered when high burst release is not favorable. In certain cases, the drug type (hydrophobic/hydrophilic) can also be chosen so that it will help to get a desired profile. It should also be mentioned that large drug crystals on the surface of the polymeric film may affect the degree of foreign body reactions and as a result, also the drug release profile. This point should also be addressed when the system for a specific application is considered.

**SUMMARY AND CONCLUSIONS**

Bioresorbable drug-loaded polymer films were prepared by solution processing. Investigation of the films focused on cumulative drug release as affected by film morphology (drug location/dispersion in the film), drug type, the host polymer, and its initial molecular weight. Two film structures were studied: a polymer film with large drug crystals located on its surface (A-type), and a polymer film with small drug particles and crystals distributed within the bulk (B-type). The basic mode of drug dispersion/location within the film (A or B-type) is determined mainly by the process of film formation and depends mainly on the solvent’s evaporation rate. The drug’s hydrophilicity has some effect on this structuring process.

In general, the drug location/dispersion in the film, the host polymer, and the drug type determine the drug’s release profile from the film. The initial molecular weight of the host polymer can help achieve the desired drug release profile in certain cases. Most release profiles from A-type films exhibited a burst effect of $\approx 30\%$ and a second release stage from these films occurs at an approximately constant rate, which is determined mainly by the polymer weight loss rate. Only a very
hydrophilic drug exhibited an extremely high burst release. In most of the studied systems, the matrix (monolithic) nature of the B-type film enabled release profiles that were determined mainly by the degradation profile of the host polymer, with a very low burst effect.

It has been shown that appropriate selection of the process parameters and film components (polymer and drug) can yield film structures with desirable drug release behaviors. This can lead to the engineering of new bioreposable drug-eluting film-based implants for various applications.

REFERENCES


