Chapter 4
A new porous polyetherurethane wound covering

Summary
A polyetherurethane (PEU) wound covering with non-interconnected micropores up to approximately 5 μm has been prepared by means of a phase inversion process. This highly elastic, very thin (15-20 μm), pliable wound covering showed good, immediate adherence to wet wound surfaces and high water vapour permeability, but was impermeable to bacteria. In guinea pigs epidermal wound healing of partial-thickness wounds under PEU wound coverings was accelerated as compared with uncovered controls and an occlusive wound covering, OpSite. Water in liquid form or wound exudate could not leak through the PEU covering, but its high water vapour permeability induced concentration of the wound exudate into a jellylike clot layer, which apparently accelerated reepithelialization.

The main conclusion from a clinical study on 20 donor sites was that the use of the PEU covering reduces pain, besides prevention of fluid retention and enhanced reepithelialization.

Introduction
The concept of a two-layer artificial skin for covering full-thickness (burn) wounds, consisting of a biodegradable, porous bottom-layer functioning as a temporary template for skin regeneration and a protective non-degradable top-layer was first described by Yannas and Burke (1). Gogolewski and Pennings constructed an artificial skin based on polyurethane/poly(L-lactide) mixtures using the above concept (2).

Our current concept of the synthetic skin substitute consists of a microporous vapour permeable polyetherurethane (PEU) top-layer and a separate bottom-layer, composed of a biodegradable polyesterurethane elastomer network, which is designed to degrade rapidly to non-toxic degradation products, not having the disadvantages like low rate of degradation and release of the toxic, carcinogenic, aromatic diamine 4,4'-methylenedianiline upon degradation of the segmented polyurethane, associated with the PU/PLLA mixture (3).
The PEU top-layer in itself can also serve as a wound covering, acting as a temporary covering of donor sites and second degree burns (partial-thickness wounds).

It is commonly accepted that such a wound covering should be adherent, elastic, pliable, impermeable to bacteria, easy to handle, non-toxic, hemostatic and also allow the proper water vapour transport through the covering (4,5). However, no data concerning the optimal water vapour permeability of wound coverings, to prevent desiccation of the wound and avoid simultaneously fluid accumulation under the covering, are available (5,6). Despite the fact that many wound coverings are commercially available (e.g., OpSite, Biobrane, Omiderm, Epigard) many surgeons still prefer treatment of donor sites and second degree burns with conventional methods like tulle gras dressing, which may indicate that the ideal, synthetic wound covering has yet to be developed (5,8). This chapter reports on the preparation and characteristics of this new polyetherurethane wound covering.

Materials and Methods

*PEU wound covering*

In this study Tecoflex EG-80A (9) (Thermedics Inc.) a so called second generation medical-grade segmented cycloaliphatic elastomeric polyetherurethane (PEU) was used as supplied. A 5% (w/w) PEU solution in tetrahydrofuran (THF), containing 1% (w/w) lithiumchloride (LiCl) was refluxed for 2 h under nitrogen atmosphere and subsequently stirred for 2 h at room temperature. A film of this polymer solution was cast on a glass plate, using a 500 μm cast-iron. The glass plate was placed just above a water layer in an open box. Within some minutes the clear film turned white. Half an hour later on, when most of the solvent had evaporated, the non-translucent film was dried in vacuo at 50 °C for 2 h and subsequently placed in water to detach the PEU film from the glass plate and to remove the salt. Finally the white elastic film was dried. The PEU covering was sterilized by means of gamma radiation (25 kGy).
Porous PU membrane
A Petri-dish containing a 7% (w/w) polyurethane (Estane, Goodrich U.S.A.) solution in 1,4-dioxane was placed above a 1:1 v/v water/1,4-dioxane mixture in a closed box. After 2 days the porous membrane was placed in water and subsequently dried.

Water vapour permeability
The wound covering was stretched in a screwed open cap onto a glass cup, which was partially filled with water and inverted so that the wound covering was in direct contact with water.

A ServoMed evaporimeter (Model EP-1C, ServoMed AB, Vallingby, Sweden) was used for measuring the water vapour transmission rate (WVTR in gm⁻²·h⁻¹) at various water vapour pressure differences across the wound covering. The measurements were performed in a closed cabinet to prevent disruptive air currents as described elsewhere in detail by Erasmus and Jonkman (6,7).

Stress-strain measurements were performed on cut specimens (5 x 20 mm) from the above described dry PEU film and the commercial wound covering OpSite (10) (thickness 28 μm, Smith & Nephew Ltd., Hull, U.K.) at room temperature using an Instron (4301) tensile tester equipped with a 10 N load-cell, at a cross-head speed of 50 mm/min.

An I.S.I.-DS 130 scanning electron microscope was used to study the microstructure of the membranes.

Animal and clinical studies
Under sterile conditions, at the back of each of 61 guinea pigs two partial-thickness wounds (2 x 2 cm) with a mean depth of 0.32 mm were made with a dermatome. The wounds were either covered with a dry, sterilized PEU membrane or with OpSite or were left uncovered. The coverings were not changed during the experiment. All wounds were evaluated histologically 1 to 14 days after excision as described in detail previously (12).

Twenty adult burn wound patients undergoing split-skin graft procedures at the Burns Centre of the Roman Catholic Hospital of Groningen were candidates for the clinical study. Skin grafts with a mean thickness of 0.30 mm were taken with a dermatome. Half of the donor site was covered.
with the PEU covering, the other half with a single layer of tulle gras dressing (paraffin gauze). The complete donor site was covered with four absorptive cotton pads, comprising 32 single layers fine mesh gauze, held in place with a crepe bandage. The cotton pads and crepe bandage above the PEU covering were cut away between 1 and 5 days after operation, thus allowing free ventilation. The PEU covering was peeled off the wound between 5 and 21 days after operation. The crepe bandage and gauzes on top of the tulle gras were removed between 7 and 10 days after operation. Biopsies were taken between 3 days to 3 months after operation and studied histologically as described elsewhere in detail (15).

Results and discussion
Figure 1 presents a scanning electron micrograph of a PU membrane, possessing a very regular pore structure. It can be seen that the large pores are interconnected with smaller ones. This porous membrane was obtained by slow evaporation of the solvent (1,4-dioxane) and simultaneously slow diffusion of water vapour (non solvent) into the polymer solution.

Figure 1. Scanning electron micrograph of a PU membrane prepared from a 7 wt% polymer solution in 1,4-dioxane using a 1:1 v/v 1,4-dioxane/water solvent/non solvent mixture. Note the regular pore structure.
Figure 2. Scanning electron micrograph of a PEU membrane prepared by casting a film from a 5 wt% polymer solution in THF, containing 1 wt% LiCl. The rough topside of the membrane is the bottomside of the PEU wound covering, which faces the wound.

Figure 3. Scanning electron micrograph of a cross-section of the PEU wound covering.
By using a more volatile solvent (THF) combined with the presence of the hygroscopic lithium chloride in the polymer solution, which might attract water vapour, the process of phase inversion was accelerated, which resulted in a different, less regular membrane structure.

Figure 2, 3 and 4 show scanning electron micrographs of the dry PEU wound covering, prepared by casting a film of a 5 wt% polymer solution in THF, in the presence of 1 wt% LiCl. The topside of the PEU membrane, which actually is the bottomside of the wound covering facing the wound, showed a rough surface, composed of pits and small pores up to approximately 5 µm (fig. 2). The membrane of thickness 15-20 µm contained micropores up to ca. 5 µm, which were not interconnected (fig. 3). The bottomface of the membrane (i.e. the topside of the wound covering), which was originally stuck to the glass plate, showed a smoother surface with pores up to ca. 5 µm (fig. 4). As a result of this structure water in liquid form (or wound exudate) could not leak through the PEU membrane, but water vapour diffused at a high rate (see below). Due to the porous structure and its hydrophilic characteristics the PEU membrane showed good adherence to wet surfaces. The dry PEU wound covering immediately adhered well to partial-thickness wound beds, thereby sealing the wound and forming a barrier against infection, since it was shown that the covering was impermeable to bacteria (12).

Figure 5 presents the water vapour transmission rate (WVTR) vs. the water vapour pressure difference across two wound coverings, namely the PEU wound covering and OpSite, measured in vitro, "upside down" (6,7). The slopes of the lines empirically found are designated water vapour permeance (WVP).

The water vapour permeability of the PEU wound covering, expressed as water vapour permeance was 20,1 gm⁻²h⁻¹kPa⁻¹, which was much higher than the corresponding value found for OpSite (5,3 gm⁻²h⁻¹kPa⁻¹), which is considered an occlusive wound covering (10), but less than Omiderm (24,6 gm⁻²h⁻¹kPa⁻¹), a commercially available polyurethane wound covering which has been grafted with polyacrylamide and which is known to be a high vapour permeable wound covering (14). It is known that the use of occlusive wound coverings in partial-thickness wounds accelerates reepithelialization, stimulates wound healing, prevents wound desiccation.
Figure 4. Scanning electron micrograph of the bottomface of the PEU membrane, showing a relatively smooth surface with pores up to ca. 5 μm.

Figure 5. Water vapour permeability of wound coverings: Water vapour transmission rate (WVTR) as a function of the water vapour pressure difference across the wound covering. The slopes of the individual lines are designated water vapour permeance (gm^{-2} h^{-1} kPa^{-1}).
and body heat loss, but has the disadvantage of accumulation of wound exudate under the covering, which may lead to infection, especially in case of occlusive film dressings like OpSite (10,18). It is suggested that a more water vapour permeable wound covering, like the constructed PEU membrane, will avoid the latter.

Figure 6 shows typical force-strain curves of the dry PEU wound covering and for comparison OpSite, a commercial, clinically used wound covering. It is clear that the dry PEU wound covering was far more elastic than OpSite, having a lower modulus, but exhibiting lower strength at break. A wound covering should be elastic if it has to be applied over bending surfaces like over joints, to facilitate an intimate cover of the wound. The thickness of the PEU membrane (15-20 μm) together with the elasticity made the PEU membrane very pliable, a property which is needed to enclose the wound surface very near (conformability (16)). The PEU covering is elastic both in the dry and wet state, in contrast to some hydrogel-based wound coverings, like Omiderm for instance, which are only elastic in the wet state and contract the wound when losing water (vapour) during the healing process (17).

The force-strain behaviour of a PEU membrane determined directly after preparation differed from an aged PEU membrane as can be seen in fig. 6. The PEU membrane was prepared by casting of a LiCl containing refluxed polymer solution. Heat treatment of a polyurethane solution will result in complete dissolving of the physically cross-linked PU chains by breaking up the existing supermolecular structure in solution. The LiCl keeps the chains from aggregation upon cooling down to room temperature by complexation to the urethane bonds, thus enhancing the solubility of the PU and leading to the formation of a new super molecular structure (13). A membrane cast from this PEU solution showed relatively high elasticity (low modulus). However, after 1 to 3 months the elasticity had decreased slightly. The at room temperature aged PEU membranes also exhibited decreased elongation at break.

Preliminary studies on wound healing of partial-thickness wounds in rats, using the PEU wound covering were encouraging (11). Extensive studies in guinea pigs (12), in which wound healing of 122 partial-thickness wounds under PEU coverings was compared with wounds covered with OpSite, an
Figure 6. Force-strain behaviour of: (a) PEU wound covering 3 months after preparation, (b) PEU wound covering directly after preparation and OpSite.

Figure 7. Fresh split-thickness donor site half dressed with the PEU membrane (right) and half with a paraffin gauze (left). Note that the PEU membrane becomes transparent when sucked to the woundbed.
occlusive film dressing, and uncovered controls, showed that reepithelialization and keratinization were enhanced in wounds covered with the high water vapour permeable, porous PEU membrane compared with wounds covered with OpSite or uncovered air exposed controls. The percentage of reepithelialization on day 2 after operation was 85% in wounds covered with the PEU membrane, whereas it was 66% and 35%, respectively in wounds covered with OpSite or exposed to air. In PEU covered wounds 100% reepithelialization was attained by day 3, one day earlier than in the other wounds. Under the PEU covering the wound exudate had turned into a jellylike clot layer by day 1 as a result of the high water vapour permeability of the porous covering. The high water vapour permeability of the PEU covering prevented fluid retention (as was observed in the case of OpSite covering) as well as complete wound desiccation (uncovered controls). The jellified clot layer underneath the PEU covering apparently provided an ideal matrix for epidermal wound healing.

In order to evaluate the clinical efficacy of the PEU wound covering, it was compared with the conventional treatment of tulle gras dressing (see fig. 7) plus absorptive gauzes and crepe bandage on split-thickness skin graft donor sites of 20 burn wound patients (15). The, initially fluid, wound exudate under PEU coverings concentrated into a jellylike clot layer after the extra gauzes had been cut away, which is needed to allow free ventilation. After 5 days already the PEU covering could be peeled off the wound without pain or epithelial damage. Clinically and histologically no significant difference was observed in the rate of healing between the PEU and tulle gras covered wounds, which may be explained by the fact that tulle gras packed in a thick layer of gauzes and bandage prevented wound desiccation, as a result of a sultry effect caused by the gauzes. Both treatments enhanced reepithelialization at a similar rate. Further it was observed that the use of the PEU wound covering reduces pain completely compared with the rather painful treatment with tulle gras. One point to note, finally, is that the PEU wound covering is not hemostatic in itself, which, however did not turn out to be a problem in the clinical situation.
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