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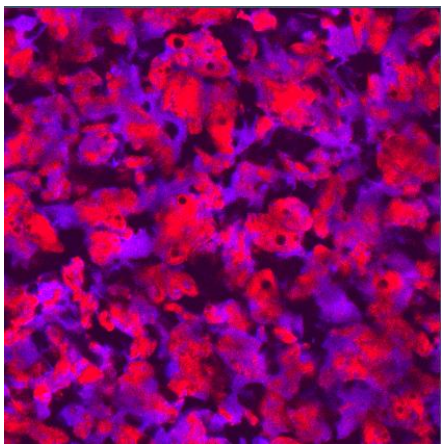
A Water Resistant Film Forming Emulsion

The First Steps towards a Topical Preventive Product against Intertriginous Dermatitis



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Abstract

Intertriginous dermatitis (Intertrigo) is a skin disease caused by friction between adjacent skin surfaces. Heat and moisture induces an inflammation, causing pain and often secondary infections. The aim of this degree project was to develop a prototype for a topical film forming emulsion for patients suffering from Intertrigo. The prototype should deposit a film on epidermis which decreases friction between the skin surfaces and prevents inflammation. The aim was to develop an in-shower product which deposited the film during the shower procedure.

Two product prototypes were evaluated. One had a microcrystalline wax as the main ingredient in the oil phase and the other used a polyamide as the film forming agent. A reference cream with no film forming ingredient was used as control in the evaluative experiments. Focus was to develop and evaluate the deposited film. The film has been characterised considering its occlusivity, water resistance and bioadhesion.

Occlusivity was tested with a gravimetrical method. Formulations were spread as a thin film on top of hydrogels and weight loss was determined as a function of time. Water vapour flux across the film could then be calculated. The wax formulation was less permeable than the polyamide formulation. However, none of the formulations exhibited excessive occlusive behaviour.

Water resistance was evaluated with a washing experiment. Roughened Poly(methyl-methacrylate) plates were used as an in vitro substitute for skin. Samples were rubbed onto the plates and washed at 170 rpm in warm water. The plates were visualised in a light microscope before and after the washing sequence. The polyamide formulation proved to be water resistant for 2 minutes and the wax formulation was still visible after 6 minutes.

Bioadhesion was tested with a texture analyser. Skin samples from pig were prepared with a dermatome and attached to a probe on the texture analyser. The probe was lowered onto the surface of the formulation and withdrawn at 0,1mm/s. A control cream and water were used as references. The force needed to withdraw the probe from the sample was measured. The wax formulation exhibited the highest tensile work to separate the probe from the sample, and water the lowest. Generally, formulations with high viscosity needed more force to separate from the probe, indicating that this might influence the results.

Sammanfattning

Intertriginös dermatit (Intertrigo) är en hudsjukdom som orsakas av friktion i hudveck. Värme och fukt inducerar en inflammation i huden som orsakar smärta och ofta leder till sekundära infektioner. Det här examensarbetet har ämnat utveckla en produktprototyp för en topikal filmdeponerande emulsion som kan användas av patienter som lider av Intertrigo. Produkten ska förebygga inflammation genom att deponera en film på epidermis som minskar friktionen. Prototypen ämnade vara en in-shower produkt där filmen deponeras under tvättprocessen.

Två produktprototyper utvärderades. En av produktera hade ett mikrokristallint vax som huvudingrediens i oljefasen och den andra innehåller en polyamid. En referenskräm utan filmbildande egenskaper användes som kontroll under utvärderingsexperimenten. Under projektet har fokus legat på att utveckla och att utvärdera den deponerade filmen i produktprototypen. Filmen har utvärderats rörande dess vattenresistans, ocklusivitet och bioadhesionsförmåga.

Ocklusivitet har bestämts med en gravimetrisk metod. Formuleringen spreds som en tunn film på toppen av en hydrogel och vägdes med förbestämda tidsintervaller. Viktminskningen bestämdes som funktion av tid och flödet av vattenånga genom filmen bestämdes. Vaxformuleringen var mer ocklusiv än formuleringen med polyamid, men ingen av produktprototyperna påvisade överdrivet ockluderande egenskaper.

Vattenresistans utvärderades med ett tvättexperiment. Plexiglasplattor användes som in vitro-substitut för hud. Proven roterade i varmt vatten under 170 rpm. Proven smörjdes in på plexiglasplattorna och fotograferades i ljusmikroskop innan och efter tvättproceduren. Polyamidformuleringen var vattenresistent i 2 minuter och vaxformuleringen kunde tydligt ses efter 6 minuters tvättid.

Bioadhesion testades med en texture analyser. Hudprover från grisöron förbereddes med en dermatom och fästes på en prob. Proben sänktes mot provytan tills att ytorna kom i kontakt. Därefter drogs proben upp från provytan (0,1mm/s). Vatten och en kontrollkräm användes som referens. Kraften som behövdes för att dra proben bort från provet mättes. Vaxformuleringen påvisade det högsta värdet för dragfasthetsarbete (arean under kraft/distanskurvan) och vatten påvisade det lägsta värdet. Generellt hade formuleringar med hög viskositet högre kraftåtgång, vilket indikerar att viskositet kan påverka resultatet.

Populärvetenskaplig sammanfattning

Filmbildande emulsioner – att tvätta fast en vattenresistent film på hud

Är det möjligt att med en kräm deponera en vattenresistent film på människohud medan man duschar? Trots flera vetenskapliga hinder är detta fullt möjligt. Det tyder resultaten från ett projekt under våren på. Två olika produktprototyper har arbetats fram med goda resultat. Produkternas bioadhesionsförmåga, vattenresistens och ocklusiva egenskaper har testats och analyserats.

Projektet har sitt ursprung i att försöka skapa ett hjälpmedel mot hudsjukdomen Intertriginös dermatit, ofta kallat Intertrigo. Sjukdomen orsakas av friktion mellan motsatta hudytor. Värme, fukt och maceration leder till inflammation i huden som i sig kan vara mycket smärtsamt. Tillståndet kan också orsakat sekundära infektioner. Patienter som redan har Diabetes eller är mycket överviktiga löper högre risk att drabbas av sjukdomen och det finns inga botemedel.

I litteraturen påpekas också att det saknas preventiva åtgärdsmedel. Generellt är det svårt att få konsumenter att använda preventiva produkter, människan har precis lärt sig att det är viktigt att borsta tänderna till exempel. Om man däremot kan göra användandet av produkten till en del av en redan existerande dagsrutin, som att duscha, borde man kunna attrahera konsumenter i större utsträckning. Därför blev målet att försöka göra en produktprototyp för en in-shower-produkt. En lotion som appliceras medan man duschar, deponerar en film på huden och sköljer bort andra överflödiga ”paketeringsingredienser” från huden. Filmen ligger osynligt kvar på huden och kan minska friktionen mellan närliggande hudytor och på så sätt mekaniskt förebygga inflammation.

Båda prototyperna bildade vattenresistenta filmer, som tålde turbulent vattenflöde i varmvatten i 2-3 eller ca 6 minuter. En referenskräm utan någon filmbildare påvisade ingen som helst vattenresistens. Resultaten observerades i ljusmikroskop. Produktprototyperna påvisade också en godtagbar permeabilitet av vattenånga. Ca 400 µm tunna filmer spreds på toppen av hydrogeler i petriskålar och viktminskningen mättes som en funktion av tid. Med resultaten kunde man sen bestämma vattenflödet genom filmen per timme och per ytenhet. Bioadhesionstesterna gav däremot något motsägande resultat, och tyvärr påverkades förmodligen experimentet av krämernas mycket varierande viskositet. En stor överraskning var också hur väldigt olika resultaten blev när man bytte en emulgator mot en annan, med exakt samma struktur så när som på ett kol i kolvätekedjan. Detta tyder på vikten av varje enskild ingrediens tillskott till en komplex formulering som dessa.

Det finns fortfarande en del arbete kvar, speciellt att se till att filmen också faktiskt mekaniskt minska friktionen, men förutsättningarna ser ljusa ut. Att deponera filmer med hjälp av en kräm och en tvättprocess kan dessutom hitta ytterligare användningsområden. Vem vet, snart finns ”tvätta-på-filmsprodukter” i en butik nära dig!

Preface

This masters engineering degree project was written at the Department of Food technology at LTH in collaboration with the pharmaceutical company Bioglan AB in Malmö. The degree project equals 30 credits.

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Ida Moen Larsson
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1. Introduction

The skin is the largest organ of the human body. It protects the body from the environment and the outermost layer of the epidermis is called stratum corneum. The skin disease Intertriginous dermatitis, commonly known as Intertrigo, is an inflammation in macroscopic skin folds caused by friction, moisture, heat and maceration between adjacent skin surfaces. Obese individuals and patients diagnosed with diabetes are more likely to develop this condition. Even though there are several suggested treatments, recurrence is high and there is no medical cure for the disease.

Literature also points out that there are no studies on preventive treatment of Intertrigo. It is very difficult to make consumers use preventive care products; this might be one reason why preventive products are not readily available on the market for this condition. If, however, the application procedure is effortless, this might be circumvented. One way to do this could be to make a preventive product more attractive by formulating it as an in-shower product.

Lotions are often emulsions. An emulsion consists of at least two immiscible liquids where one is dispersed in the other. Emulsions are thermodynamically unstable, but can be stabilised by adding emulsifying agents, such as surfactants and co-emulsifiers. If the disease Intertrigo is caused by friction, one question is if it would be possible to also prevent it by decreasing friction with a topical formulation, without the use of an active pharmaceutical ingredient (API)? If a topical product deposited a thin film which decreased friction mechanically, no API would be needed. Such a film would have to meet several criteria, such as being non-occlusive, being water resistant and adhere to the skin surface.

Creating an in-shower product which deposits a film on the skin and decreases friction involves several obstacles, and solution of these might counteract each other. An oil-in-water emulsion needs a surfactant to stabilise the system, which in turn forms micelles washing off unwanted species from the topical surface. Furthermore, increasing moisture is known to increase skin friction. The cosmetic industry also battles environmental issues and sustainable ingredients are preferable today. Moreover, some abundant ingredients traditionally used in the industry are being criticised. In this thesis, the focus was the deposition of a non-occlusive and water resistant film on the skin and the search for a well-functioning biodegradable surfactant.

Following this introduction, relevant theoretical background is presented in the theoretical chapter. The facts presented are somewhat interdisciplinary to give the reader an overview of the many dimensions this project has covered. In the methodological chapter, the methods used are explained. The result chapter follows the same disposition as the methodological chapter and presents the results. Finally, the results are analysed and discussed in the discussion chapter. In the final chapters, the report is summarized in a brief conclusion and thoughts on future research are presented.

1.1 Aim and research questions

The aim of the project was to development a product prototype of a topical formulation which intends to decrease friction in skin folds by forming a non-occlusive, water resistant film on epidermis. This led to several research questions which follow:

Can a film be deposited onto epidermis by washing?

What characteristics will the film from the product prototypes exhibit in terms of occlusivity, bioadhesion and water resistance?

2. Theoretical background

The theoretical chapter covers a wide range of fields. It is meant to give the reader substantial background information on the different areas which the products and their evaluation will concern. The chapter starts with an introduction on the human skin and some of its properties and the skin disease Intertrigo. Background concerning emulsions and special ingredients used in emulsions formulated in this project will also be presented. A brief discussion concerning sustainability and ethical considerations is also a part of this chapter.

2.1 The human skin

The skin protects the body from physical damage, microorganisms and other substances in the external environment. It consists of two main layers, epidermis and dermis, and several different bilayers. The skin plays a role in regulating body temperature and it also produces different endocrine substances (Lodén, 2013).

The top layer of the skin, epidermis, has an extremely high turnover and renewal of cells. Cells are continuously developed through mitosis in the deeper part of epidermis, the basal layer. When the cells migrate closer to the top layer and air/skin interface they die due to lack of blood circulation in epidermis. The outermost layer of the skin, called stratum corneum (SC), hence consists of old dead cells (Lodén, 2013).

The skin can be the subject of inflammation, in medical terms this is called *dermatitis*. Eczema for instance is an example of dermatitis. Worth mentioning though is that some people tend to use the words dermatitis and eczema synonymously, which is incorrect. Inflammation in the skin does not strictly imply that it is a type of eczema. Eczema is indeed a type of dermatitis, but a condition can be dermatitis without being eczema. (Lodén, 2013) This thesis focused mainly on a special form of dermatitis, namely Intertriginous dermatitis, an inflammation in macroscopic skin folds.

2.1.1 Occlusivity and transepidermal water loss (TEWL)

The stratum corneum is a responding membrane, with altering properties depending on its environment. This means that we cannot determine a fix and specific permeability coefficient for the human skin. Even though the SC prevents water from evaporating from our bodies, the transepidermal water loss (TEWL) can be estimated to approximately 100 - 150 ml/day/m^2 of the skin surface area in healthy skin. The water activity (a) inside the body (can be estimated to $a_{body} \approx 1$) is much higher than

that of the external environment, causing a gradient which drives water to evaporate through the skin. The external environment can be characterised by its relative humidity (RH) and the corresponding value of RH inside the body is ca 99,6% (Sparr, 2012).

The water activity inside our bodies remains somewhat constant, but the outer surface of the SC can be altered. Application of creams and other topical products can create occluding films which separate the SC from the external environment. Because of this, an occlusive film is a way to increase moisture in the SC by decreasing the TEWL (Sparr, 2012).

2.2 Intertriginous dermatitis (Intertrigo)

Intertriginous dermatitis, commonly called Intertrigo, is an inflammatory condition in skin folds. It may cause redness, itching and a burning sensation. The inflammation is induced when opposing skin surfaces rub against each other in the moist and warm microclimate created in skin folds. Maceration and friction are inducing factors to the dermatitis. (Medscape 2017) The condition itself can be painful and secondary infections by fungi, bacteria or viruses are common. Especially fungal infections are very common (Hidalgo, 2007). Even if treatments are available, recurrence is common, (Medscape 2017). Also, earlier review articles indicate that research concerning preventive measures is hard to find (Mistiaen and van Halm-Walters, 2010).

2.2.1 Patient group and current treatment recommendations

The disease is overrepresented among obese patients and patients with diabetes. People suffering from other skin conditions such as psoriasis also carry an increased risk of developing the condition. There is no predilection between races or sexes, however very young and old are risk groups due to weaker immunological barriers and immobility (Medscape 2017).

Even though there are various recommendations and treatments available on the market recurrence is high for Intertrigo and there is no cure. Recommendations consist of weight loss, to stay cool and dry, and to avoid tight clothing. Adjacent skin surfaces can be separated by ointments and pastes and secondary infections are often treated with topical antimycotic and/or antibacterial formulations. Intertrigo without secondary infections are commonly treated with local topical corticosteroid formulations, (Medscape 2017). In addition, there are a lot of inventive remedies available, such as applying dressings bathed in solutions or absorbing excess moisture with tea bags, (PrimeHealthChannel 2017). However, these remedies are often not compatible with everyday life and/or are difficult to use.

For a more detailed description on the state of the art of Intertrigo and business prospects concerning this patient group and this product, see Business case, Appendix A1.

2.3 Emulsions

An emulsion is a dispersion containing at least two immiscible or partly miscible liquids. One of these liquids is dispersed uniformly in the other which acts as the continuous phase. In an oil-in-water emulsion (o/w) the oil is dispersed into the continuous phase consisting of water. In a water-in-oil emulsion (w/o) the system is instead inverted, with the oil acting as the continuous phase. (Aulton and Taylor, 2013)

2.3.1 Cosmetic and pharmaceutical emulsions

One important aspect of especially cosmetic and pharmaceutical emulsions is their complexity. They are generally multi-phase emulsions with an emulsifying system containing both surfactants and amphiphilic emulsifiers, i.e. fatty alcohols. When the emulsification system is present in larger concentration than necessary to stabilize the emulsion, the emulsifiers start to interact in the water continuous phase. Sometimes, these interactions form lamellar or crystalline structures in the emulsion that not only stabilise the emulsion further, but also contribute to the consistency of the product (Eccleston, 1990).

2.3.2 Film forming agents

In both the pharmaceutical and the cosmetic industry, film forming agents of different kinds are used for a range of purposes such as increasing water resistance or forming sustained drug delivery systems. Film forming emulsions for sustained release usually consists of medium chain triglycerides (MCT), polyvinyl alcohol (PVA), a plasticiser, a surfactant and a matrix forming polymer encapsulating the oily drug (Lunter and Daniels, 2013). Schrooeder et al. (2007) performed a study where 14 different polymers were investigated concerning their film forming ability to evaluate their drug delivery potential. Both mechanical and cosmetic properties were evaluated. Among the polymers tested were Chitosan, hydroxypropylcellulose (HPC) and acrylates copolymer. Acrylates copolymer is readily used by the cosmetic industry to enhance rub-off and water resistance (ULprospector 2017). Another film forming and water resistance agent is polyamide. The polyamide with the commercial name OleoCraft forms cohesive water-resistant films on epidermis (Croda Personal Care). The product is used in cosmetic products such as sun screens or make-up. Other in-shower lotions available on the market use microcrystalline wax and mineral oil to create a smooth and water resistant surface on the skin after application (Nivea 2017).

2.3.3 Emulsifying agents

Since the polar (water) phase and nonpolar (oil) phase are immiscible, the emulsion system is thermodynamically unstable, unless an emulsifying agent is added. The free energy of the emulsion will still be high even though the emulsifier is added, but the emulsifying agent will at least delay the coalescence of the dispersed phase. Emulsifiers delay this process by either aiding to form an interfacial film surrounding the droplets or by acting on the external phase and altering its rheology. The effects of emulsifiers can be derived from either enhanced mechanical barriers at the droplet surfaces or by increasing the repulsion between droplets. Strong interfacial films form a mechanical barrier that prevents the merge of droplets. The introduction of repulsive forces counteracts the attractive forces exhibited due to the van der Waals forces. By altering the rheology and thickening the external phase it becomes more difficult for droplets to move through the external phase. Emulsifiers working in this way are generally called co-emulsifiers, auxiliary emulsifiers or viscosity enhancers, (Aulton and Taylor, 2013).

Surface active agents (surfactants) are emulsifiers and can be further classified into ionic and non-ionic surfactants depending on their molecular behaviour. Surfactants are characterised by having one hydrophilic part, and one hydrophobic part. The hydrophilic part of the molecule may be charged or not and determines if the molecule is ionic or non-ionic. Depending on the hydrophilic-lipophilic balance (HLB) of the molecule, it is more or less soluble in water (Aulton and Taylor, 2013).

Emulsions are unstable and have a high free energy. A surfactant will, due to the hydrophobic effect, face the aqueous phase with their hydrophilic part. When the concentration of the surfactant reaches a critical point, the surfactant molecules form spherical aggregates called micelles. The micelle consists of 50-100 molecules, turning the fatty tail inwards into the sphere and the hydrophilic group towards the water phase. This process decreases the surface tension between the immiscible liquids, since the immiscible liquids are no longer in direct contact. The formation of micelles occurs spontaneously, since they lower the free energy of the system. The radius of the micelle depends on the length of the hydrocarbon chain of the surfactant, and core size of the micelles hence varies (Aulton and Taylor, 2013). The usage of traditional surfactants brings us to the matter of sustainability.

2.4 Sustainability and ethical considerations

Surfactants, especially ionic surfactants, are known to be irritants and in some cases, toxic. The alkyl sulphate sodium lauryl (dodecyl) sulphate (SDS) is the most widely used anionic surfactant in different topical products (Aulton and Taylor, 2013). It is an anionic surfactant irritating properties (Aulton and Taylor, 2013). Some common types of surfactants such as nonylphenols have even been banned from several European countries due to its possible disturbance of the endocrine system in animals. Many traditionally used surfactants are also non-renewable, but are still used since they are cheap and abundant. This has raised serious environmental debate concerning surfactants, and several biodegradable and mild sugar based surfactants have been evaluated the past decades. Among the widely investigated groups of surfactants we find polyglucosides (APGs). APGs are natural emulsifiers with a wide range of application areas, where skin care is one of them (Rojas et al., 2009). They are also non-ionic and hence mild and less irritating than traditional surfactants like sodium lauryl (dodecyl) sulphate (Aulton and Taylor, 2013; Lodén, 2013).

Ethical considerations are always necessary in research involving humans and animals. Ethical considerations concerning the development of a patient survey was inevitable. In Sweden, there is a requirement by law since January 2004 that all research involving sensitive matters should be vetted and approved by the Swedish ethical review board, (EPN, 2017). The law defines “research” as scientific experiment or theoretical labour to gain new knowledge on scientific grounds. However, the “law on ethical trial of research regarding humans”, does not concern research performed by students at university on basic or advanced level, (SFS 2003:460). Even though students are spared from the requirement of an ethical vetting of their research, it is also stated that sensitive matters might need to be trialled anyway. Hence, herein lies a matter of interpretation to every project, to decide if they should be defined as research or not.

The trade association Läkemedelsindustriföreningen (LIF), (the research-based pharmaceutical industry) helps members to understand the bureaucracy and ethical demands connected to different types of research. As mentioned, market research does not require an approved enquiry from the ethical review board. A company can on its own distribute market research surveys or distribute them with aid from patient association. The aim with market research can be to gain information for development of new products. The respondent should understand where the survey has its origin and how the information will be used. Anonymity is also very important. The distributor should also be aware of the ICC/ESOMAR International Code on Market Research (LIF 2017).

2.5 Bioadhesion

Bioadhesion can be defined as the attachment of macromolecules (synthetic or natural) to biological surfaces (Vasir et al, 2003). Topical bioadhesion has many advantages such as patient compliance, local administration and avoidance of the first pass metabolism (Singh et al., 2011). Bioadhesion has been widely investigated in the pharmaceutical industry during the last decades since several bioadhesive polymers are suitable for controlled release systems (Vasir et al, 2003). Many bioadhesive formulations adhere to buccal mucosa or other tissues, but research has also been performed to investigate topical bioadhesion (Singh et al, 2011). Researchers readily use pig skin to test bioadhesion in vitro (Carvalho et al, 2013; Cintra et al, 2016). Earlier research using a tensile strength method for testing bioadhesion indicates that a low withdrawal speed is preferable and that tensile work (the area collected in the force-distance plot during withdrawal) and fracture strength (peak force divided by the contact area) are two ways to interpreting adhesiveness, (Hägerström and Edsman, 2001)

The mechanisms of bioadhesion are not yet fully understood and several theories to explain the chemical process of bioadhesion exist. Various classes of molecules have been investigated, and among known bioadhesives there are derivatives of cellulose (i.e. methyl-cellulose or hydroxypropyl-cellulose), high molecular weight polyacrylic acid (i.e. carbomer) and polysaccharides such as chitosan (Salamat-Miller, 2005). Different theories regarding bioadhesion focus mainly on the concept of mucoadhesion. Attractive electrostatic forces, chemical bonding such as covalent-, ionic-, hydrogen-bonds or van der Waals forces, entanglement and wetting are some of the plausible explanations for bioadhesion. In addition, environmental, physiological and polymer related factors affect the bioadhesion (Vasir et al, 2003), making the process even more complex and difficult to understand. Furthermore, literature on the topic is scarce.

3. Materials and methods

This chapter describes the development of methods and the experiments performed during the project. Each head section will have a corresponding section in the results chapter.

3.1 Development of topical formulations

All prepared formulations are oil-in-water emulsions. A first basic formulation was developed and by altering ingredients in the oil phase, but keeping the w/w% between the water and the oil phase constant, different film forming agents were tested. In the start of the project, film formation, foaming capacity, water resistance and decreasing friction were all focus areas for the product. After a while however, the foaming capacity was down-prioritised. This decision was made mainly because of the counteracting impact on film formation that many surfactants exhibited. The first formulations were prepared with Macrogol 100 stearate or SDS. These formulations gave no positive results concerning film deposition. When the APGs coco glucoside and lauryl glucoside replaced the earlier surfactants in the formulations, positive results regarding film forming and water resistant properties were obtained. These formulations had very low foaming capacity, but film forming and water resistance were considered more important at this stage of the project.

Commercial film forming agents for the formulations have been found in literature and many possible ingredients were tested before two final prospects were selected for further development and evaluation experiments. One of these formulations were based on a microcrystalline wax (Multiwax 180 MH, Sonneborn) and the other used a polyamide as a film former (OleoCraft LP-20, Croda). A detailed list of ingredients for the formulations is available in the Materials list, Appendix A2.

Formulations have all been prepared by mixing a water phase (continuous phase) and an oil phase (dispersed phase) separately. Ingredients for the formulations have been weighed on scales (Mettler Toledo, PB3002-S/FACT or Mettler LJ16 Moisture Analyser). The two phases have been heated to the same temperature (Thermometer IKA ETS-D5) in beakers placed in a temperature regulated water bath on top of a magnetic heating plate (IKA C-MAG HS 7). During heating the liquids were stirred with a magnetic flea and the beakers were covered with tin foil to avoid evaporation. When both phases have become completely homogenous and have the same temperature, the oil phase have been poured gently into the water phase while mixing at 13500-17500 rpm with a homogenizer (IKA, Ultra Turrax T25 basic) for 2-3 minutes. The emulsions were stirred carefully until they reached room temperature. pH was measured with a pH-meter (744 pH Meter, Metrohm).

3.2 Water vapour permeability

To determine the relative occlusivity of the samples, a modified version of the water vapour permeability experiment presented by Sparr et al. (2013) was used. It is an experimental, gravimetric method for determining the water vapour flux across the film layer. Gelatine was used as a gelling agent.

A gelatine water liquid was prepared by dissolving 4 w/w % of powdered gelatine into a small amount of cold water. The remaining water was heated to approximately 50 °C (magnetic heating plate, IKA C-MAG HS 7) and the cold water/gelatine mixture was added. The liquid was then stirred with a magnetic flea until the gelatine was completely dissolved. The beaker was always covered with tin

foil during heating. The foam created on the surface of the liquid was removed with a plastic pipette prior casting.

The hydrogel was cast in Petri dishes (diameter 5 cm). The liquid was poured into the dishes to fill the Petri dishes as close to the edge as possible, approximately 1 mm from the top edge. The gel was left to set overnight. Samples were spread with a spatula directly on top of the gel at room temperature and a lid was placed on top of each dish. The mass of applied sample on the gel was weighed (Mettler LJ16 Moisture Analyser) and the approximate thickness of the film was calculated with equation 1. The density of the emulsions was estimated to 1 g/cm^3.

$$d_{film}(m) = \frac{m\,(g)}{A\,(m^2)\,\rho\,(\frac{g}{m^3})} \qquad (1)$$

The dishes were placed in a drying cabinet (Termarks Cooling Incubator KBP 6151) set at 32 °C to mimic skin temperature. The lids of the dishes were removed at t = 0 and weighed at predetermined time intervals. The weight loss $\Delta m\,(g)$ was determined as function of time, and the slope $\Delta m\,(g)/\Delta t\,(h)$ from the plots divided by the area of the gel surface $A\,(m^2)$ gives the water flux $J\,\left(gm^{-2}h^{-1}\right)$ through the film, equation 2 (Sparr et al., 2013). Relative humidity was determined with a RH-meter (Testo 363).

$$J\,(gm^{-2}h^{-1}) = \frac{Slope\,(\frac{\Delta m\,(g)}{\Delta t\,(h)})}{A\,(m^2)} \qquad (2)$$

The experiment was optimised considering thickness of the applied film and the amount of gel cast in the petri dishes. The gels were cast and used as soon as possible since older gels caused unwanted errors, such as the rupture seen in figure 1. A film thinner than used in results in this report resulted in cracks in the films causing unreliable results, figure 2. For the final experiment, films of approximately 400µm were spread onto the hydrogels. Too little gel in the petri dishes also resulted in vast difficulties of spreading an even film of the samples on top of the gel.

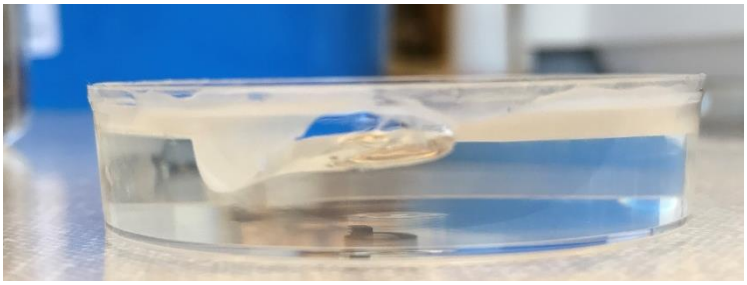


Figure 1: a gel with large crack in both the film as well as the gel itself resulting in inaccurate results. The dish had been cast a week prior the experiment, and the experiment was optimized to use as freshly cast gels as possible for the evaporation experiment. That also ensured as high water activity as possible in the gels.

Figure 2: to the right the film has cracked during the experiment and film thickness was adjusted to avoid ruptures of the film during the evaporation test.

3.3 Microscopy

3.3.1 Light microscopy

Samples were examined in a light microscope (Zeiss, Axiostar Plus) with a digital camera (Canon PowerShot G9) connected to a PC. Pictures were taken with the camera and software (RemoteCapture DC) and were thereafter analysed and labelled in the software AxioVision LE. The light microscope was also used when evaluating the water resistance of the formulations (3.4 Water resistance).

3.3.2 Confocal microscopy

For the fluorescence confocal microscope (Zeiss, LSM 510 META), the samples were rubbed with a plastic pipette onto a sterile disposable sample holder and a few drops of immersion oil was added on top of the objective (40x). The laser used were a DPSS 561-10 laser and one HeNe 633 laser (different laser were needed because of the different excitation wavelengths of the fluorescent probes used). The settings of the confocal microscope and the analysis of the obtained pictures were performed by the software Zen 2009. Snap photographs and stack sequences were taken to examine the structure of the formulations and their 3D appearance. The stack pictures were taken with 25 slices with 0,49 µm intervals.

To distinguish the structure of the samples, two different staining probes were used. Nile red, (λ_{ex} 530 nm; λ_{em} 635 nm) (Sigma Aldrich 2017) and Nile blue (λ_{ex} 633 nm; λ_{em} 672 nm) (Interchim 2017) are fluorescent probes used to stain hydrophobic and hydrophilic substances respectively. The molecular structure of Nile red and Nile blue can be seen in figure 3. 0,1 w/w% of the water phase was added of Nile blue to the water phase and 0,1 w/w% of the oil phase was added of Nile red to the oil phase. Otherwise, the formulations were prepared as described in chapter 3.1 Development of topical formulations. The samples were wrapped in tin foil after preparation.

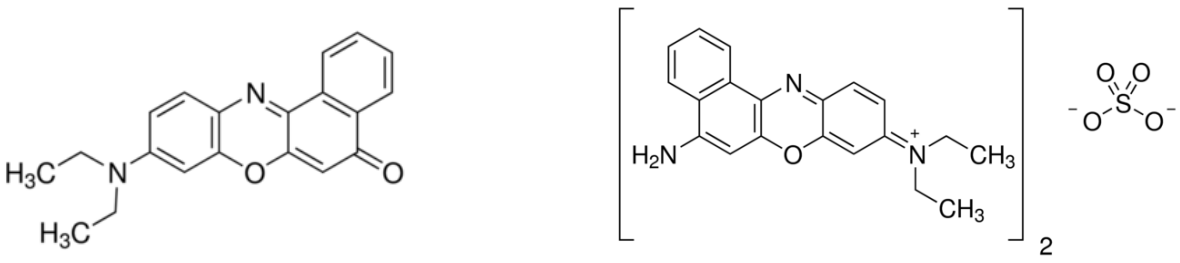


Figure 3: to the left: the molecular structure of Nile red. To the right: the molecular structure of Nile blue. The Nile blue molecule is more polar than the Nile red molecule, and will therefor stain hydrophilic compounds while the Nile red will stain lipophilic substances (Sigma Aldrich 2017.)

3.4 Water resistance

Poly (methyl methacrylate) plates, (PMMA plates), were kindly donated by Schönberg GmbH & Co. KG, Hamburg. UV transparent PMMA plates with one roughened side are commonly used in Europe for acting as a skin imitating substrate when performing in vitro water resistance tests on sun screens. No substrate is known to replicate the in vivo situation perfectly, but these plates are easily handled, cheap, abundant and non-reactive. Most importantly, the plates allow a distribution of creams in a way that mimics that of human skin (Pissavini et al, 2007). The exact surface roughness index of the plates was unfortunately unknown. However, earlier studies have evaluated the surface structure of different PMMA plates from Schönberg GmbH & Co, figure 4, (Ferrero et al., 2007). The plates obtained were all cut from the same larger plate and hence hade the same roughness index. All plates were examined in a light microscope prior the experiment.

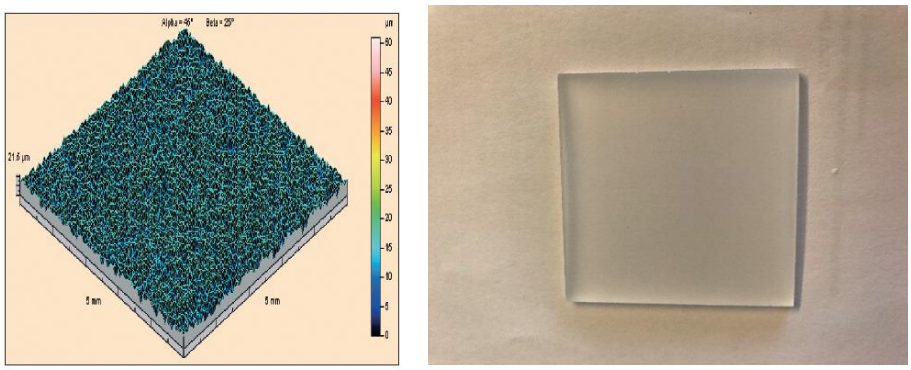


Figure 4: To the left; a topographic picture of the PMMA plates from Schönberg GmbH & Co. The scale bar has the unit of µm. The dimensions of the plate on the picture are 5x5 mm and it has a depth of 21,5 µm. To the right; a clean PMMA plate in dimensions 5x5 cm, height 3 mm (Ferrero et al., 2007).

The experimental setup was a modified version of that explained by Ahn et al. (2008). The setup is shown in figure 5. Approximately 60 -70 mg of sample were rubbed onto ~5 cm^2 the roughened side of the PMMA slides with a gloved finger and pictures were taken in a light microscope. The plates were either dry or wet when sample was applied. When the plate was wetted, a couple of drops of water were rubbed onto the slide simultaneously as the cream. A plastic pipette was used to measure the amount of water. The PMMA plate was fastened with scotch tape to a paddle (figure 5) and lowered into a water bath. The rod which held the paddle was connected to a motorised stand (IKA RW20DZM.n) and the plates were left to rotate in the water bath (tap water, ~38 °C) for different times and at a high rotation speed (~170 rpm). Once every minute, the samples were emerged from

the water and rubbed with a gloved finger, to simulate a shower procedure. The rubbing continued also when cream was no longer visible. The plates were left to air dry and again analysed in the light microscope. A control formulation was also used in the experiment with no film forming water-resistant ingredient.

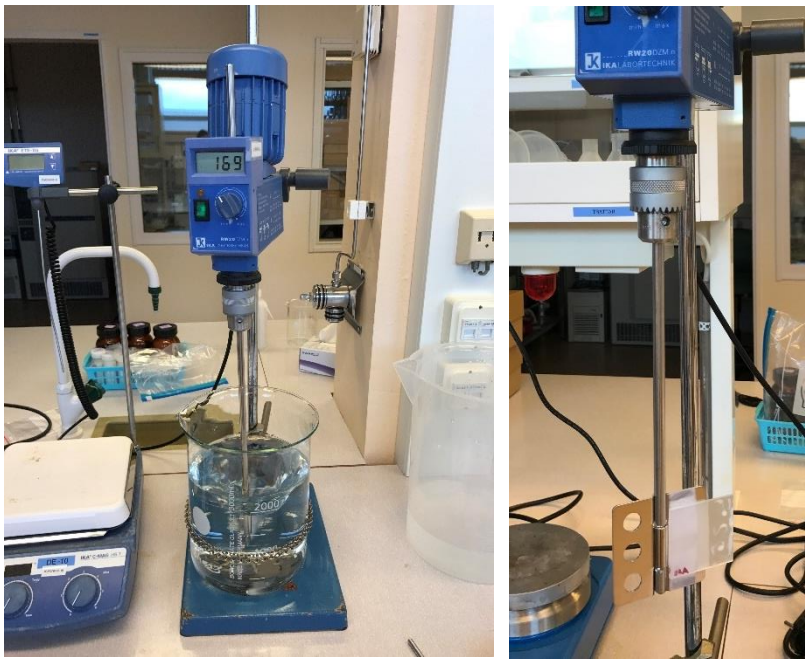


Figure 5: To the left: the experimental setup for the water resistance test. The motor kept the rotation speed constant at approximately 170 rpm as indicated by the display. The beaker was filled with tap water at ca 38 °C and left to rotate for different time intervals. To the right: the PMMA plate attached to the paddle on the rod with scotch tape.

3.5 Bioadhesion – a tensile strength method

The method was a modified version of an earlier experiment used to characterize bioadhesion of hydrogels and surfactant systems (Carvalho et al, 2013; Cintra et al, 2016). A texture analyser (TA-XT2*i*, Stable Micro Systems) was used to evaluate the bioadhesive properties of the formulations through a tensile test method. The texture analyser was connected to a stationary computer that collected data which were analysed by the software Exponent (Stable Micro Systems). In addition to the wax and the polyamide formulations, water and a control cream were used as reference.

3.5.1 Preparation of pig ear skin

Fresh pig ears were obtained from a local butcher and frozen immediately to -18 °C. The ears were then thawed, washed, gently shaved and cut with a surgical scalpel into smaller strips of approximately 15-20 cm^2. The pieces were fixed to a Styroform block with pins and dermatomed to approximately 500 µm (Dermatome set to 510µm) thick skin pieces. (Integra Dermatome, Model B, Integra LifeScience, Padgett Instruments). Dermatomed skin pieces were immediately placed with the dermal side downwards on a filter paper wetted with phosphate buffered saline solution (PBS solution) to prevent the skin from drying. The filter papers with the dermatomed skin pieces were wrapped in tin foil and directly transferred to a freezer.

3.5.2 The tensile test procedure

The formulations were spread as evenly as possible in a beaker or petri dish and placed on the static part of the texture analyser. High viscosity formulations were placed in a petri dish and a spatula was used to create an even surface, whereas more liquid products spontaneously spread evenly. On the day of the experiment, dermatomed pig ear skin was thawed at room temperature with PBS solution. The thawed skin pieces can be seen in figure 6. Skin pieces were attached to the flat cylindrical probe (diameter 24 mm) and fastened with Transpore™ tape. The cylindrical probe was mounted onto the upper flexible arm, illustrated in figure 6. The tool was calibrated regarding force and height before the experiment. The dynamic arm was lowered against the sample with the constant speed of 1 mm/s until the skin touched the sample surface, indicated by a trigger force of 1 mN. The probe continued at 0,5 mm/s another 2 mm into the sample after the trigger force had been detected to ensure that the entire probe surface was immersed in the cream. The skin and sample were kept in contact for 10 or 60 seconds with no additional force applied. The probe arm was then elevated at 0,1 mm/s. The force was detected by the software Exponent during the experiment and the tests were performed at room temperature and in triplicates.

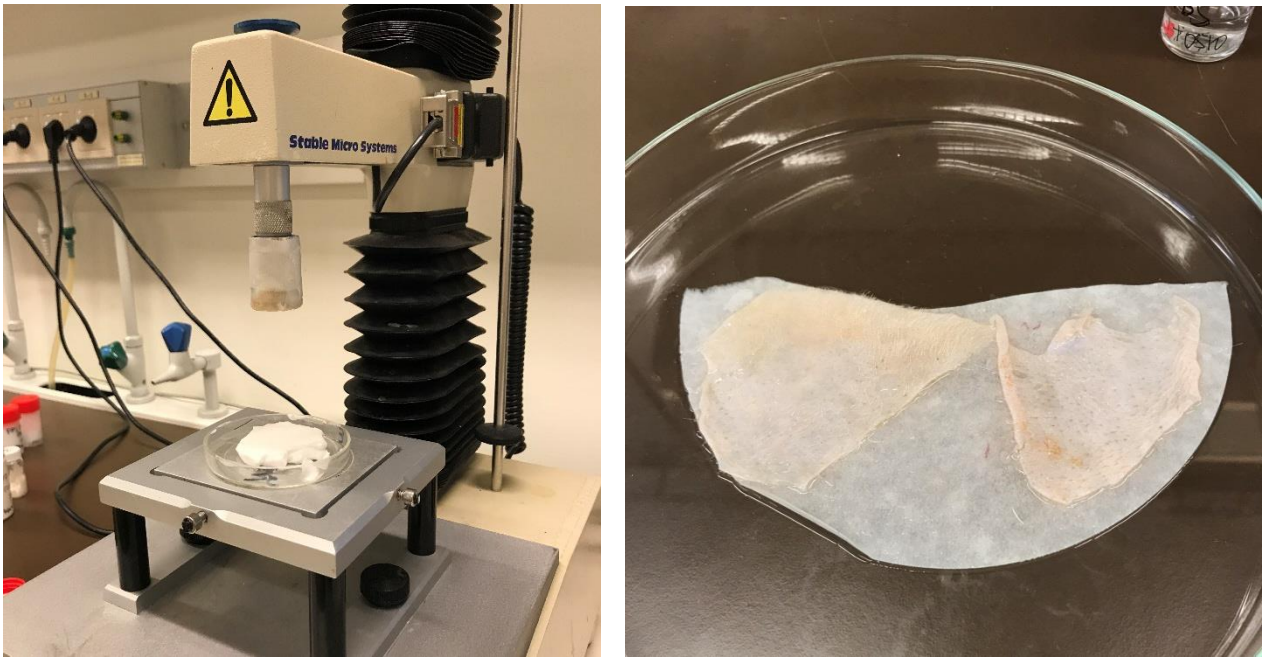


Figure 7: to the left, the experimental setup for the tensile strength experiment to evaluate the bioadhesive properties of the formulations. The cylindrical probe on the flexible arm is lowered into a beaker of water. To the right: the thawed pig skin on a filter paper soaked with PBS.

Two tests were excluded from the results due to obvious failures during the test procedure. Issues mainly arose from differences between the skin samples such as hair straws getting stuck in the creams or that the skin was not attached properly to the probe as seen in figure 7.

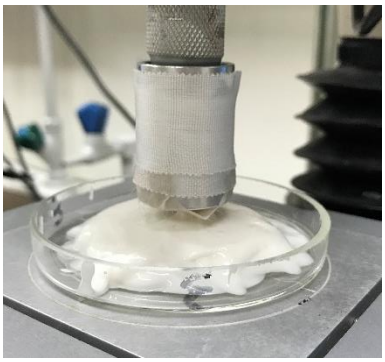


Figure 6: the skin sample attached to the probe is no longer correctly in place, yielding errors in the results from that test sequence.

3.6 Sensory evaluation study, market research survey and business case

An evaluation study for the two final products was developed, see Appendix A3. Questions were based on previous evaluation studies performed at Bioglan AB and respondents were asked to perform the application of each product on separate days.

The patient survey was categorized as a market research survey, and thus did not require the involvement of the ethical review board. The market research survey, see Appendix A4, aimed to gain understanding of the preferences regarding a possible product to treat Intertrigo. The compilation of the survey followed the guidelines of ICC and ESOMAR for market research (Esomar 2017) and the ethical advice accessible at the web page of LIF.

During the project, a business case was developed for the possible end product. The business case investigates the state of the art concerning Intertrigo and the treatments available. It also discusses possible target groups, marketing concerns and analyses the future positioning of the product on today's market. In addition, it presents statistics of the relevant market and patient group. The business case is based on a model used by the marketing department on Bioglan AB. The business case is summarised briefly in the results chapter and presented in its full version in Appendix A1 – Business case.

4. Results

For a detailed overview of the evaluation experiments performed, read the Traceability Matrix, Appendix A5. In Appendix A2, Materials, the w/w% distribution of the ingredients in each formulation is presented in a table.

4.1 Development of topical formulations

Two formulations met the criteria of forming a noticeable film on human skin after application to wet hands and rinsing with warm tap water. Both had the same ingredients in the water phase but different ingredients in the oil phases. One oil phase was based on a microcrystalline wax (Multiwax, Sonneborn) and the other was based on addition of a polyamide (OleoCraft LP-20, Croda). The reference formulation contained no film forming agent or ingredients known to increase water resistance.

Formulation containing microcrystalline wax
The formulation exhibited high viscosity and is pale yellow in colour due to the yellow colour of the microcrystalline wax. The texture was smooth. It was odourless and has a pH of 7,69. Light microscope pictures of the formulation are available in figure 8.

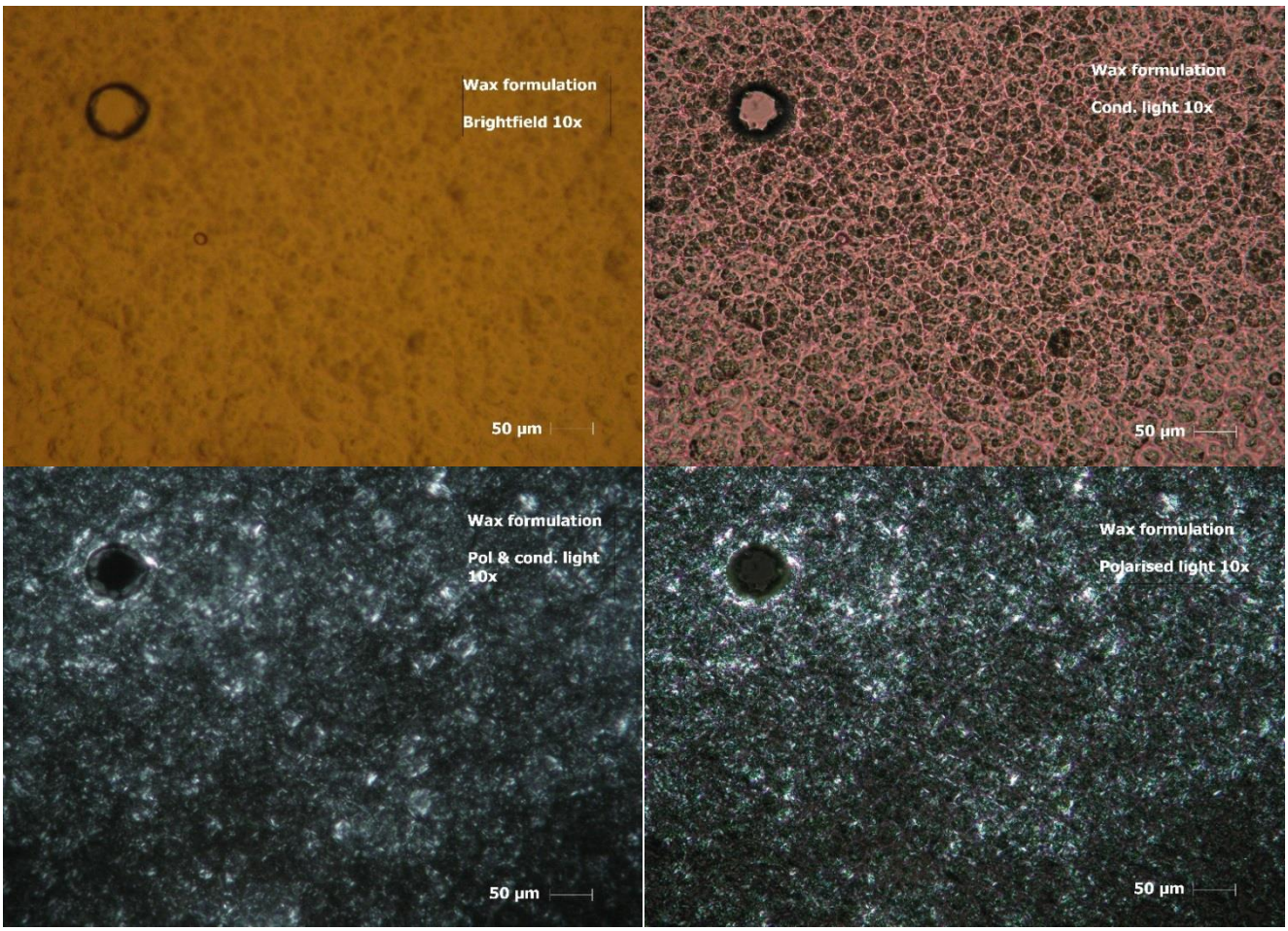


Figure 8: the results of pictures taken in a light microscope of the wax formulation. The different modes used of the microscope was: top left brightfield mode, top right condensated light, bottom left polarised and condensated light and bottom right polarised light only. The large circle in the top left corner of each figure is an air bubble.

Formulation containing polyamide

This formulation had a lower viscosity and was white in colour. The product was more lotion like and pourable. It is odourless and has a pH of 6,57. The structure was hard to visualise in the light microscope and it is barely visible in figure 9.

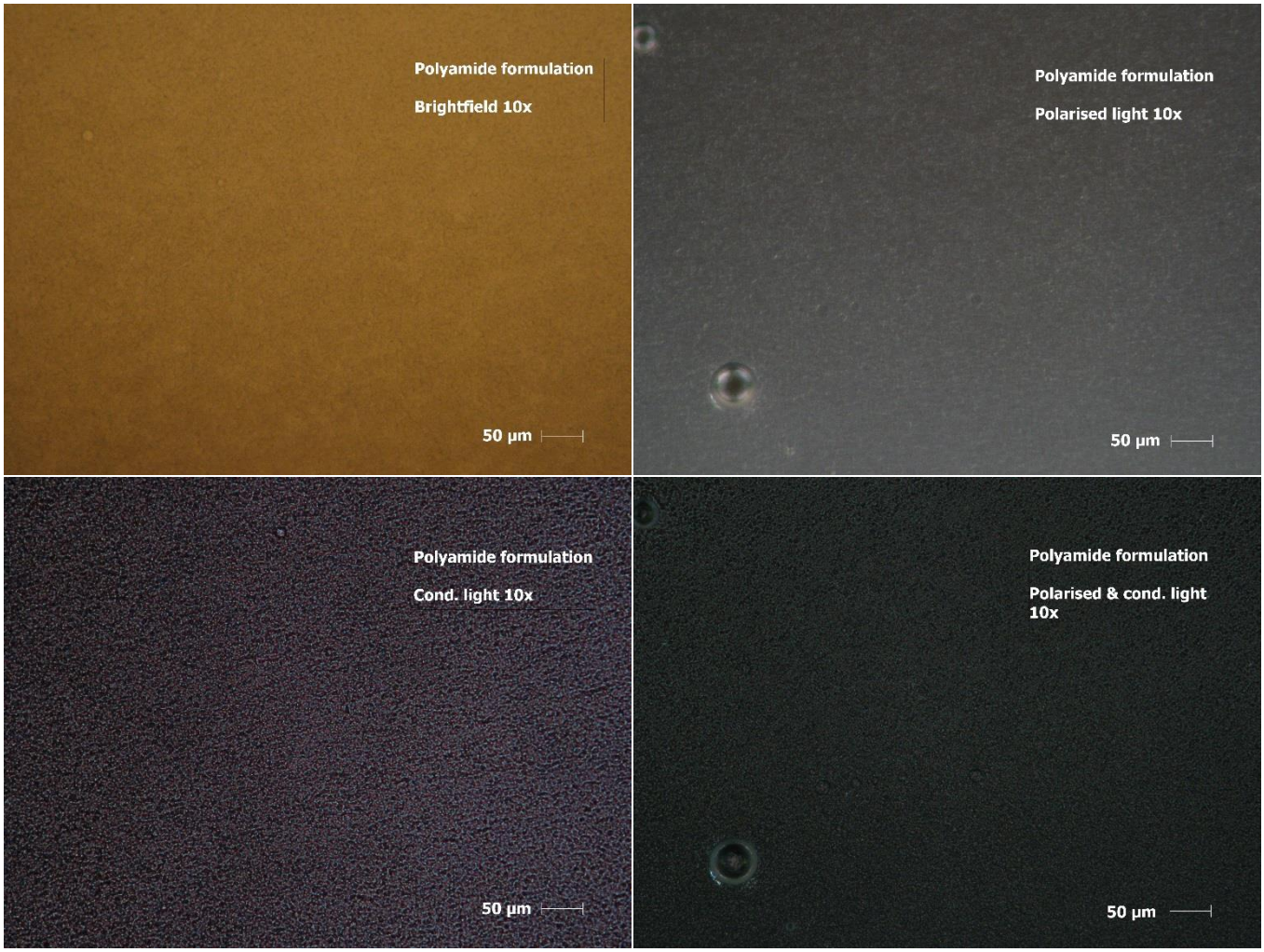


Figure 9: the results from light microscope pictures of the polyamide formulation. Different modes of the microscope were used: top left picture brightfield mode, top right polarised light, bottom left condensated light and bottom right polarised and condensated light. Especially this formulation was hard to examine in the light microscope and the pictures give little information on the structure of the emulsion. On the two pictures to the right an air bubble is also visible in the pictures.

Formulation used as a reference cream

The reference cream had a high viscosity and is bright white. It was a smooth, odourless cream, and has a pH of 3,56. Light microscopy pictures of the reference cream are available in figure 10.

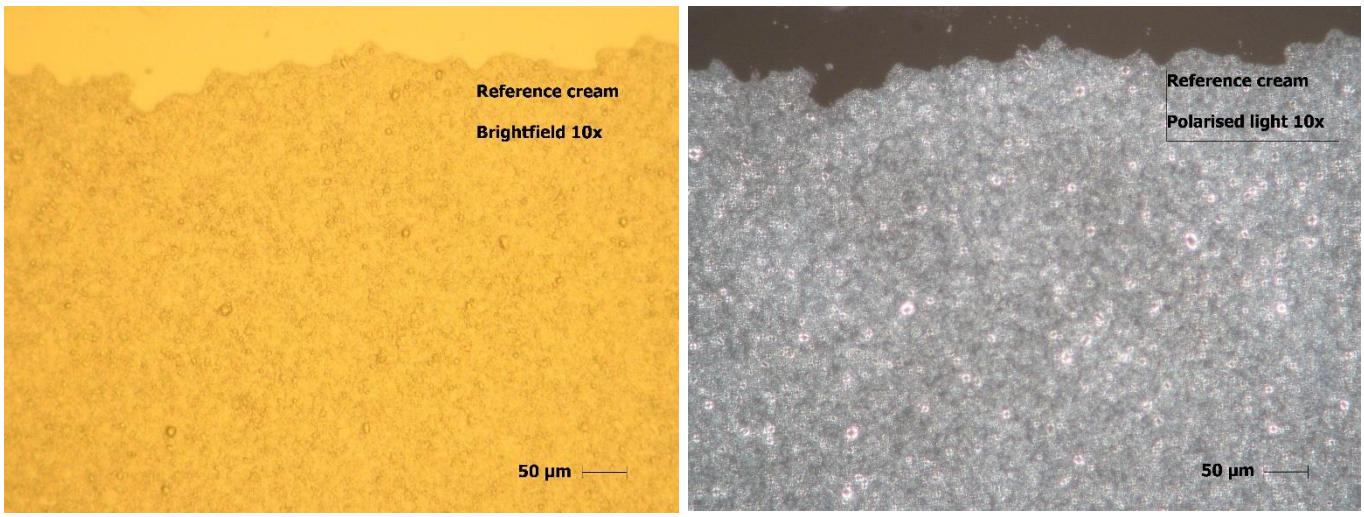


Figure 10: the results from pictures taken of the reference formulation in brightfield (to the left) and polarised light mode (right picture). The top part of the pictures is the interface between the cream and the clean glass slide.

Note that the stability of each formulation has not been determined. After a couple of weeks, the wax formulation started to bleed, and the polyamide formulation indicated tendencies to separation. pH has not been adjusted to wanted level.

4.2 Confocal microscopy

The staining of the formulations was successful and results from pictures taken with the florescence confocal microscope can be seen in figure 11 - 15. Nile red which should stain the more lipophilic parts of the sample is shown as red colour in the pictures. Nile blue, staining the hydrophilic parts can be seen as blue areas. In both 2D pictures of the samples, figure 11 and 12, the Nile red and Nile blue channels are shown separately and overlaid, resulting in three separate pictures in each figure. Black white areas in all pictures from the confocal microscope can be air, or parts of the sample that has not been stained. This will be further discussed in the discussion chapter.

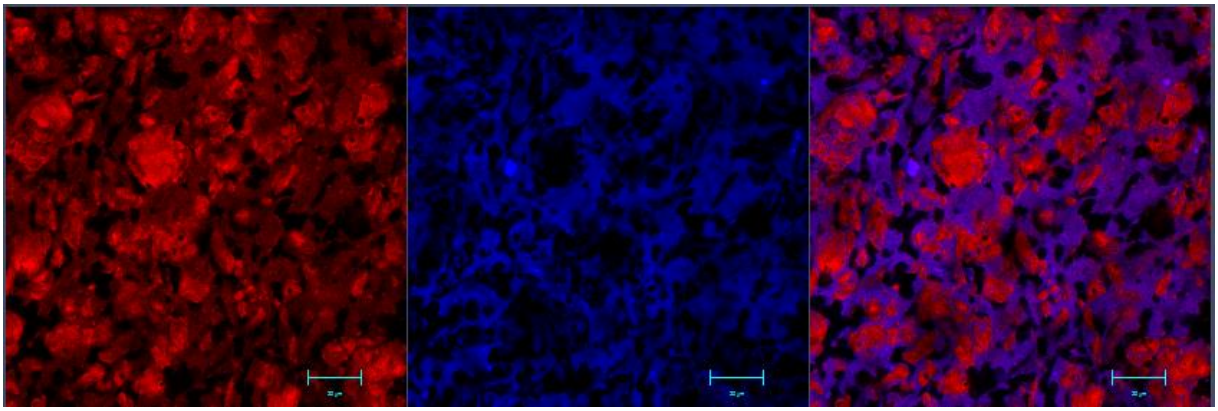


Figure 11: the 2D picture of the wax formulation taken with a confocal microscope using two fluorescent stains. To the left the part of the emulsion that has been stained with Nile red is shown. In the middle we see the exact same area of the sample stained with Nile blue. To the far right the red and blue pictures are merged. The scale bar indicates a distance of 20 µm.

In the pictures of the wax formulation (figure 11), there are some areas stained by only Nile red, and some with only Nile blue. Some areas also overlap. In the pictures of the polyamide formulation, the situation is different. Here the Nile red and Nile blue have stained more or less the same areas, resulting in three somewhat identical pictures, but in different colours.

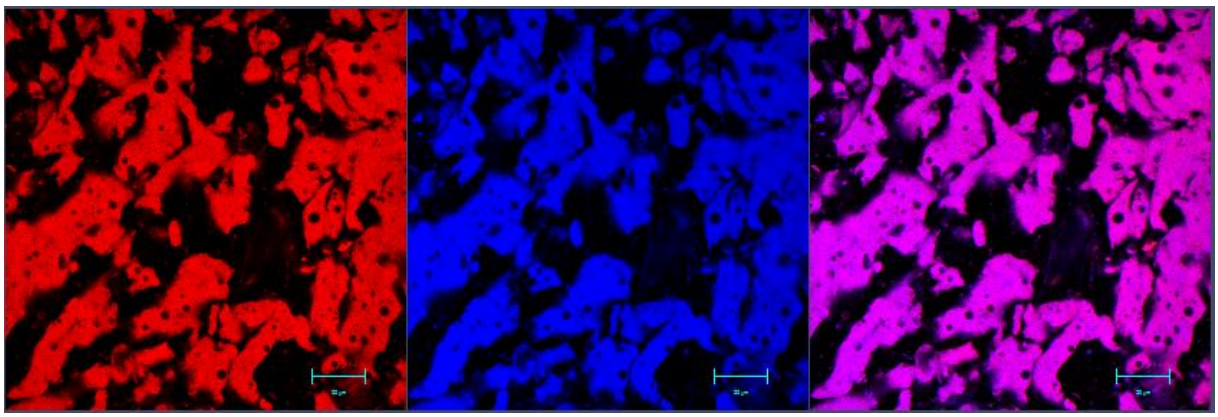


Figure 12: the 2D picture of the polyamide formulation taken with a confocal microscope using two fluorescent stains. To the left the part of the emulsion that has been stained with Nile red is shown. In the middle we see the exact same area of the sample stained with Nile blue. To the far right the red and blue pictures are merged. The scale bar indicates a range of 20 µm.

3D pictures of the formulations are seen in figure 13 and 14. The 3D picture of the wax formulation can be seen in figure 13. The structure clearly contains some lipophilic particles and some more hydrophilic sections.

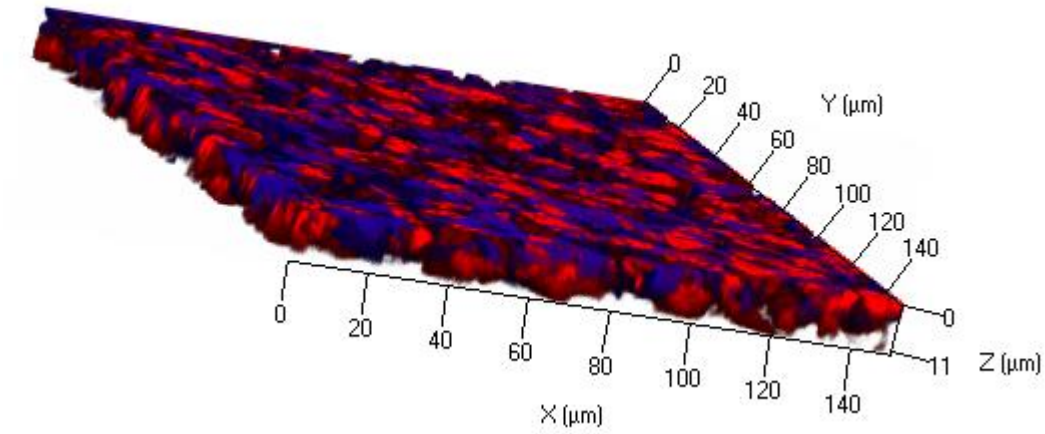


Figure 13: the 3D figure of the wax formulation. The x, y and z axes are indicated by the scale bars in each direction. The stack picture was taken in 25 separate slices with an interval of 0,49 µm.

In figure 14, we see the 3D stack picture of the polyamide formulation. It is almost completely impossible to distinguish what part of the sample that has been stained with Nile red or Nile blue.

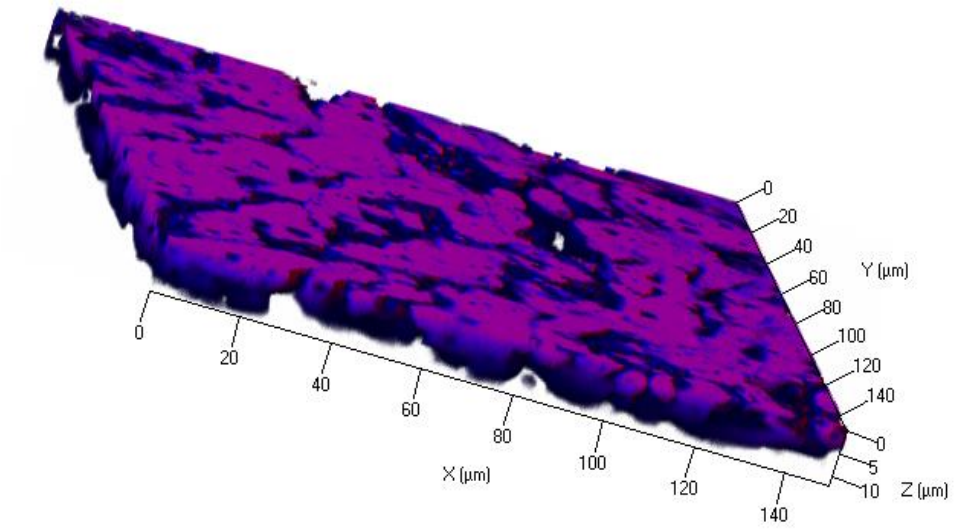


Figure 14: the 3D figure of the polyamide formulation. The x, y and z axes are indicated by separate scale bars for each axis. The stack picture was taken in 25 separate slices with an interval of 0,49 µm.

A zoomed version of the 2D picture of the polyamide formulation can be seen in figure 15. Here, a slight distinction between the two stains can be seen.

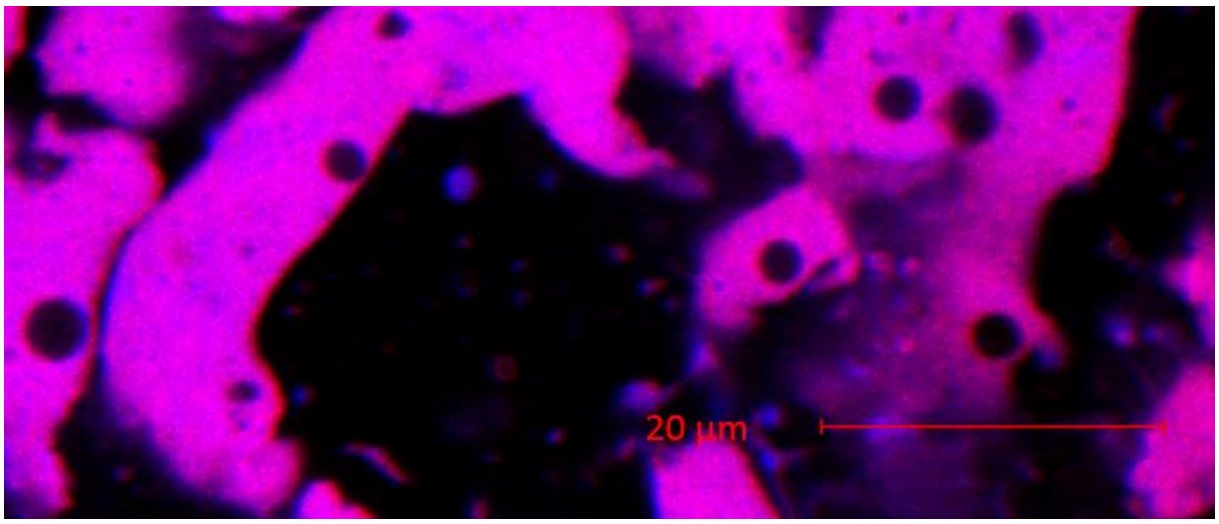


Figure 15: the zoomed 2D picture of the polyamide formulation. The Nile blue and the Nile blue seem to have stained almost the same areas but some differences are visible in the picture. The scale bar indicates 20 µm.

4.3 Water vapour permeability

The results from the experiments are shown in figures 16 - 20 and in table 1. The experiment was performed at 32 °C and at 15,7% RH. All samples were tested in triplicates, indicated by A, B and C in graphs and table 1. The first wax sample is named W1 and the second wax formulation is named W2. The first polyamide formulation is named PA1 and the second formulation is called PA2. The first wax formulation and the first polyamide formulation, W1 and PA1 respectively, contain the APG coco glucoside as the main surfactant. The formulations W2 and PA2 contain lauryl glucoside as the main surfactant.

The results for the complete experiment including all formulations tested and in triplicates are shown in figure 16. The control plates are bare gel casts with no cream on top and exhibit the highest weight loss due to evaporation, as expected. The weight loss is higher for all samples the first 1-2 hours of the experiment, due to evaporation not only from the gel cast, but also from the formulations.

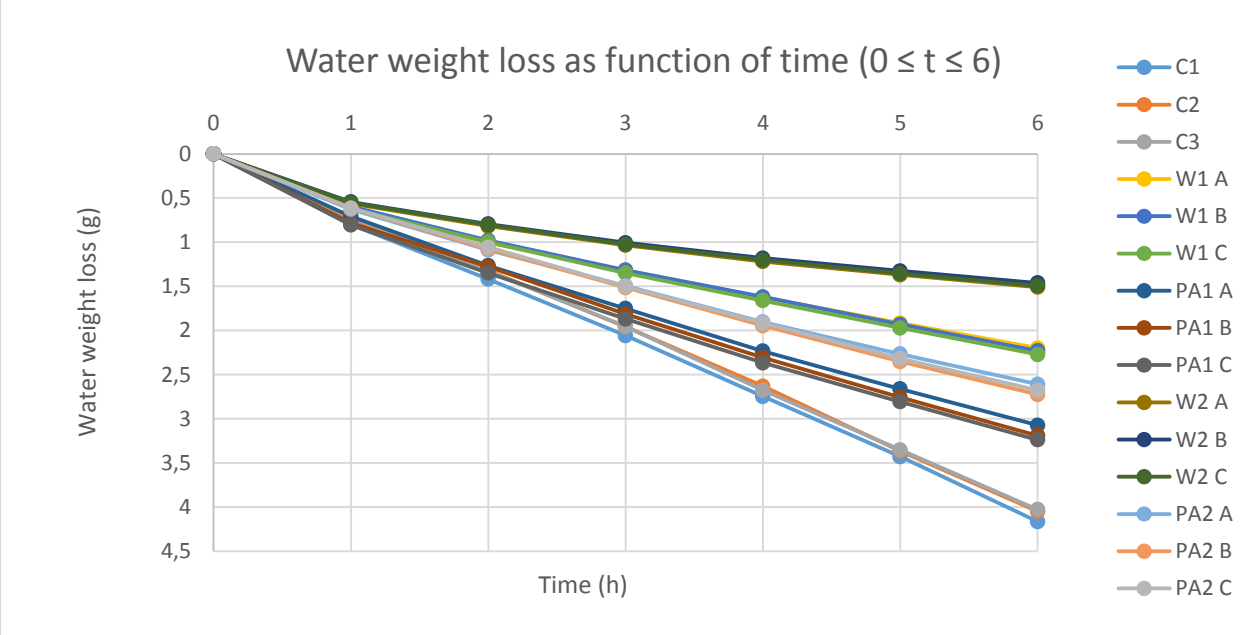


Figure 16: The water weight loss as function of time for all formulations used in the experiment. C = control, W1 = Wax formulation with coco glucoside, W2 = wax formulation with lauryl glucoside, PA1 = Poluamide with coco glucoside and PA2 = polyamide with lauryl glucoside. All samples were tested in triplicates (A, B and C).

Standard deviations from data plotted in figure 16 are shown in table 1.

Table 1: The standard deviations from each sample and measuring point during the experiment can be seen in this table.

	Standard deviations				
Time (h)	*Control*	*Wax 1*	*Wax 2*	*Polyamide 1*	*Polyamide 2*
0	0	0	0	0	0
1	0,033	0,01	0,01	0,041	0,006
2	0,044	0,011	0,01	0,037	0,012
3	0,048	0,014	0,011	0,048	0,008
4	0,047	0,018	0,015	0,054	0,018
5	0,033	0,023	0,018	0,06	0,035
6	0,06	0,029	0,019	0,07	0,048

To easier distinguish the formulations from each other, the mean values of the triplicates were calculated and are displayed in figure 17. The first polyamide formulation (PA1) reaches steady state later than the other three formulations.

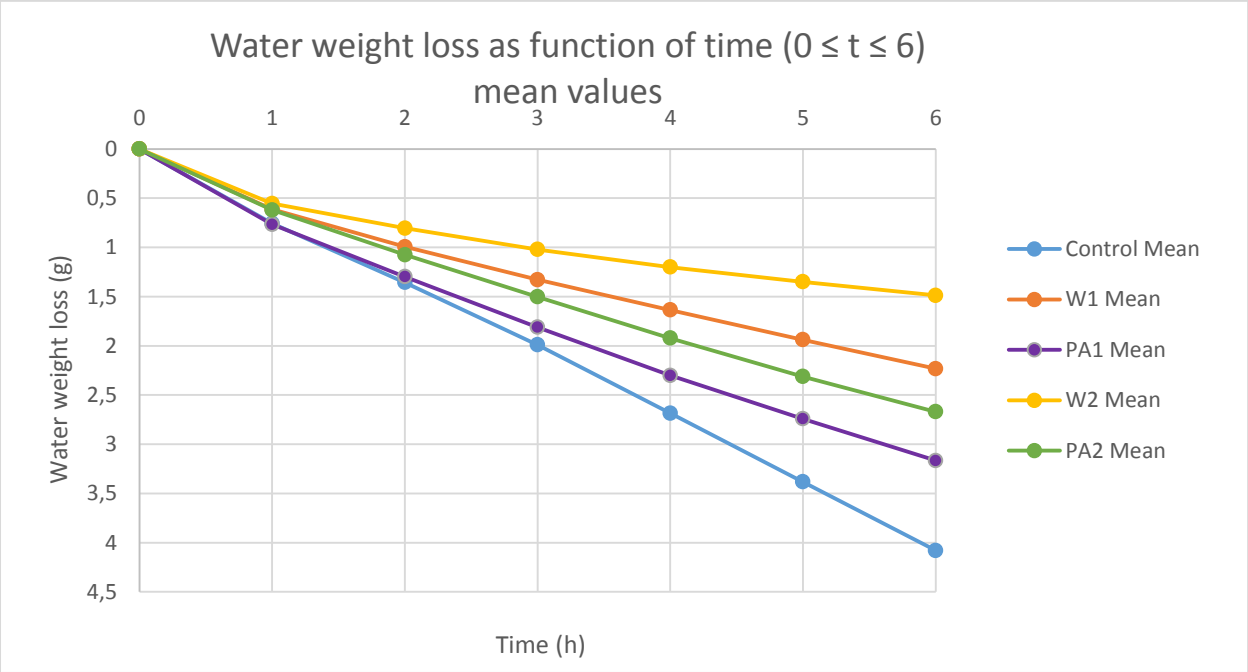


Figure 17: The water weight loss as function of time for all mean values of each formulation used in the experiment. C = control, W1 = Wax formulation with coco glucoside, W2 = wax formulation with lauryl glucoside, PA1 = Poluamide with coco glucoside and PA2 = polyamide with lauryl glucoside.

To ensure that steady state has been reached; the slope of the functions was taken from the time interval of $2h \leq t \leq 6h$. The plot from which the slopes were obtained is shown in figure 18. Since the Y-axis is inverted, a high slope indicates a large water weight loss. Hence, the formulation with the lowest slope is the least permeable film former.

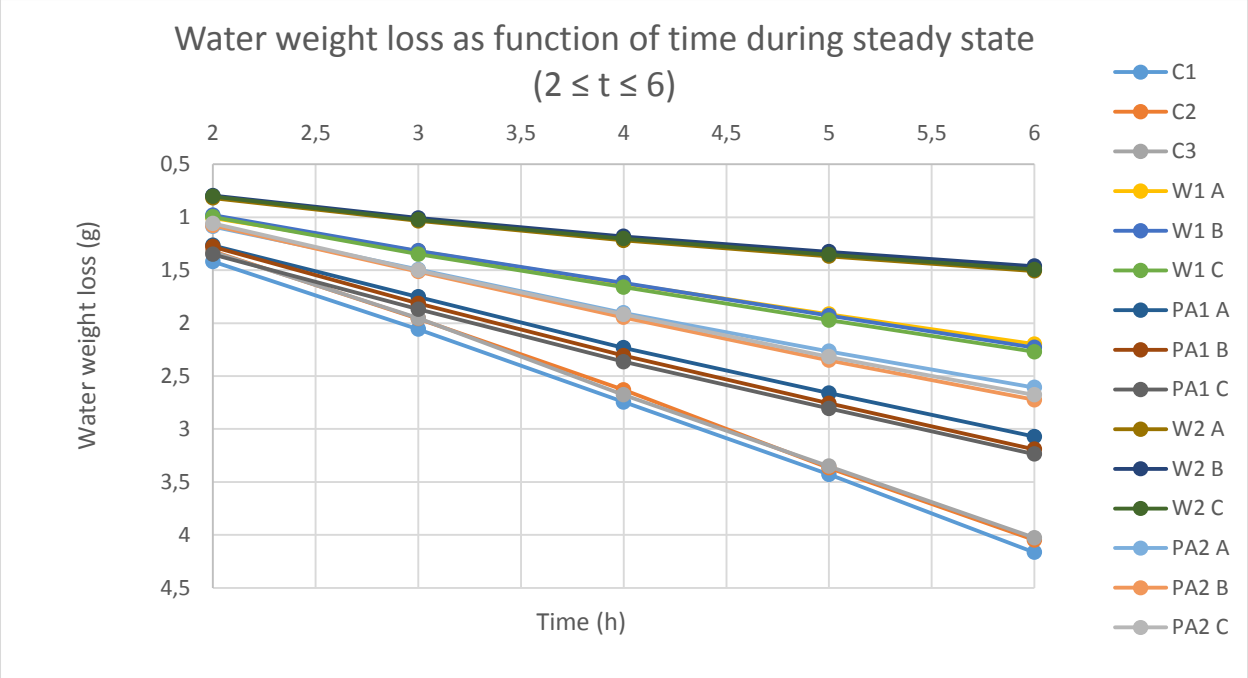


Figure 18: The water weight loss as function of time between 2 and 6 hours for all formulations used in the experiment. C = control, W1 = Wax formulation with coco glucoside, W2 = wax formulation with lauryl glucoside, PA1 = Poluamide with coco glucoside and PA2 = polyamide with lauryl glucoside. All samples were tested in triplicates (A, B and C).

The slopes and calculated water flux *J* are shown in table 2. Equation 2 was used to calculate the water flux through the film. The wax formulations both have lower slopes than the two polyamide formulations.

Table 2: the slopes of each sample were obtained from figure 15. The water flux was calculated for each sample using equation 2. W1 = wax formulation with coco glucoside, W2 = wax formulation with lauryl glucoside, PA1 = polyamide formulation with coco glucoside, PA2 = polyamide formulation with lauryl glucoside, C = control (bare gel with no sample film). Each sample was tested in triplicates A, B and C. Hence W1 A, W1 B and W1 C indicate the three samples of wax formulation with coco glucoside.

Formulation	**Sample**	**Slope**	***J* ($gh^{-1}m^{-2}$)**	**Gel area (cm^2)**
Wax coco glucoside	*W1 A*	0,2982	151,95	19,625
Wax coco glucoside	*W1 B*	0,3113	158,62	19,625
Wax coco glucoside	*W1 C*	0,317	161,53	19,625
Wax lauryl glucoside	*W2 A*	0,1715	87,39	19,625
Wax lauryl glucoside	*W2 B*	0,1653	84,23	19,625
Wax lauryl glucoside	*W2 C*	0,1712	87,24	19,625
Polyamide coco glucoside	*PA1 A*	0,4523	230,47	19,625
Polyamide coco glucoside	*PA1 B*	0,4768	242,96	19,625
Polyamide coco glucoside	*PA1 C*	0,4711	240,05	19,625
Polyamide lauryl glucoside	*PA2 A*	0,3812	194,24	19,625
Polyamide lauryl glucoside	*PA2 B*	0,4131	210,50	19,625
Polyamide lauryl glucoside	*PA2 C*	0,4057	206,73	19,625
Control	*C1*	0,6813	347,16	19,625
Control	*C2*	0,6676	340,18	19,625
Control	*C3*	0,6675	340,13	19,625

In figure 19 the weight % loss as a function of time during steady state is displayed for the mean values of the formulations and the bare gel control. The slopes of the trendlines correlating to each plot are displayed in figure 20.

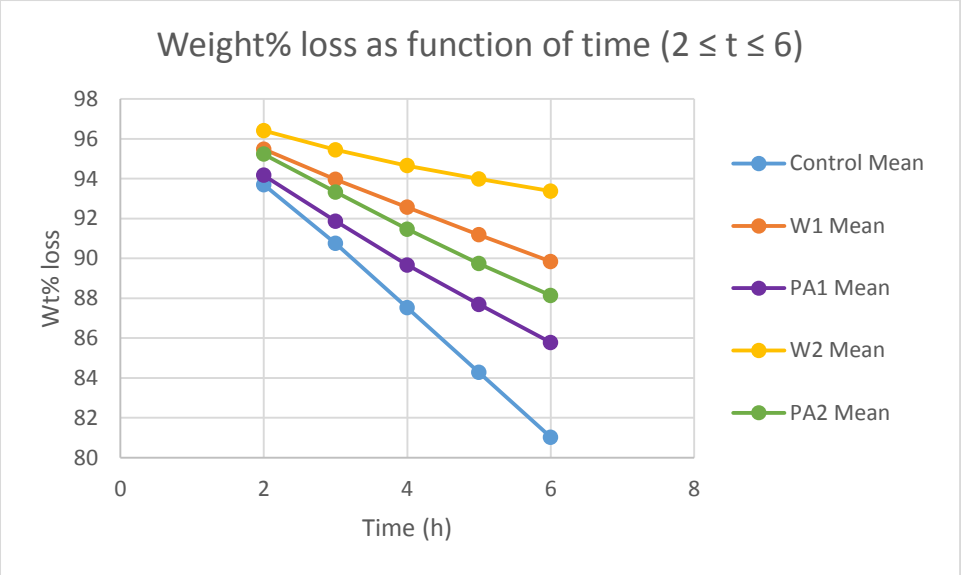


Figure 19: in the graph, the wt% loss as function of the mean values of the samples is plotted as a function of time. The slopes are obtained when samples have reached steady state. The slopes of each sample plot are shown below in figure 17.

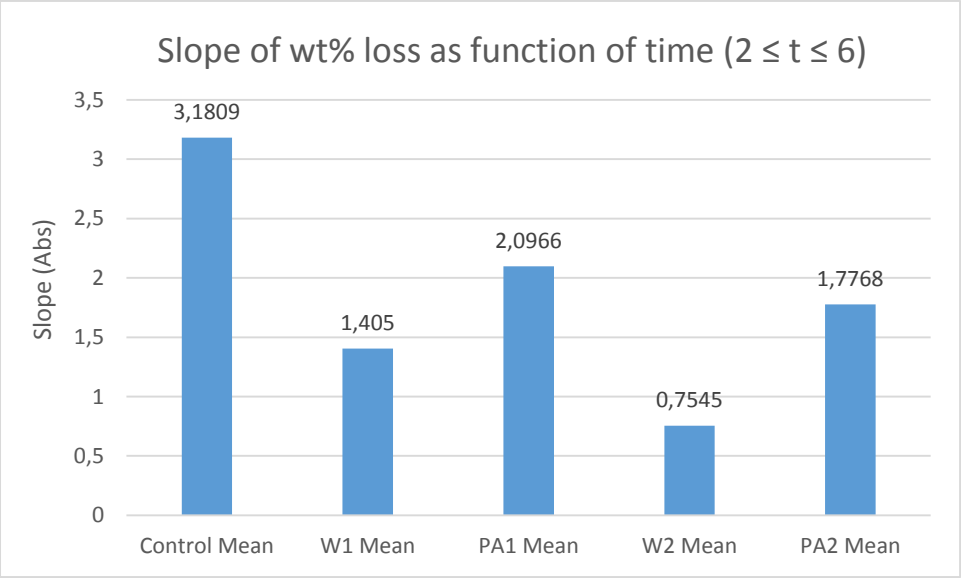


Figure 20: the slopes of each sample mean are shown as absolute amounts in the figure above. The control clearly has the highest slope, indicating the highest permeability. The second wax formulation has the lowest slope, thus being the most occlusive sample.

4.4 Water Resistance

Results from the water resistance test indicate that the wax formulation was more water resistant than the polyamide formulation. The reference cream showed no water resistance. Results were not affected by plates being wet or dry prior the application. Pictures of clean PMMA plates before application of product are seen in figure 4 in the method chapter. A light microscope picture of the clean surface structure of the plates is seen in figure 21.

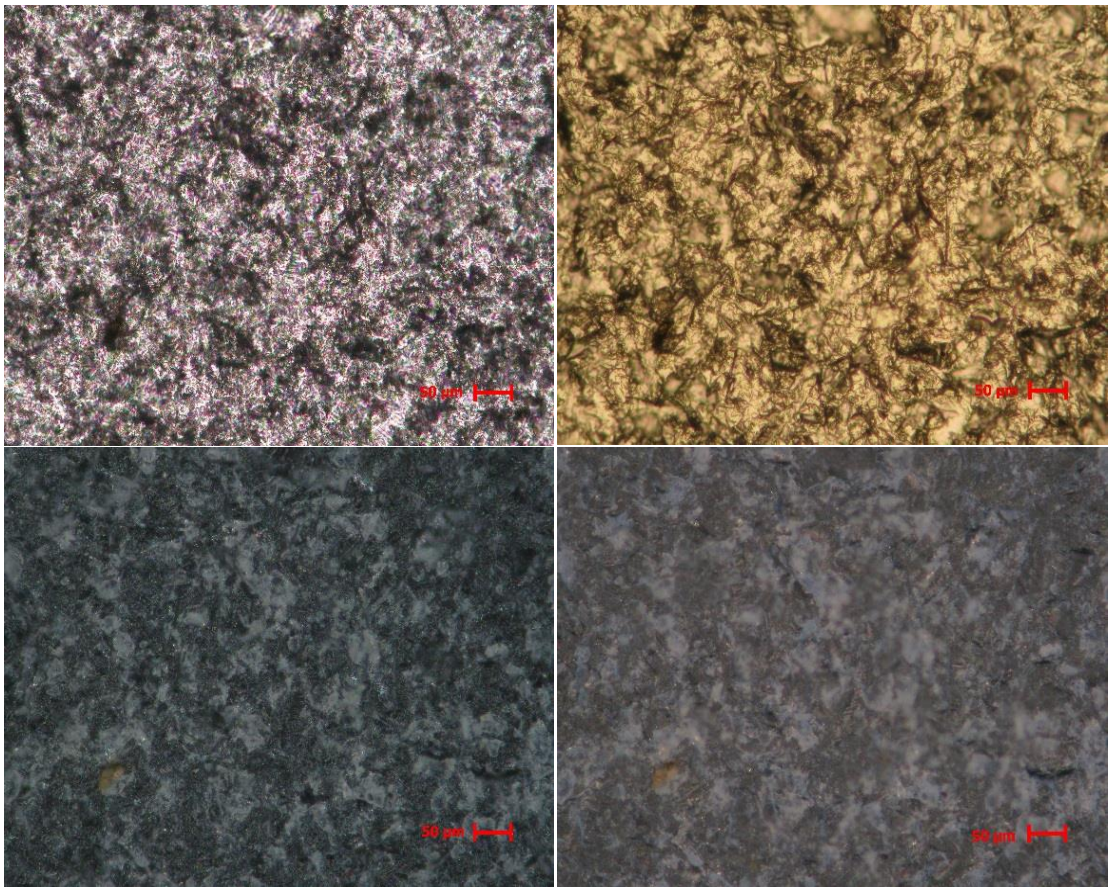


Figure 21: The surface of the clean PMMA plates. Top right: brightfield mode, bottom right: polarized light, top left: condensated light and bottom left: polarised and condensated light. All pictures are taken with a 10x objective. Scale bar indicates a length of 50 µm.

Water temperature, rotation speed, applied amount of cream and immersion time can be seen in table 3. The table presents an overview if the formulation gave positive film forming results after the experiments.

Table 3: the table displays the different washing times and if positive results concerning water resistance were obtained or not. The results are also visualised by pictures taken with a light microscope.

Sample	**Time (min)**	**RPM**	**Water temperature °C**	**Results obtained indicating water resistance (Yes/No)**
Dry plates				
Reference	2	171±3	38,4±0,4	No
Wax formulation	2	171±3	38,4±0,4	Yes
Polyamide formulation	2	171±3	38,4±0,4	Yes
Reference	4	171±3	38,4±0,4	No
Wax formulation	4	171±3	38,4±0,4	Yes
Polyamide formulation	4	171±3	38,4±0,4	No
Reference	6	171±3	38,4±0,4	No test performed
Wax formulation	6	171±3	38,4±0,4	Yes
Polyamide formulation	6	171±3	38,4±0,4	No
Wet plates				
Reference	2	171±3	38,4±0,4	No
Wax formulation	2	171±3	38,4±0,4	Yes
Polyamide formulation	2	171±3	38,4±0,4	Yes
Reference	4	171±3	38,4±0,4	No
Wax formulation	4	171±3	38,4±0,4	Yes
Polyamide formulation	4	171±3	38,4±0,4	No
Reference	6	171±3	38,4±0,4	No test performed
Wax formulation	6	171±3	38,4±0,4	Yes
Polyamide formulation	6	171±3	38,4±0,4	No test performed

Directly after application, the interface between the clean surface and the film on top of the acrylic glass plate are seen in the microscopic pictures, figure 22, 23 and 24.

Pictures taken before the washing procedure

The reference cream is applied to a dry PMMA plate in figure 22. The cream can be seen to the right in the figure. A red line was drawn on the clear backside of the plate to easily indicate the interface after washing. The red line is slightly visible in the two top pictures.

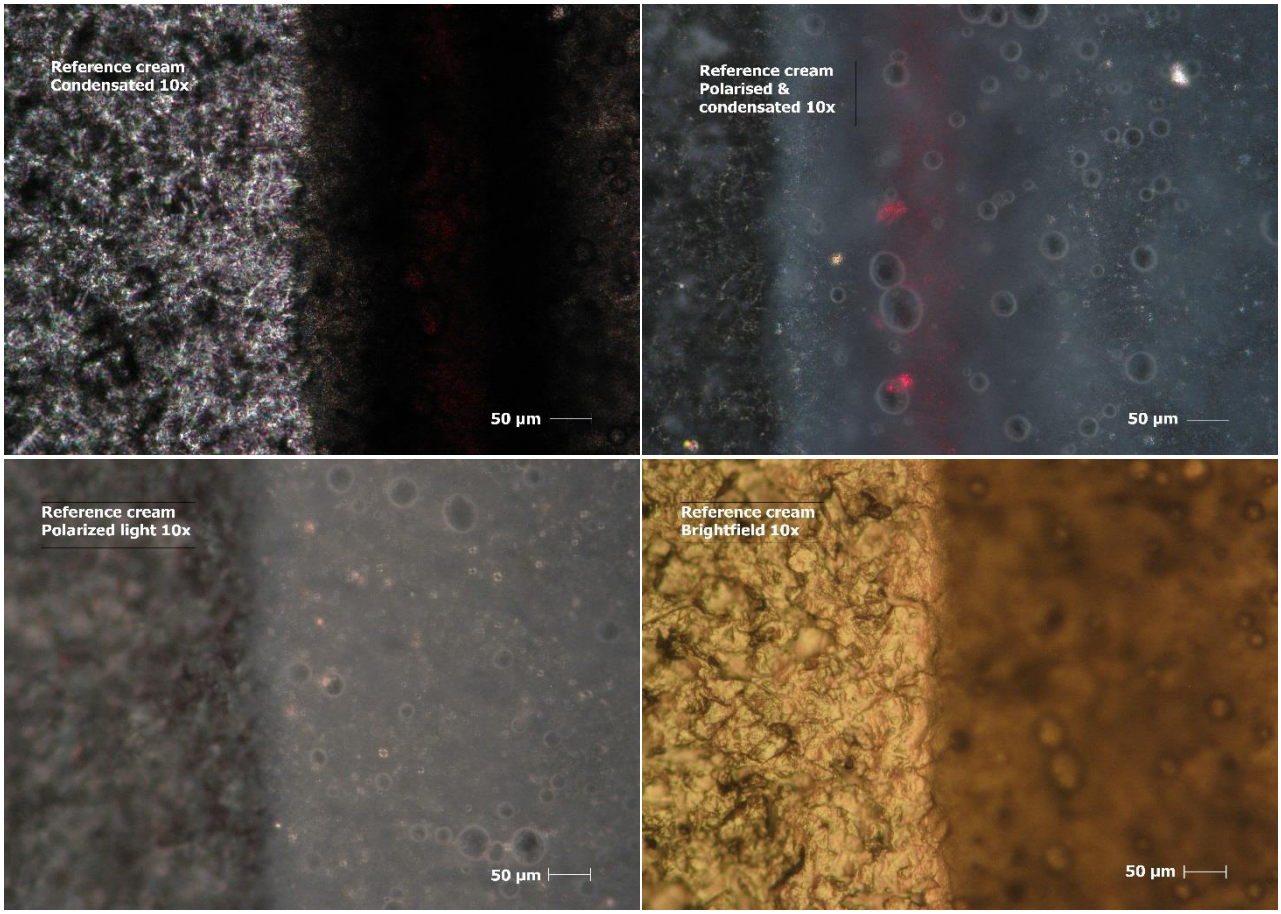


Figure 22: Pictures taken in a light microscope after application of a reference cream with no film forming agent incorporated. Pictures are taken in different modes of the microscope; top left: condensated light, bottom left: polarized light, top right: polarised and condensated light and bottom right: brightfield mode. All pictures are taken with a 10x objective. Scale bar indicates a length of 50 µm.

The figures displaying the applied wax- and polyamide formulations do not indicate as clear interface as the reference cream does in figure 22. This is due to the water applied on the plates which dilutes the creams. In figure 23 the interface between the wax formulation and the clean PMMA plate is visualised. The sample is visible to the right in the pictures. Some larger circles are also visible; they are entrapped air bubbles. In figure 24, the polyamide formulation has been rubbed on a wet PMMA plate. The cream is visible to the left in the pictures.

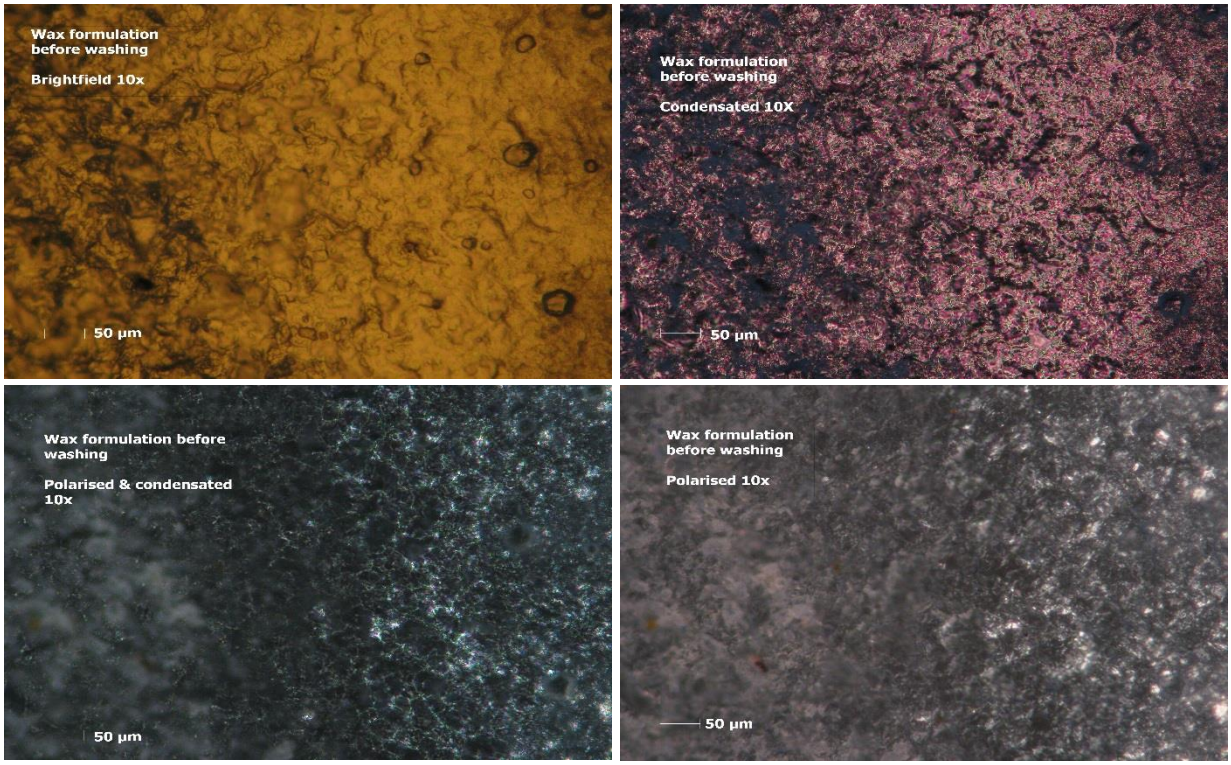


Figure 23: Pictures taken in a light microscope after application of the formulation containing microcrystalline wax on a wet PMMA plate. Pictures are taken in different modes of the microscope; top left: brightfield mode, bottom left: polarized and condensated light, top right: condensated light and bottom right: polarised light only. All pictures are taken with a 10x objective. Scale bar indicates a length of 50 µm.

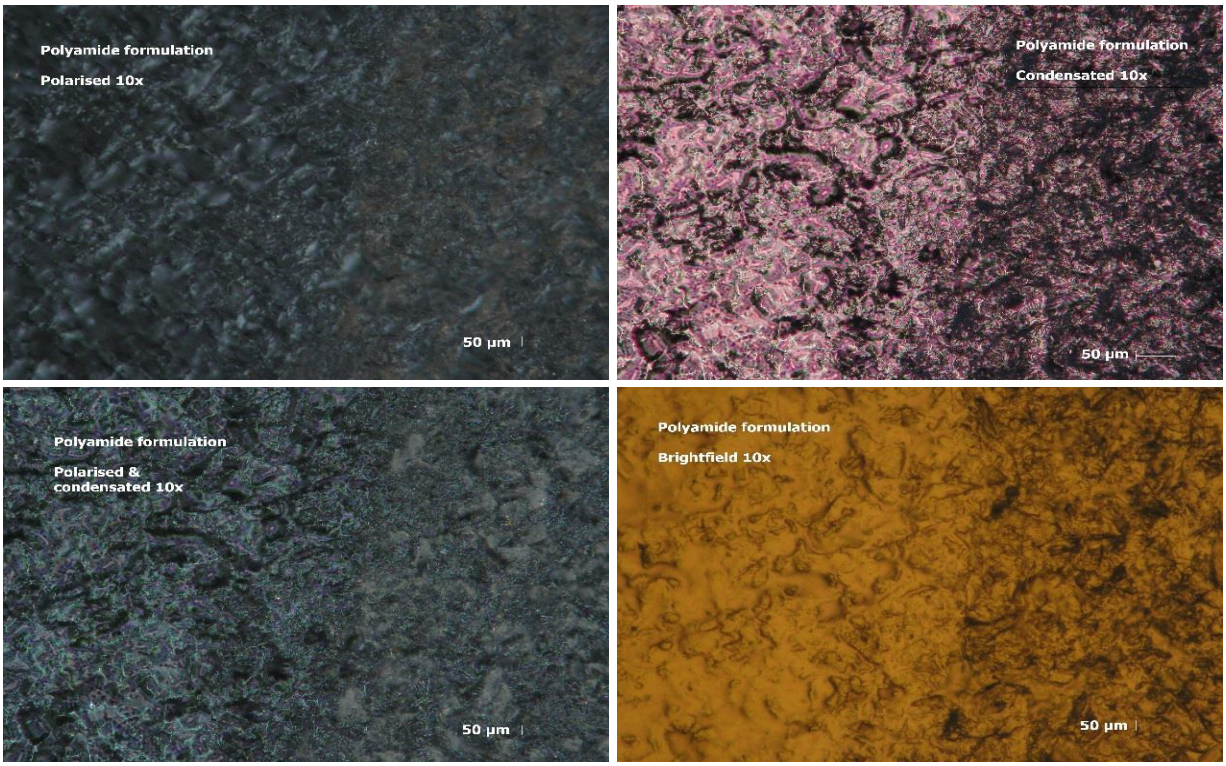


Figure 24: Pictures taken in a light microscope after application of the formulation containing polyamide on a wet PMMA plate. The sample is applied on the left hand-side of each picture. Top left: polarised light, bottom left: polarised and condensated, top right: condensated light and bottom right brightfield mode. All pictures were taken with a 10x objective. Scale bar indicates a length of 50 µm.

Pictures taken after the washing procedure

After washing, the interface between the surface where cream was applied and the clean PMMA plates are seen in figure 25 below. Cream has been applied to the left on the plate and the whole plate has been washed as described in the method chapter.

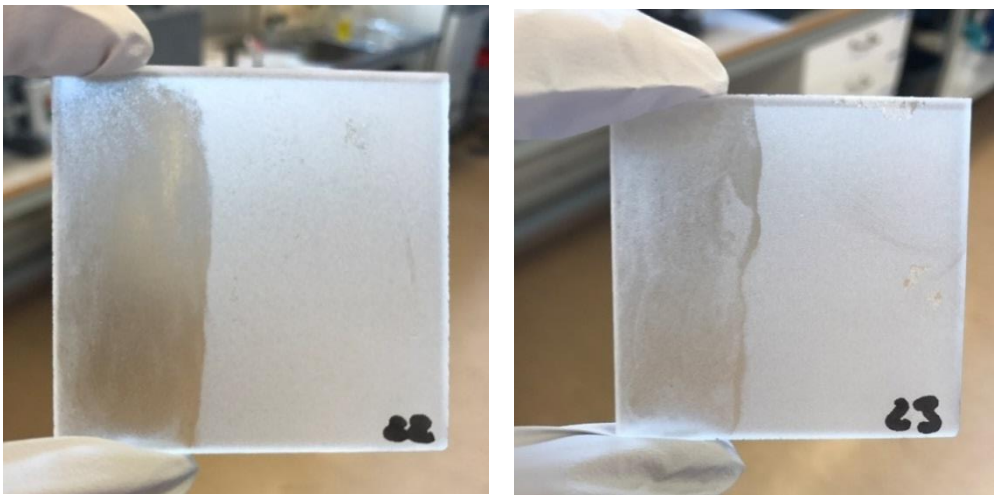


Figure 25: pictures of wax and polyamide formulations having been washed of the PMMA plate after 2 minutes, but a film is remaining visible by the eye. To the left, the wax formulation, to the right the polyamide formulation is seen. The samples have been applied to the left side of each plate.

However, other samples were hard to evaluate using only the human eye, and the light microscope was used for evaluation of the water resistance by taking pictures of the interface of the clean plate and the area where formulation had been applied. Microscopic results of film duration on the plates are shown in figures 26, 28 and 29. The best results obtained are those visualised in the figures.

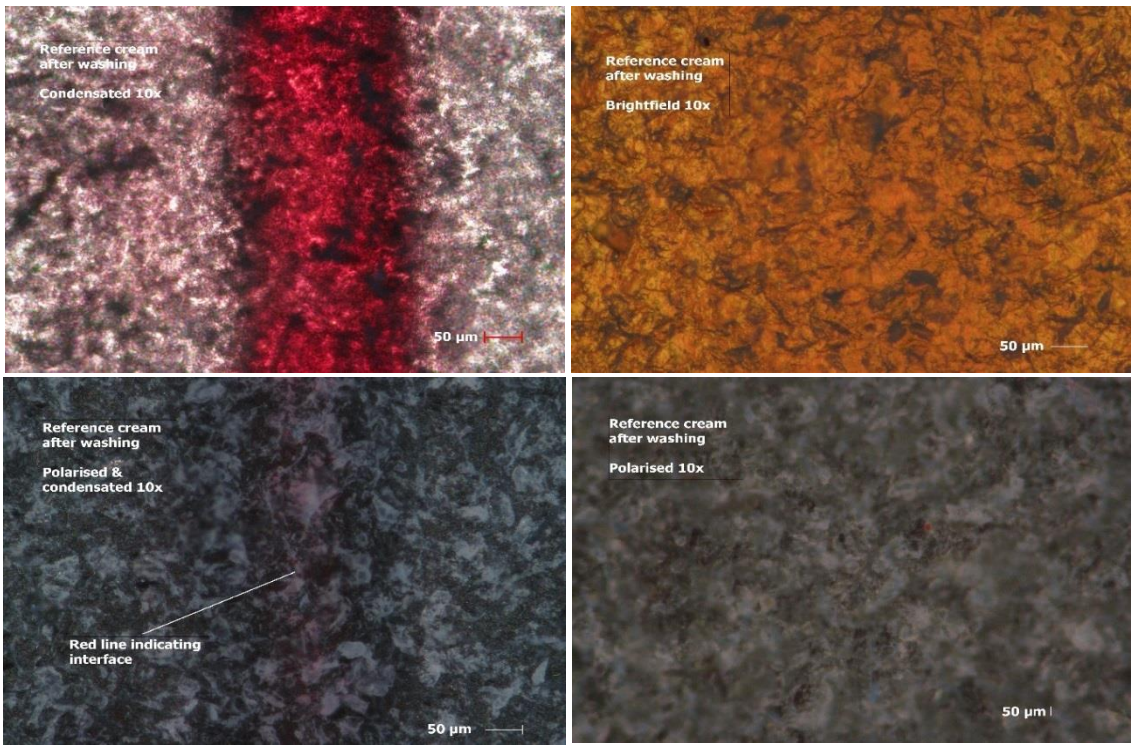


Figure 26: reference sample has clearly been washed off after only 2 minutes after application on a dry PMMA plate. Top left: condensated light, bottom left: polarised and condensated, top right: brightfield mode and bottom right polarised light only. All pictures were taken with a 10x objective. The red line indicates the interface between the former area of applied cream and the clean plate. Scale bar indicates a length of 50 µm.

The control formulation leaves no or very little traces of film on the plates, figure 26. The cream leaves no film on the PMMA plate after being applied to a dry PMMA plate and washed/rubbed for only 2 minutes. The red line is the same line as visualised before in figure 22 prior the washing experiment. All photographs were taken of the same area of the PMMA plate, but due to optical effects the red line is only visible or partly visible in certain microscopic modes.

However, the control formulation displayed a more flake like behaviour when being washed away, figure 27, but still left no or limited traces behind on the plates. The wax and the polyamide had a more erosion like behaviour when being washed off, leaving a water resistant film behind on the plates.

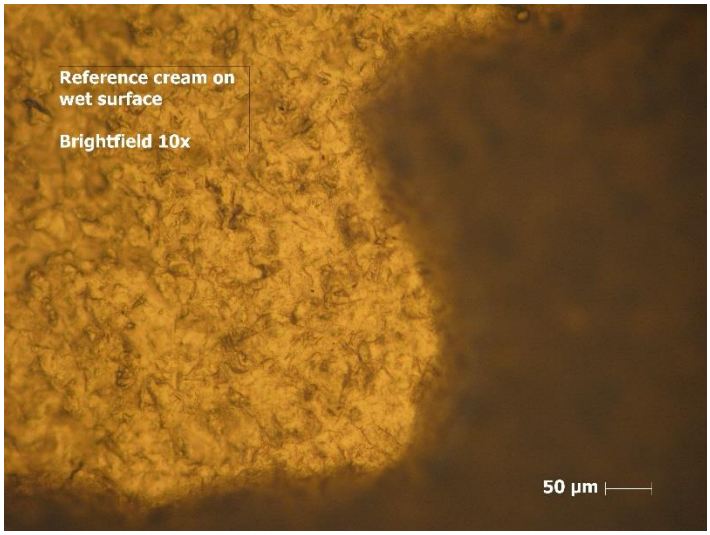


Figure 27: in contrary to the two more water resistant formulations which both displayed a more erosion like behaviour during the washing procedure, the reference cream was torn of in small pieces creating interfaces as can be seen in the picture. The dark area to the right is covered with cream and to the left we see the clean rough surface of the PMMA plate. Scale bar indicates a length of 50 µm.

The formulation containing microcrystalline wax was the most water resistant of all samples. The interface between the film left behind after a washing procedure of 6 minutes and the clean PMMA plate can be seen in figure 28. The sample can be seen to the right in the pictures.

The formulation with polyamide was water resistant up to two minutes both when applied on wet and dry PMMA plates. In figure 29 we see the interface between the polyamide formulation and the clean surface of the PMMA plate after having been applied to a wet PMMA plate and washed for 2 minutes.

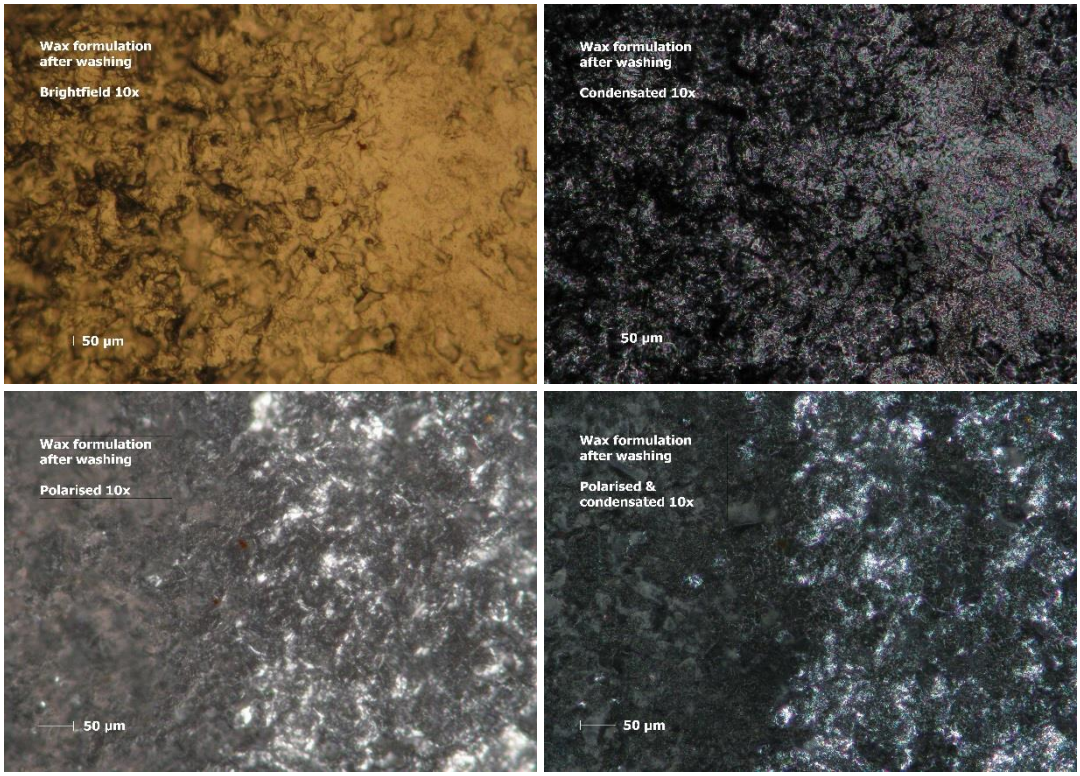


Figure 28: The result after 6 minutes of washing after applying the wax formulation to a wet PMMA plate. The remaining film is visible on the right hand side. Top left: brightfield mode, bottom left: polarised light, top right: condensated light and bottom right polarised and condensated light. All pictures were taken with a 10x objective. Scale bar indicates a length of 50 µm.

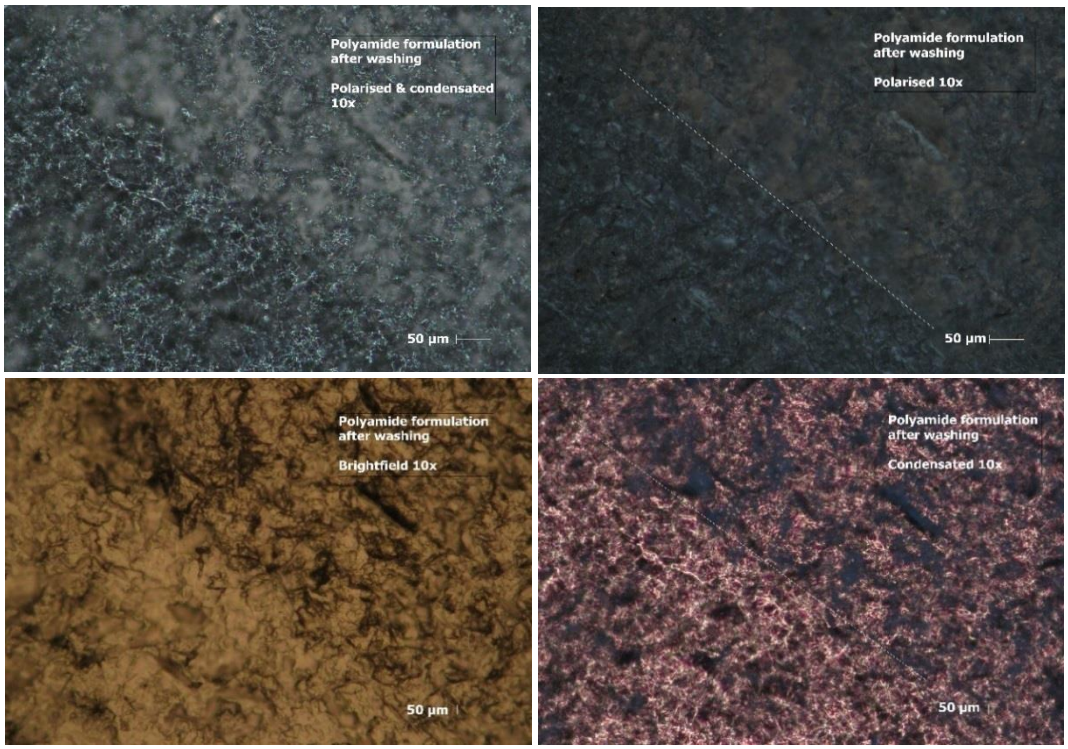


Figure 29: Results after washing a wet PMMA plate for 2 minutes after application of the polyamide formulation. The remaining film is visible on the bottom left hand side. It is barely visible in the microscopic pictures. The interface is indicated by a thin white line in the two pictures to the right. Top left: polarised and condensated light, bottom left: brightfield mode, top right: polarised light and bottom right condensated light. All pictures were taken with a 10x objective. Scale bar indicates a length of 50 µm.

4.5 Bioadhesion

The results from the bioadhesion tests can be seen graphically in figures 30 – 45. For each test substrate, two plots are presented; one where force is plotted as a function of time, and one where force is plotted as function of distance. Both plots start the moment the probe senses the trigger force of 1 mN and ends when the probe reaches its original position. In the force vs. distance plots, the tensile work (i.e. the area beneath the force/distance curve) is indicated by green colour. The original position is determined manually, and can therefor vary between each test cycle. The values of the peak force, tensile work and calculated fracture strength are represented in tables 4 and 5. All values are shown as absolute amounts. The results of the tests with a hold time of 10 seconds are presented first. Two test result values are of interest for analysing the bioadhesiveness, the tensile work, and the fracture strength.

Test results for hold time of 10 seconds
Water exhibited the lowest fracture strength, and the reference cream the highest. The wax formulation exhibited approximately the same fracture strength as the reference cream and the polyamide formulation was close to the value for the water test result. The tensile work results however, do not give the same result. Equally, the water test gave the lowest tensile work and the test with the wax formulation yielded the highest tensile work. All values are shown in table 4.

Test results for hold time of 60 seconds
The results regarding the fracture strength are different than those from the 10 second hold time tests. The reference cream had the highest value, and the polyamide formulation the lowest. The wax formulation had the second highest value. Equally as for the 10 second hold time tests, the wax formulation resulted in the highest tensile work and the water lowest value for the same parameter. All values are highlighted in table 5.

Interpretation of graphs
The force vs. time plots start at the time when the probe senses the trigger force. After that the probe continues to penetrate 2 mm down into the sample, hence the force increases. During the hold time, the force relaxes and drops exponentially. After the hold time, the probe is withdrawn and the force drops below 0 (since the probe is withdrawn in the opposite direction). The force increases until it reaches a peak value, the highest force required during the separation of the skin surface from the sample. A high peak value thus indicates higher bioadhesion strength.

In the force vs. distance plot, the plot starts at the trigger force and the probe penetrates 2 mm down into the sample. The force increases during that process and the force than drops below 0 when the probe starts its withdrawal phase. The peak force is visible also in these plots. When the probe is elevated to its original position above the sample (a negative x-value), the test is finished. A large tensile work indicates high bioadhesiveness.

Table 4: the results from the test performed with a 10 seconds hold time before withdrawal can be seen below in the table. Tensile work and fracture strength are two measures of bioadhesive strength.

Water 10 s.				
Test no.	**Peak force (N)**	**Tensile work (N mm)**	**Probe area (mm^2)**	**Fracture strength (N mm^{-2})**
1	0,022	0,060	452,16	0,489E-04
2	0,021	0,058	452,16	0,473E-04
3	0,021	0,054	452,16	0,457E-04
Average:	**0,021**	**0,057**	452,16	**0,464E-04**
S.D.	0,001	0,003		

Wax form. 10 s.				
Test no.	**Peak force (N)**	**Tensile work (N mm)**	**Probe area (mm^2)**	**Fracture strength (N mm^{-2})**
1	0,106	0,365	452,16	2,343E-04
2	0,109	0,309	452,16	2,407E-04
3	0,121	0,432	452,16	2,665E-04
Average:	**0,112**	**0,369**	452,16	**2,472E-04**
S.D.	0,008	0,062		

Polyamide form. 10 s.				
Test no.	**Peak force (N)**	**Tensile work (N mm)**	**Probe area (mm^2)**	**Fracture strength (N mm^{-2})**
1	0,024	0,097	452,16	0,520E-04
2	0,022	0,079	452,16	0,492E-04
3	0,021	0,063	452,16	0,468E-04
Average:	**0,022**	**0,080**	452,16	**0,494E-04**
S.D.	0,001	0,017		

Reference formulation 10 s.				
Test no.	**Peak force (N)**	**Tensile work (N mm)**	**Probe area (mm^2)**	**Fracture strength (N mm^{-2})**
1	0,125	0,225	452,16	2,757E-04
2	0,119	0,215	452,16	2,632E-04
3	0,113	0,205	452,16	2,506E-04
Average:	**0,119**	**0,215**	452,16	**2,632E-04**
S.D.	**0,006**	**0,010**		

Figures for the test with 10 seconds hold time are visible below in figures 30 - 37.

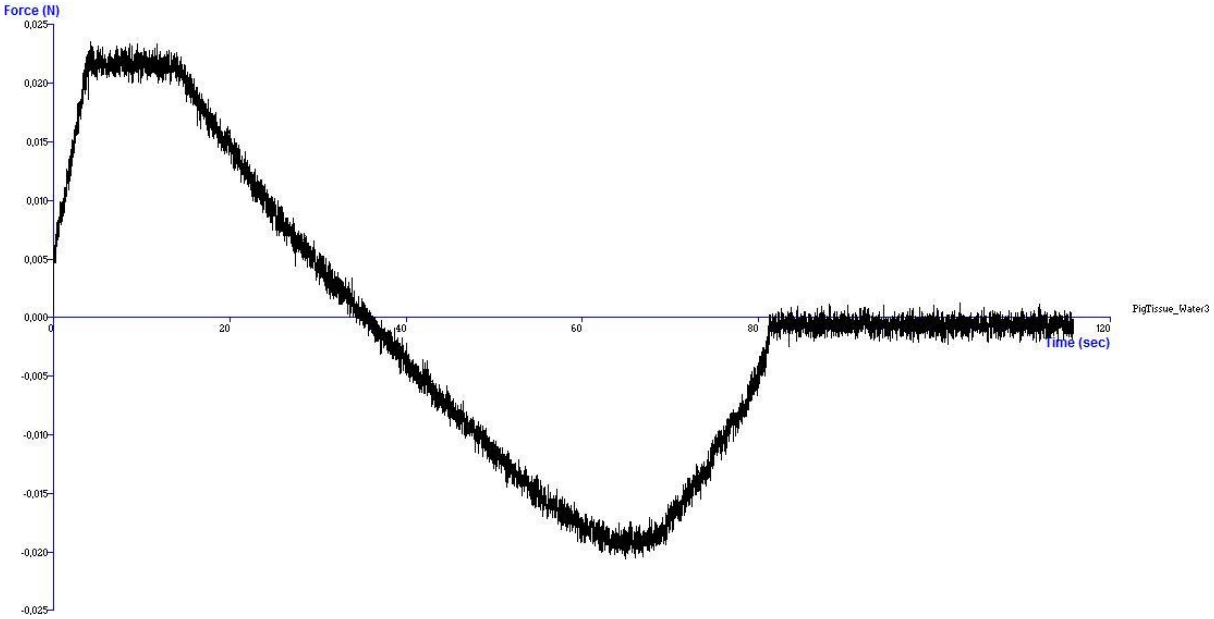


Figure 30: the force as function of time curve for one of the test of water as test substrate. The curve starts when the trigger force has been detected by the texture analyser. After 10 seconds hold time, the probe was withdrawn from the water at 0,1mm/s.

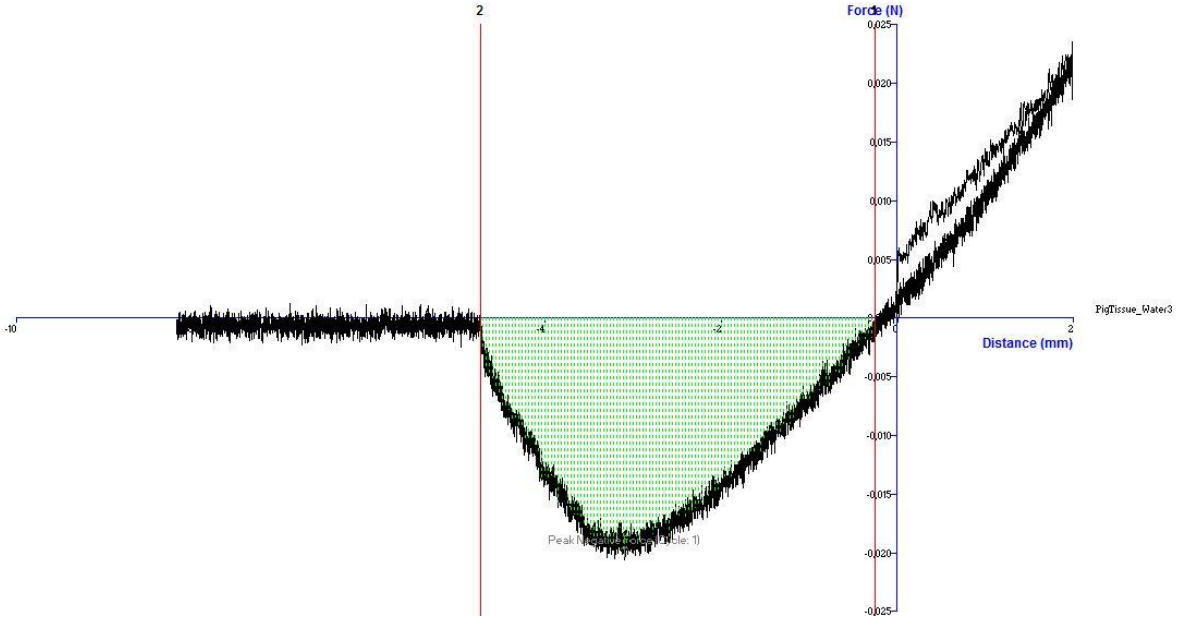


Figure 31: the force as the function of distance curve for the same test of water as seen above. The negative area coloured green indicate the tensile work for separating the pig skin tissue from the water surface.

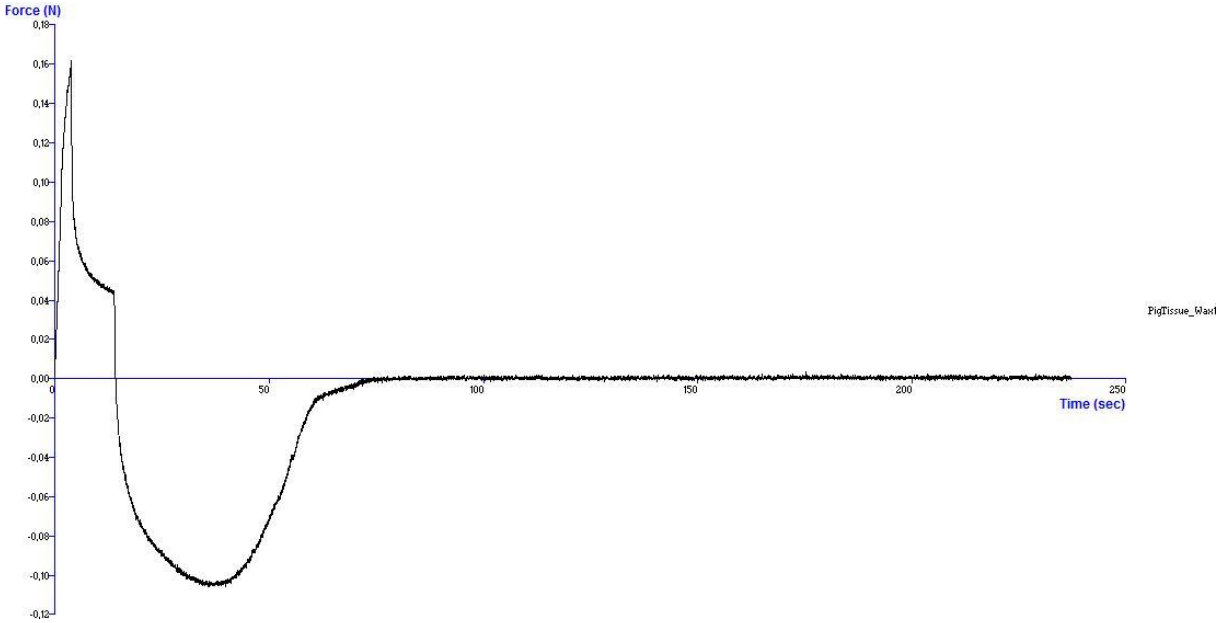


Figure 32: the force as function of time curve for one of the test of the wax formulation as test substrate. The curve starts when the trigger force has been detected by the texture analyser. After 10 seconds hold time, the probe was withdrawn from the water at 0,1mm/s.

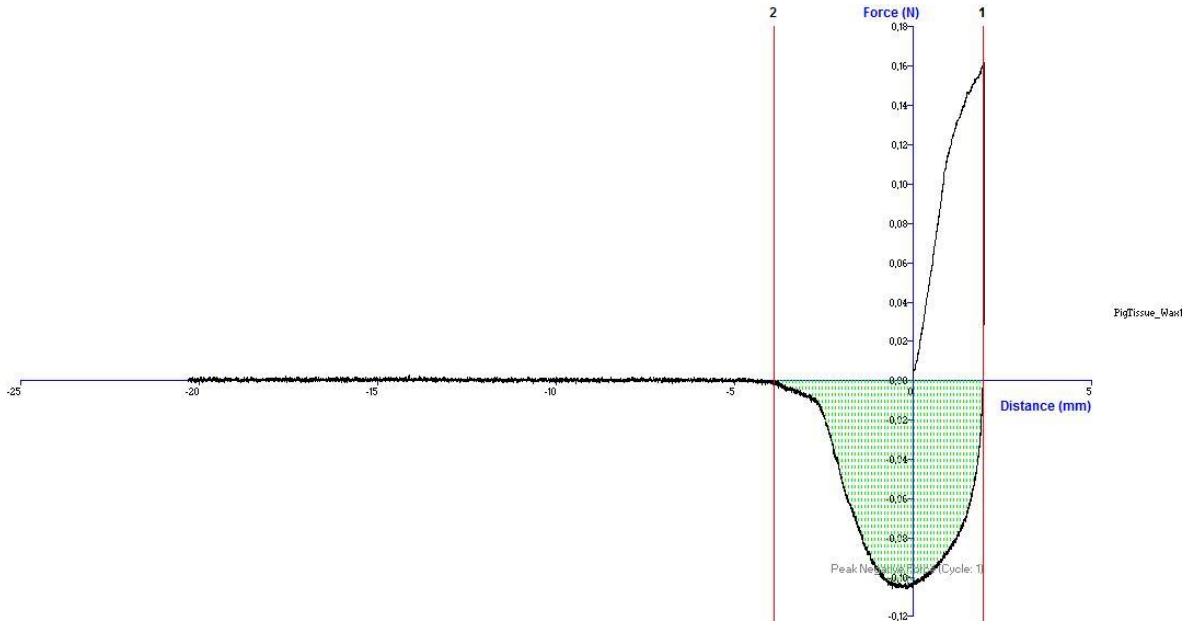


Figure 33: the force as the function of distance curve for the same test of the wax formulation as seen above. The negative area coloured in green indicates the tensile work for separating the pig skin tissue from the sample surface.

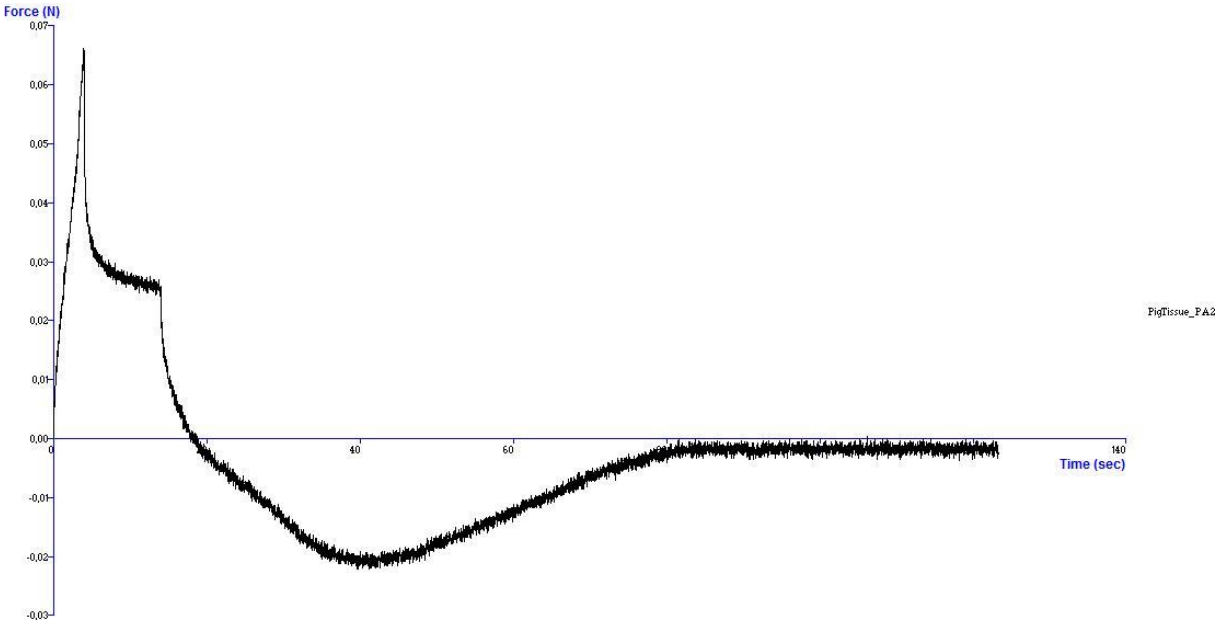


Figure 34: the plot shows the results from the experiment with the polyamide formulation and force is plotted as a function of time. The plot starts at the time when the probe detects the trigger force.

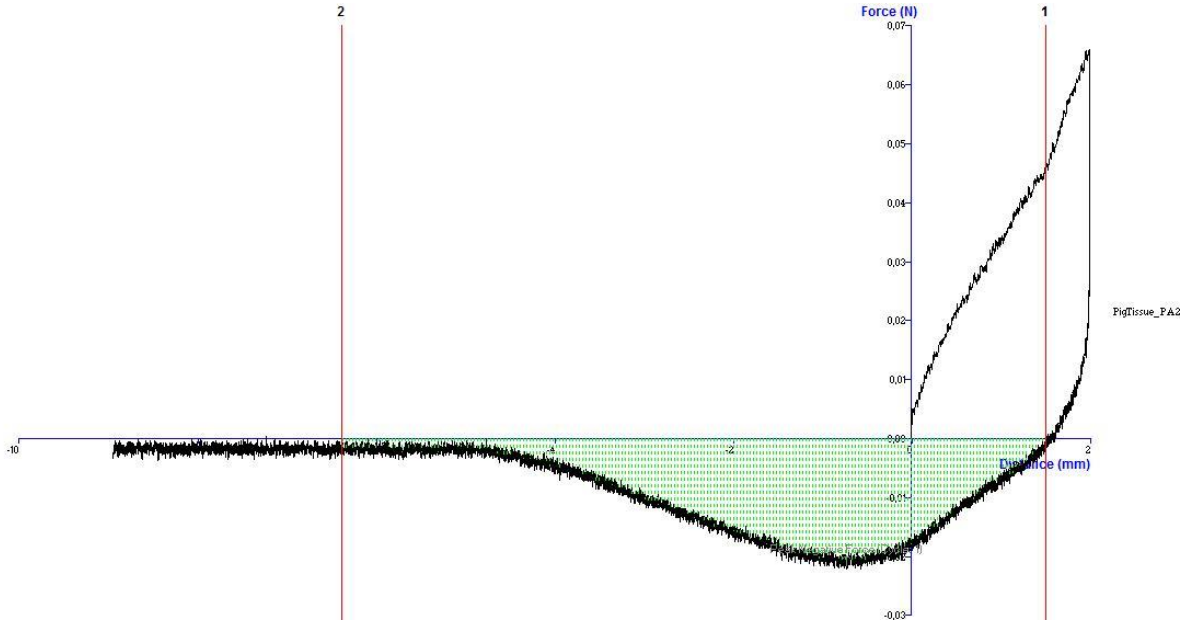


Figure 35: the force as the function of distance curve for the same test of the polyamide formulation as seen above. The negative area coloured in green indicates the tensile work for separating the pig skin tissue from the sample surface.

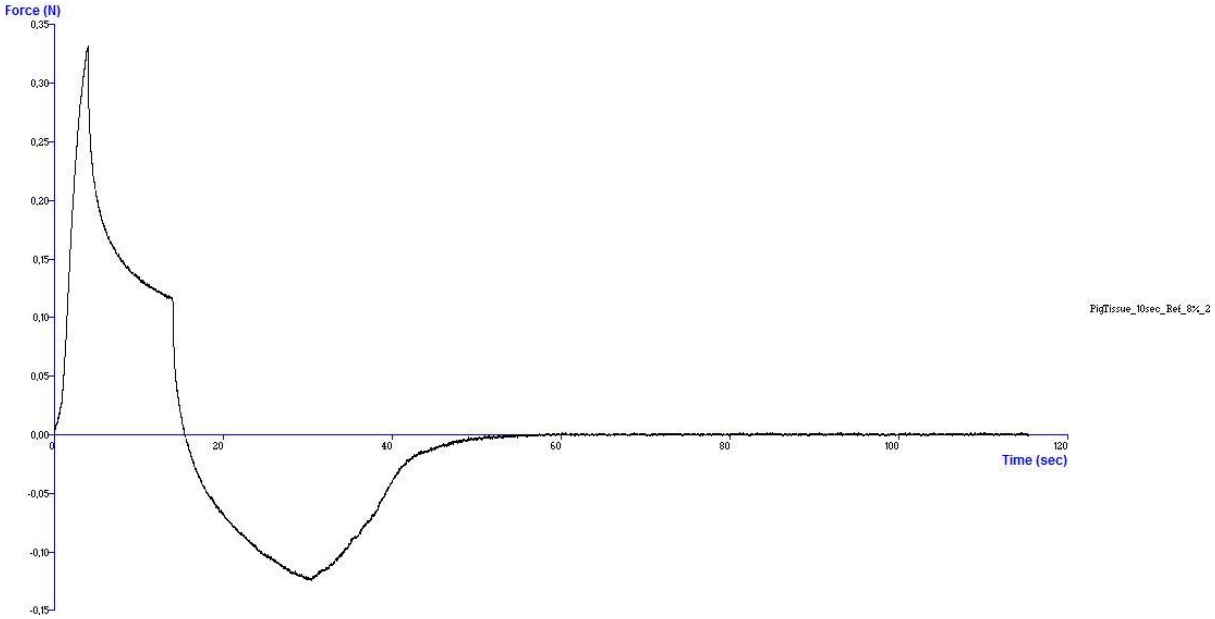


Figure 36: the force as function of time curve for one of the test of the reference formulation as test substrate. The curve starts when the trigger force has been detected by the texture analyser. After 10 seconds hold time, the probe was withdrawn from the water at 0,1mm/s.

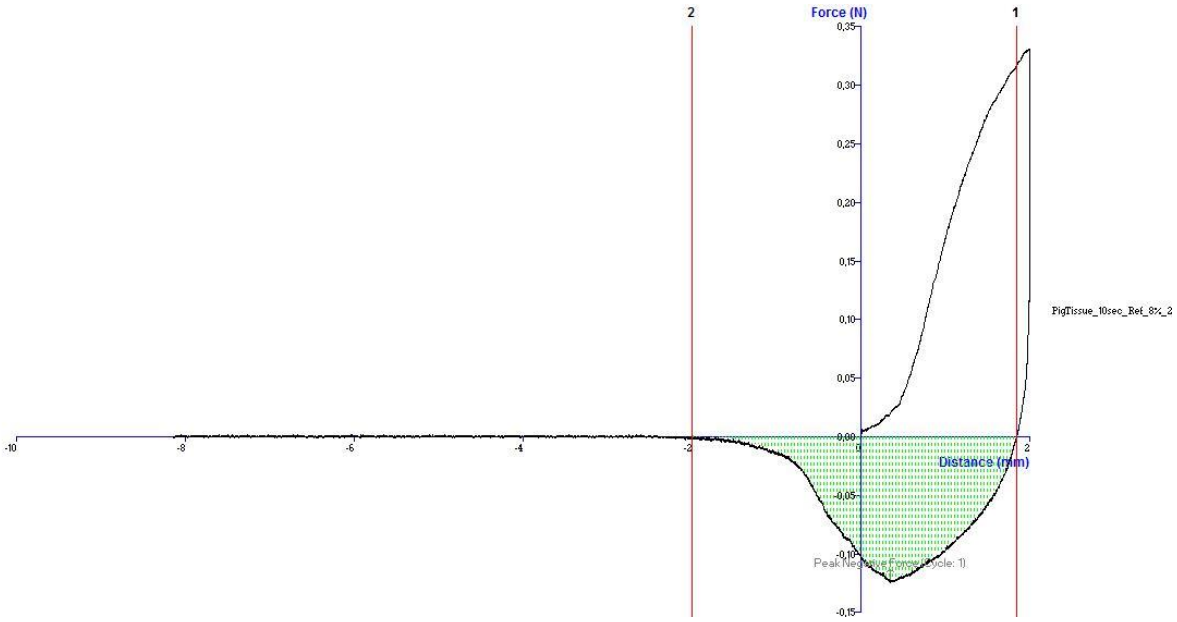


Figure 37: the force as the function of distance curve for the same test of the reference cream as seen above. The negative area coloured in green indicates the tensile work for separating the pig skin tissue from the sample surface.

Table 5: the results obtained from the test with a 60 seconds hold time are summarized in this table. Tensile work and fracture strength are two different measurements of bioadhesiveness.

Water 60 s.				
Test no.	**Peak force (N)**	**Tensile work (N mm)**	**Probe area (mm^2)**	**Fracture strength (N mm^{-2})**
1	0,025	0,094	452,160	0,558E-04
2	0,022	0,069	452,160	0,497E-04
3	0,024	0,079	452,160	0,527E-04
Average:	**0,024**	**0,081**	452,160	**0,527E-04**
S.D.	0,001	0,013		

Wax form. 60 s.				
Test no.	**Peak force (N)**	**Tensile work (N mm)**	**Probe area (mm^2)**	**Fracture strength (N mm^{-2})**
1	0,082	0,361	452,160	1,814E-04
2	0,084	0,480	452,160	1,868E-04
3	0,086	0,436	452,160	1,908E-04
Average:	**0,084**	**0,426**	452,160	**1,863E-04**
S.D.	0,002	0,060		

Polyamide form. 60 s.				
Test no.	**Peak force (N)**	**Tensile work (N mm)**	**Probe area (mm^2)**	**Fracture strength (N mm^{-2})**
1	0,024	0,116	452,160	0,523E-04
2	0,022	0,099	452,160	0,497E-04
3	0,020	0,063	452,160	0,445E-04
Average:	**0,022**	**0,093**	452,160	**0,488E-04**
S.D.	0,002	0,027		

Reference formulation 60 s.				
Test no.	**Peak force (N)**	**Tensile work (N mm)**	**Probe area (mm^2)**	**Fracture strength (N mm^{-2})**
1	0,139	0,302	452,16	3,07769E-04
2	0,146	0,326	452,16	3,22302E-04
3	0,127	0,241	452,16	2,81516E-04
Average:	**0,137**	**0,290**	452,16	**3,03862E-04**
S.D.	0,009	0,044		

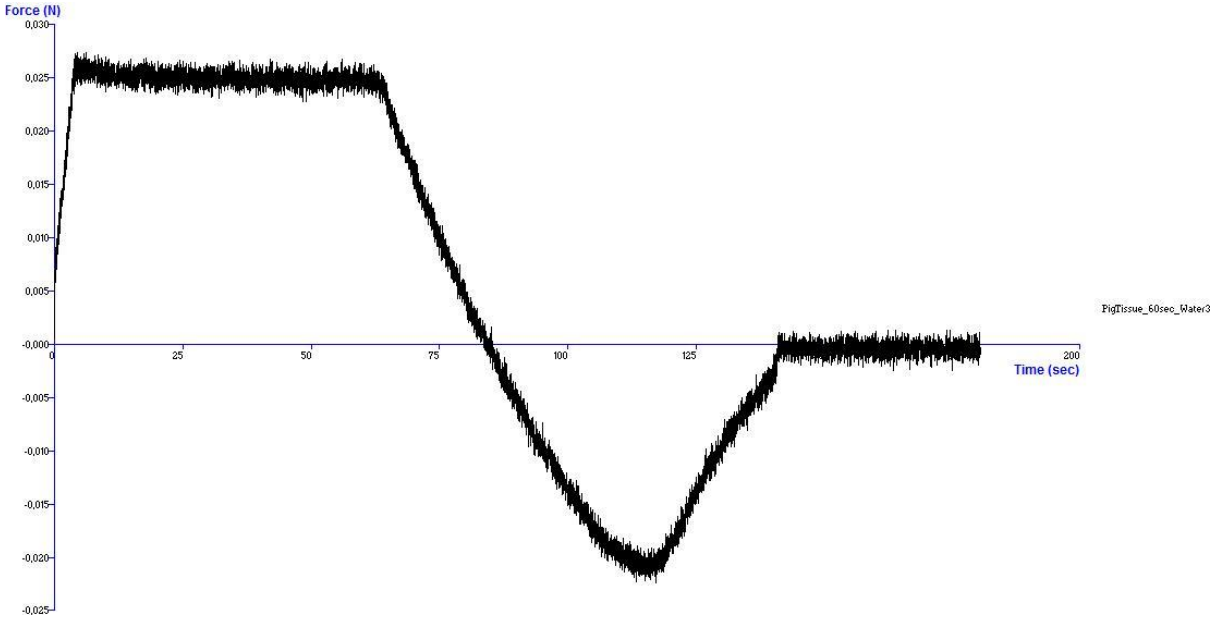


Figure 38: the force as function of time curve for one of the test of the reference formulation as test substrate. The curve starts when the trigger force has been detected by the texture analyser. After 60 seconds hold time, the probe was withdrawn from the water at 0,1mm/s.

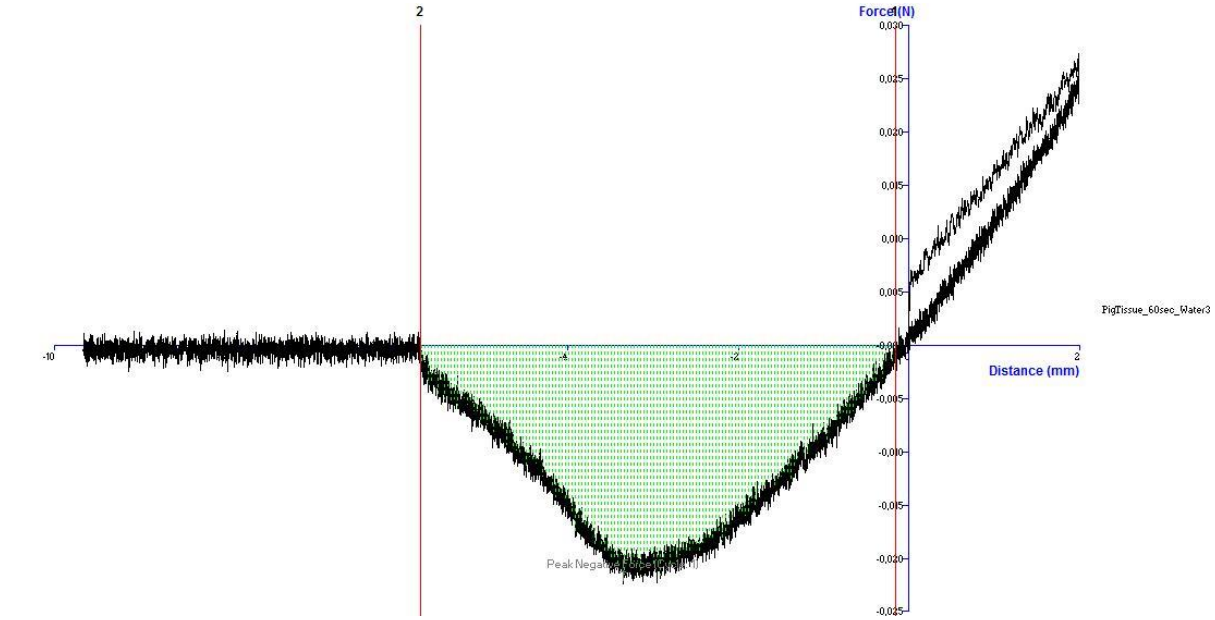


Figure 39: the force as the function of distance curve for the same test of the water sample as seen above. The negative area coloured in green indicates the tensile work for separating the pig skin tissue from the sample surface.

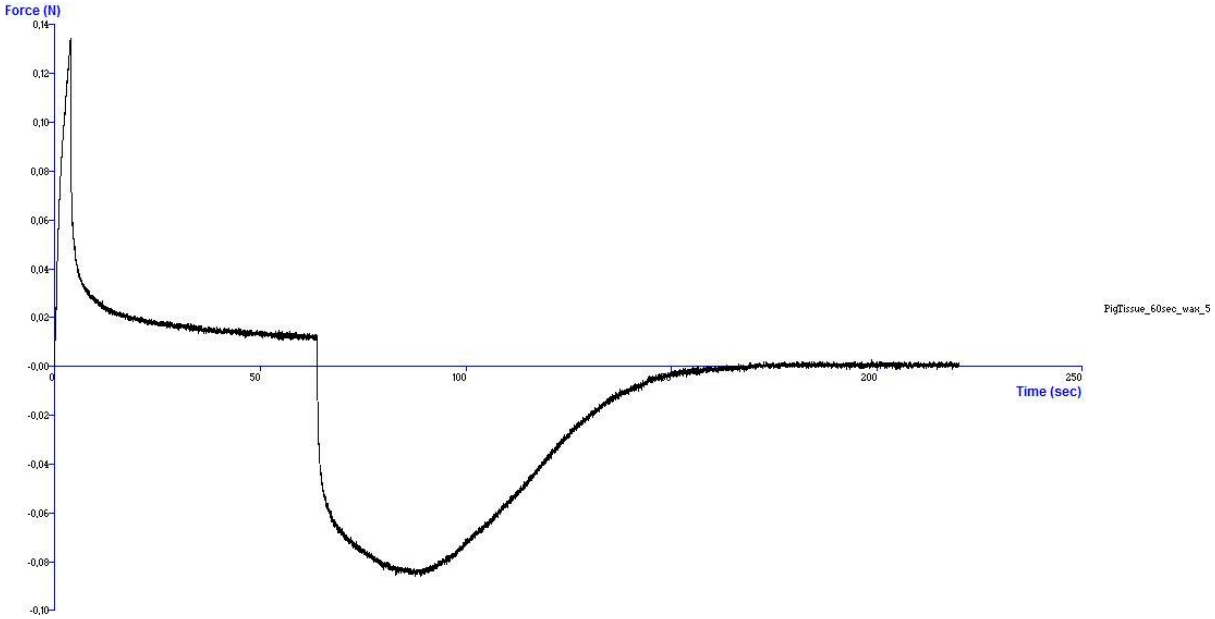


Figure 40: the force as function of time curve for one of the tests of the wax formulation as test substrate. The curve starts when the trigger force has been detected by the texture analyser. After 60 seconds hold time, the probe was withdrawn from the water at 0,1mm/s.

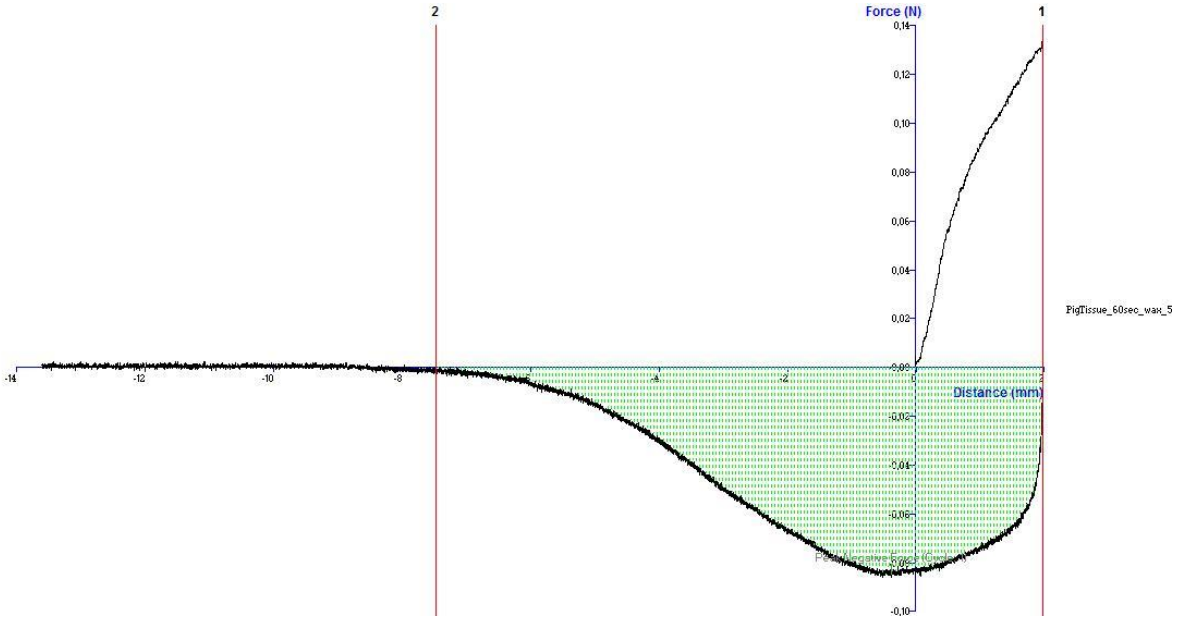


Figure 41: the force as the function of distance curve for the same test of the wax sample as seen above. The negative area coloured in green indicates the tensile work for separating the pig skin tissue from the sample surface.

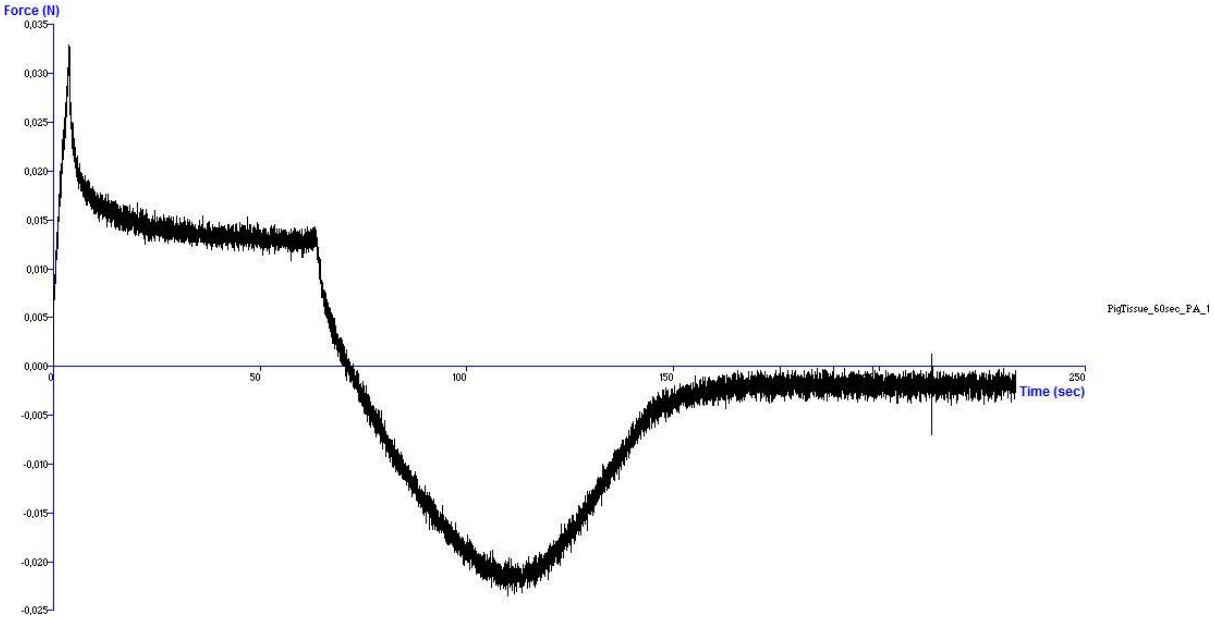


Figure 42: the force as function of time curve for one of the tests of the polyamide formulation as test substrate. The curve starts when the trigger force has been detected by the texture analyser. After 60 seconds hold time, the probe was withdrawn from the water at 0,1mm/s.

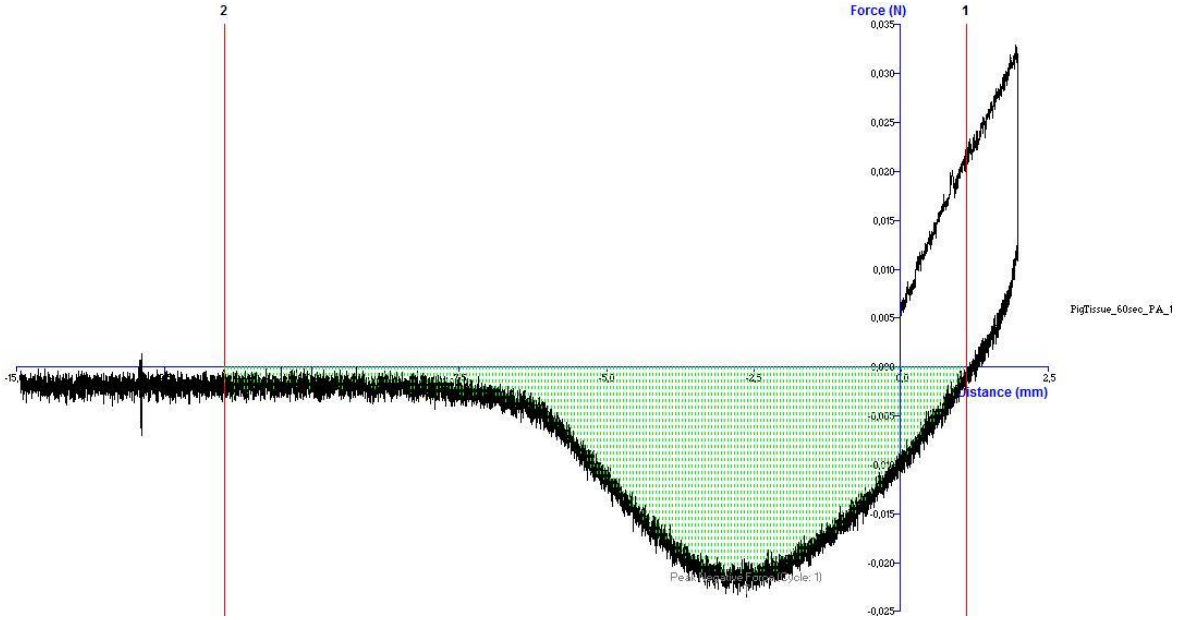


Figure 43: the force as the function of distance curve for the same test of the polyamide sample as seen above. The negative area coloured in green indicates the tensile work for separating the pig skin tissue from the sample surface.

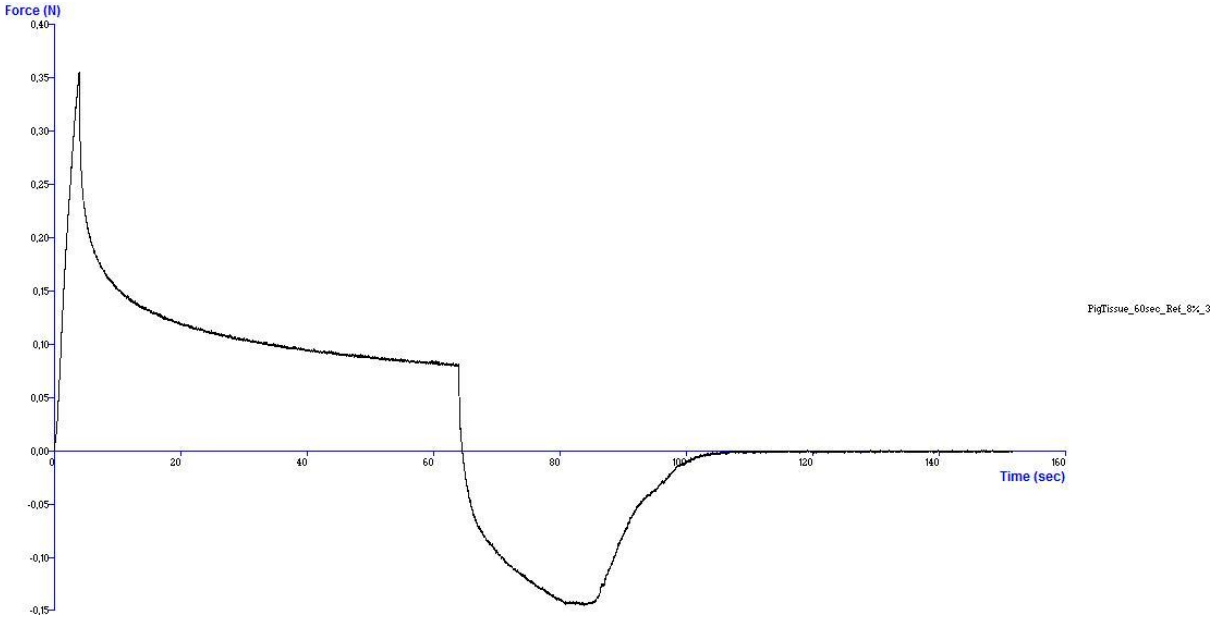


Figure 44: the force as the function of time plot for the reference cream after 60 seconds hold time.

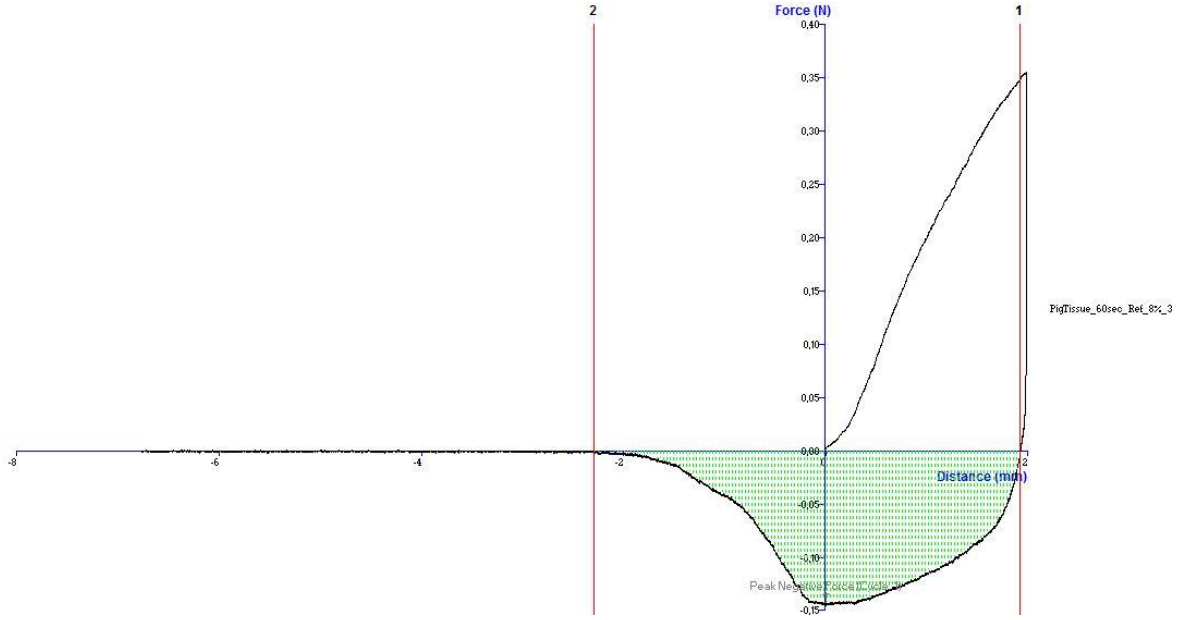


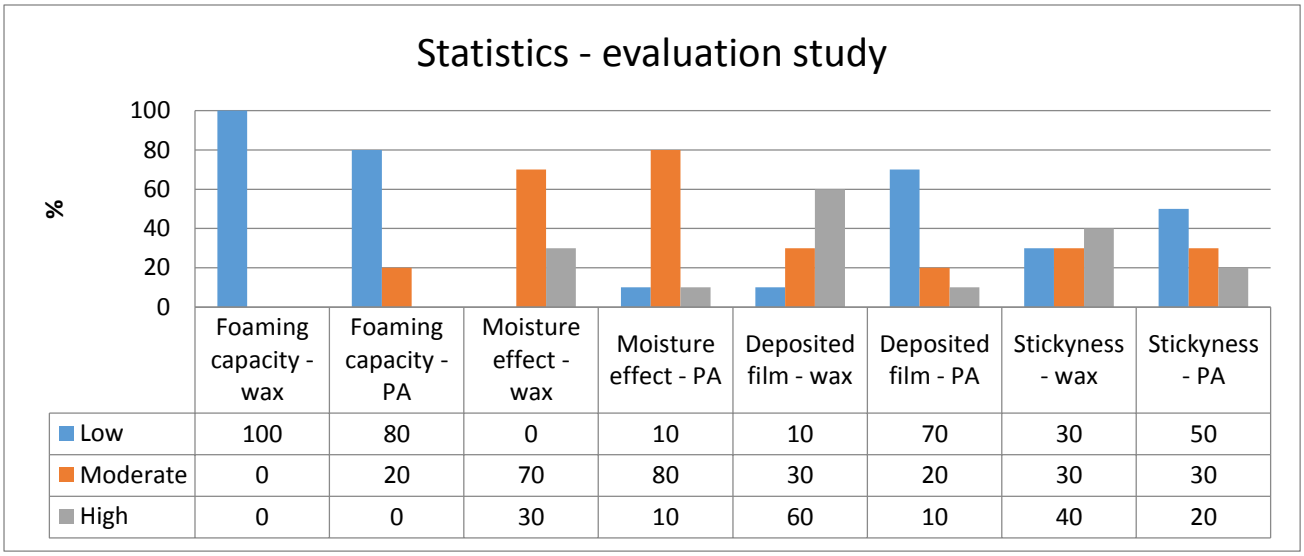
Figure 45: the force as the function of distance curve for the same test of the reference sample as seen above. The negative area coloured in green indicates the tensile work for separating the pig skin tissue from the sample surface.

4.6 Sensory evaluation study, market research survey and business case

The result from the sensory evaluation study are summarised verbally below and in figure 46. In total, 10 respondents completed the evaluation study.

The majority answered that the wax formulation deposited a more noticeable film than the polyamide formulation. Several respondents described the film deposition from the wax formulation as high, while the polyamide formulation was only slightly noticeable. The texture of both formulations was described as smooth (wax formulation 90%, polyamide formulation 80%) and respondents thought the creams had an at least moderate moisturising effect and did not foam during usage.

Most respondents also thought that the feeling directly after application was somewhat unpleasant, but became much more pleasant with time. Several respondents described the formulations as "sticky" and some participants thought that the formulations had an at least moderate friction decreasing property. However, the results concerning friction were too varied to be able to draw any conclusions.



	Foaming capacity - wax	Foaming capacity - PA	Moisture effect - wax	Moisture effect - PA	Deposited film - wax	Deposited film - PA	Stickyness - wax	Stickyness - PA
Low	100	80	0	10	10	70	30	50
Moderate	0	20	70	80	30	20	30	30
High	0	0	30	10	60	10	40	20

Figure 46: the statistics from important results from the evaluation study are presented in the diagram above. PA = polyamide formulation, wax = wax formulation. The questions were answered on a scale between 1 and 5 where 1-2 were considered as low, 3 moderate and 4 and 5 as high when summarising the statistical results.

Even though the market research survey was sent digitally and distributed to patients in the patient organisation Hälsa Oberoende av Storlek (HOBS) and in several Facebook groups after approval from the administrator, unfortunately no respondents handed in the survey. Contact was also established with the Obesity clinic in Malmö and Viktväktarna but unfortunately they could not participate in helping distributing the survey.

The business case can be read in its complete version as appendix A1. However, a brief summary of the case is worth mentioning. There are several remedies available aiming to treat Intertrigo, however none of them cures the disease and recurrence is high. Different topical formulations such as corticosteroids or antifungal/antibacterial products are commonly used. Statistics show that 36 000 people alone in Sweden were diagnosed with Intertrigo or similar skin disease in 2014 and globally 334 million people suffer from some type of dermatitis. Literature highlights the need for clinical

work concerning the disease and currently no preventive products are available on the market. This product also has the advantage of being more easy to use than already existing products and remedies.

The product fits well into the portfolio of Bioglan AB. Major market hurdles identified was the need to get customers to use a preventive product and the price.

5. Discussion

Development of product prototypes
The difficulty during the formulation development is that there is very little scientific information available on how different film forming ingredients react together and what chemical properties they have. When working with emulsifiers the hydrophilic-lipophilic balance (HLB) value is an indicator on the chemical behaviour and overall structure of the molecule, a similar indicator is not available for film forming agents. Hence, the development process became very much a "trial and error" project, where little help could be found in literature. As mentioned by Eccleston (1990) cosmetic emulsions like these are extremely complex, and there is no simple way to circumvent that.

The pictures taken with the confocal microscope confirms the complexity of at least the wax formulation. The wax formulation has areas in the aqueous phase stained both by the Nile red and Nile blue, indicating a crystalline structure in the continuous phase possibly caused by interactions between the excess emulsifiers and the water. The wax and other fatty particles can be seen as red droplets dispersed in the continuous phase. The polyamide formulation only had areas stained by both dies, and neither the confocal pictures can tell us very much about the sample structure. The magnification is not optimized for this sample. However, if you look closely in the zoomed picture of the sample, one can get a slightly better impression of the contrast between the two stains. Overall though, the polyamide formulation behaves more homogenously amphiphilic than the wax formulation. From this point of view, the polyamide has better properties to incorporate several other substances, both hydrophilic and lipophilic.

Both formulations also depict irregular black areas in the pictures. This is probably air spaces caused by poor wettability of the samples on top of the glass substrate. Very little amount of sample was applied, and the possibility that the sample contracted and left microscopic areas on the glass uncovered is high.

The first batches of test formulations used other surfactants such as Macrogol (PEG) 100 stearate and SDS. Initially, foaming capacity was meant to be tested and analysed for different surfactants. However, it was abandoned in favour of the film forming capacity and evaluation of this property. SDS was an unwanted ingredient, due to its negative properties (Aulton and Taylor, 2013), even if it has a fantastic foaming capacity. The formulations eventually used for experiments had no or little foaming and the foaming experiments were never performed. The APGs used though, are known to have excellent foaming capacity when combined with cocoamidipropyl betaine as a secondary surfactant. The APGs such as Coco glucoside and Lauryl glucoside are biodegradable and mild compared to for instance SDS, (NaturallyThinking, 2017). These two APGs works well in maintaining a stable emulsion, but the foaming capacity without a secondary surfactant is low when used in lower concentrations as they have been in this project.

The reason to why the APGs were introduced to the project has to do with their molecular size. Since surfactants form micelles and the size of the micelle depends on the length of the fatty tail of the molecule, (Aulton and Taylor, 2013), a smaller surfactant should be optimal for this formulation. A smaller micelle would probably rinse of less material per micelle, and hence allow for more material to deposit on the skin. It is hard to know whether the positive results obtained from the smaller APGs are because of their size, but it is one possible explanation.

Water vapour permeability
Results indicate that the wax formulations are more occlusive than the formulations using polyamides as the film forming agent. This can be the result of two aspects, where one obviously is the difference of the oil phase and wax seems to be a more occlusive ingredient than the polyamide. Secondly, the wax formulation also has slightly higher w/w% of the oil phase, which also will affect the permeability.

The formulations exhibit no extraordinary behaviour compared to other topical products when it comes to permeability. This experiment has been performed earlier at Bioglan and has yielded similar result for a wide range of non-occlusive o/w creams with varying compositions (Bioglan 2014). It is also important to remember that these films were much thicker than the film that would be left on skin after application and that no membrane acting as the stratum corneum was used. We can assume that, if this relatively thick film used in the experiment has acceptable permeability behaviour, the very thin film deposited on top of the skin will not be less permeable.

In both cases, the formulations with coco glyceride as the emulsifier are more permeable to water vapour. However, these formulations had a much higher level of air incorporated into them, which caused a more uneven film spread on to the gel. It is therefore doubtful if the altering permeability is due to the chemical difference of the molecules. More likely, it is caused by the air bubbles incorporated into the formulations. After the conclusion that both the APGs created formulations with approximately the same level of occlusivity, only the samples containing lauryl glucoside were evaluated, since the formulations with coco glucoside were difficult to handle due to all the air incorporated in the creams.

Water resistance
Once could argue that the rough surface of the PMMA plates gives pictures with poor resolution. However, for the purpose they are used for in this experiment, it is not essential. A binary result in this case where you can distinguish the interface also after the washing procedure indicates a deposited film, which is a sufficient result. It is of course not the same as performing in vivo experiments, but literature prompts this to be a good in vitro alternative. It has also been difficult to apply the formulations in a perfectly reproducible manner (considering force applied by the stroking finger et. c). This could be of less importance since the shower procedure for possible consumers would have great inter-individual variation. The fact that most respondents in the evaluation survey said that the wax formulation left more product behind after washing also correlates with the result from the water resistance experiment. This also indicates that the PMMA plates do not give false or unreliable results as an in vitro substitute for human skin.

Bioadhesion
The main issue with the bioadhesion experiments is that there is a risk that the test results are connected to viscosity differences between the samples, which is also mentioned in literature earlier (Cintra et al., 2016). It was also difficult to get a completely even surface of those samples with higher viscosity. The polyamide formulation in turn did not yield a rupture between the skin surface and the cream as the other formulations did. After the test with the polyamide sample was completed, there was lotion still attached to the skin probe. This was not the case with the wax formulation or the reference cream. The results also indicate that viscosity has had major effect on the results. The reference cream had the highest viscosity and was similar to the wax formulation, while the polyamide lotion is very liquid and had results in the same range as water. Also, the penetration depth could be modified. When penetrating 2 mm into the sample, the edges of the skin covered became a

source of error, since edges varied between test rounds. Future development prospects could be to modify the penetration depth to 0,5 mm and maybe centrifuge the samples to ensure a completely even surface. Another possible modification of the experiment could be to form a hydrous gel of those components thought to aid the bioadhesion in the formulation and test the adhesion properties of that gel. This could also be a way to tackle the issue with varying viscosities. The viscosity issue could also be ruled out by using skin tissue on both the flexile probe arm and the static part of the texture analyser. If a thin film was deposited on top of the skin tissue and they were pressed together, the force needed to withdraw the skin pieces from each other could be measured. A higher value would indicate a stronger bioadhesion without heavy influence of rheological properties of the sample. Possibly, the method could also be used to indicate the degree of skin friction once the product reaches that stage. If skin tissue covered both parts of the texture analyser as recently described, and *both* surfaces were covered with the presumed low friction film a small withdraw or slide/peel force would indicate low friction. This experiment would also present a situation similar to the in vivo skin fold with adjacent skin surfaces rub against each other.

Other reflections

Something that has not been considered during the development procedure is the microclimate of skin folds which are moist, warmer that average body temperature and can have altering pH depending on secondary infections.

The starting point of this project was to begin with a basic cosmetic formulation, and to add different components that literature suggests to be effective film formers and skin feel enhancers. After reading a lot of literature in the field of bioadhesion and film forming emulsions, another way to commence might have been to start in the other end. To start with film formers and investigating their properties and how the behave in presence of different emulsifying agents could be an alternative option to work with the project. When a couple of prospering options were found, one could try to develop a cosmetic emulsion with the film former as a starting point. One difficulty in this project has been to extract the film itself from the formulations to investigate its' properties. That might have been easier if the project had started off by investigating only the film formers.

The project started by creating the "packaging" rather than finding good options for the film forming procedure. It began with a basic formulation and then added different ingredients with film forming prospects and refined those formulations where the film former was successful. Maybe this is also the back side and disadvantage when working with cosmetic formulations and medical devices? Since there is no API present which is often the starting point for drug development otherwise, it's hard to know where to start and what to focus on. In this project, selection of surfactants, film formers, foaming and the in-shower application method have all been major focus points making it difficult to determine where to start and isolating the core of the product.

If more conclusions are wanted from the evaluation study, more respondents are needed. Also, the questions in the evaluation are answered subjectively and how somebody apprehends a product will always be a subjective matter. This became very evident for instance when analysing the results for the question of stickiness of the products, answers were spread evenly on the whole answering scale. The water resistance test with the wet PMMA plates and the evaluation study however, indicate that it is indeed possible to apply a film through a washing procedure.

6. Conclusion

Two product prototypes met the first basic criteria and were further developed and evaluated. One contained a microcrystalline wax as the main ingredient and the other a macromolecule of polyamide. A reference cream was also developed and used in several experiments. The two formulations both exhibited water resistant properties in an in vitro washing experiment. However, the wax formulation proved to be far more water resistant than the polyamide product. The reference cream had no water resistant properties.

The wax formulation proved to be more occlusive than the polyamide product. None of the formulations had remarkable behaviour concerning occlusivity, and the conclusion was drawn that the formulations both had acceptable permeable properties.

Bioadhesion experiments gave conflicting results both when analysing results after tests with 10 and 60 seconds hold time, but also when comparing the values for fracture strength and tensile work for the different experiment cycles. Generally, high viscosity gave a higher value of both the fracture strength and the tensile work. The experiment needs to be further optimised before one can ensure that result values correlate to bioadhesion, and is not a result of rheological properties of the samples.

The prototypes are not yet finished products, but they do exhibit a film forming behaviour on wet surfaces and have proved to be water resistant. Respondents of the user study also confirmed this and highlighted the pleasant moisturising after-feel the products left behind. The majority of the respondents preferred the wax formulation. The prototypes definitely have the possibility to become successful in-shower products, but they need to be optimised concerning properties such as long term stability, viscosity, pH and film duration. Also, the major hurdle of decreasing friction is yet to be investigated.

7. Future research

Even though these formulations create a film on the skin, different derivatives of cellulose, carbomers and chitosan could be further investigated as film forming agents and bioadhesive agents. The carbomer Acrylates/C10-30 Alkyl Acrylate Crosspolymer and other similar crosspolymers are readily used in other in shower lotions. Another interesting dimension is the thermosensitive behaviour which some of these compounds exhibit. It might be possible to take advantage of the increased temperature when showering and at the skin surface compared to room temperature. If a thermosensitive film former could be incorporated in the formulation, this could precipitate when temperature is increased upon application. The matrix formed by the polymers could carry other substances that aim to decrease friction while the water rinses away those substances only incorporated in the formulation to make it stable and attractive for the customer.

Even though a film was formed, the issue of decreasing friction remains. This is a challenge, since increased skin moisture lead to increased skin friction. Skin friction can be measured by a frictional feel analyser to test different friction lowering ingredients, (Egawa et al., 2002).

Furthermore, incorporation of anti-inflammatory, antifungal or antibacterial substances could be an option. However, I am uncertain if the application method of this product is suitable for a product with active ingredients.

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9. Appendix

A1 Business case

A2 Materials

A3 User evaluation study

A4 Market research survey

A5 Traceability matrix

9.1 A1 - Business case

Business Case

Product: In-shower lotion depositing water resistant film on epidermis

Author: Ida Moen Larsson

Intertriginous dermatitis (Intertrigo)

Dermatitis, commonly also called eczema, is a collective term for several inflammatory skin conditions. There are numerous types of eczema, which are all types of dermatitis, but note that all dermatoses are not eczema (i.e. dermatitis caused by sun exposure is not a type of eczema even though it is an inflammation), (Lodén, 2013).

Intertrigo (Intertriginous Dermatitis) is a skin condition caused by inflammation in the top outermost layer of the epidermis. The rash often appears in skin folds and is common between toes, beneath breasts or the belly, between inner thighs and surrounding genitalia. The rashes are reddish and can be very painful. Intertrigo is induced and/or triggered by heat, moisture, friction and poor air circulation. This inflammatory dermatitis is common and patients already suffering from diabetes and/or obesity are more prone to develop the condition, (Medscape 2017). Other risk factors increasing possibility of Intertrigo are incontinence, malnutrition, extreme sweating, reduced immune system due to e.g. HIV or chemotherapy or other skin conditions such as Psoriasis, (WebMD 2017).

The issues of Intertrigo

Recurrence: even though treatment for simple cases of Intertrigo has good prospects, recurrence is common (Medscape, 2017). Data available suggests that prevalence has been evident at 6% of hospitalised patients, 17% for nursing home patients and 20% in cases observed during home care (Mistiaen & van Halm-Walters, 2010).

Fungal infections: the intertriginous areas are often infected by fungi, such as Candida.

Secondary bacterial/viral infections: if the skin condition is not treated or becomes more and more severe, a secondary bacterial or viral infection might become a critical condition for the patient.

Moisture in the intertriginous areas: since the condition is aggravated by moisture and heat it is crucial for the patients to try to constantly keep areas clean and dry, which can be very difficult.

Clothing: patients should avoid tight clothing but can with advantage use cotton or linen fabric to separate adjacent skin surfaces. Avoid all fabrics that encapsulate air and prevent the flow through of air and materials that cause friction. (Medscape, 2017)

Preventive interventions: In more than one review article authors mention that no studies on preventive treatments could be found (Mistiaen & van Halm-Walters, 2010; Mistiaen, Poot, Hickox, Jochems & Wagner 2004).

Treatment and recommendations

As mentioned, a lot of the treatment today is based on general recommendations to patients considering hygiene and clothing. Showering on a regular basis and keeping affected areas cool, dry and clean is essential. Avoiding maceration between adjacent areas is also important. There are no preventive medications against Intertrigo and no preventive treatments except for the general recommendations mentioned exist. Obese patients are advised to try to lose weight, (American Osteopathic College of Dermatology 2017).

Depending on the state of the condition there are different recommendations for treatment. If the condition is worsened by fungal infection or other infections the treatment takes on different characters. See table 1.

Table 1. Different treatments against Intertrigo. (Medscape 2017; Vårdguiden 1177 2017; Akademiska sjukhuset 2017; Fass 2017)

Condition	**Treatment**	**Example product**	**Comments**
Intertrigo	Smooth protective clothing	DermaSilk	Specially developed material aiming to avoid causing skin friction.
	Local treatment with glucocorticosteroid	Betametason, Hydrokortison, Mometason	Glucocorticosteroids are available in different strengths on a scale I-IV.
	Solution of 10% mg/ml aluminium acetotartrate	Alsollösning kutan	Can be used to dab affected areas or as a soaked dressing 15-20 minutes. Remove and dry with cold hair dryer.
	Stay dry, clean, cool. Avoid maceration, friction and tight clothing. Use open toed shoes. Lose weight.	No medication, behavioral recommendations for patients.	Preventive causes done by patient.
	Provide protective barrier with hydrophobic cream.	Active substance Dimethicone (international drug: Tetrix), in Sweden Silon.	
	Immunosuppressants	Protopic salva	**Note!** In Sweden suggested as treatment for Atopical dermatitis but internationally also recommended for Intertrigo.
	Mixture of petrolatum, zinc oxide paste, and aluminum acetate solution or nystatin	Triple paste, Greer goo.	To avoid skin frition this paste can be rubbed on several times a day. **Note!**

	powder, hydrocortisone powder, and zinc oxide paste.		International treatments and recommendations. These pastes are combinations of protective agents, antimycotic agents and cortisone.
Intertrigo Candida or other fungal infection	Local steroid in combination with antifungal agent such as imidazole	Daktacort and Cortimyk	Risk of striae of skin if used in longer periods. Can start with stronger corticosteroid and decrease strength after a couple of days of treatment.
Intertrigo with secondary bacterial infection	Antibiotics or cortisone (sometimes combined in one product)	Fucidin, Fucidin-hydrocortisone, Heracillin	Often antibiotics with fusidic acid or flucloxacillin targeting staphylococcus since these bacteria is present in skin.

Product

Market potential and attractiveness

In 2015, prescripted products for skin conditions in Sweden were sold for approximately 600 million SEK (excluding VATs) (eHälsomyndigheten, 2017). We can assume that the market for over-the-counter (OTC) products concerning skin conditions also is fairly large. Globally 334 million people are estimated to suffer from some type of dermatitis (Vos et al. 2015). Statistics concerning eczema published by the Public Health Agency of Sweden reveals that 22% of the people that took part in the statistical survey during 2016 suffered from some type of eczema and 2% considered their issues to be severe (Folkhälsomyndigheten, 2017). Almost 36 000 patients in Sweden alone were diagnosed with Intertrigo or similar skin related diseases in 2014 (Socialstyrelsen, 2017). Statistics from 2010 - 2014 also indicate that the number of patients obtaining the diagnosis increases every year (Socialstyrelsen, 2017). Atopic dermatitis, another condition closely related to Intertrigo which also often appears in folds and creases of the skin, were diagnosed on around 23 500 patients in Sweden during 2014 (Socialstyrelsen, 2017).

Market trends and drivers

Medical

Currently there are no known preventive medical treatments against Intertrigo. Several authors also highlight the need for professional clinical studies of products and daily habits to establish what actually helps this patient group. Also, studies that have been performed have had severe methodological deficiency or have been considered to be biased (Mistiaen & van Halm-Walters, 2010; Mistiaen, Poot, Hickox, Jochems & Wagner 2004).

Economy

In 2009 the pharmacies in Sweden were released from being strictly state owned and pharmacies now work on an open and competitive market. This means that pharmacies today in Sweden compete not only with each other concerning their OTC products, but they also compete with other department stores, health food stores and cosmetic department stores.

Technology/method of use

A lot of those techniques and rituals today recommended to patients are time consuming and uncomfortable, pastes or creams are to be rubbed on several times each day and it is not possible to walk around publically with tea bags under your armpits. Patients suffering from Intertrigo already often have other medications to take and other problems to take care of. A product like this in-shower lotion is easy to use and adds no or very little extra effort to everyday-tasks, since showering is most commonly a part of the patient's life already.

Strategic fit in the portfolio of Bioglan AB

Bioglan has a strong over-the-counter portfolio which mainly focuses on topical formulations. The portfolio consists of medicines, medical technological products but also cosmetics and dietary supplements. Bioglan has high expertise in topical formulations and has the skills and means to distribute and market another topical product.

Bioglan has staff that is experienced in working with marketing OTC products and has the knowledge on how to reach target groups for the product. In addition, the company has a lot of experience working with and developing treatments for skin conditions involving infections, such as Impetigo (treated with Microcid).

Target groups for indirect marketing

Pharmacists

As mentioned, the Swedish pharmacy monopoly was phased out for not so many years ago. Today, a pharmacy is not only a place to fetch one's prescript medications, but also a place for buying a wide range of OTC products as well as cosmetic products. Hence, pharmacists today are also focusing on sales profits from these products. Many pharmacy chains also have bonus systems to benefit customers and attract more consumers. These bonus systems do not however give bonus points on prescript drugs (Apoteket Hjärtat, 2017), and having a variated and broad range of products is essential.

Health care staff

Health care staff should be informed about the existence of the product. If staff working in health care recommends the product the patient is more likely to buy it when he or she goes to the pharmacy or other vendors of the product.

Cosmetic stores/beauty departments

Since the product is an in-shower lotion, it has the advantage of not only having the patients suffering from Intertrigo as a target consumer. It can also be attractive for people with generally irritated skin or simply being used as a product giving enhanced skin sensation. This aspect could make it desirable for cosmetic vendors and beauty departments or larger shopping facilities.

Health food stores

The treatment recommendations found for Intertrigo today often consist of home cures and remedies. Health food stores as a franchisee could target those groups visiting these stores regularly.

Competitors

Currently there are no products exclusively developed for the condition Intertrigo. Furthermore, as mentioned, there are no preventive products on the market apart from those instructions concerning the daily routines of the patient (clothing, showering, staying cool et c). It becomes difficult to isolate one or two largest competitors, but creams containing corticosteroids are common and antimycotic creams are also hard to compete with since this in-shower lotion does not contains any API, but again, these are competitors of another part of the market.

Market intelligence

Estimated Intertriginous dermatitis market size: 35 000 patients diagnosed in Sweden only during 2014 → market probably several times larger.

Estimated Intertrigo-shower cream market size: market can be expanded to other types of dermatitis/eczema such as atopic dermatitis and market towards people with generally irritated skin.

Window of Opportunity: Pre-study including Feasibility report with FLE and FRP for laboratory exercises of the formulation and Design and Development plan should be finished during Q2 2017.

Commercial Risk

For each Key Factor – each most appropriate response is highlighted

Key Factors	Very Low	Low/Average	High/Average	Very High
Product Attractiveness; how compelling is the product's value proposition	Minimal apparent need. No improvement in customer economics	Need must be highlighted for or taught to customers.	Clear customer need: benefits over existing products.	Product meets strong identified unmet customer need. Enabling features with major economic advantages vs. existing products
Market development needed	No products sold today in the application; need not recognized in market	Emerging application with a few first adopters; few products sold	Established application with several recognized products in the market	Well established and understood application; products sold for some time
Sales force & distribution capability and capacity	Must develop sales organization and skills base--new to COMPANY	New Sales function needed with some leveraging of existing organization	Can use existing skill base but need more resources	Already in place
Leverage/Synergistic Opportunities	None - standalone product	Little potential to drive synergistic sales	Identified limited potential synergistic sales opportunities	Product will certainly drive major synergistic sales

Major market hurdles

- It is difficult to get patients to use preventive products.
- Price. This product will probably not be as cheap as other shower gels, and then it might be difficult to persuade consumers to buy this product instead if they don't have severe problems with Intertrigo.

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9.2 A2 - Materials

Materials used for development of different formulations

Table 2: the different chemical ingredients for the produced formulations are shown below. The two product prototypes have the same ingredients in the water phase. The reference cream has fewer ingredients.

Wax formulation	**w/w%**	**##**	**Polyamide formulation**	**w/w%**	**##**	**Reference formulation**	**w/w%**
Water phase			**Water phase**			**Water phase**	
Water purified	55,27		Water purified	61,2		Water purified	78,6
Citric acid, anhydrous	0,46		Citric acid, anhydrous	0,5		Metylparaben	0,75
Sodium hydroxide	0,27		Sodium hydroxide	0,3		Citric acid, anhydrous	0,009
Hydroxyetylcellulose	0,5		Hydroxyetylcellulose	0,5			
Metylparaben	0,25		Metylparaben	0,25			
Glycerin	5		Glycerin	5			
Lauryl glucoside	10		Lauryl glucoside	10			
Oil phase			**Oil phase**			**Oil phase**	
Paraffinum Liquidum	10		Paraffinum Liquidum	3		Paraffinum Liquidum	15
Hard fat (hydrogenated coco-glyderides)	4		Triglycerides medium chain	6		Polysorbate 60 (Tween 60)	2,5
Multiwax (Microcrystalline wax)	10		Isostearyl isostearate	1		Sorbitan monostearate (Span 60)	2,5
Dimethicone 350	1		Dimethicone 350	2		Cetostearyl alcohol	8
Cetostearyl alcohol	2		Polyamide (OleoCraft LP-20)	8		Etylparaben	0,75
Etylparaben	0,25		Cetostearyl alcohol	2			
Glycerol monostearate	1		Etylparaben	0,25			

Equipment used for the formulation development:

- Homogenizer: IKA Ultra Turrax T25 basic
- Scales; Mettler Toledo, PB3002-S/FACT or Mettler LJ16 Moisture Analyser
- Thermometer: IKA ETS-D5
- Magnetic heating plate: IKA C-MAG HS 7
- pH-meter: 744 pH Meter, Metrohm

Equipment used for the water vapour experiments:

- Powdered gelatine, Haugengruppen AS
- Water
- Petri dishes (diameter 5 cm)
- Magnetic heating plate: IKA C-MAG HS 7
- Drying cabinet: Termarks Cooling Incubator KBP 6151
- Scales: Mettler LJ16 Moisture Analyser
- RH-meter: testo 635
- Spatula

Equipment used for microscopy:

- Light microscope: Zeiss, Axiostar Plus
- Digital camera: Canon PowerShot G9
- Fluorescent stains: Nile red and Nile blue (Sigma Aldrich)
- Confocal microscope: Zeiss, LSM 510 META

Equipment used for the water resistance experiments:

- In vitro skin substitute: Poly (methyl methacrylate) plates, (PMMA) (Schönberg GmbH & Co. KG, Hamburg)
- Digital thermometer
- Motorised test stand: IKA RW20DZM.n
- Light microscope: Zeiss, Axiostar Plus

Equipment used for the bioadhesion experiments:

- Texture analyser: TA-XT2*i*, Stable Micro Systems
- Pig ear skin
- Dermatome: Integra Dermatome, Model B, Integra LifeScience, Padgett Instruments
- PBS solution
- Adhesive tape: Transpore^{TM} tape
- Filter paper
- Tweezers

9.3 A3 - User evaluation study

Användarstudie FPL17-012

Bakgrund

Tack för att du deltar i denna användarstudie.

Du kommer att få testa två produkter, produkt nr 1 och produkt nr 2. Tanken är att detta ska vara en receptfri in-shower-produkt som ska minska irritation i hudveck. Det är viktigt att du följer appliceringsinstruktionen nedan. Läs genom alla frågorna innan du påbörjar testet, eftersom det är en del frågor som berör appliceringen i sig och efterkänsla direkt efter appliceringen.

När du ska testa produkterna är det viktigt att du först tvättar händerna med tvål och noga sköljer bort tvålen. Huden ska vara blöt då krämerna appliceras och därefter sköljas av med **enbart** vatten. Applicera ca 1/2 tsk kräm, smörj in och skölj med kranvatten. Låt händerna lufttorka och besvara frågorna i formuläret.

Applicera produkterna på två **separata dagar**! Detta för att undvika att produkterna påverkar varandra.

Hudstatus före användning, välj ett (1) av nedanstående alternativ som passar dig bäst:

Torr/fnasig ☐

Röd/irriterad ☐

Normal/mjuk ☐

Utseende

Vad tycker du om krämens utseende?

Inte alls tilltalande	1	2	3	4	5	*Mycket tilltalande*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

Kladdighet

Hur kladdig/klistrig upplevs produkten under appliceringen?

Inte alls klistrig	1	2	3	4	5	*Mycket klistrig*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

Hur kladdig/klistrig upplevs produkten medan den torkar?

Inte alls klistrig	1	2	3	4	5	*Mycket klistrig*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

Konsistens

Hur beskriver du konsistensen på produkten? Markera med kryss i tabellen vilket altenativ som stämmer bäst överrens med produkterna.

Tjockhetsgrad	*Mycket tunnflutande*	*Lotion*	*Fast kräm*
Produkt nr 1			
Produkt nr 2			
Textur	*Jämn*	*Grynig/kornig*	*Luftbubblor*
Produkt nr 1			
Produkt nr 2			

Rengöring

Hur pass rengörande effekt/fräschhetskänsla upplever du att produkten har/ger?

Ingenting	1	2	3	4	5	*Väldigt mycket*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

Appliceringsegenskaper

Kryssa i vilken eller vilka egenskaper du anser att produkten uppfyller.

Skumning	*Mycket*	*Medel*	*Ingenting*
Produkt nr 1			
Produkt nr 2			
Mjukgörande känsla			
Produkt nr 1			
Produkt nr 2			

Torktid

Hur snabbt upplever du att produkterna torkar?

Mycket långsamt	1	2	3	4	5	*Mycket snabbt*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

Efterkänsla

Hur mycket av produkten bedömer du finns kvar på huden efter sköljning?

Lite	1	2	3	4	5	*Mycket*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

Hur behaglig känns huden omedelbart efter att den blivit behandlad?

1 minut efter applicering

Inte alls behaglig	1	2	3	4	5	*Mycket behaglig*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

10 minuter efter applicering

Inte alls behaglig	1	2	3	4	5	*Mycket behaglig*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

2 timmar efter applicering

Inte alls behaglig	1	2	3	4	5	*Mycket behaglig*
Produkt nr 1						Produkt nr 1
Produkt nr 2						Produkt nr 2

Hur bedömer du känslan av det behandlade området när produkten har torkat helt?

Mycket sträv	1	2	3	4	5	*Mycket len*
Produkt nr 1						
Produkt nr 2						

Hur lång tid tog det för produkten att torka helt? _____

Andra synpunkter_____

_____

Reaktioner i huden
Påverkar krämerna huden på några andra sätt? Markera med kryss i tabellen.

Produkt nr 1

Typ av känsla	Ingen alls	Knappt märkbar	Måttlig	Intensiv
Sveda				
Klåda				
Minskad torrhet				
Minskad irritation				
Minskad friktion/strävhet				
Hinna applicerad på huden				
Annat: …….				

Produkt nr 2

Typ av känsla	Ingen alls	Knappt märkbar	Måttlig	Intensiv
Sveda				
Klåda				
Minskad torrhet				
Minskad irritation				
Minskad friktion/strävhet				
Hinna applicerad på huden				
Annat: …….				

Vilken produkt tycker du bäst om? Varför?

Vad upplever du vara de viktigaste skillnaderna mellan produkterna?

Övriga kommentarer (frivilligt)

9.4 A4 - Market research survey

Problem med irriterade eller inflammerade hudveck?

Besvara den här enkäten och bidra till ett utvecklingsprojekt för en ny produkt som lindrar besvär med inflammerade hudveck!

2017-03-06
Lämna ditt svar senast 2017 -04-13
Bioglan AB, Borrgatan 31, Malmö

Konsumentundersökning - inflammation i fuktiga hudveck

Du tillfrågas härmed om att besvara en konsumentundersökning. För att kunna besvara enkäten måste du ha fuktiga hudveck som ibland besvär dig. Vecken kan finnas spridda på olika delar av kroppen.

Bakgrund

Enkäten har utformats i samband med ett masterarbete på Lunds tekniska högskola, i samarbete med ett läkemedelsföretag i Malmö. Syftet med projektet är att göra en förstudie för produktutveckling av en ny hudprodukt som ska lindra besvär för patienter med irriterade/inflammerade hudveck. Resultatet av enkätundersökningen ska bidra till förståelse för patientgruppens besvär och konsumentpreferenser kring en ny produkt. Enkäten besvaras anonymt och svaren kommer att användas internt i projektet och eventuellt i arbetets slutrapport.

Den huvudsakliga patientgruppen som produkten riktar sig mot är personer som lider av sjukdomen Intertrigo (Intertriginös dermatit). Intertrigo är en inflammation i huden som uppstår i hudveck som följd av friktion, fukt och värme. Respondenter som inte är drabbade av Intertrigo men har andra besvär med fuktiga hudveck är också inkluderade i målgruppen för enkäten. Dagens behandlingar innefattar olika typer av salvor/krämer och icke medicinska lindrande åtgärder som att försöka hålla sig torr, sval och undvika stramt åtsittande kläder.

Kvinna ☐ **Man** ☐

Ålder:_____ år **Vikt:**_____ kg **Längd:**_____ cm

Besvara följande alternativ:

Du är diagnostiserad med sjukdomen Intertrigo	Ja ☐	Nej ☐
Du tycker att dina besvär uppfyller ovan nämnda kriterier	Ja ☐	Nej ☐

1. **Är du diagnostiserad med andra hudsjukdomar än Intertrigo? (Om du svarar Nej, hoppa till fråga 3).**

Ja ☐ Nej ☐
Om du har svarat Ja ovan, vilken/vilka sjukdom/sjukdomar:_____
_____
_

2. **Tar du för tillfället några mediciner mot dina andra hudsjukdomar?**

Ja ☐ Nej ☐
Om du har svarat Ja ovan, vilka mediciner:_____
_____
_

3. **Hur stora besvär med hudveck bedömer du att du har idag?**

☐	☐	☐	☐
Inga besvär alls	Lindriga besvär	Stora besvär	Mycket stora besvär

4. Var på kroppen anser du att du har mest problem?

_____

_____

__

5. Hur behandlar du dina problem med hudveck i dagsläget?

- Enbart med icke medicinska kurer (badda med alsollösning, lösa kläder, undvik att bli varm, kroppspuder osv) ☐
- Preparat med antimykotisk verkan (preparat mot svampinflektioner) ☐
- Preparat med antibakteriell verkan (preparat som motverkar bakterier) ☐
- Preparat med glukosteroider (ex hydrokortisonsalva) ☐
- Immunoreglerande preparat (praparat som påverkar immunsystemet) ☐
- Annat:_____

6. Om du hade fått erbjudande om att prova en ny produkt mot Intertrigo/irriterade hudveck, hade du provat den nya produkten?

Ja ☐ Nej ☐

7. Om du svarat Ja på fråga 6, vilken typ av produkt hade du i så fall föredragit?

- Kräm/lotion ☐
- In-shower produkt ☐
- Kroppspuder ☐
- Plåster/tejp ☐
- Sprayprodukt ☐
- Annat:_____

8. Hade du kunnat tänka dig att använda en förebyggande produkt mot Intertrigo/irriterade hudveck?

Ja ☐ Nej ☐

9. Numrera alternativen inbördes på en skala 1 – 7, där 1 är viktigast och 7 minst viktigt, hur du hade prioriterat egenskaper hos en ny potentiell behandling mot dessa hudproblem? (Använd varje siffra enbart till ett alternativ).

- Tidsåtgång för användande ☐
- Långvarig verkan ☐
- Doft/färg på produkten ☐
- Sensorisk känsla vid användning ☐
- Användarvänlighet/enkelhet ☐
- Förpackningens utseende & storlek ☐
- Direkt/snabb effekt ☐

10. Hur ofta per dag hade det varit acceptabelt för dig att använda produkten?

☐ 1 gång/dag ☐ 2 ggr/dag ☐ 3 ggr/dag

11. Vad tycker du hade varit ett rimligt månadspris för produkten?

☐ 50 – 100 SEK ☐ 101 – 150 SEK ☐ 151 – 200 SE ☐ 200 SEK eller mer

Tack för din medverkan!

9.5 A5 - Traceability matrix

	Traceability matrix for FPL17-012:23 Polyamide lotion						
	User requirement/need		Design input/Technical Requirement	Target value (%)	Verification method	Design output	Comments
1	Be an oil-in-water emulsion preventing inflammation/irritation in adjacent skin folds.	a	Apperance: white, homogenous lotion/cream.	NA	Visual inspection	Liquid, very white with low viscosity. Pourable.	
		b	Oil-in-water emulsion containing:				
		c	Water purified	61,2			Formulation has not been optimised concerning pH, comments on target value regards effect on differences in water w/w%.
		d	Buffer base: Natruim hydroxide	0,3			
		e	Buffer acid: Citric acid	0,5			
		f	Humecant: glycerine	5			
		g	Thickener/rheology modifier: hydroxyetylcellulose	0,5			
		h	Preservative: metylparaben	0,25			
		i	Surfactant: Lauryl glucoside	10			
		j	Emollient: paraffinum liquidum	3			
		k	Emollient: isopropyl isostearate	1			
		l	Emollient: triglycerides medium chain	6			
		m	Skin conditioner: Dimethicone 350	2			
		n	Co-emulsifier: cetostearyl alcohol	2			
		o	Film former: Polyamide OleoCraft LP-20	8			
		p	Preservative: etylparaben	0,25			
			Total:	**100**			
2.	Deposit water resistant film on epidermis	a	See 1.o		Verification method	Design Output	Comments

			Film must be non-occlusive		Water vapour evaporation test	Non-occlusive relative other creams done with the experiment.	Experiment could be optimized further - maybe test with method present in British Pharmacopoeia where reference value exist to determine if film formed is permeable or not.
			Film must adhere to skin even when skin is wetted		Sensory evaluation study/water resistant test	Adheres on wet skin and PMMA plates.	Further iv vivo studies needed to establish amount needed, effect of water temperature etc.
			Film must remain intact until next application the following day		Not tested.	-	-
			Film should not be sticky when dry		Sensory evaluation study		Very subjective answers, need more objective test method. Could test as mentioned in literature - use cotton pads and see if some of the cotton sticks to the skin or not.
			Surfactant must not wash off the deposited film		Sensory evaluation study/water resistant test	Washed off from PMMA plates after 2-4 minutes in water at 38 °C.	In vivo study needed. Maybe also test further with in vitro method. Pig skin tissue? Label sample with fluorescent probes and investigate after washing in epifluorescence microscope.

3	Must be drug free and free from surfactants known to be environmentally discussable	a	No Pharmaceutical active ingredient. See 1X-X.		Formulation developed without API	Drug free product.	
		b	Biodegradable surfactant used, see 1X.		Formulation developed without non-biodegradable surfactants	Biodegradable surfactant.	
4	Must reduce friction between adjacent skin surfaces.	a	Reduction of friction directly after application.				Project has not focused on decreasing friction, film forming has been the target.
		b	Reduction of friction after several hours after application.				See above.
		c	Make skin feel smooth and dry.				See above.
5	Attractive packaging and easy to use	a	Pump flask for fix dosage				
			Pump flask with attractive label and colour				
6	Product should be able to pump from a pump flask	a	Viscosity needs to be compatible with pump flask requirements		Rheology tests	Not tested.	
7	Product should be stable	a	Should be stable for a certain amount of time		Stability study	Separates after 2-4 weeks.	Specific stability study not performed, only visual inspection.
			Should be stable at elevated temperatures				

	Traceability matrix for FPL17-012:22 Wax formulation						
	User requirement/need		Design input/Technical Requirement	Target value (%)	Verification method	Design output	Comments
1	Be an oil-in-water emulsion preventing inflammation/irritation in adjacent skin folds.	a	Apperance: white, homogenous lotion/cream.		Visual inspection	Cream, pale yellow with high viscosity. Smooth and creamy.	
		b	Oil-in-water emulsion containing:				
		c	Water purified	55,27			Formulation has not been optimised concerning pH, comments on target value regards effect on differences in water w/w%.
		d	Buffer base: Sodium hydroxide	0,27			pH needs adjustment.
		e	Buffer acid: Citric acid	0,46			pH needs adjustment.
		f	Humecant: glycerine	5			
		g	Thickener/rheology modifier: hydroxyetylcellulose	0,5			
		h	Preservative: metylparaben	0,25			
		i	Surfactant: Lauryl glucoside	10			Add cocoamiopropyl betaine for foaming?
		j	Emollient: paraffinum liquidum	10			
		k	Emollient: hydrogenated coco-glycerides	4			
		l	Dimethicone 350	1			
		m	Co-emulsifier: cetostearyl alcohol	2			
		n	Film former: Microcrystalline wax, Multiwax	10			Very high w/w% of wax, could a crosspolymer or cellulose derivative be added and wax concentration decreased?
		o	Preservative: etylparaben	0,25			
		p	Emulsifier: glycerol monostearate	1			

			Total:	**100**			
2.	Water resistant film	a	Film must deposit on epidermis, see 1 n.		Verification method	Design Output	Comments
		b	Film must be non-occlusive		Water vapour evaporation test	Non-occlusive relative other creams done with the experiment. The most occlusive of the formulations tested.	Experiment could be optimized further - maybe test with method present in British Pharmacopoeia where reference value exist to determine if film formed is permeable or not.
		c	Film must adhere to skin even when skin is wetted		Sensory evaluation study/water resistant test	Adheres on wet skin and PMMA plates.	Further iv vivo studies needed to establish amount needed, effect of water temperature etc.
		d	Film must remain intact until next application the following day		Not tested.	-	-
		e	Film should not be sticky when dry		Sensory evaluation study	Respondents say the formulation is sticky at first, and pleasant after a while.	Very subjective answers, need more objective test method. Could test as mentioned in literature - use cotton pads and see if some of the cotton sticks to the skin or not.
		f	Surfactant must not wash off the deposited film		Sensory evaluation study/water resistant test	Washed off from PMMA plates after at least 6 minutes in water at 38 °C.	In vivo study needed. Maybe also test further with in vitro method. Pig skin tissue? Label sample with fluorescent probes and investigate after washing in epifluorescence microscope.
3	Should be drug free and free from surfactants known to be environmentally discussable	a	No Pharmaceutical active ingredient. See 1c-p.		Formulation developed without API	Drug free product.	

		b	Biodegradable surfactant used, see 1i.		Formulation developed without non-biodegradable surfactants	Biodegradable surfactant.	
4	Must reduce friction between adjacent skin surfaces.	a	Reduction of friction directly after application.				Project has not focused on decreasing friction, film forming has been the target.
		b	Reduction of friction after several hours after application.				See above.
		c	Make skin feel smooth and dry.				See above.
5	Attractive packaging and easy to use	a	Pump flask for fix dosage?				
			Pump flask with attractive label and colour				
6	Product should be able to pump from a pump flask	a	Viscosity needs to be compatible with pump flask requirements		Rheology tests	Not tested.	
7	Product should be stable	a	Should be stable for a certain amount of time		Stability study	Separates after 2-3 weeks.	Specific stability study not performed, only visual inspection.
			Should be stable at elevated temperatures				