Novel Biodegradable Composite Wound Dressings With Controlled Release of Antibiotics: Microstructure, Mechanical and Physical Properties

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Abstract: Wound dressings aim to restore the milieu required for skin regeneration and protect the wound from environmental threats, including penetration of bacteria. The dressings should be easy to apply and remove and maintain a moist healing environment. In this study, novel biodegradable composite wound dressings based on a polyglyconate mesh and a porous PDLGA binding matrix were developed and studied. These novel dressings were prepared by dip-coating woven meshes in inverted emulsions, followed by freeze-drying. Their investigation focused on the microstructure, mechanical and physical properties, and the release profile of the antibiotic drug ceftazidime from the binding matrix. The mechanical properties of our wound-dressing structures were found to be superior, combining relatively high tensile strength and ductility, which changed only slightly during 3 weeks of incubation. A range of dressing formats based on films, hydrophilic gels, and foams are available or have been investigated. Films and gels have a limited absorbance capacity and are recommended for light to moderately exudating wounds, whereas foams are highly absorbent and have a high WVTR and are, therefore, considered more suitable for wounds with moderate to heavy exudation. The characteristics of the latter are controlled by the foam texture, pore size, and dressing thickness.

INTRODUCTION
The main goal in wound management is to achieve rapid healing with functional and esthetic results. An ideal wound dressing can restore the milieu required for the healing process, while protecting the wound bed against penetration of bacteria and environmental threats. The dressing should also be easy to apply and remove. Most modern dressings are designed to maintain a moist healing environment and to accelerate healing by preventing cellular dehydration and promoting collagen synthesis and angiogenesis. Nonetheless, overrestriction of water evaporation from the wound should be avoided, as accumulation of fluid under the dressing may cause maceration and facilitate infection. The water vapor transmission rate (WVTR) from the skin has been found to vary considerably depending on the wound type and healing stage, increasing from 204 g m⁻² day⁻¹ for normal skin to 278 and as much as 5138 g m⁻² day⁻¹ for first degree burns and granulating wounds, respectively. The physical and chemical properties of the dressing should therefore be adapted to the type of wound and to the degree of wound exudation.

A range of dressing formats based on films, hydrophilic gels, and foams are available or have been investigated. Thin semipermeable polyurethane films coated with a layer of acrylic adhesive, such as Optsite® (Smith & Nephew) and Bioclusive® (J & J), are typically used for minor burns, postoperative wounds, and a variety of minor injuries including abrasions and lacerations. Gels such as carboxymethylcellulose-based Intrasite Gel® (Smith & Nephew) and alginate-based Tegagel® (3M) are used for many different types of wounds, including leg ulcers and pressure sores. These gels promote rapid debridement by facilitating rehydration and autolysis of dead tissue. Foam dressings, such as Lyofoam (Mölnlycke Healthcare) and Allevyn (Smith & Nephew), are used to dress a variety of exuding wounds, including leg and decubitus ulcers, burns, and donor sites.

Films and gels have a limited absorbance capacity and are recommended for light to moderately exudating wounds, whereas foams are highly absorbent and have a high WVTR and are, therefore, considered more suitable for wounds with moderate to heavy exudation. The characteristics of the latter are controlled by the foam texture, pore size, and dressing thickness.

Bacterial contamination of a wound seriously threatens its healing. In burns, infection is the major complication after the initial period of shock, and it is estimated that about...
75% of the mortality following burn injuries is related to infections rather than to osmotic shock and hypovolemia. Bacteria in wounds are able to produce a biofilm within ~10 h. This biofilm protects them against antibiotics and immune cells already in the early stages of the infection process. The rapidity of biofilm growth suggests that efforts to prevent or slow the proliferation of bacteria and biofilms should begin immediately after creation of the wound. This has encouraged the development of improved wound dressings that provide an antimicrobial effect by eluting germicidal compounds such as iodine (Iodosorb<sup>®</sup>, Smith & Nephew), chlorohexidine (Biopatch<sup>®</sup>, J & J), or most frequently silver ions (e.g., Acticoat<sup>®</sup> by Smith & Nephew, Actisorb<sup>®</sup> by J & J, and Aquacell<sup>®</sup> by ConvaTec). Such dressings are designed to provide controlled release of the active agent through a slow but sustained release mechanism which helps avoid toxicity yet ensures delivery of a therapeutic dose to the wound. Some concerns regarding safety issues related to the silver ions included in most products have been raised. Furthermore, such dressings still require frequent change, which may be painful to the patient and may damage the vulnerable underlying skin, thus increasing the risk of secondary contamination.

Bioresorbable dressings successfully address this shortcoming, as they do not need to be removed from the wound surface once they have fulfilled their role. Biodegradable film dressings made of lactide-caprolactone copolymers such as Topkin<sup>®</sup> (Biomet) and Oprafol<sup>®</sup> (Lohmann & Rauscher) are currently available. Bioreosorbable dressings based on biological materials such as collagen and chitosan have been reported to perform better than conventional and synthetic dressings in accelerating granulation tissue formation and epithelialization. However, controlling the release of antibiotics from these materials is challenging because of their hydrophilic nature. In most cases, the drug reservoir is depleted in less than 2 days, resulting in a very short antibacterial effect.

There is currently no available synthetic dressing that combines the advantages of occlusive dressings with biodegradability and intrinsic topical antibiotic treatment. We have recently reported the development of biodegradable composite core/shell fibers loaded with antibiotics which could potentially be used as a basic unit for such wound dressings. In this study, we developed a composite wound dressing based on this concept. We propose a plain-woven textile made of biodegradable polyglyconate fibers bound together with a continuous porous matrix that affords the dressing an occlusive nature. The reinforcing fibers’ excellent mechanical properties afford good mechanical strength, whereas the continuous binding matrix can be tailored to produce the desired effect: e.g., drug release kinetics, water absorbance, and other physical properties that promote wound healing. The goal of this study was, therefore, to develop this type of dressing and characterize its main features: mechanical and physical properties and drug release profile to elucidate whether it may have better wound healing properties.

### MATERIALS AND METHODS

#### Materials

**Polymers.** Maxon<sup>TM</sup>, polyglyconate monofilament sutures with a diameter of 0.20–0.25 mm, United States Surgical, USA, were woven to produce a mesh.

Bioresorbable porous structures (binding matrices) were made of 50/50 poly(α-lactic-co-glycolic acid) (PDLGA), inherent viscosity (i.v.) = 0.56 dL/g (in CHCl<sub>3</sub> at 30°C, MW ~ 100 KDa), Absorbable Polymer Technologies, USA.

**Drug.** Ceftazidime hydrate, 90–105%, Sigma (C-3809).

**Surface active agent.** Bovine serum albumin (BSA), MW = 66,000 Da, Sigma (A-4503).

Sorbitan monooleate (Span 80), MW 428.608 g mol<sup>−1</sup>, Sigma (85548).

**Reagents.** 1,1,3,3,3-Hexafluoro-2-propanol (H1008) was purchased from Spectrum Chemical Mfg. Corp.

#### Wound dressing preparation

**Fiber surface treatment.** The sutures were surface treated to dispose of the original fiber coating and enhance adhesion between the core fiber and the binding porous matrix. The Maxon<sup>TM</sup> fibers were gently wrapped around flexible Teflon frames and dipped in 1,1,3,3,3 hexafluoro-2-propanol for 40 s. The fibers were then washed with 70% ethanol and dried. The surface treated Maxon fibers were hand- woven into a plain-woven fabric (the most basic fundamental textile weave) with 1.5 mm gaps between adjacent fibers.

**Inverted emulsion formation.** An organic solution was prepared by dissolving a known amount of PDLGA (15% w/v) in chloroform. An aqueous solution was obtained by dissolving 1% w/v (relative to the polymer load) and surfactant. The aqueous solution was then poured into the organic solution (in a test tube) and homogenized to an inverted emulsion using a Kinematica PT-3100 Polytron homogenizer operating at 18,000 rpm for 1.5 min. Three formulations were prepared:

a. Formulation with organic–aqueous phase ratio (O:A) = 6:1 containing 1% w/v BSA (relative to the aqueous volume) as surfactant. This formulation is termed BSA1.

b. Formulation with O:A = 12:1 containing 1% w/v BSA (relative to the aqueous volume) as surfactant. This formulation is termed BSA2.

c. Formulation with O:A = 12:1 containing 1% w/v Span 80 (relative to the organic phase volume) as surfactant. This formulation is termed SPAN.

The woven structure was then dip coated (while placed on holders) in fresh inverted emulsions and then immediately frozen in a liquid nitrogen bath. The samples were then placed in a precooled (−105°C) freeze-dryer (Virtis 101 equipped with a nitrogen trap) and freeze-dried to preserve the microstructure of the emulsion-based structures. Drying was performed in two stages: The freeze-dryer chamber pressure was reduced to 100 mTorr while the
temperature remained at –100°C. After 3 h a hot plate was turned on to –45°C for an additional 12 h. The condenser was then turned off and its plate temperature gradually increased to room temperature while the pressure was monitored between 100 and 700 mTorr. During this step, the liquid nitrogen trap condensed the excess water and solvent vapors. The dried samples were stored in desiccators until use.

Morphological characterization
The morphology of the wound dressing’s structures was observed using a Jeol JSM-6300 scanning electron microscope (SEM) at an accelerating voltage of 5 kV. Cryogenically fractured surfaces were Pd-sputtered before observation.

In vitro changes in the morphology of wet wound dressing structures were characterized using an environmental SEM (Quanta 200 FESEM) at an accelerating voltage of 10 kV and a pressure of 4.5 Torr. Specimens were fixed to a special base, fractured surface facing up, and maintained in PBS (37°C, pH 7.0) for 14 days. Initial fractographs were taken and coordinates were recorded so as to enable return to these coordinates at 2, 4, and 14 days after immersion in PBS.

The mean pore diameter \( (n = 100 \text{ pores}) \) and porosity of the observed morphologies was analyzed using the Sigma Scan Pro software and statistics were calculated using the SPSS 10 software. Statistical significance was determined using the ANOVA (Tukey-Kramer) method. The area occupied by the pores was calculated for each SEM fractograph using the Sigma Scan Pro software to evaluate the porosity of the samples. Porosity was determined as the area occupied by the pores divided by the total area.

Water vapor transmission rate
The moisture permeability of the wound dressing was determined by measuring the WVTR across the dressing. A Sheen Payne permeability cup with an exposure area of 10 cm² was filled with 10 mL PBS and covered with a circular wound dressing. The cup was placed in a straight position inside an oven at 37°C, containing 1 kg of freshly dried silica gel to maintain relatively low humidity conditions. The weight of the assembly was measured every hour for 12 h and a graph of the evaporated water versus time was plotted. WVTR was calculated by the formula:

\[
\text{WVTR} = \frac{\text{slope} \times 24}{\text{area}} \left[ \frac{g}{m^2 \cdot \text{day}} \right]
\]  

Water uptake ability
The fluid absorbing capacity of a wound dressing is an important criterion for maintaining a moist environment over the wound bed. Water uptake was measured over 7 days. Dry wound dressings were cut into 1 cm × 1.5 cm rectangles, weighed, and placed in bottles containing 2 mL PBS (pH 7.0). The bottles were closed and placed in an incubator at 37°C. The weight of the samples was measured after 6 h, 12 h, 1, 2, 3, and 7 days by removing the PBS and blotting them gently to remove excess fluid. The water uptake was calculated as:

\[
\text{Water uptake (\%) } = \frac{W_{\text{wet}} - W_{\text{dry}}}{W_{\text{dry}}} \times 100
\]  

Tensile mechanical properties
The wound dressing’s tensile mechanical properties were measured at room temperature, under unidirectional tension at a rate of 10 mm/min, using a 5500 Instron machine. Each wound dressing sample was cut into a dog bone shape (neck length 5 cm, width 1 cm). The tensile strength was defined as the maximum strength in the stress-strain curve. The maximal strain was defined as the breaking strain. Young’s modulus was defined as the slope of the stress-strain curve in the elastic (linear) region. Four samples were tested for each type of specimen. Additional specimens were immersed in phosphate buffered saline (PBS), pH 7.0, at 37°C for 1, 2, and 3 weeks, after which they were dried and tested in the same manner.

The means and standard deviations were calculated using the SPSS 10 software. ANOVA (Tukey-Kramer) was used for group comparison.

In vitro drug release studies
The composite wound dressings were immersed in PBS at 37°C for 28 days to determine the various drug release kinetics from these structures. The release studies were conducted in closed glass vessels containing 1.5 mL PBS. The medium was removed (completely) periodically, at each sampling time (6 h, 1, 2, 3, 7, 14, 21, and 28 days), and fresh medium was introduced.

Ceftazidime assay. The medium’s ceftazidime content was determined using a Jasco HPLC with a UV 2075 plus detector and a reverse phase column (Intersil® ODS-3V 5 μm, inner diameter \( d = 4.6 \) mm, length = 250 mm), kept at 25°C. The mobile phase consisted of a mixture of PBS and acetonitrile (95/5, v/v) at a flow rate of 1 mL/min with a quaternary gradient pump (PU 2089 plus) without gradient. Twenty microliters of samples were injected with an autosampler (AS 2057 Plus). The column effluent was eluted for 22 min and detected at 254 nm. The area of each eluted peak was integrated using EZstart software version 3.1.7. A calibration curve was prepared for concentrations ranging from 1.0 to 200.0 μg/mL (correlation coefficient > 0.999, slope: 0.0000318).

Residual drug recovery from composite dressings
Residual drug recovery from the composite dressings was measured as follows: the fibers were placed in 1 mL methylene chloride to dissolve the remaining PDLGA coating. Two milliliters of water was then added to dissolve the hydrophilic drug residues. The materials were vortexed for 30 s and then left to stand until phase separation occurred.
The aqueous phase was filtered to dispose of polymer particles. The drug concentration was estimated using the aforementioned assays.

RESULTS
Morphological characterization of dry wound dressings
A composite wound-dressing construction composed of a plain-woven mesh of polyglyconate fibers bound by a continuous PDLGA porous matrix loaded with the antibiotic ceftazidime was developed and studied. A SEM fractograph showing a basic unit structure of the wound dressing is presented in Figure 1(a). The PDLGA matrix adhered well to the fibers, forming a skin layer ~60 μm thick, as demonstrated in Figure 1(b).

The freeze-drying of inverted emulsions technique that was used to create the PDLGA-binding matrix resulted in a porous microstructure [shown in Figure 1(c,d)] which also acts as a reservoir for the antibiotic that is incorporated in it. Three different emulsion formulations were used in this study, as listed in Table I. These three formulations yielded different resultant matrix microstructures. The microstructure of the BSA1 sample is highly porous [Figure 2(a)] with an average porosity of 63 ± 4% and pore diameter of 1.4 ± 0.3 μm (Table I). An increase in the emulsions’ organic-aqueous phase ratio from 6:1 to 12:1 (formulation BSA2) resulted in larger polymer domains between pores, less pore connectivity, and a lower porosity of 35% ± 2% [Figure 2(b) and Table I]. However, it did not significantly affect the pore size, which remained 1.4 ± 0.3 μm. When the surfactant BSA which was used to stabilize the emulsion was replaced with Span 80 (formulation SPAN) for the same O:A phase ratio (12:1), the mean pore size decreased to 1.1 ± 0.3 μm, whereas porosity increased to 45% ± 7% [Figure 2(c) and Table I].

Water vapor transmission rate
WVTR was measured for the three types of dressings, based on the formulations in Table I. Evaporative water loss through the various dressings [Figure 3(a)] was linearly dependant on time ($R^2 > 0.99$ in all cases), resulting in a constant WVTR. A WVTR of 3452 ± 116 g m⁻² day⁻¹ was measured for a dressing based on the BSA1 formulation. When the O:A phase ratio was increased to 12:1 (BSA2), the WVTR decreased significantly to 480 ± 69 g m⁻² day⁻¹. A WVTR of 2641 ± 42 g m⁻² day⁻¹ was measured when the surfactant BSA was replaced with Span 80 (SPAN). The WVTR was determined experimentally also for a dense non-porous PDLGA film, prepared using the solution casting technique as described elsewhere, to serve an analogue for biodegradable films currently in use for wound care, as well as to elucidate the effect of porosity on the WVTR. A WVTR of 356 ± 106 g m⁻² day⁻¹ was measured in this case. The WVTR of an exposed aqueous surface was also determined experimentally, in order to simulate a condition in which no dressing is applied to the wound surface. In this case, the WVTR was 6329 ± 725 g m⁻² day⁻¹.

![Figure 1. SEM fractographs of a ceftazidime-loaded composite wound dressing: (a) A representative plain-weave basic unit structure, (b) a cross section view of the reinforcing fibers and binding drug-loaded porous matrix, (c) and (d) detailed views of the continuous porous matrix structure.](image)

![Table I. Structural Characteristics of the Ceftazidime-Loaded Porous Matrix](table)

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Organic–Aqueous Phase Ratio</th>
<th>Drug Loadinga (w/w)</th>
<th>Polymer Content in the Organic Phaseb (w/w)</th>
<th>Surfactantb</th>
<th>Freeze-Dried Emulsion</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>BSA (1% w/v in the aqueous phase)</td>
<td>63 ± 4% 1.4 ± 0.3 μm</td>
</tr>
<tr>
<td>BSA1</td>
<td>6:1</td>
<td>5%</td>
<td>15%</td>
<td>BSA (1% w/v in the aqueous phase)</td>
<td>35 ± 2% 1.4 ± 0.3 μm</td>
</tr>
<tr>
<td>BSA2</td>
<td>12:1</td>
<td></td>
<td></td>
<td>Span80 (1% w/v in the organic phase)</td>
<td>45 ± 7% 1.1 ± 0.3 μm</td>
</tr>
<tr>
<td>SPAN</td>
<td>12:1</td>
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a Relative to the polymer weight.  
b Relative to a liquid phase volume (organic or aqueous).
Water uptake

BSA1 (O:A = 6:1) and BSA2 (O:A = 12:1) formulations were used to measure the fluid absorption capacity of our new wound dressings. Samples were placed in PBS (pH 7.0) to simulate the water absorption behavior in the presence of wound fluids. Water absorption ability was calculated according to the formula described in Experimental Section. Both types of dressings displayed similar temporal water absorption patterns, consisting of the following stages [Figure 4(a)]:

1. A rapid initial water uptake within the first 24 h. A considerable share of the initial water uptake actually occurred during the first 6 h [Figure 4(a), inset]. A 65% (w/w) increase in the weight of the BSA1 type dressings was observed at this stage, whereas dressings of type BSA2 increased by 56%.
2. A slight decrease in water content during the following 3 days, reaching ~45% w/w for both types of dressings.
3. A steady increase over the next 2 weeks, reaching a 125% increase in weight after 3 weeks, for both types of dressings.

The changes in the microstructure of the wet matrix samples because of water uptake showed initial reorganization of the porous structure with a small decrease in pore size, followed by gradual thickening of the polymeric walls, as presented in Figures 4(b–e). These changes led to coarser porous structures.

Tensile mechanical properties

The effect of polymer degradation on the wound dressing’s mechanical properties was determined using the BSA1 formulation. The results are presented in Figure 5. Dressings incubated for 1, 2, and 3 weeks displayed similar tensile strengths (21–27 MPa) and strains at break (55–63%). When failure occurred, it was initiated because of break of the reinforcing fibers and not by the matrix. The initial Young’s modulus of the dressing (126 ± 27 MPa) was preserved for 1 week of incubation (117 ± 19 MPa) and then decreased to ~70 MPa after 2 weeks.

In vitro drug-release studies

The release profile of antibiotics from wound dressings varied considerably with the changes in formulation (Figure 6). Ceftazidime release from the dressings based on the BSA1 formulation was relatively short, reaching almost complete release of the encapsulated drug within 24 h. An increase in the emulsion’s O:A phase ratio from 6:1 to 12:1 reduced the burst release. Specifically, burst release values of 97 and 57% were recorded after 6 h for formulations BSA1 and BSA2, respectively, after which the release of the antibiotics from BSA2 dressings continued for 5 days at a decreasing rate. The ceftazidime release profile from the SPAN formulation was totally different. It exhibited a low burst release of 6% during the first 6 h of incubation and then a release pattern of a nearly constant rate for 10 days.

DISCUSSION

A composite wound dressing based on a fibrous polyglyconate mesh embedded within a porous drug-loaded PDLGA porous matrix was developed and studied. Composites are made up of individual materials, matrix, and reinforcement. The matrix component supports the reinforcement material by maintaining its relative positions and the reinforcement material imparts its special mechanical properties to enhance the matrix properties. Taken together, both
materials synergistically produce properties unavailable in the individual constituent materials, allowing the designer to choose an optimum combination. In our application, the reinforcing polyglyconate mesh affords the necessary mechanical strength to the dressing, whereas the porous PDLGA binding matrix is aimed to provide adequate moisture control and release of antibiotics to protect the wound bed from infection and promote healing. Both structural

![Figure 3](https://www.interscience.wiley.com)

**FIGURE 3.** (a) Water loss versus time plots: Uncovered surface, BSA1 formulation, BSA2 formulation, SPAN formulation, and dense (non-porous) PDLGA (50/50, MW 100 KDa) film, (b) Water vapor transmission rates for the various wound dressings. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

![Figure 4](https://www.interscience.wiley.com)

**FIGURE 4.** (a) Water uptake by two dressing formulations containing: 5% w/w ceftazidime, 15% w/v polymer (50/50 PDLGA, MW 100 KDa), stabilized with 1% w/v: BSA1 (O:A = 6:1) and BSA2 (O:A = 12:1). (b–e) E-SEM fractographs of BSA1, recorded during the water uptake experiment at 0 (b), 2 (c), 4 (d) and 14 days (e). In addition, larger domains of (b) and (e) are presented. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
constituents are biodegradable, thus enabling easy removal of the wound dressing from the wound surface once it has fulfilled its role.

The freeze-drying of inverted emulsions technique which was used to create the porous binding matrix is unique in its ability to preserve the liquid structure in the solid state. The viscous emulsion, consisting of a continuous PDLGA/chloroform solution phase and a dispersed aqueous drug solution, formed good contact with the mesh during the dip-coating process. Consequently, an unbroken solid porous matrix was deposited by the emulsion following freeze-drying, as demonstrated in Figure 1(a).

The freeze-drying of inverted emulsions technique has several advantages. First, it enables attaining a thin uninterrupted barrier, which unlike mesh or gauze alone can better protect the wound bed against environmental threats and dehydration. Second, it entails very mild processing conditions which enable the incorporation of sensitive bioactive agents such as antibiotics and even growth factors to help reduce the bio-burden in the wound bed and accelerate wound healing. Third, the microstructure of the freeze-dried matrix can be customized through modifications of the emulsion’s formulation to exhibit different attributes, namely different porosities or drug release profiles. Three formulations were used in this study and their effects on the microstructure, the resulting physical and mechanical properties, and the drug release profile were studied.

**Microstructural and physical properties**

In this study, we focused on three matrix formulations (listed in Table I), which display distinctly different microstructural features (Figure 2 and Table I). The effect of the O:A phase ratio was examined on formulations containing BSA as surfactant. As expected, a higher O:A phase ratio, i.e. lower aqueous phase quantity, resulted in a smaller porosity of the solid structure. However, both microstructures were homogenous and characterized by a similar average pore size. The stabilization effect of Span 80 was even higher than that obtained using BSA and therefore resulted in a smaller pore size (Table I).

Successful wound healing requires a moist environment. Two parameters must therefore be determined: the water uptake ability of the dressing and the WVTR through the dressing. An excessive WVTR may lead to wound dehydration and adherence of the dressing to the wound bed, whereas a low WVTR might lead to maceration of healthy surrounding tissue and buildup of a back pressure and pain to the patient. A low WVTR may also lead to leakage from the edges of the dressing which may result in dehydration.

![Figure 5](https://example.com/fig5.png)

**FIGURE 5.** (a) Tensile stress–strain curves for wound dressings immersed in PBS for 0 (–0–), 1 (–1–), 2 (–2–), and 3 (–3–) weeks. (b) Young’s modulus, (c) tensile strength, and (d) maximal tensile strain as a function of immersion time. Comparison was made using ANOVA and significant differences are indicated (*). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

![Figure 6](https://example.com/fig6.png)

**FIGURE 6.** Cumulative release of ceftazidime from wound dressings based on the following formulations: •-BSA1, ■-BSA2, ▲-SPAN. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
and bacterial penetration.\textsuperscript{3,13} It has been claimed that a wound dressing should ideally possess a WVTR in the range of 2000–2500 g m\(^{-2}\) day\(^{-1}\), half of that of a granulating wound.\textsuperscript{13} In practice, however, commercial dressings do not necessarily conform to this range and have been shown to cover a larger spectrum of WVTR, ranging from 90 (Dermiflex\textsuperscript{10}, J & J\textsuperscript{14}) to 3350 g m\(^{-2}\) day\(^{-1}\) (Beschitin\textsuperscript{9}, Unika\textsuperscript{15}). Clearly, the WVTR is related to the structural properties (thickness, porosity) of the dressing as well as to the chemical properties of the material from which it is made. The results for our dressings, shown in Figure 3, demonstrate how the WVTR can be customized based on modifications of the porous matrix’s microstructure. In this study, we examined what we consider the upper (12:1) and lower (6:1) O:A phase ratio boundaries which would be suitable for this type of application, in terms of emulsion stability and in terms of the desired drug release profiles. We were able to cover a large range of WVTRs, between 480 and 3350 g m\(^{-2}\) day\(^{-1}\).

The lowest value is similar to that reported for film-type dressings (e.g., Tegaderm, 491 \pm 44 g m\(^{-2}\) day\(^{-1}\)),\textsuperscript{10} whereas the highest value is similar to that of foam-type dressings (e.g., Lyofoam, 3052 \pm 684 g m\(^{-2}\) day\(^{-1}\)).\textsuperscript{16} Based on our previous results, where it was shown that the porosity of freeze-dried emulsions can be altered progressively by modification of the emulsions’ O:A ratio,\textsuperscript{10} there is good reason to believe that a WVTR in this range can be fine tuned by altering the O:A phase ratio of formulations which include BSA as surfactant anywhere between 6:1 and 12:1, and specifically to the 2000–2500 g m\(^{-2}\) day\(^{-1}\) range. A WVTR of 2641 \pm 42 g m\(^{-2}\) day\(^{-1}\) that was achieved with the SPAN formulation is close to this range and seems the most appropriate.

Water uptake by the wound dressing may occur either as the result of water entry into accessible voids in the porous matrix structure (hydration effect) or as the polymer matrix material gradually uptakes water and swells (swelling effect). Our water uptake patterns for wound dressings based on the BSA1 and BSA2 formulations (Figure 4) demonstrated both these effects. As mentioned in the results section, both types of wound dressing demonstrated a three-stage water uptake pattern. Examination of the water uptake process through temporal microstructural changes in the polymeric matrix sheds light on these stages, as follows:

Stage 1 (governed by hydration): during this stage of water uptake, a quick flux of water associated with hydration of the porous structures was measured within 6 h after immersion in PBS for both types of dressings, as demonstrated in Figure 4(a). Water content then plateaued at values of 65% for the BSA1 formulation with the higher porosity (63%) and 55% for the BSA2 formulation with the smaller porosity (35%).

Stage 2: A small decrease in water content during days 2–4, probably due to gradual shrinkage of pore walls and reorganization of the porous matrix [Figures 4(b–d) and Table II]. Such changes could be provoked by a combined effect of the polymer’s glass transition temperature that is very close to the incubation temperature (37 °C) in combination with a softening effect of water on the polymer. It has been shown, for instance, that amorphous electrospun PDLGA fibrous mats undergo drastic shrinkage after 1 day of in vitro incubation because of the relaxation of extended amorphous chains.\textsuperscript{17} A 26% decrease in the void fraction of the polymer matrix [Figure 4(e) and Table II] evidently caused a reduction in the water volume contained within the matrix (~20%) during this phase.

Stage 3 (governed by swelling): After the 4th day of immersion in the aqueous medium, water uptake increased gradually and similarly for both types of dressing over the duration of 3 weeks, ultimately reaching a twofold increase. The process of swelling is dependent on the polymer’s water affinity. As PDLGA is not as hydrophilic as hydrogels or natural polymers used in this application, swelling occurred slowly. It is believed that the swelling effect was enhanced over time as hydrophilic end groups became more abundant because of polymer degradation by hydrolysis. This stage is also characterized by gradual thickening of the polymer walls because of the increased water uptake and creation of larger voids in the matrix because of polymer degradation [Figure 4(e)]. The combination of these two changes, which occurred in parallel, resulted in a coarser microstructure.

We appreciate that the gradual increase of porosity because of degradation would consequently result in an increase over time in the WVTR values presented thus far. Such changes in WVTR are not a matter for concern as it is expected that the barrier properties of the regenerating skin would be restored at a corresponding rate. Furthermore, a gradual increase in WVTR over time could encourage wound closure as shown by Schunck et al. (2005) in a recent study comparing in vivo response to occlusive versus nonocclusive dressings.\textsuperscript{18} They discovered that the use of occlusive dressings during the entire or 2 weeks of the healing period promotes cell migration but delays wound closure and so a gradual reduction in the dressing’s barrier properties over 1–2 weeks could have a beneficial effect on wound closure.

It should also be mentioned that delamination of the fiber-matrix interface may affect the integrity of the wound dressing as well as barrier properties. We have, therefore, examined the effect of degradation on the interface and found that the dressing material maintained its integrity for the duration of at least 2 weeks exposure to aqueous medium, despite a gradual ongoing process of degradation of the matrix component. SEM observations [Figure 7] showed high quality fiber-matrix interface, i.e. contact between the two components still exists as degradation proceeds.

<table>
<thead>
<tr>
<th>Incubation Time (Days)</th>
<th>Porosity (%)</th>
<th>Pore Diameter (µm)</th>
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<tbody>
<tr>
<td>0</td>
<td>63 ± 4</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>2</td>
<td>53 ± 6</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>4</td>
<td>37 ± 2</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>14</td>
<td>57 ± 3</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

TABLE II. Structural Characteristics of the BSA1 Wound Dressing at Various Times of Incubation in Aqueous Medium
Tensile mechanical properties

The mechanical properties of a wound dressing are an important factor in its performance, whether it is to be used topically to protect cutaneous wounds or as an internal wound support, e.g. for surgical tissue defects or hernia repair. Furthermore, in the clinical setting, appropriate mechanical properties of dressing materials are needed to ensure that the dressing will not be damaged by handling. Porous structures typically possess inferior mechanical properties compared to dense structures, yet in wound healing applications porosity is an essential requirement for diffusion of gasses, nutrients, cell migration, and tissue growth. Most wound dressings are, therefore, designed according to the bilayer composite structure concept and consist of an upper dense "skin" layer to protect the wound mechanically and prevent bacterial penetration and a lower spongy layer designed to adsorb wound exudates and accommodate newly formed tissue. Our new dressing design integrates both structural/mechanical and functional components (e.g. drug release and moisture management) in a single composite layer. It combines relatively high tensile strength and modulus together with good flexibility (elongation at break). It actually demonstrated better mechanical properties than most other dressings currently used or studied, as demonstrated in Table III.

The initial mechanical properties of natural polymers such as collagen or gelatin can be satisfactory. However, considerable degradation of these properties is expected to occur rapidly due to hydration and enzymatic activity. The results of the 3 weeks degradation study of our wound dressings show a significant decrease only in Young's modulus (Figure 5). The maximal stress and strain of our composite wound dressing (24 MPa and 55%, respectively) are dictated mainly by the mechanical properties of the reinforcing fibers which fail first during breakage. At these time periods, they are not subjected to considerable degradation, which explains the constancy in these properties. In contrast, the Young's modulus of the dressings is considerably affected by the properties of the binding matrix that makes up the largest part of the cross-sectional area. The degradation of the matrix material which is clearly in

![FIGURE 7. SEM fractographs demonstrating the interface between the reinforcing fiber and porous matrix for specimens based on formulation BSA1, immersed in aqueous medium for: (a) start point, (b) 1 week, and (c) 2 weeks.](image)

### TABLE III. Mechanical Properties of Various Wound Dressings

<table>
<thead>
<tr>
<th>Material/Format</th>
<th>Elastic Modulus (MPa)</th>
<th>Tensile Strength (MPa)</th>
<th>Elongation at Break (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA1 (composite polyglyconate mesh, coated with PDLGA porous matrix)</td>
<td>126 ± 27</td>
<td>24.2 ± 4.5</td>
<td>55 ± 5</td>
</tr>
<tr>
<td>Electrospun poly-(L-lactide-co-ε-caprolactone) (50:50) mat</td>
<td>8.4 ± 0.9</td>
<td>4.7 ± 2.1</td>
<td>960 ± 220</td>
</tr>
<tr>
<td>Electrospun gelatin mat</td>
<td>490 ± 52</td>
<td>1.6 ± 0.6</td>
<td>17.0 ± 4.4</td>
</tr>
<tr>
<td>Electrospun collagen mat</td>
<td>11.4 ± 1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolut® LT regenerative membrane (Gore). Glycolide fiber mesh coated with an occlusive PDLGA membrane</td>
<td>11.7</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Kaltostat® (ConvaTec) Calcium/Sodium Alginate fleece</td>
<td>1.3 ± 0.2</td>
<td>0.9 ± 0.1</td>
<td>10.8 ± 0.4</td>
</tr>
</tbody>
</table>
progress after 2 weeks of exposure to PBS [Figure 4(e)] thus leads to a decrease in Young’s modulus. The mechanical properties of our wound dressings are superior to those reported before and remain good even after 3 weeks of degradation (Young’s modulus of 69 MPa, maximal stress 24 MPa and maximal strain 61%), as demonstrated in Figure 5.

**In vitro drug-release studies**

The incorporation of broad-spectrum antibiotics such as cef-tazidime in wound dressings can help reduce the bio-burden in the wound bed and thus prevent infection and accelerate wound healing. The controlled release of this antibiotic may help prevent the occurrence of complications associated with conventional topical treatments. The local antibiotic release profile should potentially exhibit a considerable initial burst release rate to respond to the elevated risk of infection from bacteria introduced during the initial trauma, followed by a release of antibiotics at an effective level long enough to inhibit latent infection. With characteristic healing reported to take 3–7 weeks (depending on the location, size and degree of injury, as well as the rate of tissue regeneration), our aim would be to maintain effective antibiotic levels for at least 2–3 weeks.

The main challenge in designing a device for the release of low molecular weight hydrophilic antibiotics is to overcome the rapid discharge of the drug from the device. Common strategies that have been described in an attempt to overcome the problem of rapid drug release include entrapment of the hydrophilic drug within a hydrophobic substance as a means for delaying water penetration and outward drug diffusion or enhancement of drug bonding to the carrying matrix. These strategies are usually contrary to basic requirements from wound dressings such as porosity and hydrophilicity, desired to provide adequate gaseous exchange and absorption of wound exudates. A delicate balance between the two must clearly be achieved.

The advantage of the freeze-drying of inverted emulsions technique used in our study is that the drug is incorporated within a porous structure during the fabrication process, to obtain its release in a controlled desired manner. Our results show that the highly porous (63%) matrix based on the BSA1 formulation (with an O:A phase ratio of 6:1) exhibited a very high burst release of antibiotics and total release of the encapsulated drug within 24 h. Lower porosities, achieved by employing emulsions with a higher 12:1 O:A phase ratio, reduced the burst release and prolonged the antibiotic’s release (Figure 6). Dressings based on the BSA2 and SPAN formulations displayed a burst release of 57 and 6% and overall release spans of 5 and 10 days, respectively. Replacing the hydrophilic surfactant albumin with the hydrophobic Span 80 resulted not only in a considerable 10-fold decrease in the antibiotic’s burst release but also in a twofold increase in total elution span. A finer microstructure with thicker polymer walls between pores thus enables slower diffusion of the hydrophilic antibiotic molecules to the surrounding. The incorporation of a surfactant may contribute to more than just a stabilizing (microstructural) effect or serve as a chemical moderator. By binding to various drugs through specific interactions, we have demonstrated that albumin, a predominant drug-binding protein in the body may reduce the burst release of antibiotics and contribute to a more moderate release rate overall, making it an attractive surfactant with a dual role.

**SUMMARY AND CONCLUSIONS**

Novel biodegradable occlusive wound dressings based on a polyglyconate mesh and a porous PDLGA binding matrix were developed and studied. These composite dressings were prepared by dip-coating woven meshes in inverted emulsions, followed by their freeze-drying. Their investigation focused on the microstructure, mechanical and physical properties, and the release profile of the antibiotic drug cef-tazidime from the binding matrix.

The physical properties of the wound dressing (water absorbance and WVTR) as well as drug release profile can be controlled by changes in the inverted emulsion’s formulation. An increase in the emulsion’s O:A phase ratio resulted in decreased porosity of the matrix, and thus in a lower WVTR and some reduction in the initial water uptake. It also reduced the burst release of antibiotics from the matrix. The surfactants used for stabilizing the inverted emulsion significantly affected the microstructure and the resulting physical properties. Specimens containing albumin as surfactant exhibited a relatively high burst release and low WVTR at a 12:1 O:A phase ratio, whereas specimens with a similar O:A ratio containing Span 80 produced an optimal WVTR of 2641 ± 42 g m⁻² day⁻¹ and a very low burst release followed by a moderate and constant release rate for 7 days.

The initial mechanical properties of our wound-dressing structures were found to be superior in combining resistance to tear (tensile strength of ~24 MPa) and ductility (elongation at break of ~55%). Three weeks of *in vitro* incubation in PBS did not affect these properties, and we, therefore, conclude that adequate strength retention is promised during the anticipated duration of usage as a wound dressing.

Our novel composite structures combine good mechanical properties with desired physical properties and controlled release of the antibiotic drug ceftazidime from the binding matrix and are therefore potentially very useful as burn and ulcer dressings. Changing the emulsion formulation enables adapting the desired properties to the wound characteristics and can thus enhance wound healing.

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**REFERENCES**


