Bachelor-thesis:

‘Which pressure-sensitive adhesives are used in medicine?’

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Major: Biomedical engineering

Bachelor thesis: ‘Which pressure-sensitive adhesives are used in medicine?

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Summary

Pressure-sensitive adhesives (PSAs) are a broad department of adhesives with a lot of application possibilities. This could be in industry, but also in medicine. The main question for this thesis is:

'Make an overview of pressure sensitive adhesives used in medicine.'

To answer the main question, the definition of PSAs is given first. After this the applications of PSAs are explained. To know the properties of an adhesive to adhere with a surface or substrate a chapter is made to explain the important properties of PSAs. After the important properties, testing methods are explained and at last the future directions in PSAs.

A general definition to define an adhesive is:
'A material capable of bonding and holding adherents together by means of surface attachment (1)*.'*

To distinguish PSAs from general adhesives two essential requirements are important and have always been remembered when choosing or developing a PSA (4;5):

- The adhesive have to stick firmly to a difficult surface like human skin.
- The adhesive should be easily and cleanly removed from the substrate when desired. It will not cause skin irritation due stripped Corneocytes.

The applications for PSAs on the market are mostly for wound protection. The applications for PSAs are (3):

- Drug delivery systems.
- Moisture vapor permeable (MVP).
- Traumaless removable.
- Water resistant.
- For electro-medical applications.

Pressure-sensitive adhesives have to adhere to the human skin and need some properties to make an adhesive bond. These properties are (7):

- Surface free energy
- Polarity
- Rheological properties

Many testing methods are available to quantitatively characterize the interfacial strength between the substrate or surface and the PSA. Among all tests the peel and the blister tests are the most popular ones, in the industry and in the academy (12;13).

In literature there are a few future directions available:

- Problem in repeated removal of adhesives, with as result stripped corneocytes. This can be solved by using a water solvable PSA. The adhesive will lose its adhesiveness and can be removed easily (3).
- Impregnating the adhesive with a broad spectrum antibiotic or use drug delivery systems as specific antibiotics delivery through the skin (18).
- Bio-engineered tissue with stem cells (18).
- Another new type of medical adhesives, for instants the hydro gels (18).

Samenvatting

Drukgevoelige hechtmiddelen (PSAs) vallen onder een brede tak van hechtmiddelen met grote toepasbare mogelijkheden. Niet alleen in de industrie, maar ook in de gezondheidszorg.
De hoofdvraag voor de scriptie is:

'Maak een overzicht van drukgevoelige hechtmiddelen gebruikt in de gezondheidszorg'

Om de hoofdvraag te beantwoorden wordt eerst de definitie van PSAs gegeven. Na dit uitgelegd te hebben worden verschillende toepasmogelijkheden gegeven. Verschillende eigenschappen zijn nodig om de hechting mogelijk te maken tussen een PSA en het oppervlak. Dit wordt als volgende uitgelegd. Hierna worden uitgelegd welke testen er gedaan kunnen worden om de adhesiemogelijkheden te kunnen meten, waarna de toekomstmogelijkheden uitgelegd worden van PSAs.

De definitie om een hechtmiddel weer te geven is:
'Een materiaal die gebruikt wordt voor binding en het aan elkaar bevestigen van materialen door gebruik te maken van oppervlaktehechting (1).'

Om PSAs van normale hechtmiddelen te onderscheiden zijn 2 eigenschappen belangrijk die alleen gelden voor PSAs. Deze zullen altijd onthouden moeten worden wanneer gekozen wordt voor het ontwikkelen van een PSA:

- Het hechtmiddel zal sterk moeten hechten aan een moeilijk oppervlak, zoals de menselijke huid.
- Het hechtmiddel moeten bij wens makkelijk en zonder resten verwijdert kunnen worden van een oppervlak en zal geen huidirritatie veroorzaken(4;5).

De toepasmogelijkheden voor PSAs op de markt zijn vooral voor wondprotectie. De belangrijkste mogelijkheden voor PSAs zijn(3)::

- Medicijn diffusie systemen
- Vocht, damp permeabel
- Zonder schade verwijderen
- Waterbestendig
- PSAs voor electro-medische toepassingen.

PSAs voor medische toepassingen zullen moeten hechten aan de menselijke huid en Zullen bepaaldde eigenschappen moeten bezitten om een binding te kunnen maken. Deze eigenschappen zijn:

- Oppervlakte energie
- Polariteit
- Rheologische eigenschappen

Verschillende testmethoden zijn aanwezig om de grensvlak energie tussen het oppervlak van de huid en het oppervlak van de PSA te meten. De 'peel' en 'blister' test zijn de meest populaire testen. Niet alleen in industrie, maar ook op de onderzoekscentra (12;13).

In literatuur zijn een aantal toekomstmogelijkheden beschreven voor PSAs:

- Het probleem door beschadiging van de huid kan opgelost worden door wateroplosbare PSA te gebruiken (3).
- Impregneren van de PSA met antibiotica (breed spectrum of specifiek) (18)
- Bio-engineerd weefsel met stamcellen. Gehecht door een PSA (18).
- Een nieuw type PSA, zoals bijvoorbeeld een hydrogel (18).

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1. Introduction

1.1. Main introduction

Pressure-sensitive adhesives (PSAs) are a broad department of adhesives with a lot of application possibilities. This could be in industry, but also in medicine. Early adhesives consist of a natural rubber with a resin as tackifier (3). Nowadays adhesives with intrinsic tack are available on the market. The biggest part of the PSAs made today are from an acrylic origin. PSAs are adhesives that adhere to a surface or substrate when pressure is executed on top of the adhesive, for instants a plaster. A plaster can adhere to your skin, but when pressure is executed for a period of time, the plaster is adhered stronger. Until Recently PSAs are labeled as a not-difficult technology, but this label is fading out, because of the new application possibilities and studies made on PSAs (3), for instant more difficult applications like drug delivery systems (nicotine plasters). The greatest difficulty in PSAs is in the attachment of human skin where also rheological, moisture or sebum and reattachment (irritation of skin) are variables. Due to the strong growth of knowledge in polymer chemistry the possibilities and applications are endless and will still grow in the future.

To answer the main question, the definition of PSAs is given first. After this the applications of PSAs are explained. To know the properties of an adhesive to adhere with a surface or substrate a chapter is made to explain the important properties of PSAs. After the important properties, testing methods are explained and at last the future directions in PSAs.

1.2. Main question

Make an overview of pressure sensitive adhesives used in medicine.

1.2.1. Sub questions

- What types of adhesives are available?
- What applications are there for pressure sensitive adhesives?
- Which properties are important to form an adhesive connection for pressure sensitive adhesives?
- How to test on adhesiveness?
- What are the future directions for pressure-sensitive adhesives?

2. What types of adhesives are available?

In this paragraph the term adhesive is explained in general. An adhesive is a broad term and includes a lot of different attachment methods. A general definition to define an adhesive is:

'A material capable of bonding and holding adherents together by means of surface attachment (1)*.'*

Surface attachment is defined further in chapter 3.

There are two different major classes of medical adhesives available: (2)

- Permanent or tissue adhesives(glue)
- Removable adhesives (pressure sensitive adhesives)

The objective for tissue adhesives is to attach two objects together without the aim of separating. Tissue adhesives are used inside the body to attach tissue together. These types of adhesives are more difficult to study, because they have to attach in the presents of water. In the surgical field stitches and staples are still the leading attachment methods for tissue. Pressure sensitive adhesives (PSAs) have the opposite objective of tissue adhesives. These adhesives should be able to remove without causing damage to the substrate, They are demanding as they are able to adhere to (3):

- varying skin types (moisture and dry skin)
- removable without the remaining of residue
- cause no irritation to the skin

2.1. Pressure-sensitive adhesives

Pressure-sensitive adhesives are used in a great variety of applications (see chapter 3: Applications for pressure sensitive adhesives?). This great variety requires many different properties of the polymers used in PSAs. The most used polymer type in PSAs is the acrylics. This is because of their good adhesive qualities and low levels of allergenicity (3). There are also other types of polymers used in PSAs, but their only used for special applications. These are (3):

- Silicone-based adhesives, which are used in transdermal drug delivery systems (see chapter 3.1: Drug delivery). These devices are in need of an inert adhesive and biocompatible system.
- Polyvinyl ether-based adhesive, which are used in permeable skin patches.
- Polyvinyl pyrrolidone-based adhesives, which are used for high moisture absorption applications, such as ostomy bags and mounts, without the loss of adhesion.
- Urethane- based adhesives, which are used for sustained released wound dressings and urethane implants.

It is important to know that PSAs must do more then only adhere well to human skin. They must have specific properties tailored to their final application (3).

Two essential requirements of medical pressure-sensitive adhesives are important and have always been remembered when choosing or developing a PSA:

- The adhesive have to stick firmly to a difficult surface like human skin.
- The adhesive should be easily and cleanly removed from the substrate when desired. It will not cause skin irritation due stripped Corneocytes(4;5).

These two requirements should give a conflict, because with a high peel force usually signals the ability to stick firmly, while a low force is needed to peel of the tracheostoma valve and/or filter (5;6) Tokumura has suggested that these two properties could not give a conflict when using a softener. This causes anchors in the Sulcus cutis, which give an increase in surface free energy.

Many studies are made to develop a PSA which are strong enough to attach, but leave no damage to the substrate when removed. To cause no damage to the substrate different methods are studied (6):

- An increase of water vapor permeability by forming pore structures into the adhesives.
- An increase of conformability to skin movement by using an elastic non woven fabric by backing of tapes.
- A decrease in ripped corneocytes by using a gel adhesive. Corneocytes are skin cells.

2.2. Tissue adhesives

In this paragraph the tissue adhesives are short explained to achieve a full view of the 'medical adhesives' in the further chapters of this thesis the pressure sensitive adhesives are explained in depth.

The various types of tissue adhesives can be subdivided into two major classes of adhesives: (18)

- Synthetic adhesives: Cyanoacrylate derivatives
  - Butyl-2-cyanoacrylate
  - 2-octyl cyanoacrylate
- Biologic adhesives: Fibrin-based adhesives

The first synthesized Cyanoacrylate was already in 1949 (21). Cyanoacrylates are investigated and used as a medical adhesive since the 1960s (19;21).

To know further on the properties of Cyanoacrylates it is important to know something about the synthesis of the polymer. Cyanoacrylates are synthesized by reacting formaldehyde with alkyl cyanoacetate. This reaction will obtain a prepolymer what is by heating depolymerized into a liquid. Upon application of the adhesive the monomers with the alkoxycarbonyl group (-COOR) undergoes an exothermic hydroxylation reaction that results in polymer chains with different lengths. For application it is important to know that shorter polymers have a higher degree of toxicity then longer polymers (21).

Cyanoacrylates are compounds that form a very high tensile strength adhesive. This compounds also polymerize very fast when it comes in contact with water and blood to form a strong bond.

Cyanoacrylate adhesives are biodegradable, but usually used on an external surface and may induce subcutaneous an inflammatory foreign body reaction, what includes inflammation, neovascularization, wound breakdown and tissue necrosis (18;21). This is related to the byproducts of degradation, cyanoacetate and formaldehyde. Slower degradation rates will reduce the foreign body reaction. This is the reason why shorter chains have a higher degree of toxicity then longer chains, because longer chains are more difficult to degrade. A slower degradation rate will reduce the accumulation of the toxic byproducts (21).

Butyl-2-cyanoacrylate is used and effective in superficial lacerations under low tension. The wound breaking strength of Butyl-2-cyanoacrylate is very low and even lower than that made by sutures. The breaking strength of Butyl-2-cyanoacrylate compared to sutures is only 10-15% (21). After polymerization the adhesive becomes brittle and can get loose on skin creases or long incisions. The areas were Butyl-2-cyanoacrylate could be used is on low tension incisions like: (21)

- Facial skin closure
- Scalp wound closure
- Upper lid blepharoplasty.

A replacement cyanoacrylate for Butyl-2-cyanoacrylate is 2-octyl cyanoacrylate. The slower degradation rate of this polymer will decrease the accumulation of toxic byproducts, resulting in a foreign body reaction. Also plasticizers can be added to the polymer what increases the

flexibility of the adhesive and decreases the risk of breaking. For example the 3-dimensial breaking strength of 2-octyl cyanoacrylate is 3 times higher than at Butyl-2-cyanoacrylate. The stronger, flexible bond of 2-octyl cyanoacrylate could be used in longer incisions (21). Octyl cyanoacrylates are the only tissue adhesives in the cyano-groups that are approved by the FDA for use in the human body (21).

Fibrin based adhesives are biologic and biodegradable and have, by contract, a lower tensile strength and slower polymerization then Cyanoacrylates. These types of adhesives induce a minimal inflammation. Unfortunately fibrin glues use human thrombin, this blood product still carries a small risk of infection due a contaminated donor pool (18). The principal components of all fibrin adhesives are: (20)

- Fibrinogen
- Thrombin

These two components are used as a 2-component kit. The properties of the adhesives are influenced by the quantities of each of the components. The mechanical strength is influenced by the proportion of fibrinogen, Factor XIII and adhesive proteins in the fibrin adhesive. A higher dose of fibrinogen will increase the mechanical strength, whereas adhesives containing higher concentrations of thrombin tend to form clots more easily and add to clot adhesion (20).

Adhesion of tissue adhesives is especially taken place by the mechanism called ‘interlocking’ (figure 1). Interlocking is a mechanism what uses the roughness of the surrounded tissue for adhesion, instead of the surface free energy what is the main adhesion mechanism used by pressure sensitive adhesives. By interlocking the soft adhesive, mostly monomer, flows into the roughness of the surface. Due to water the monomers start to polymerize and get cured. The stiff polymer gets stuck inside the roughness of the tissue due to polymerization.

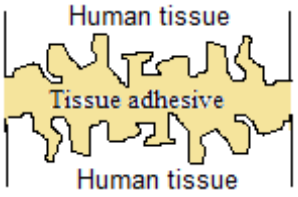

Figure 1: schematic viewing of an adhesive adhered with human tissue due to the mechanism ‘interlocking’.

A second adhesion mechanism for tissue adhesives is a covalent bond with the amino-groups of proteins inside the body.

3. Applications for pressure sensitive adhesives?

The biggest amount of the pressure-sensitive adhesives on the market is for wound protection. The applications for PSAs are (3):

- Transdermal drug delivery
- Adhesive bandage or plasters
- Adhesive drapes
- Ostomy bag mounts: Construction of an opening in the human skin. For example a tracheostomy.
- Intravenous needle attachments, like morphine perfusion.
- Electro medical procedures
- Micro porous tapes

3.1. Drug delivery systems

Because of the high progress of transdermal drug delivery the last few years this application is explained further in this chapter. Transdermal drug delivery is mostly used against antianginal problems, motion sickness, hypertension, pain problems by using analgesia, smoking problems, pregnancy. In drug delivery systems the drug is transmitted through the skin with the use of a patch at a controlled way (3). There are many advantages for transdermal drug delivery. These advantages are (3):

- Constant diffusion of the drug through the skin. Transdermal drug delivery is only possible when there are a low dose is necessary.
- There is a lower dose needed then when oral dispensed.
- There is a higher accomplishment by patients when using a transdermal drug delivery system then an oral drug.

There are 2 methods available for a controlled transdermal drug delivery. The drug may either may held in the drug reservoir of a patch that is adhered to the skin with the use of a PSA (Figure 2) or the PSA may act as a mechanism for adhesion as well as a carrier for the drug (Figure 3) (3).

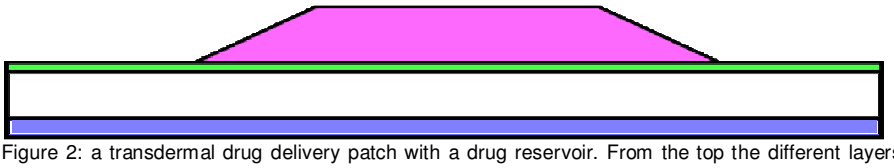

Figure 2: a transdermal drug delivery patch with a drug reservoir. From the top the different layers are: the drug reservoir, a permeable membrane, pressure sensitive adhesive and a release liner. The release liner takes care of a constant diffusion rate of the drug through the skin.

Figure 3: a transdermal drug delivery patch without a drug reservoir. From the top the different layers are: the backing, a drug caring pressure sensitive adhesive and a release liner. The release liner takes care of a constant diffusion rate of the drug through the skin.

For the use of a transdermal drug delivery patch the PSA should have some good properties. These properties are:

- Good attachment with the skin
- Compatible with the drug
- The drug should not change the properties of the PSA
- The drug should solve well into the polymer. Mostly an acrylic polymer is used. This is because of its polar properties. A non polar material like silicone rubber or a hydrophobic polymer like Polyisobutylene is less suitable.

The polymers used for transdermal drug delivery mostly are silicone polymers. Silicone polymers are widely used in medicine as transdermal PSAs (3). Polysiloxane based adhesives have proved to be permeable to low molecular weight polymers like drugs whilst showing good adhesion to human skin causing almost non irritation and being easily removable(3).
Also acrylic adhesives have been used, like they have been used in almost every PSA. These are often used in a copolymer as a acrylate esther/vinyl pyrrolidone. This is due to their ability to form complexes with certain antimicrobial agents. This results in a more controlled release (3).

3.2. Moisture vapor permeable (MVP) PSAs

PSAs which are adhered to human skin will always come in contact with a moisture or vapor environment. An application which should be present at all PSAs, which come in contact with human skin, should be moisture vapor permeable. Moisture under for example an adhesive bandage will soften the skin and reduces the surface free energy (see chapter 4.1: Surface free energy). This will decrease the adhesive properties and will result in loosening of the adhesive. When an adhesive has a high moisture vapor transmission rate, it shows a reduction in skin lesions (3).

The moisture vapor permeability is caused by the producing of hydrophilic polymers to form the PSAs. This PSAs consist of an acrylic base with hydrophilic groups attached. These hydrophilic groups are hydroxyl or carboxylic acid groups, polyurethanes or vinyl-ethers (3). Other methods used to increase the water permeability of PSAs are: (3)

- Alginates blended with a polyisobutylene adhesive.
- Gel adhesives based on acrylates. Gel adhesives can store a lot of water so the skin will stay dry.
- Polyurethanes, that can remain adhered to the skin even if the patient sweats abundantly.

The loss of water vapor by human skin is approximately 200 till 600 mg/m^2/24h (3). The loss of liquid may be much higher. The consequence for this high numbers is that the MVP PSAs must have a moisture vapor permeable rate of at least 600 mg/m^2/24h without sacrificing its bacterial barrier properties (3).

3.3. Traumaless removal of PSAs

Traumaless removal of PSAs is important in medicine, because they will be always attached to human skin. This is particularly required with wound care products used at children with a delicate skin and elderly. This is also required at products what are repeatedly removed from one area. These are seen at ostomy products, like a tracheostoma filter.

Different methods are available for traumaless removal. Crosslink activation (3;4), which causes a decrease in glass temperature and a decrease in 'tack'. A decrease of 'tack' results in a decrease of adhesion. Also thermally deactivated by heating or cooling during removal is possible. This is caused by using side chain crystallisable polymers that crystallize below that of use (cool-off adhesive) (4) or melt at temperatures above that of use (warm-off adhesive) that results in a less tacky adhesive (3;4). Crystallization will cause a lower glass transition temperature what results in a stiffer material and lowers the adhesion, like increasing crosslinks (4). Melting will decrease the viscosity and causes the PSA to flow, what results in a lower adhesion (see chapter 4.3: Rheological properties. Water use is also a possiblity for traumaless removal . Due to water the PSA gets deactivated. This is caused by a water soluble tackifier. The tackifier gets solved in the water and will result in a decrease in adhesion (3). Tackifiers are used in PSAs which are originally not good adhesives, like natural rubber. At last a softener can be used. Tokumura et al has studied the amount of softener (Isopropyl myristate) that should be used to avoid stripped corneocytes, which causes skin irritation. Tokumura et al found that the amount of stripped Corneocytes on the removed adhesives was correlated with the amount of skin irritation(4). Also the level of pain decreased when the adhesives were removed with the increase of the softness. The peeling force decreases with a small amount, but this was not significant. This suggests that the lack of significant change of peeling force was caused by penetration of the soft adhesives containing Isopropyl myristate into the outer skin layer (Sulcus cutis). The penetration of soft adhesive into the Sulcus cutis would increase the contact area between the adhesive and the skin surface and would act as anchors (4). The surface free energy is increased.

3.4. Water resistant PSAs

Water resistant PSAs are as the name says PSAs which keeps their adhesive strength when there is al large amount of water around, like for instants blood. This PSAs are aimed in use for surgical/medical dressings or plasters (3). The degree of water resistant can be changed by using different kind of polymer formulation. This formulations vary from crosslinked vinyl lactam copolymers, these polymers are capable of tolerating lots amounts of water, to emulsion polymerized adhesives made from water insoluble monomers in the presence of a water soluble surfactant, converted in a water insoluble adhesive after polymerization(3).

3.5. PSAs for electro-medical applications

These adhesives are designed to provide an electrical connections between the medical electrode and the skin. It is possible that the PSA is only used as an adhesive patch by keeping the device on the skin, but can also be used as a conductive medium and adhesive for the electrode (3). Mostly used PSA for this application is a polymer gel. A gel is a lightly crosslinked polymer, which can carry lots of water. This water can be made conductive of course. The rate water/polymer can be up to 99/1(3).

4. Which properties are important to form an adhesive connection for pressure sensitive adhesives?

To develop strong adhesive connections, intermolecular contact is necessary (7). Adhesive connections are a composite structure whose properties depend upon the bulk properties of both adhesive and adherent and the interfaces which join these bulk phases (1). Renvoise et al says that with the use of soft adhesives the performance is not only depended on interfacial properties, but also strongly on the rheological behavior (1;9). Thus the bonding state of an adhesive is rheological distinguished from the holding state, because an adhesive must have the properties to wet, spread and penetrate the surface roughness to adhere. To provide the holding capability it must display the viscoelastic properties of the substrate to provide strength and creep resistance to the adhesive joint (1). The relationship between rheological behavior and peeling performances is quite clear when the adhesive is used on a non-deformable substrate. The adhesive must also have a high affinity with the substrate. This means a high surface energy for the substrate. In the case the surface energy becomes lower or/and the elasticity of the substrate becomes higher the case becomes much more complex (8) .

Derail has studied the rheological properties. It is important that the elastic modulus of the adhesive is higher than the elastic modulus of the substrate. When it is other way around the adhesive properties get unstable and could lose its properties (9). Derail (9) has also studied the adhesiveness of an adhesive in a wet environment. A wet environment is possible on a sweaty human skin. He studied the elastic modulus changes in a wet environment. The elastic modulus decreased when an adhesive absorbs a liquid. It is possible that the elastic modulus decreased to the same level as the substrate. The adhesive get unstable and could lose its properties.

A good intermolecular contact or interfacial property means that the adhesive has to be spread out over the surface. There must be also displace of air or other contaminates that are present on the substrate surface. An adhesive which confirms to all this conditions must have: (7)

- A contact angle of zero or near to zero
- At some time during the bonding operation have a relative low viscosity of no more than a few centipoises.
- Be brought together with the substrate in a way that there is no entrapped air between the adhesive and the substrate.

In the particular case of a visco-elastic substrate, like the human skin, the adhesive - - properties depends strongly on: (8)

- Mechanical properties of the substrate
- Adhesion properties of the adhesive

The properties what causes an adhesive bond are (7):

- Surface free energy
- Polarity
- Rheological properties

In the following paragraphs this properties are explained.

4.1. Surface free energy

Every material wants to be at its lowest energy state. The lowest energy state is received by keeping the surface as little as possible. In nature the lowest energy state will be at the spherical form. For example water in oil. Water will transform to spherical drops when it get in contact with oil. In a sphere the surface energy is higher then the energy in the middle of the sphere. The amount of energy on the surface is called the surface free energy. (11) The energy of the surface layers is the result of the attraction of the bulk material for the surface layer and this attraction tends to reduce the number of molecules in the surface region resulting in an increase in intermolecular distance. This requires work within the material and this explains why there is energy on the surface of every material. This work can be translated in the amount of energy needed to keep the energy in the surface. This is called the surface free energy. (7) Every substance has a different surface energy. This is part of the material properties.

4.2. Polarity

The most well-known type of a physical attractive force are the Van der Waals forces. There are two different types:

- Dispersion (or London) forces, also known as non-polar, these arising van internal electron motions which are independent of dipole moments.
- Polar (or Keesom) forces, these arising from the orientations of permanent electrical dipoles and the induction effect of permanent dipoles on polarize-able molecules (7).

The dispersion forces are usually weaker then the polar forces, but there more universal. All materials exhibit them (7).

The larger the surface, the larger the work of adhesion will be. It is important to know that the surface of a structure is always larger then there is to see with the naked eye. If a surface is investigated under a microscope a mountain landscape is seen. Because of this mountain landscape the surface is much larger than at assumption was in the beginning. It is important to make your advantage with this phenomenon. A good wetting will help. Wetting is the degree the fluid will divide over the surface of a solid material. With a good wetting the fluid will spread over the surface of the solid material and gets deep into the pores. With a good wetting the interaction will increase and the connection between the two materials stronger. De extent of the wetting is depending of the surface energy of the two materials. A good wetting will take place with a low surface energy of the fluid and/ or a high surface energy of the solid. In this case the fluid will extend over the surface of the solid. A solid with a fluid spread out over the surface has a lower surface energy, namely the surface energy of the fluid. As said earlier a material wants to be in its lowest energy state. With a bad wetting the surface energy of the solid is low and the fluid will not spread out over the surface. The fluid will stay as a droplet on the surface of the solid. Figure 4 represents the wetting of a fluid on a material (11).

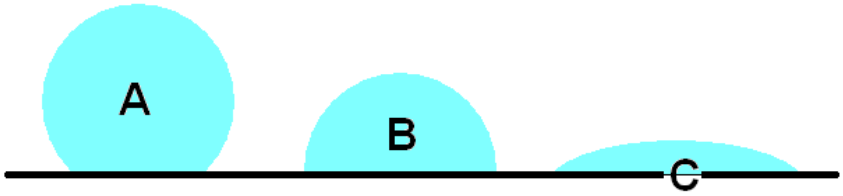

Figure 4: A has a bad wetting (Less than 90 degrees contact angle), B an average wetting (90 degrees contact angle) and C a good wetting (more the 90 degrees contact angle). (11)

4.3. Rheological properties.

Renvoise et al mentioned it already in chapter 3: the adhesive properties of PSA's are not only dependent of surface free energy and polarity, but also on rheological properties (8). Rheological properties are the mechanical properties of the adhesive. The 'tack' of the adhesive is dependent of the way an adhesives is produced. Figure 5 shows the correlation between Elastic modulus and temperature. The T_g is the temperature were the molecules are not moving anymore and the material is solid. Above this temperature the material is in its fluid state. For adhesives it is important that they have a large mol mass. With the use of a large mol mass the chain length of the polymer is large. How larger the polymer, how larger the change is to form entanglements. Entanglements are physical crosslinks what limits the mobility of the polymers and results in a rubber like structure (8). In Figure 5 a plateau is shown. This plateau represents the entangled structure. This plateau represents the area of the adhesives. A polymer in its entangled state is called visco-elastic. Visco-elastic is the state were polymers are fluid, but kept together with the use of entanglements. It is also called its rubbery state. This is important for the adhesive properties, because when the adhesive is too much a fluid it flows away and the adhesive properties are lost. The height of the plateau represents the entanglement density. How higher the plateau, how lower the T_g and higher the T_f will be. With a decrease of the T_g the 'tack 'of the adhesive will increase. This will say that how lower the plateau, how larger is the 'tack' (9).

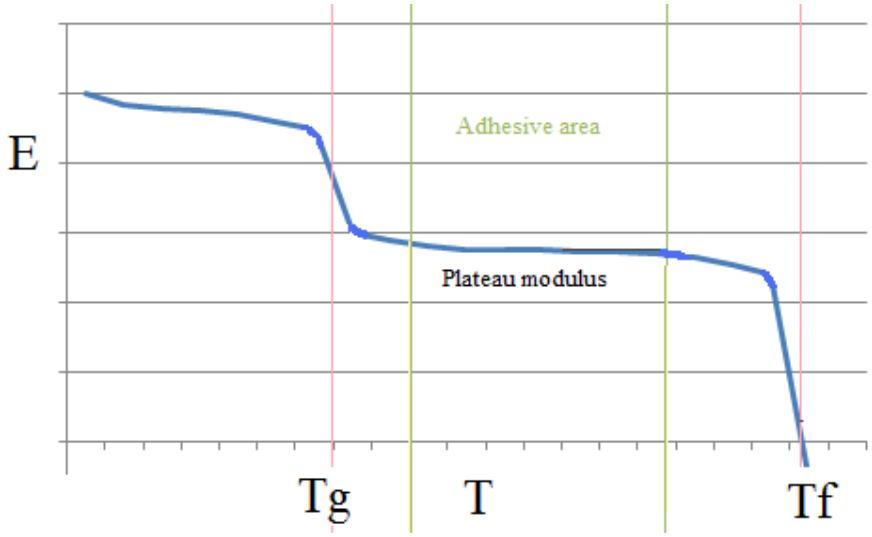

Figure 5: adhesive area. T_g represents the glass temperature. T_f represents the flow temperature.

The following rheological properties will determine the 'tack' (4;9):

- Soft or hard monomers. A hard monomer has a high T_g and has a lower 'tack'. A soft monomer has the opposite properties.
- Polar monomers increases the T_g and has as consequence a decrease of 'tack'.
- Crosslinking agents are increasing the T_g and lower the 'tack' of the adhesive.
- The layer thickness of the adhesive will increase the 'tack'

5. How to test on adhesiveness?

Many testing methods are available to quantitatively characterize the interfacial strength. Among all tests the peel and the blister tests are the most popular ones, in the industry and in the academy (12;13).

5.1. Peel test

The peel test is a test what normally is executed on a stiff substrate, like metal. On metal, because it's non deformable, it is possible to calculate the strength necessary to peel of the adhesive. For medical adhesives this is not possible, because of the deformability of human skin. Human skin is highly deformable up to a limit. The skin should first be kept tight before the peeling is executed (4). For example before ripping of a plaster the skin is kept tight. Before peeling off of the adhesive a force is already taken on the skin. Another difficulty is that the elasticity is nowhere the same on human skin. This makes it difficult to collect some data (4). The deformability of the skin might be harmful to the wound. It is only possible to say that an increase of peel force will induce an increase in pain (4). The peel angle is at influence for the peel force on the adhesive material. The peel angle is defined as the angle through which the backing is bent from its original adherent state (4). The peel force decreases with increasing peel angle up to 135°. After 135° to peel force is levels up. Figure 6 represents the peel test on human skin with an angle of 135°. Another factor that will influence is the amount of peeling experiments on human skin. Bothwell has notices that the peeling force of adhesive strips is increasing when repeated for 24 hour on the back of volunteers (9). This is caused by stripped corneocytes. After the 24 hours a plateau is reached for a couple of days, depending on the subject. This result means that skin can adapt toward the aggressive way of peeling. Skin can modify the complex structure of the stratum corneum (9).

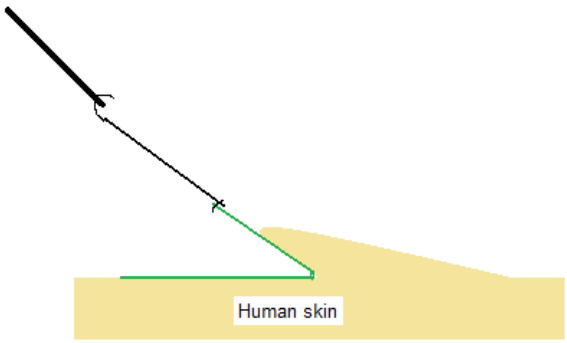

Figure 6: A peel test of an adhesive adhered to human skin. This figure shows the elasticity of human skin. This peel test is executed at an angle of 135° (4).

In the peel test the measured interfacial strength is termed the adhesive fracture energy $G_{a,}$ which is defined as the energy required separating the object attached with an adhesive to the substrate. When carrying out the peel test, however, the peel test adherent requires a certain mechanical strength to avoid the failure of the adherent itself. Otherwise, the failure locus is not at the interface, but in the film or object itself, which makes the measurement of the interfacial strength unfeasible (13). It is also possible to calculate the interfacial strength

theoretically. The advantage for this method is that you only need a few variables and it will not cost a lot of time. The disadvantage is that environmental variables can't include the test.

5.2. Blister test

In the blister test, a hole filled with fluid or air is overlaid with a thin film. Blister tests are often used for measuring the fracture energy between a coating film and the substrate(14). Since the time that the standard blister test (SBT) first was reported by Dannenberg, many improvements and refinements of the blister test have been made (15). With a continuous pressure the fluid or air is pressurized to form a blister. A circular blister is formed due to the pressure on the underside of the thin film. The adhesive keeps the thin film on his place till a critical point is reached(12;13;16).The values of adhesive fracture energy and residual stress of the thin film can be deduced by measuring: (13)

- the height of the blister
- radius of the circular blister
- pressure inside the blister

There are 4 different types of blister tests possible: (13)

- constraint blister test
- unconstrained blister test or standard blister test (SBT): (15;17)
  - Pressurized blister test
  - Shaft loaded blister test
- Island blister test
- Peninsula blister test

The constrained and the unconstrained blister tests are the most used blister test. These two tests are explained further.

The constrained blister test is divided in two different tests. The pressurized blister test and the shaft loaded blister test. The pressurized blister test is a test where the blister is formed by a hydrostatic pressure. The shaft loaded blister test is a test where the blister is formed by subjecting a central load on the thin film. The most conventional one is the pressurized blister test. In this blister test a hydrostatic pressure is produced under the thin film through a tight hole and forces the film to form a blister. The shaft loaded blister test is a test to form a blister by using a force by a small shaft on the thin film. This forces the thin film to form a blister (13).

The constrained blister test is similar to the unconstrained blister test, but with the addition of a plate positional parallel to the substrate restricting the vertical deflection of the film. Figure 7 presents the unconstrained and constrained blister test.

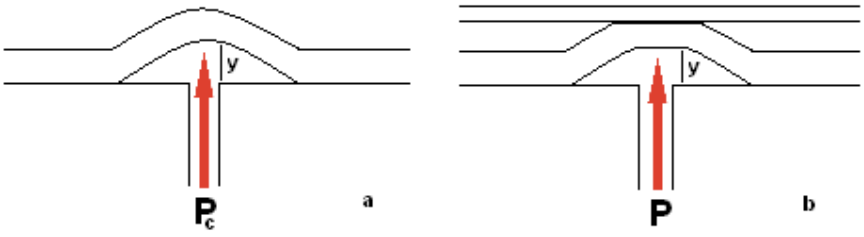

Figure 7: Types of blister tests: Unconstrained blister test (a) and constrained blister test (b) (the blister height is constrained to prevent rupture of the liner

Compared with the unconstrained blister test, where the maximum stress occurs in the center of the blister, the constrained blister test reduces this stresses minimizing the risk of film rupture.

6. Future directions?

For future directions of PSAs in medicine, there are different possibilities. Current PSAs are far from perfect. The main reason is the difficulty of adherence to human skin. Human skin surface free energy, polarity and rheological properties, the three factors to influence the adhesive capabilities to human skin, are different per person, per place on person and time. To solve the problems and overcome the difficulties a lot of progress can and should be made.

An important problem is repeated removal of adhesives, for instants at ostomy bags. A simple solution could be removal of the PSA with the use of water. Water is available in high amounts and the costs are low. Removal due decrease of peel force when washed off with water is a possibility. The adhesives what are studied at the moment is based on salt of a uncrosslinked copolymer that contains enough carboxylic acid that it is water soluble in the salt form (3). When water is come in contact with the PSA it will solve in the water and the peel force decreases. The only problem is how to overcome the water excretion of human skin?

PSAs are used for example on a plaster, bandages and drapes and comes in contact with blood. It could be possible to help the immune system of the human body due impregnating the adhesive with a broad spectrum antibiotic (18). Another applications for antibiotics is to use them in drug delivery systems (18). At the moment drug delivery is only capable for low molecular weight molecules (18). Antibiotics are larger and are more difficult to diffuse through the patch and skin. With the use of antibiotics in drug delivery patches it is possible to induce a constant diffusion instead of injecting in one time a high amount what can affect the human body. Of course the possibilities should be studied in further results.

Also bio-engineered tissue with stem cells could be surrounded by an adhesive and implanted into the body or used as patch for a skin template. When the adhesive is degraded the stem cells will form a new tissue (18). This is possible when a porous polymer is used, like for instants polyurethane.

Another new type of PSAs or tissue adhesives are the hydro gels (18). Hydro gels exist for 99% of water. They can carry this amount of water, because they can swell. This could be important for drapes or plasters. In tissue adhesives the foreign body response will reduce, because of the low quantity of polymer used. One example is used to show the endless possibilities in polymer chemistry for PSAs and tissue adhesives in the future. Figure 8 represents an hydro gel what could be used in the future as a tissue adhesive. This figure represents a tri block polymer what has acrylic end groups for the mechanical and adhesive properties, water soluble polyethylene oxide chains, which can be excreted by the kidneys after degrading and not water soluble polylactic acid chains, which are harmful for the human body (18).

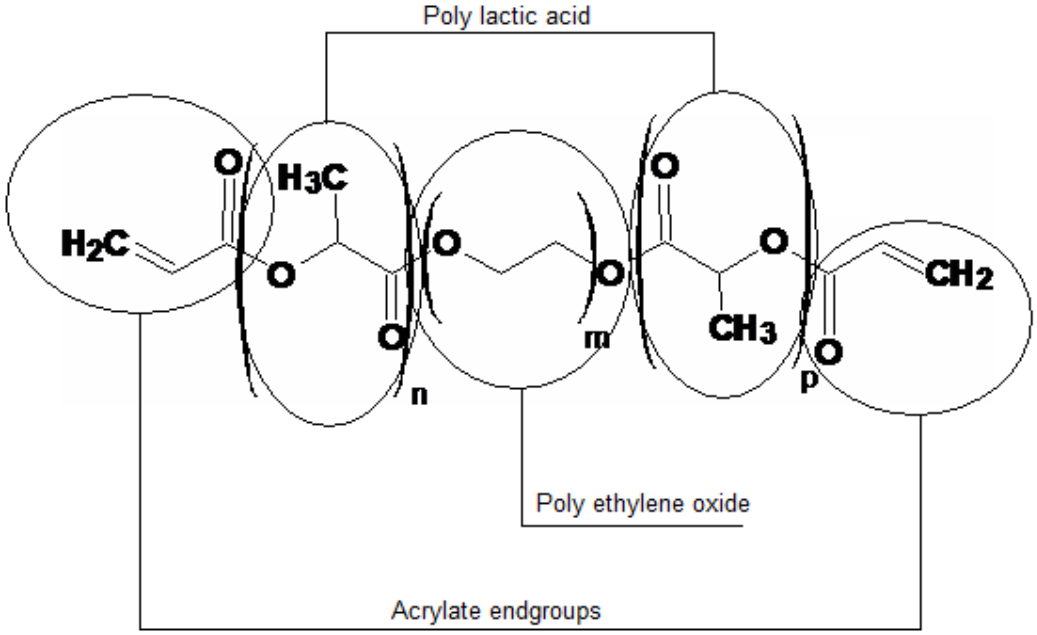

Figure 8: a tri block polymer of polyethylene, poly lactic acid and acrylate end groups. The poly lactic acid polymers are not water soluble, but are degradable and harmful for the human body. Polyethylene oxide (PEG) is water-soluble and can be removed by the kidneys . The cyano end groups give the polymer its mechanical properties.

7. Conclusion

7.1. What types of adhesives are available?

The general definition to define an adhesive is: *'A material capable of bonding and holding adherents together by means of surface attachment* (1)*.'* Two major classes can be distinguished (2):

- Permanent or tissue adhesives(glue)
- Removable adhesives (pressure sensitive adhesives (PSAs))

Removable adhesives or PSAs are developed to adhere on the human skin. Tissue adhesives are developed to be implanted in the human body. For example to replace staples. The surface attachment is totally different between the two classes of adhesives. PSAs make use of:

- Surface free energy.
- Polarity.
- Rheological properties.

The tissue adhesives make use of the mechanism named 'interlocking'.

7.2. What applications are there for pressure-sensitive adhesives?

PSAs on the market are used mostly for wound protection (3). Different properties for PSAs are:

- Drug delivery
    - Transdermal drug delivery systems like for instants nicotine plasters.
- Moisture vapor permeable (MVP)
    - All applications which come in contact with human skin, like:
        - Adhesive bandage or plasters
        - Adhesive drapes
- Trauma less removal PSAs
    - Important for all PSAs attached to human skin, but must important by repeated use of PSAs like for instants ostomy bag mounts.
- Water-resistant PSAs
    - Important for surgical/medical dressings or plasters which come in contact with large amounts of blood, sweat or water.
- PSAs for electro-medical applications
    - This is important for PSAs that carry electrodes for electro medical procedures, which are adhered to human skin. This application can be divided in two classes:
        - Adhesives that keeps the electrode only at his place. A non adhesive gel is used for conductivity.
        - Adhesives that keeps the electrode at his place and adhesives which are used as a conductive adhesive.

7.3. Which properties are important to form an adhesive connection for pressure-sensitive adhesives?

For the adhesiveness of PSAs three main properties are important to form an adhesive connection. These properties are:

- Surface free energy.
    - The amount of energy on the surface is called the surface free energy. (11) The energy of the surface layers is the result of the attraction of the bulk material for the surface layer and this attraction tends to reduce the number of molecules in the surface region resulting in an increase in intermolecular distance. Due to this work different surfaces can adhere (11).

- Polarity
    - Polarity can be subdivided in to two classes, polar and non polar. A material can be only non polar or both (bipolar). Polar components will only adhere to other polar components. This is the same for non polar. Human skin is bipolar. The polarity is caused due to the proteins available on the skin. Most adhesives are made of silicones or acrylates. These are non polar. This has as consequence that only the non polar sides can adhere. This has a influence on the adherence capacity.

- Rheological properties
    - PSAs are adhesives that are fluids, but due to entanglements their rubber-like. Entanglements will give their mechanical properties. When a PSA is put on a substrate or surface and a pressure is pushed onto it the adhesive will flow over the substrate and will induce a good wetting. The surface energy will rise and the adhesiveness of the PSA is increased.

7.4. How to test on adhesiveness?

Two tests are available for testing the adhesion of PSAs, which are used in industry and medicine. These testing methods are the:

- Peel test
- Blister test

The peel test is a test which can be executed on human skin (in vivo) as on a model (in vitro). Under an angle a sample is peeled from a substrate of surface and the peel force is measured.

The blister test is a test which only can be executed on a model (in vitro). A film of PSA is adhered to a surface, which contains a hole. Through this hole a pressure is induced on the film. This pressure is mostly induced by an airflow. The amount of pressure that is induced to let loose the film is called the fracture energy.

7.5. What are the future directions for pressure-sensitive adhesives?

For future directions of PSAs in medicine, there are different possibilities. Current PSAs are far from perfect. The main reason is the difficulty of adherence to human skin. Human skin surface free energy, polarity and rheological properties, the three factors to influence the adhesive capabilities to human skin, are different per person or per place and time. To solve the problems and overcome the difficulties a lot of progress can and should be made. For example:

- Problem in repeated removal of adhesives, with as result stripped corneocytes. This can be solved by using a water solvable PSA. The adhesive will lose its adhesiveness and can be removed easily.
- Impregnating the adhesive with a broad spectrum antibiotic or use drug delivery systems as specific antibiotics delivery through the skin.
- Bio-engineered tissue with stem cells.
- Another new type of medical adhesives, for instants the hydrogelen.

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