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Surfactants and their role in wound cleansing and biofilm management

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Surfactants and their role in wound cleansing and biofilm management

Abstract: Surfactants are widely used as detergents, emulsifiers, wetting agents, foaming agents and dispersants in the cosmetics, hygiene, food and oil industries. Their use in a clinical setting is also common, particularly within the field of wound care. Many wound cleansers contain surfactants and subsequently there is available data that shows the growing potential of these wound cleansers in the enhancement of wound closure. The presence of microorganisms in wounds has been recognised as a significant factor that delay healing. In complex or chronic wounds that are complicated by biofilms, persistent inflammation or the production of non-viable tissue and slough, the use of surfactants has been shown to aid in the removal of these barriers to wound healing. The use of concentrated surfactant(poloxamer) based wound dressings represent an important component of wound management. Consequently, this article will discuss the effect of clinically used surfactants, with specific focus on a concentrated poloxamer for use against wound biofilm.

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biofilms • cell repair • surfactants • wound cleaning • wound healing

Many wounds become stalled or do not progress through the normal stages of wound healing. The longer a chronic wound remains open, the greater the likelihood of biofilm formation.[1,2] While antibiofilm strategies are complex and multifaceted, their key components comprise wound cleansing, regular debridement and the use of antimicrobial dressings to prevent its reformation. The most common options for debridement are surgical and sharp and dressings that promote autolysis. The latter can be used in conjunction with surgical and sharp debridement, or as an alternative when they are not available or desired. Recently, surfactants have been promoted as another option as they can cleanse, remove slough and most types of necrotic tissue and are active against biofilm.

Surfactants are used extensively in all walks of life and are often applied to the skin, clothes and other materials to remove dirt, reinforcing their role as cleaning agents. Soap is one of the earliest examples of a surfactant: its ability to increase the miscibility (how completely two or more liquids dissolve in each other) of dirt and oils enhances their removal from the skin surface. As well as removing dirt, surfactants have also been reported to enhance the removal, via sequestration (the uptake, trapping and locking in) of microorganisms. This indicates that they can play a major role in biofilm management and infection control. Surfactants can be chemically synthesised (synthetic) or occur naturally. Surfactants such as poloxamer 188 are used widely in medicine.

This paper will explore the literature on surfactants, in particular poloxamer-based products and describe the potential mechanisms behind their role in enhancing wound healing. The effect of concentrated (poloxamer-based) surfactants on microbial biofilms will also be discussed.

Wound biofilm

Biofilms are communities of microbes that are either associated with biotic or abiotic surfaces (not necessarily solid) or are attached to themselves. They are encased in a matrix of extracellular polymeric substance (EPS), including, polysaccharides, nucleic acids, extracellular DNA (eDNA), proteins, metal ions.[3,4]

Compared with their free-floating or planktonic counterparts, the attached (sessile) microbes that grow within a biofilm community demonstrate increased tolerance to immunological clearance, antibiotics and

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antiseptics.[2] Consequently, biofilms need to be removed from non-healing, at-risk and infected wounds.

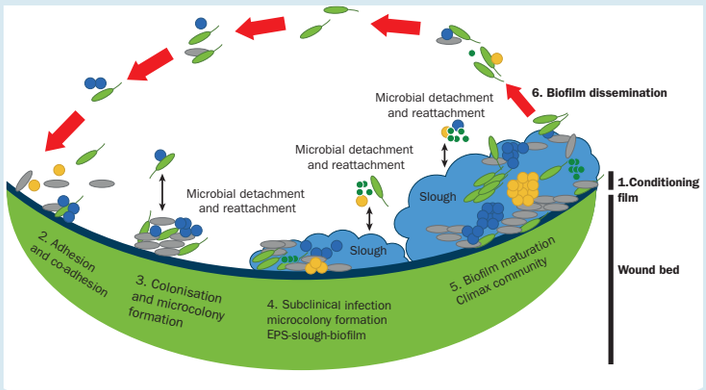
The first stage in biofilm formation involves the development of a conditioning film, whereby a surface (biological or non-biological) is bathed within milliseconds in proteinaceous material (Fig 1). Pioneering (the first to adhere) microbes attach to the conditioned surface and release extracellular material that helps to 'cement' them to the surface. [3,4] Providing conditions are favourable, these microbes begin to multiply, forming cellular aggregates or microcolonies. Further microbes, referred to as secondary and tertiary colonising microbes, are chemotactically attr°acted to the developing biofilm.

As the biofilm ages and matures, the microbiology becomes more diverse and further extracellular polymers are secreted, resulting in the formation of a highly recalcitrant 'climaxed polymicrobial community'.

At least five different biofilms can be found within the wound ecosystem: in the wound bed, deep within tissue, within and on slough and necrotic tissue, and on wound dressings (Fig 2).

As parts of the biofilm detach (referred to as desloughing), or are dispersed or disseminated, and enter the wound exudate, they remain within the sessile (attached) state. They stay within this state until a microbial division occurs, after which the microbes

Fig 1 Biofilm development in wounds[2]



to remove or sequester non-viable tissue, which can contain biofilm. These include autolytic debridement, desloughing (the removal of slough),[5] or the combined use of antimicrobials and autolytic agents. These techniques have also been shown to be effective in cleansing the wound and removing biofilms.[7]

Surfactants containing betaine, polyhexamethylene biguanide (PHMB) or poloxamer 188 can be used not only to facilitate wound cleansing and aid autolytic debridement, but also to support wound healing at the cellular level.[12] In addition, concentrated surfactants can

Fig 2. Proposed sites of microbial adhesion and formation of biofilms within chronic wounds. 1. Biofilm formation on wound bed; 2. Biofilms residing in slough; 3. Biofilms suspended as microcolonies within the wound exudate; 4. Biofilms attached to wound dressings/wound dressing fibres/foreign objects, and 5. Biofilms on the surface of necrotic tissue

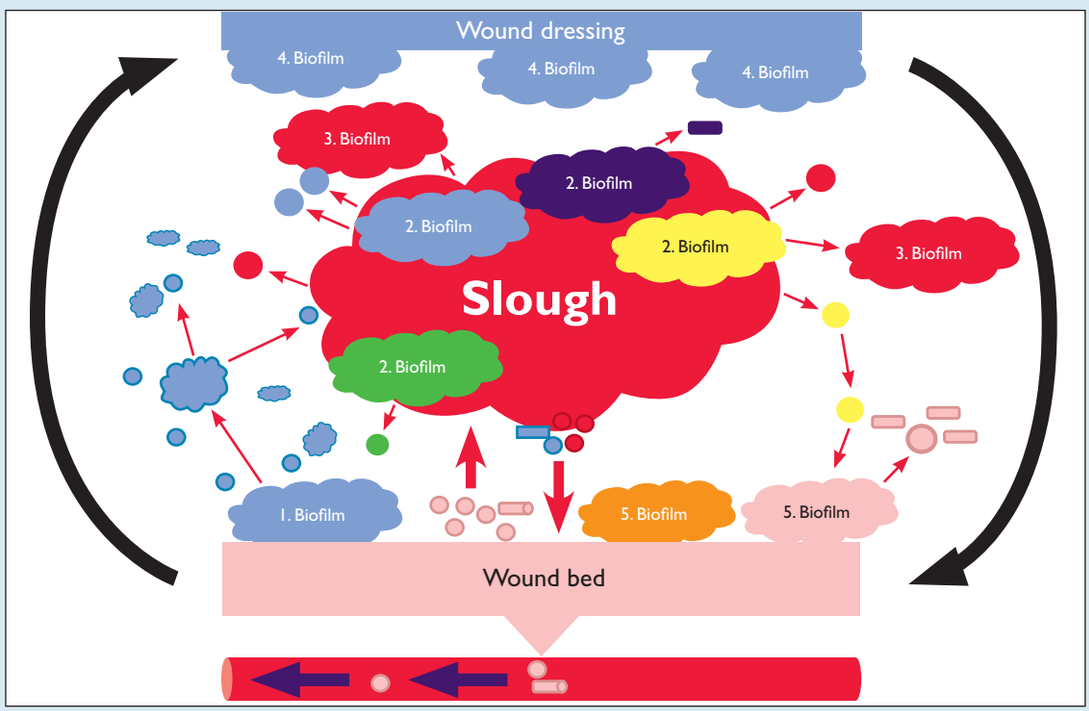
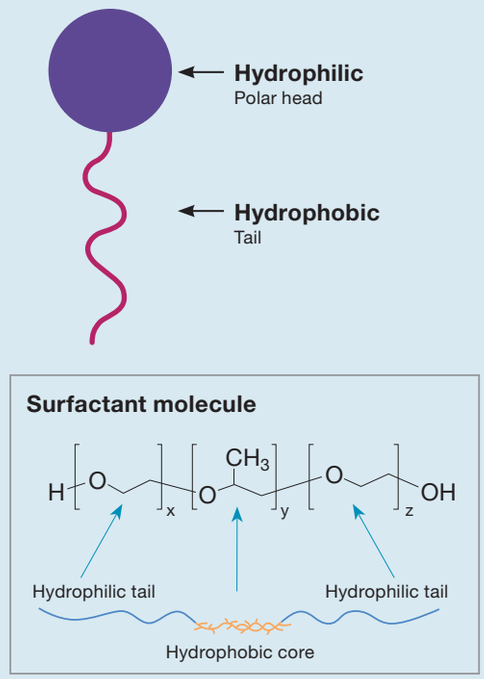


Fig 3. Example of a surfactant molecule



be considered useful for painful or ischaemic wounds.

Surfactants

Surfactants are a group of agents that can increase the wettability of a surface and the solubility of materials that are otherwise non-miscible (i.e. do not dissolve into each other). Referred to as surface active agents, surfactants are structurally defined as amphiphilic agents, which means they contain both water-soluble elements (hydrophilic) and water-insoluble (hydrophobic) structures (Fig 3).

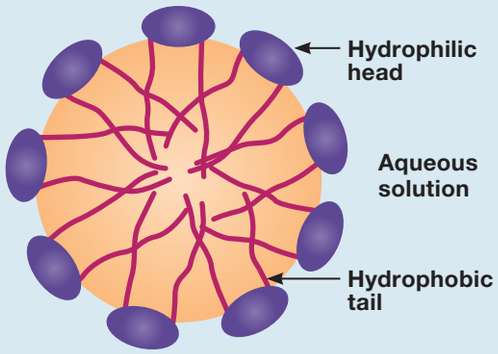
Surfactants reduce the surface tension between liquids and the surface, allowing for greater penetration of fluids including solvents and antimicrobial agents. By lowering the surface tension of liquids, a surfactant makes molecules more 'slippery', so they are less likely to stick together. Surfactants, therefore, allow biological materials to be carried away by irrigating agents such as water or saline. Within an aqueous solution, surfactants form structures called micelles that have a hydrophobic core and a hydrophilic component on the outside (Fig 4).

Surfactants interfere with the potential for microbes to adhere to surfaces, thereby reducing their ability to populate within a wound.[13] They can work in combination and synergistically with antimicrobial agents.[14]

Use of surfactants in wound care

Historically, surfactants were principally added to wound irrigating/cleansing agents and incorporated into surgical scrub solutions.[15–17] In an animal study,

Fig 4. An illustrative example of the structure of a generic micelle



Howell et al.[18] found that pre-treatment with a poloxamer-based surfactant before the use of an iodine-based surgical scrub enhanced the performance of the povidone iodine (PI).

Some surfactants, such as poloxamer-based non-ionic ones, are used to carry drugs, antibiotics and antiseptic agents. A concentrated poloxamer-based wound dressing impregnated with 1% silver sulfadiazine (SSD) is indicated for wounds that are at risk of or show clinical signs of infection.[19,20] Results of a case series showed that its use was associated with better healing rates compared with standard care, as well as an associated reduction in pain.[20] Similarly, a randomised trial by Black and Drake found that the SSD-impregnated concentrated poloxamer-based surfactant reduced the time required to perform dressing changes.[19]

The use of surfactants to prevent and control wound biofilms is a relatively new concept. There is little evidence in the literature on their efficacy on wound biofilms, even though other industries have successfully used it for this purpose for decades. Non-ionic surfactants, which includes poloxamer, are reported to be effective in the solubilisation and disaggregation of proteins, with evidence demonstrating that they block adhesion of certain proteins and help prevent microbial adhesion.[21] (Using a fluid jet-based cleaning device, poloxamer-based surfactants have been shown to help remove 'immature' (24-hour old) biofilms on orthopaedic implants.[22] The positive effects of surfactants on biofilm management have also been reinforced in *in vitro* studies by Yang et al.[23] and Percival et al.[14]. Unfortunately, data on the use of poloxamer-based surfactants within *in vivo* models are limited.

Mechanism of action

Surfactants function by their ability to serve as an 'adaptor' (a device used to connect entities that are not designed to be joined) at the interface between two liquids, such as water and oil (Fig 5), or between a solid and a liquid. They can do this because they contain both hydrophilic and hydrophobic structures. For

example, surfactants can breakdown the interface between water and oil, and can hold oil in suspension. Molecules that are water insoluble congregate near the hydrophobic groups.

In solution, depending on concentration and temperature, surfactants structurally form a spherical micelle called a 'unimer'. The micelle structure changes over time, collapsing and expanding to form a multimer (Fig 6a). In this way, it constantly traps wound debris, creating a rinsing action (Figs 6b-e). As the surfactant lowers the surface tension between the wound bed and a cleansing liquid, the cleansing liquid comes into intimate contact with the wound bed. This facilitates the separation of loose, non-viable tissue and microbial particles from the viable wound bed, which will help prevent biofilm formation and assist the eradication of older, more recalcitrant biofilms. Post-debridement, surfactants also appear to disrupt and prevent the reformation of biofilm.[24]

Classification of surfactants

Surfactants can be divided into synthetic (poloxamers) and non-synthetic/natural surfactants (biosurfactants).

Man-made/synthetic surfactants

These can be classified as either (Fig 7):

- Non-ionic surfactants: these have no electrical charge in their hydrophilic head. They do not ionise in water due to the hydrophilic groups. Examples are poloxamer, polysorbate and tween 80. Numerous long-chain alcohols such as oleyl alcohol demonstrate surfactant properties
- Ionic surfactants: anionic and cationic surfactants, where the hydrophilic head is negatively and positively charged, respectively. Examples and characteristics are summarised in Box 1
- Amphoteric: these have both anionic and cationic charges on their hydrophilic end, giving them a net charge of zero (Box 1).

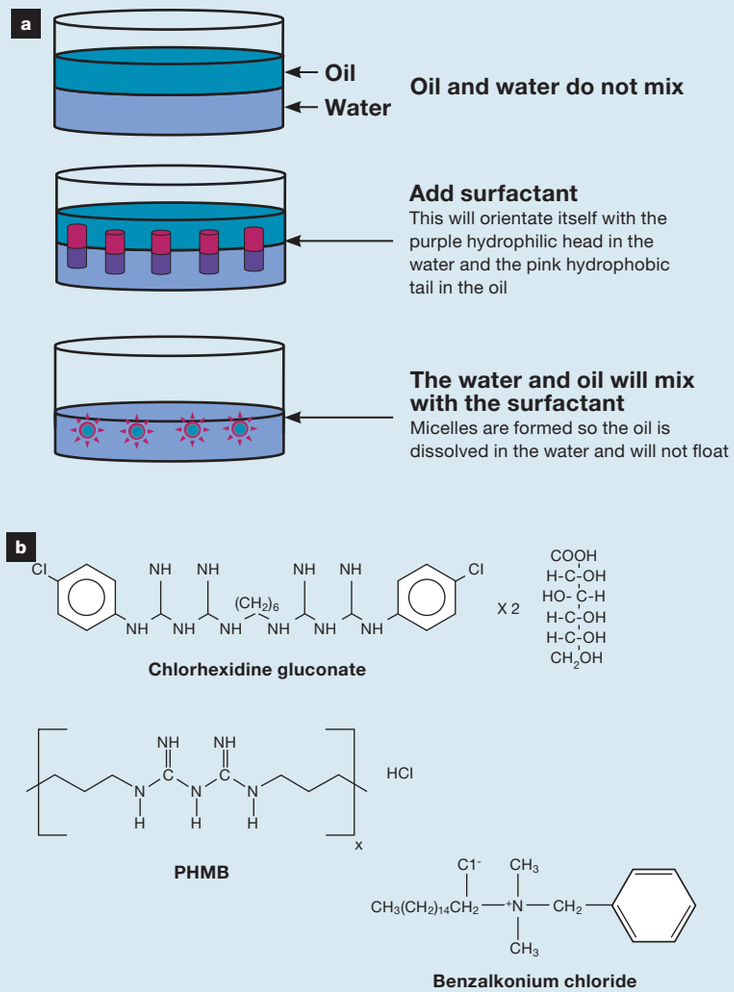
Non-synthetic surfactants

Examples of non-synthetic surfactants include pulmonary phospholipids and biosurfactants. Biosurfactants are amphiphilic compounds produced by microorganisms such as *Pseudomonas aeruginosa*. They contain a hydrophilic (polar or non-polar) and a hydrophobic (lipid) region. Characterisation of biosurfactants is based on their origin and chemical composition. They are produced extracellularly or as part of the cell membrane by bacteria, yeasts and fungi. Many different types of microorganisms can produce surface active agents. It is their ability to produce biosurfactants that gives opportunist pathogens, such as *Pseudomonas aeruginosa,* a competitive advantage.[25]

Rhamnolipds, which are produced by *Pseudomonas aeruginosa,* represent one of the most common and widely studied biosurfactants.[26] These naturally occurring biosurfactants are constructed of rhamnose sugar molecules and β-hydroxyalkanoic acids. The exact physiological functions of these molecules have not yet been precisely defined, but they are reported to promote uptake and biodegradation of poorly soluble agents and to provide antimicrobial properties.[27] When biosurfactants contain more than the critical micelle concentration—the concentration above which stable micelles form in an aqueous environment—the solubility of organic compounds increases. This enhances their availability for microbial uptake.[28] Rhamnolipids have been used to treat full-thickness burns in rats, where the intervention increased wound closure rates by 32% compared with the control.[29]

The role of biosurfactants as antibiofilm agents has been reviewed by Banat et al.[30] Biosurfactants produced

Fig 5. The action of surfactants on an oil and water mixture (**a**). Structures of some antimicrobials that kill bacteria by acting as local surfactants on bacterial plasma membranes* (**b**)



When used in high concentrations, these agents demonstrate surfactant characteristics. In addition, they are routinely used in low concentrations as preservatives in wound-care products

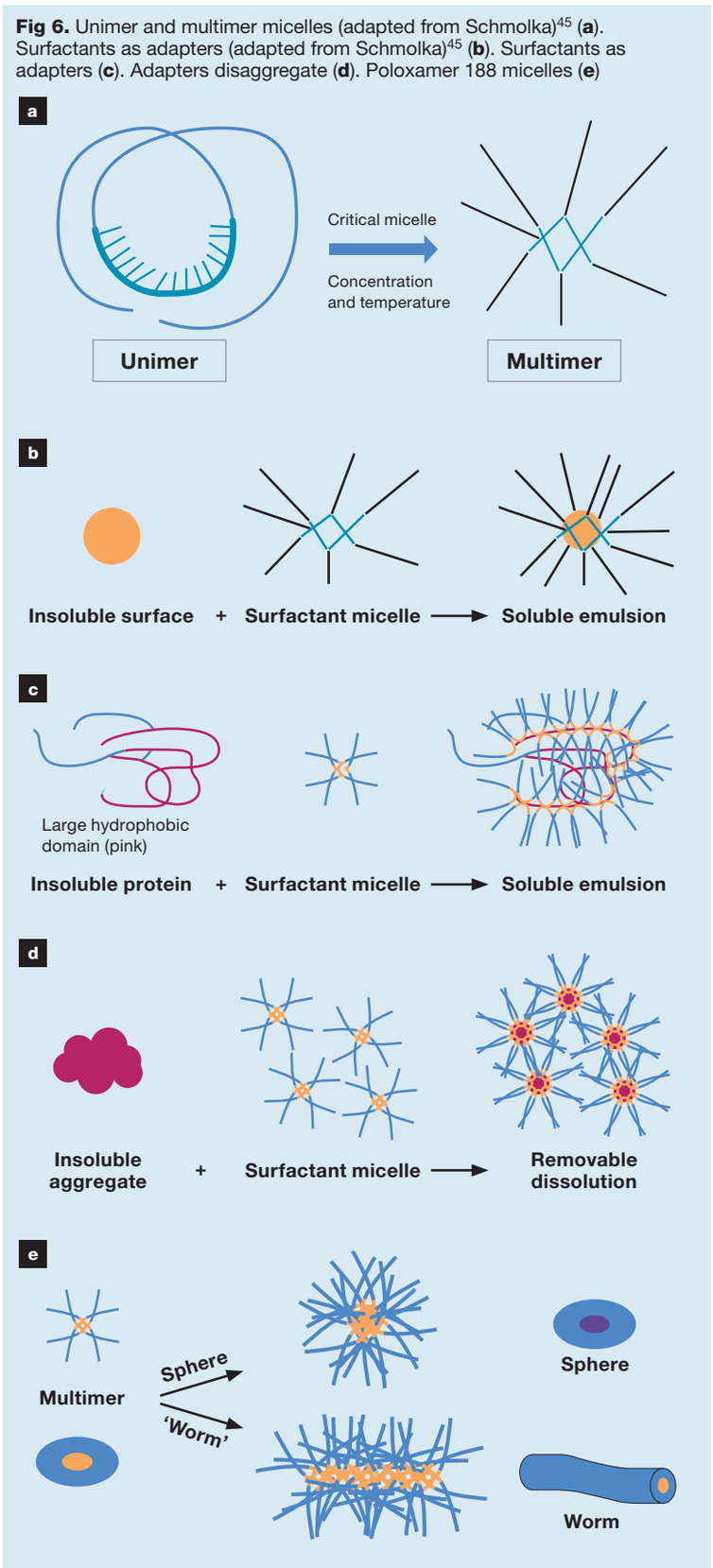


Fig 6. Unimer and multimer micelles (adapted from Schmolka)[45] (**a**). Surfactants as adapters (adapted from Schmolka)[45] (**b**). Surfactants as adapters (**c**). Adapters disaggregate (**d**). Poloxamer 188 micelles (**e**)

by probiotic bacteria were shown to reduce microbial adhesion, particularly on oral strains.[31] The biosurfactant produced by *Bacillus licheniformis* has been shown to reduce bacterial adhesion and biofilm formation of *Candida albicans* and meticillin-resistant *Staphylococcus aureus* (MRSA).[32]

It is thought that biosurfactants reduce microbial adhesion and biofilm formation by altering cell surface characteristics, including carbohydrate and proteins levels, within the biofilm matrix.[32] It is proposed that this reduces the strength and longevity of adhesion to a surface.

Poloxamers

Poloxamers are non-ionic synthetic surfactants and are referred to as triblock copolymers: they are composed of a central hydrophobic chain of polyoxypropylene flanked by two hydrophilic chains of poloxyethylene. Poloxamer is a common ingredient in mouthwashes, laxatives and toothpastes, and is used by the pharmaceutical industry for drug delivery. It has been found to prevent the deterioration of second-degree burns.[33] The mechanism of action of poloxamers has not yet been fully evaluated, but they are thought to incorporate themselves directly into the phospholipid bilayer, helping to resuscitate cells.[34,35]

Cellular effects of poloxamer 188

Poloxamer 188 (P188) also often referred to as pluronic F68, is a non-ionic linear copolymer. It has a long history of safe use, being approved by the FDA over 50 years ago. It was originally used to reduce the viscosity of blood before transfusions. It can also be used to repair cells with a damaged membrane.[36]

Poloxamer 188 is used in cellular bioreactors to improve cell viability. It is also reported to 'patch' cell membranes[36,37] by acting as a membrane resealing agent.[35] There is documented evidence that poloxamer 188 is able to 'insert' itself into eukaryotic membranes.[37,38] Various theories have been proposed suggesting they are able to 'shove out' the unimers after repair,[36,37] although there is insufficient published evidence to draw any firm conclusions.

In *in vitro* and experimental models, carbopol-based hydrogels (thickening agents used in lotions and gels that help to control the release of active agents) containing poloxamer 188 have been shown to enhance cellular migration, angiogenesis and protein expression.[39] Furthermore, poloxamer 188 has been reported to improve microvascular blood flow in animal and *in vitro* studies,[40,41] increase biofilm breakdown and prevention, and restore denatured proteins.[14,23,42] Poloxamer 188 (0.1mM) has also been shown to repair the damage of cell membranes caused by reactive oxygen damage.[38] Investigating its effect on protease activity, Jeong et al.[43] found it drastically increased the activity of gelatinases and decreased the activity of collagenases. They hypothesised that it boosts matrix metalloproteinase (MMP)-2 and MMP-9,

which degrade denatured extracellular matrix, and so might aid autolytic debridement.

Poloxamer 188 has been shown to have an excellent safety profile, with low cytotoxicity on fibroblasts and keratinocytes,[44] and to decrease inflammation by capturing bradykinins.[45]

Surfactants and wound cleansing

Agents such as saline are not considered to be effective for removing debris and biofilms.[46] However, wound irrigation solutions containing surfactants have been demonstrated to effectively cleanse and remove debris from wounds. For example, a recent 289-patient study comparing the effects of a propylbetaine-polyhexanide (betaine) solution with those of saline demonstrated that the surfactant-based solution decreased inflammation and increased granulation tissue formation and wound closure.[47] A retrospective analysis comparing the same surfactant-based irrigation solution with Ringer's solution or saline on venous leg ulcers healing rates found it was associated with a 97% faster healing rate than the comparators.[48] These and two other clinical studies[49,50] highlight the benefits of surfactant-based irrigation solutions for wound cleansing, indicating that they are an important component of any standard protocol of care, whether used with or without antimicrobial agents.

The process by which a surfactant interacts with a material to be removed from a surface is called emulsification. This process requires direct contact between the agent and material, which can take time as the surfactant diffuses beyond the immediate surface. Topical application of concentrated poloxamer-based wound dressings has been shown to soften, loosen and trap necrotic tissue and debris, and to disperse as well as, in some cases, to kill microbes.[14,23]

Johani et al.[51] found that antimicrobial irrigation solutions (with or without surfactants) performed poorly against microbial biofilms. They proposed that the 15-minute exposure time of many commonly used antimicrobial solutions is too short to be effective against wound biofilms, and concluded that longer exposure times (>24 hours) are required.

Effect of poloxamer-based surfactants on biofilms

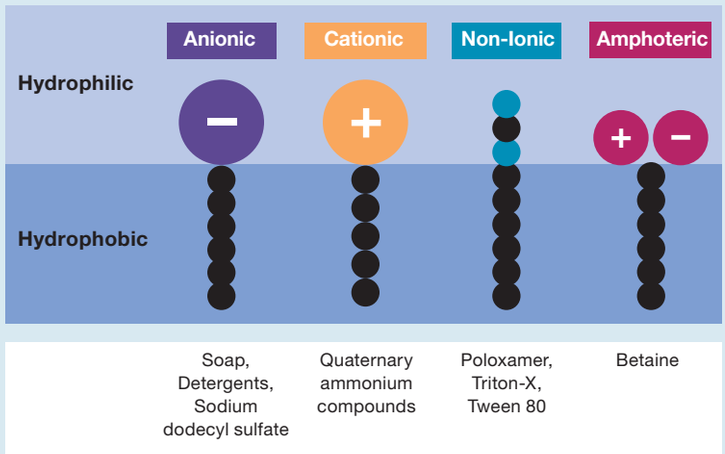
In vitro studies have investigated the effects of poloxamer-based surfactants on biofilms. Yang et al.[23] investigated the effects of a concentrated surfactant-based wound dressing on bacterial biofilms in a porcine skin explant model. After 1 day's treatment, in which the model was wiped with poloxamer 188-moistened gauze, the biofilm had reduced to undetectable level.

Percival et al.[14] evaluated, in different biofilm models, the effectiveness of a concentrated poloxamer-based surfactant in breaking down, dispersing and sequestering *Pseudomonas aeruginosa*, *Enterococcus* spp., *Staphylococcus epidermidis*, *Staphylococcus aureus* and meticillin-resistant *Staphylococcus aureus* (MRSA) biofilms.

Results of a animal study comparing porcine skin explants treated with a concentrated poloxamer 188-based surfactant gel versus a control found that the surfactant prevented biofilm formation over a 3-day period. However, it had to be applied with antibiotics to *Acinetobacter baumannii* biofilm formation.[52]

Topical application of poloxamer-based surfactants are highly tolerated and well accepted by patients[53] and have been shown not to impair general wound healing.[54,55] Interestingly, they have also been demonstrated to promote healing when applied to full-thickness rat excisions:[55] topical application of pluronic F-127 gel (once daily) significantly increased wound closure on days 11 and 14.

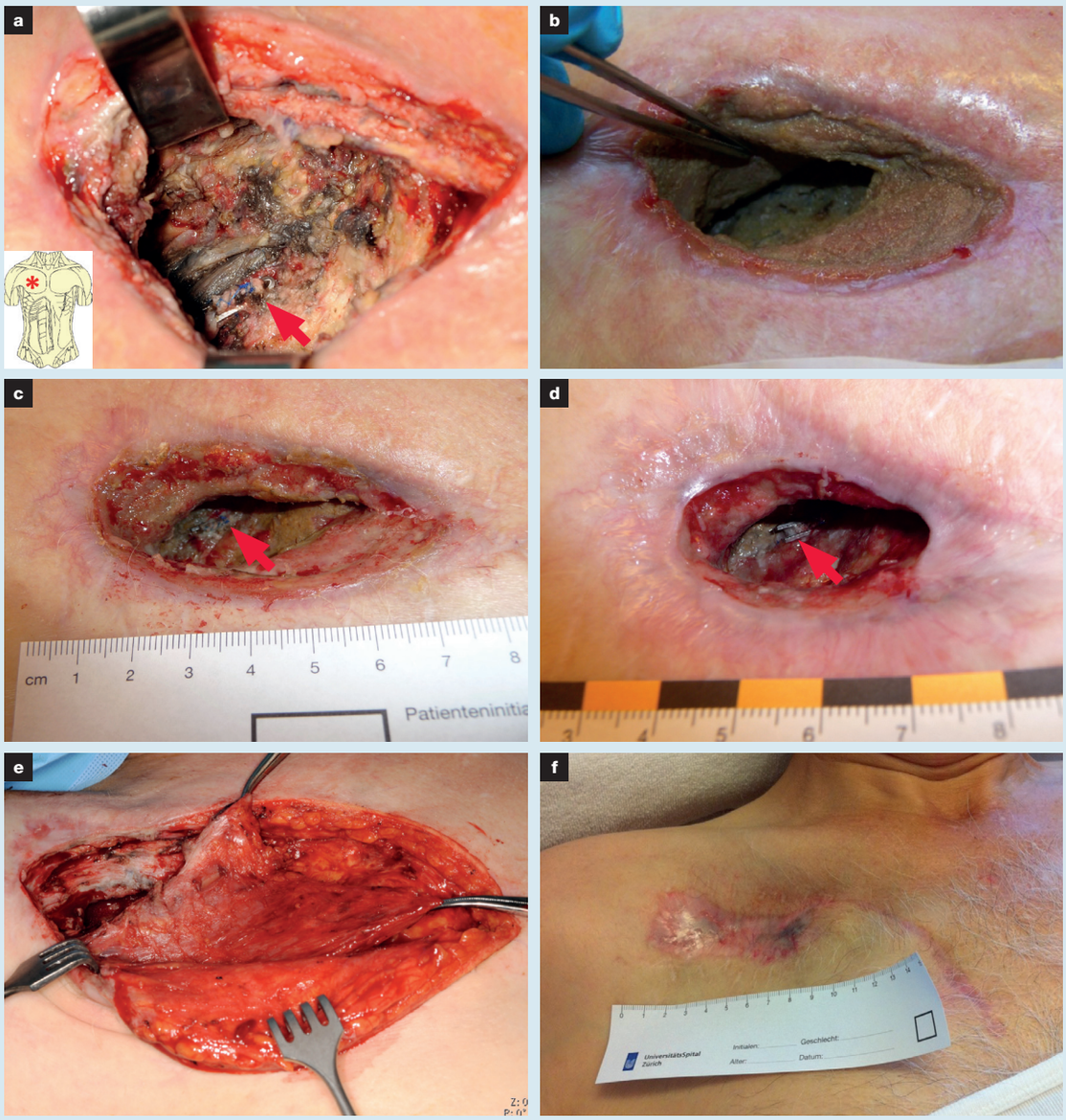
Fig 7. Types of surfactants



Box 1. Ionic and amphoteric surfactants

Anionic surfactants
Negative charge at the hydrophilic head
These are the most commonly used surfactants
Well-known anionic surfactants include sodium dodecyl sulfate (SDS) and sodium lauryl sulfate (SLS)
Other examples include alkylbenzene sulfonates, alcohol sulphates, carboxylic acid salts and alkyl sulphates. For example, alkyl sulphates are found in toothpaste
Cationic surfactants
Positive charge at the hydrophilic head
As they are more expensive to produce than anionic surfactants, they are not widely used
Examples include cetylpyridinium chloride, benzalkonium chloride and benzethonium chloride, which can be found in mouthwashes, toothpastes and throat sprays
Amphoteric surfactants
Have both a positive and negative charges at their hydrophilic head, giving them a net zero charge
An example is betaine

Fig 8. Example of clinical application of a concentrated poloxamer-based gel impregnated with 1% silver sulphadiazine (SSD). A 58-year-old man presented with an infraclavicular pectoral (asterisk) deep wound infection following a lung transplantation involving a Dacron patch and clipped stump (arrow) for cardiopulmonary bypass. Resection was not possible due to inflammation and the creation of a plexus lesion while attempting to resect the patch (**a**). The wound became infected with a biofilm, which is seen here after 10 weeks of antibiotic treatment and negative pressure wound therapy, followed by honey dressings (**b**). Biofilm clearance and granulation tissue formation after 1 week of daily applications of a concentrated poloxamer-based gel impregnated with 1% SSD (**c**). The wound after nine weeks' of daily applications of the gel: complete bacterial clearance and progressive wound healing has been achieved without the use of antibiotics, the pectoralis major flap healed (**d**). The pectoralis major flap after 27 weeks of treatment with the gel (**e**). The flap one year after surgery and treatment with the gel (**f**)



A non-comparative, European, multicentre evaluation of a concentrated poloxamer-based wound dressing containing 1% SSD demonstrated that, of 1036 patients with wounds of over 3 months' duration that had not responded to standard care, 70% achieved wound closure, with a concomitant reduction of malodour and inflammation Of these, 56% closed within 11 weeks. No complications or adverse effects were reported.[56]

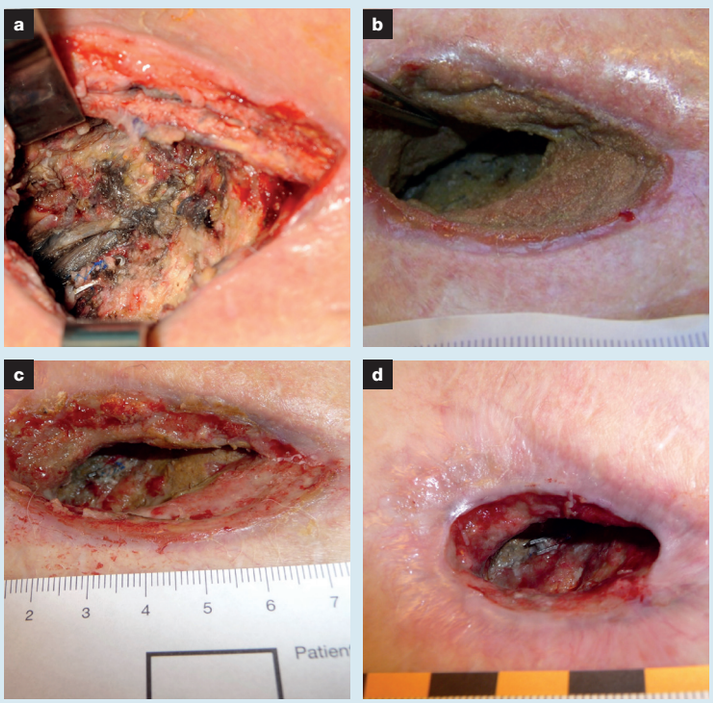
Clinical findings of a concentrated poloxamer 188 gel

Plurogel (Medline) is an amorphous, water-soluble concentrated poloxamer 188-based hydrogel that is

Box 2. Treatment protocol for the use of poloxamer 188 surfactant gel in wound care

Application
Before application, the wound should be assessed and the principles of wound bed preparation applied
Standard aseptic techniques should be used to apply the gel. Application can be individualised according to the size, location and level of exudate
Primary dressings
If used as a primary dressing, the gel can be applied: Directly to a dressing, such as gauze or foam, with a tongue depressor or similar Directly to the wound with a sterile device
At present, the gel is provided in a 50g jar, so care must be taken to avoid cross-contamination
The amount of gel required will depend on the anticipated frequency of dressing changes, but is generally: Adults: 5–10mm layer of gel Padiatrics: 2–3mm layer of gel
Secondary dressing requirements
These will depend on the wound location, dressing change frequency, patient preference/tolerance and the exudate level
Dressing removal
Dressing change frequency ranges from daily to three times a week
When removing the dressing, the level of exudate on the secondary dressing, and any strikethrough, should be noted. If the latter occurs, check when the dressing was last changed
Cold solutions will decrease the viscosity of the gel, facilitating atraumatic removal

Fig 9. Example of clinical application of a concentrated poloxamer-based gel impregnated with 1% silver sulphadiazine (SSD). A 62-year-old male underwent an infrainguinal bypass for a non-healing infected foot ulcer (peripheral arterial disease Fontaine stage IV) with deep inguinal graft infection Szilagyi grade III (multi-resistant coagulase-negative *Staphylococci)* (**a**). Persisting chronic fistula 1.3cm deep, two months after antibiotic treatment with rifampicin and local treatment with an iodine dressing. The patient was scheduled for surgical revision (**b**). A preoperative local bridging treatment was started with daily application into the fistula of a concentrated poloxamer-based gel impregnated with 1% SSD. Slow progressive healing was observed within 4 weeks (**c**). After two months of treatment with the gel, the wound is healing and it was deemed that surgery was no longer required (**d**). There was no recurrence of infection during long-term follow-up.



used as a primary dressing in inpatient and outpatient settings. Its principal function is to provide a moisture barrier and cleansing effect, which is facilitated by its micelle gel matrix formation. At room (ambient) temperature, poloxamer micellar solutions form an extremely disordered state that results in the formation of a thin flowing gel. When the temperature increases, the core of the micelle becomes dehydrated,[57] resulting in the formation of a more ordered crystalline gel state.[58] Consequently, when liquid poloxamers encounter the human body, they rapidly form a more solid gel structure. At a lower temperature, when the micelles are disorganised, they can flow like a liquid.

Indications for the gel

There are times when surgical/sharp debridement are not possible due to patient comorbidities, which may preclude any form of anaesthesia or prohibit the cessation of anticoagulants, or lack of access to a suitably qualified professional. Moreover, surgical/sharp debridement is often is painful and cumbersome for the patient, and cannot always be performed in the community setting.

In this context, surfactant (chemical) debridement might be considered as an alternative to autolytic or other non-sharp methods of debridement. As yet, there is limited clinical evidence on the use of poloxamer 188 gel, although there is anecdotal evidence, based on the experiences of one of the authors (DM), who has used it to debride, prevent and treat biofilm and control inflammation in variety of wound types in a university wound centre for the past sevem years. The author reports that these clinical objectives were achieved in 75% of these wounds and no adverse events were reported. Some examples are given in Figs 8 and 9. This appears to support the data by Palumbo et al.[56] Clearly, more clinical research studies are required to establish an evidence base for this gel. Box 2 outlines treatment protocol for the use of poloxamer 188 surfactant gel in wound care.

Conclusion

There are numerous reports demonstrating the efficacy of poloxamer-based surfactants in wound and cellular

healing, with several *in vitro* studies demonstrating their ability to disperse microbial aggregates and biofilms and to sequester disrupted biofilm.[14,23] Yang et al.[23] demonstrated that surfactants help remove biofilms within an *ex vivo* model and, when used in combination with debridement, can sensitise the microorganisms in the biofilm. Percival et al.[14] have demonstrated the ability of concentrated poloxamer-based wound dressings, with and without silver sulphadiaizne (SSD), to prevent and control biofilms and help lower inflammatory markers within numerous biofilm and wound models. As slough and biofilms within the wound are often held together by non-covalent forces surfactants, particularly poloxamers in high concentrations, are likely to interfere with these associative non-covalent forces, helping to remove them from a surface. Consequently, the use of surfactants will aid their removal, particularly when a mechanical element, such as rinsing or wiping, is also applied.

Overall, in complex or chronic wounds complicated by problematic biofilms, persistent inflammation or the production of non-viable tissue and slough, the use of surfactant-based wound dressings will aid in the removal of these barriers and debris resulting in enhanced wound healing. This paper highlights the use of concentrated (poloxamer-based) surfactants as important components of an anti-biofilm management and wound cleaning strategy. **JWC**

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