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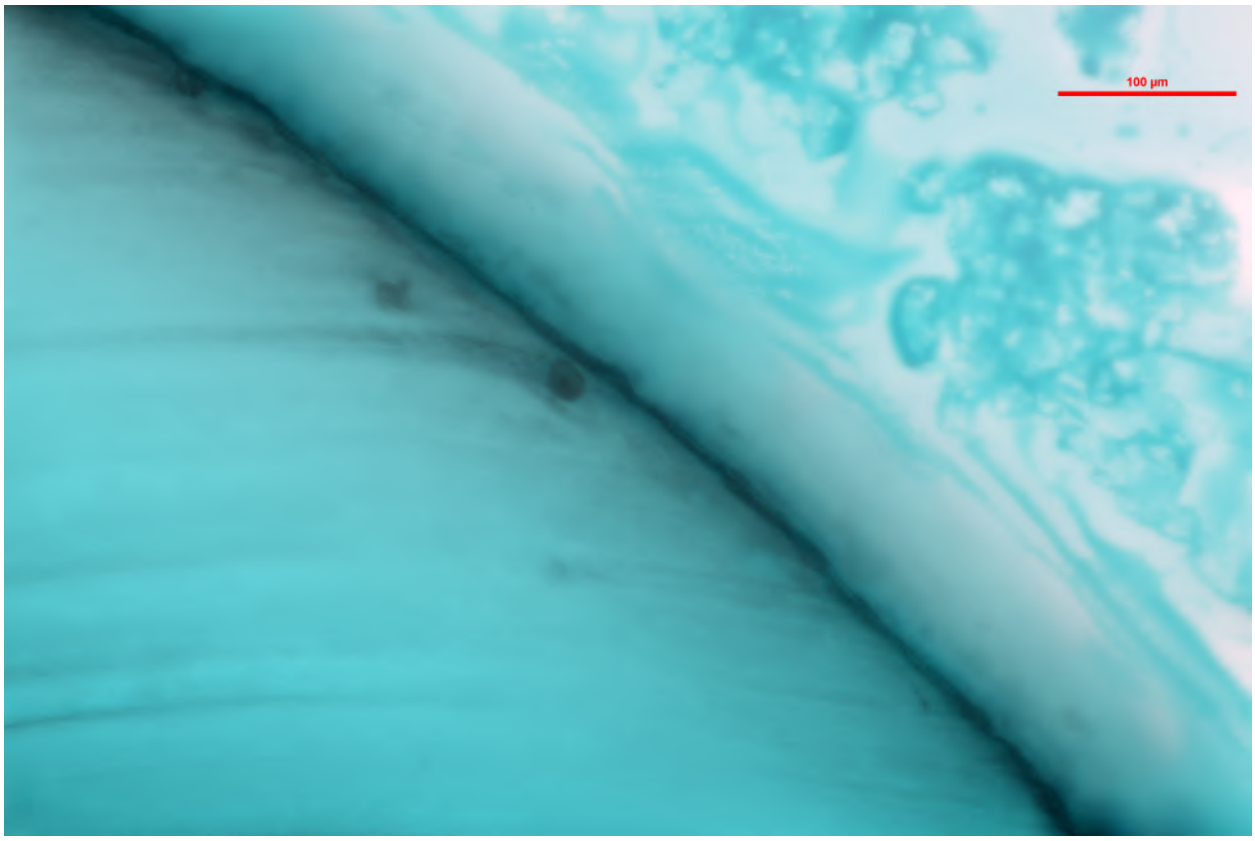

Analysis of Cellulose Ether Hydrogels for Medical Device Application

Master's thesis in Materials Chemistry

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Cover: Optical microscope picture, 10x enlargement, of the cross-section of a wetted carboxymethyl cellulose hydrogel, crosslinked with citric acid, coated polyolefin-based elastomer catheter. Coloured to provide contrast.

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Abstract

Intermittent catheterisation is done with a single-use catheter, by persons that, for some medical reason, cannot urinate voluntarily. At Wellspect HealthCare intermittent catheters are produced, under the name of LoFric®. Even though the company already has put a lot of effort in reducing its carbon footprint there is a great interest in making the catheters partly or wholly biobased. The catheter is coated with a hydrogel, polyvinylpyrrolidone (PVP), a fossil-based, hydrophilic and slippery coating attached to a fossil-based polyolefin-based elastomer (POBE) catheter tube. There are a lot of biobased material replacement options. Nevertheless, there are specific and high demands on a medical product that must be met. In turn, this puts specific and high demands on a possible biobased replacement.

The aim of this study was to investigate biobased polymers as candidates for the hydrogel coating and for the catheter tube, and to evaluate their properties and compare them to the coating properties of PVP and POBE. It was discovered that cellulose ethers could easily form hydrogels with citric acid and successfully coat the POBE catheter. Cellulose ethers crosslinked with citric acid have previously been used as hydrogels for medical applications, but, to the extent of our knowledge, not as coatings for intermittent catheters. Thermoplastic starch (TPS) showed potential as a future POBE replacement, but is in need of further investigation. Neither cellulose-based hydrogels or TPS catheter reached the standard of the LoFric® materials but showed great promise and potential for improvement.

These biobased materials, analysed in this study, showed potential to, in future, possibly replace the fossil-based parts of the current LoFric® catheter. This might improve the sustainability of the product further. However, a conversion to a biobased material does not guarantee improvement in sustainability. A life cycle assessment should eventually be carried out.

Keywords: cellulose ether, hydrogel, medical device, materials chemistry.

Acknowledgements

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Secondly, we would like to give a special thanks to Linn Persson, Philip Bjellheilm, Rebecca Suljo and Fariba Jam for the help you have been given us in the different techniques used throughout this spring. Further we would like to extend a thanks to all the colleagues at Wellspect HealthCare, and especially everyone at R&D and the C3 lab, for your contributions throughout this study. Whether it has been by learning a new technique or good company throughout lunch and coffee breaks, we are grateful for getting to know you. Thank you also to Frida Wallström at Dentsply Sirona, for helping us with the SEM analysis.

Thirdly, we would like to thank our examiner Anette Larsson, for great support during this thesis work, and for introducing the FibRe network to us. FibRe, has provided a great source of knowledge in lignocellulosic materials. Through this network we came in contact with Leif Karlson at Nouryon, who shared some of his knowledge about cellulose ethers.

Lastly, we would like to thank our family and friends for all the encouragement, support and laughter you have given us during our five years at Chalmers.

Sofia Hellström and Linnea Sjölander, Gothenburg, June 2022

List of Abbreviations

Below is the list of abbreviations that have been used throughout this thesis listed in alphabetical order:

CIC	Clean intermittent catherisation
CMC	Carboxymethyl cellulose
COF	Coefficient of friction
DP	Degree of polymerisation
DS	Degree of substitution
HA	Hyaluronic acid
HEC	Hydroxylethyl cellulose
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methyl cellulose
LCA	Life cycle analysis
MS	Molar substitution
POBE	Polyolefin-based elastomer
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
SEBS	Styrene-ethylene-butylene-styrene
SEC	Size exclusion chromatography
SEM	Scanning electron microscope
TPS	Thermoplastic starch

Contents

1

Introduction

When the bladder functions normally, emptying it is one of the most fundamental and taken for granted actions of a person's day. The bladder contracts and internal and external sphincter muscles relax as they should. If not properly emptied remaining urine could cause urinary tract infection, urinary incontinence or permanent damage to the bladder or the kidneys that could in the worst case lead to death. If the bladder and subsequently muscles do not function as they should, this action is all but taken for granted [1]. One of the most common and used methods for patients to deal with bladder management and urinary retention themselves is intermittent catheterisation. The ability for the user to, by their own accord, manage their needs has shown to improve their self-care and independence and overall quality of life [1]. There are different reasons to why one would need intermittent catheterisation, mainly connected to an illness or injury. These could include firstly, neuronic injuries such as spinal cord injury, multiple sclerosis, Parkinson's disease or stroke. Secondly, non-neuronic injuries connected to outlet obstruction due to e.g. prostate enlargement or prostate cancer complications [2].

One of the most prominent providers of catheters used for clean intermittent catherisation (CIC) is the medical device company Wellspect HealthCare with their LoFric® products. Their current product is constituted from a tube made from polyolefin-based elastomer (POBE) and a polymer coating, made from the hydrophilic polyvinylpyrrolidone (PVP) creating a slippery hydrogel. At Wellspect HealthCare the LoFric® products are manufactured by dipping uncoated catheters into a PVP solution, followed by drying and curing steps. The development for a greener and safer production is a continuous process, and in the last couple of years the coating process was completely altered. Wellspect HealthCare is striving towards more sustainable products and processes with a low environmental footprint. To move forward with the aspect to not rely too much on fossil oil, one or more key elements of the LoFric® product could be replaced, the PVP coating and/or the POBE tube.

1.1 Aim

The aim of this master's thesis is to conduct a study to evaluate biobased polymers as alternatives to the current PVP coating. Furthermore, the possible replacement

of the current POBE tube, with biobased alternatives will also be evaluated. In the future this could hopefully make the LoFric® intermittent catheters more biobased.

1.2 Limitations

This study attempted to make improvements to the LoFric® catheter to make it more biobased. However, there was no Life Cycle Analysis (LCA) done in this study, simply some discussion regarding manufacturing of biobased polymers in comparison to the current coating process. Nevertheless, simply making a product more biobased is not a guarantee for improving its sustainability. A material may be biobased but require complicated and resource consuming process steps, resulting in a higher climate impact than a fossil-based material. It may also require hazardous chemicals in its synthesis, or need environmentally toxic solvents in order to be processed. Any allergic reaction from the user would also make a material unsuitable. Therefore, any materials chosen should be already approved for use in the medical field and preferably be available in medical grade. The application also requires certain regulatory requirements to be fulfilled, to make it appropriate for its users and not cause damage or injuries.

To simplify the comparison of the different coatings only one type of uncoated catheter, in terms of length and width, was used in the study. It was manually coated in a lab scale to mimic the current process as much as possible. There might be more optimised coating processes for some of the biobased polymers, but they were not evaluated in this study. The analysis focused on the surface properties of the coating soon after the coating process. The properties after sterilisation or long-term stability of the coating, which would be important for storage capability, were not investigated in this study. The suitability of the biobased coating for a large-scale production was not assessed.

1.3 Specification of Issue under Investigation

This study tried to answer the question of whether there is any possible biobased candidate, that could replace either the PVP coating or the POBE tube in the future. This was done initially by screening different alternatives, to finally put the biobased alternatives through some of the same surface analysis as the original. This thesis work used the knowledge, and connections within the network of the competence centre FibRe. FibRe provides connections and collaborations between academia (Chalmers University of Technology, KTH Royal Institute of Technology), industry (i.a. Wellspect HealthCare, AstraZeneca and Nouryon) and Public Organisations partners. The conceptual vision for FibRe is to help forward a sustainable society, in which fossil-based thermoplastics are replaced with lignocellulose-based ones [3].

2

Literature Review

This chapter contains the theoretical background on the urinary system, intermittent catheterisation and the requirements for this product. It will then briefly discuss Wellspect HealthCare's current process and LoFric® catheters together with the current tube and polymer coating. Then possible biobased alternatives that were chosen in this study will be presented, followed by a brief theoretical background on some of the productional and analytical methods. The chapter will finish with a review of the current applications of these biobased materials, mainly in the medical field.

2.1 The Urinary System

The urinary tract, or system, is divided into two parts; the upper tract which contains the kidneys and ureters, and the lower tract which consists of the bladder and the urethra. Figure 2.1 shows the urinary systems created by NIH Medical Arts [4].

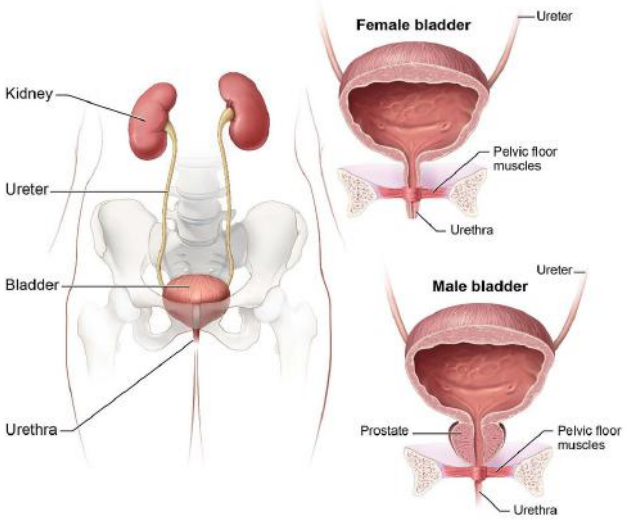


Figure 2.1: The female and male urinary system, showing the upper and lower parts: kidneys, ureters, bladder and urethra, picture created by NIH Medical Arts.

The overall purpose of the urinary system is to process blood and clear it of waste. Residual products is left behind both in the bowel, but are also transported from the cells in the body via the blood. The kidney's purpose is to discard substances such as urea, a residual from foods made out of protein. They also make sure that the concentration of various electrolytes, such as sodium and potassium is correct. Urea is collected through the blood and delivered to the kidneys, to be excreted with water and other residuals in urine. The tubes that connect the kidneys to the bladder are called ureters, which continuously provide the bladder with urine [5]. When functioning properly and hydrated, 0.5 ml of urine is produced per kg body weight and hour [6]. The body collects and stores the urine in the bladder, which can be voided at an appropriate time and place via the urethra. The urethra is about 4 cm in length for females, and 18-20 cm for males [7].

There are two sets of muscles involved when voiding: the bladder and sphincter muscles. The bladder muscles will tighten to excrete the urine out of the bladder, and the sphincter muscles, in Figure 2.1 referred to as the pelvic floor muscles, between the bladder and urethra, will relax in order to let the urine pass through [5]. When one or both of these muscles don't work as they should due to brain, spinal cord or nerve problem it is known as Neurogenic Bladder. It could be because of multiple sclerosis, Parkinson's disease, stroke, spinal cord injury or prostate cancer [8]. This could result in a bladder which either is overactive or underactive. Incontinence is the result of an overactive bladder, which starts voiding involuntary and at times when the bladder isn't full. The underactive bladder won't void even though the bladder is full, because the sphincter muscles around the connecting parts of the urethra and bladder won't relax. One way of treating an underactive bladder is catheterisation, in which the catheter tube will pass through the sphincter muscles and make voiding possible.

2.2 Intermittent Catheterisation

Intermittent catherisation is done with a single-use product, shown in a rough sketch in Figure 2.2 below. The product consists of three parts, a plastic tube and a funnel for urine outlet and attachment to e.g. a urinary collection bag. The funnel can also provide a handle for insertion and a safety stop to not let the tube glide into the body. Lastly, a hydrophilic coating, which when wetted will swell and provide very low friction when inserting the catheter. The catheter is either stored in a sterile water solution or comes with a sachet filled with sterile water solution. To wet the catheter the sachet is broken before the packaging is opened.

Figure 2.2: Simplified picture of a catheter for intermittent use, the funnel in green, the plastic tube in light grey and the coating in dark grey.

By using clean intermittent catheterisation (CIC) the person inserts the catheter through the urethra, empties the bladder and then removes the catheter. This is a significantly different method compared to the indwelling catheters, where it will have to be placed and attached into the bladder and remain there for up to one month. CIC is to be done approximately five times a day, in order to empty the bladder in a naturally intermittent way [1] and to not cause stress or trauma on the urinary tract, this demands a smooth surface and low friction properties. This is why a catheter could be coated with a crosslinked hydrophilic polymer network, which when wetted with water forms a hydrogel.

The hydrogel obtained should reduce friction and thereby also reduce discomfort for the user as well as prevent possible complications [9]. There are other specific demands on medical devices, for example sterility. But in the case of CIC products a rather specific demand must be met. The concentration of osmotically active particles, i.e. ions or other small molecules, on the surface of the catheter, must be in balance with the body's osmolality. That means that when the catheter is inserted into the body, salts and/or solutes have to be incorporated into the hydrogel in order to keep the osmolality higher than the body's. Otherwise, if the osmolality isn't correct, water could transfer from the catheter to the body and dry out, which in turn could cause the catheter to stick to the urethra. The particles could either be present in the hydrogel, or in the water solution used for wetting.

2.3 Catheter Coating Process

The current production process for LoFric® catheters at Wellspect HealthCare is the starting point for alternative materials. Figure 2.3 shows the process from an uncoated catheter to a coated one ready for packaging and sterilisation. The catheter is first dipped in the coating solution to then be dried and cured, which induces the crosslinking in the hydrogel. A second layer of coating solution is then added atop of the first, by the same technique, and then it is dried and cured a second time. As mentioned in the introduction the current process uses POBE as the uncoated catheter material and the coating is a solution of PVP.

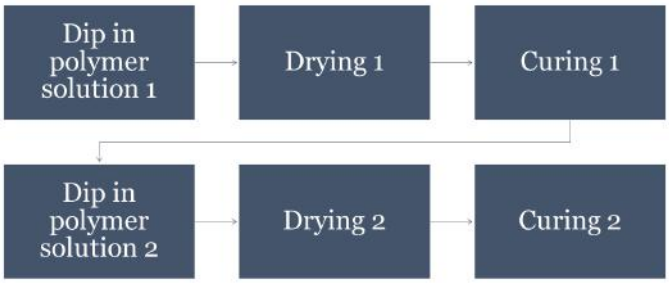


Figure 2.3: Simplified flow chart showing the current coating process at Wellspect HealthCare.

2.4 Uncoated Catheter

The most important mechanical property of the uncoated catheter is the flexibility of the tube. It should be flexible enough to be inserted into the urethra without causing damage, but not so flexible that it is difficult to maneuver and insert. The polymer used should be appropriate for extrusion processing, in order to shape it into hollow tubes.

2.4.1 Polyolefin-based Elastomer

The uncoated catheters used in the current production at Wellspect HealthCare are made of a styrene-ethylene-butylene-styrene (SEBS)-based thermoplastic elastomer, which is internally known as POBE (polyolefin-based elastomer). This material can be extruded into a thin-walled tube. The POBE tubes are colourless and slightly opaque. The flexibility of the tube can be tuned by the material composition. The POBE uncoated catheters are not produced on site but are instead purchased.

2.5 Hydrogel Coating

A hydrogel is usually defined as a crosslinked polymer network, that due to its hydrophilicity can swell and take up water into its structure. The crosslinks hinder the polymer from dissolving in the water. Hydrogels can be found both in nature and in synthesised materials. The synthetic gels tend to have a higher capacity for water absorption and a higher gel strength [10].

There are many ways of crosslinking a polymer. The gels are often classified depending on if the crosslinks are physical or chemical. Physical crosslinks are temporary and are caused by chain entanglements or physical interactions, such as hydrogen bonds or ionic interactions. Chemical crosslinks are permanent and caused by covalent bonds. In this case the polymer chains can be directly linked to each other via functional groups, or a crosslinking agent. This is usually a molecule or a polymer of low molecular weight, used to act as a connecting bridge. The hydrogel may be constructed from monomers or from already formed polymer chains [10].

By controlling the crosslinking conditions, the properties of hydrogels can be tuned. The crosslinking density, how many network points are present, is a key property as it dictates the degree of swelling that is possible for the gel. Too low crosslinking density and the polymer network will not be sufficiently formed. Too high and the network will be too rigid to take up a lot of water, which hinders the diffusion of water into the network, and the swelling will be limited [11].

2.5.1 Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) is a polymer made from the monomer N-vinylpyrrolidone, both of which are illustrated in Figure 2.4. PVP is water soluble and hydrophilic, and it can absorb up to 40 % of its own weight in water. It readily forms

films, which makes it ideal for coating. The polymerisation is usually a process involving free-radical polymerisation. PVP is used in various biomedical applications [12]. During both the curing steps, in the current process at Wellspect HealthCare, chemical and physical crosslinks are formed between the different PVP molecules, and between PVP and the POBE catheter. When wetted this coating takes up water and swells to a significant degree.

(a) N-vinylpyrrolidone. **(b)** Polyvinylpyrrolidone.

Figure 2.4: Molecular structure of the monomer N-vinylpyrrolidone and its polymer polyvinylpyrrolidone.

2.6 Biobased Alternatives

To find biobased alternatives to purely petrochemically derived polymers, a common place to start is the biobased polymers, also called biopolymers. Biopolymers are macromolecules synthesised by plants, animals or microbes. They usually have structural purposes, e.g. cellulose, or nutritional purposes, e.g. starch [13]. The sustainability of these biopolymers varies depending on the source and the extraction process. For example, a biopolymer from a plant or microbe is usually regarded as more sustainable than one from an animal. Some biopolymers require an energy intensive process for industrial extraction and purification, due to the complex hierarchies of the biobased material they build up. In this study the focus was put on biopolymers from plants and microbes, which quickly lead to the subgroup of polysaccharides.

A polysaccharide is a biopolymer based on carbohydrates, usually containing carbon, oxygen and hydrogen. A carbohydrate is a carbon chain with at least one aldehyde-, or keto group and several hydroxyl groups. The carbon chain is commonly between three and six carbons. According to standard, each of the carbons are given a number, starting with the carbon of the aldehyde-, or keto group as C1, to then move along the chain. In this manner the carbons of the chain are referred to as C1, C2, C3 and so on. The locations of e.g. hydroxyl, or other function groups, attached to these carbons are identified in the same way. Most of the carbons on the chain are chiral, giving rise to a vast variation of carbohydrates [14].

Carbohydrates derived from nature commonly take the form of monosaccharides. These are formed by a ring closing reaction within the carbohydrate chain, between a nucleophilic hydroxyl group and an electrophilic carbonyl group. The formation of the ring creates a new chiral centre, giving rise to two possible isomers. These two

isomers are referred to as α and β. The difference between them is the orientation of the hydroxyl group on C1 [14]. In Figure 2.5 the difference of α and β in glucose, a common monosaccharide, is displayed. In this image the numbering of the carbons is also visualised.

Monosaccharides become polysaccharides via a glycosidic bond. The hydroxyl groups on the monosaccharides can easily form covalent bonds with each other, via condensation reactions. In this covalent bond the hydroxyl group attached to the chiral carbon, either α or β isomer (C1), is always involved. Because of this it will in the case of e.g. glucose result in a polysaccharide that forms a helix structure (for the α isomer) or a straight chain (for the β isomer). The first creates the structure of starch, while the latter creates the structure of cellulose. The notation used for this bond is "1,4-glycodisic bond", indicating that the linkage is formed between carbons one (C1) and four (C4) in the different glucose rings [14].

The configuration of the hydroxyl group (α or β), along with the molecular weight, monosaccharide composition, branching and charging properties, all determine the properties of the polysaccharide, such as its solubility and hydrophobicity [15].

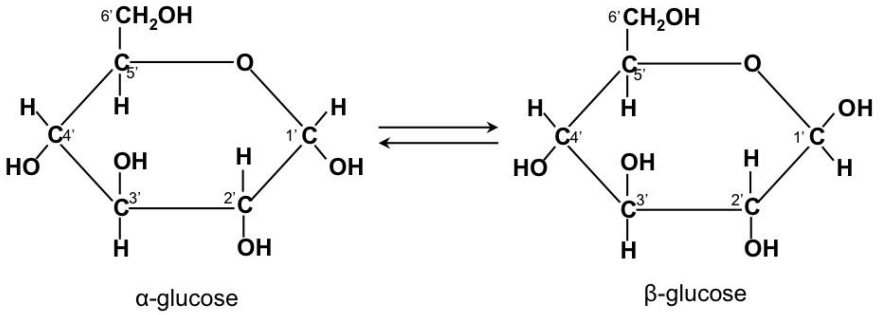


Figure 2.5: Molecular structures of the two α and β isomers of glucose.

2.6.1 Alginate

Alginate is a biopolymer derived from brown seaweed. It is a polysaccharide made up of two main monosaccharides, forming a block copolymer. The two building blocks are α-L-guluronate (G) and β-D-mannuronate (M), linked together with 1,4-glycosidic bonds, as illustrated in Figure 2.6. The composition of the monosaccharides varies between different species of seaweed. The polysaccharide forms a hydrogel under mild conditions in the presence of divalent cations, such as Ca^{2+}. It is believed that the G-blocks in the molecules coordinate with the ions, forming so called ionic crosslinks. The way the alginate chains arrange themselves around the ions is termed the "egg-box model of crosslinking", since it encapsulates the ions [16].

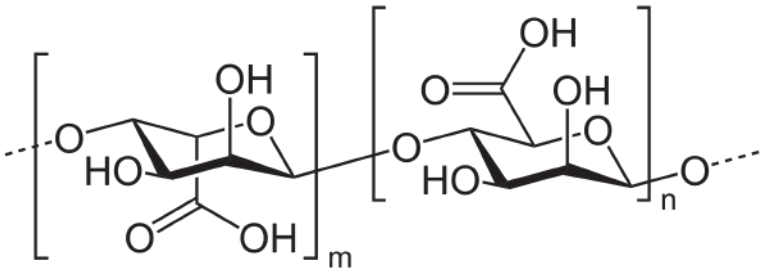


Figure 2.6: Molecular structure of alginate, with monomers of G (left) and M (right).

2.6.2 Cellulose

Cellulose is one of the most abundant biopolymers on earth. It is mainly found in the cell walls of plants, where it acts as a structural molecule. It is a linear homopolymer polysaccharide where the repeating building block is β-D-glucose linked together with 1,4 glycosidic bonds, as illustrated in Figure 2.7. The molecules straight chains allows close packing, which is why cellulose is arranged in fibrils and fibres in nature. The most common applications for cellulose are in pulp and paper [13].

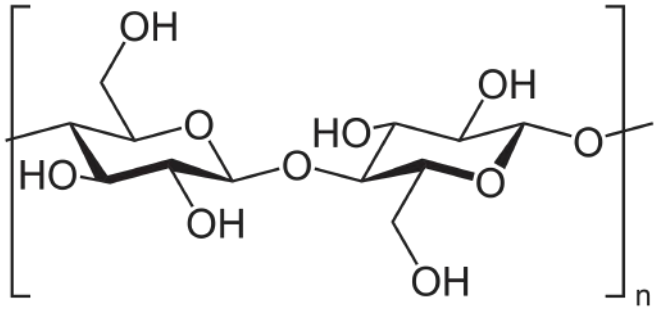


Figure 2.7: Molecular structure of cellulose.

Cellulose is generally water insoluble but hygroscopic, meaning it will absorb moisture into its structure and hold it there. This is due to the high concentration of hydroxyl groups, which facilitate hydrogen bonding between the polymer chains. On each glucose ring there are three hydroxyl groups, attached to C2, C3 and C6. These hydroxyl groups are optimal for modification with other functional groups resulting in various cellulose derivatives. The properties of these depend on their degree of polymerisation (DP), the number of monomeric units in the polymer, as well as their degree of substitution (DS), which is the number of substituted groups on each monomer. Out of these derivatives one of the main groups are cellulose ethers. These are non-toxic and usually water-soluble, which makes them excellent for uses such as thickeners. The most common use for these cellulose ethers are in the pharmaceutical, food, paint and adhesives industries [17]. This study will focus on four different cellulose ethers as possible hydrophilic coating materials.

2.6.2.1 Carboxymethyl Cellulose

The first cellulose ether is carboxymethyl cellulose (CMC), or sodium carboxymethyl cellulose (NaCMC) as it is often referred to its salt. It is polyanionic, due to the presence of carboxyl groups in the carboxymethyl side chains added in the derivatisation. An image of its structure is presented in Figure 2.8. It is the most important ionic cellulose ether commercially [18]. Since it is a polyelectrolyte it has a high affinity for water, starting at a DS of about 0.4. It is difficult to synthesise a CMC grade with DS higher than 1.3 - 1.5 in a one-step reaction. This is due to the decrease in entropy, caused by an increased need of counter ions in order to keep electroneutrality of the polyelectrolyte [19].

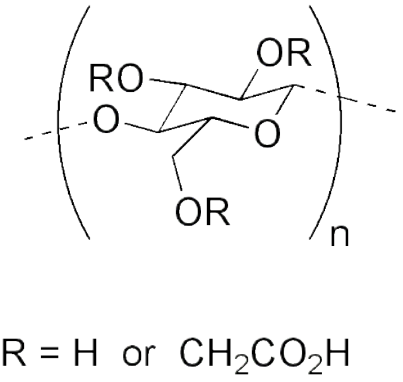


Figure 2.8: Molecular structure of carboxymethyl cellulose (CMC).

In short, a charged polymer in a solution will attain charged counter ions around its charged substituents, preventing the ions to move freely in the solution. This phenomenon is called counter ion binding. When the charge on the polymer increase, or e.g. in the case of CMC, the DS increases, the counter ion binding increases causing a loss in entropy for the system [19]. To prevent this, the polymer extend in the solution, the radius of gyration (R_G) increases, not because of the repulsion between its charged substituents, but rather due to the effect that the counter ions have on the entropy and charge distribution [19]. In other words, if a charged polymer expands, the counter ion binding will decrease, the counter ions are able to move about more freely, and thus a higher entropy will be reached. But there is a geometrical limit to how much a polymer can conform. The entropy gained from the expansion is countered by the loss of entropy for the polymer itself. This will prevent the polyelectrolyte from becoming a stiff rod. In fact, at a point of DS of charged substituents it won't increase its R_G anymore, and instead gain an entropy loss due to counter ion binding [19]. In Figure 2.9 this phenomenon is explained. The term degree of ionisation is used instead of DS, but in the case of CMC this is the same principle.

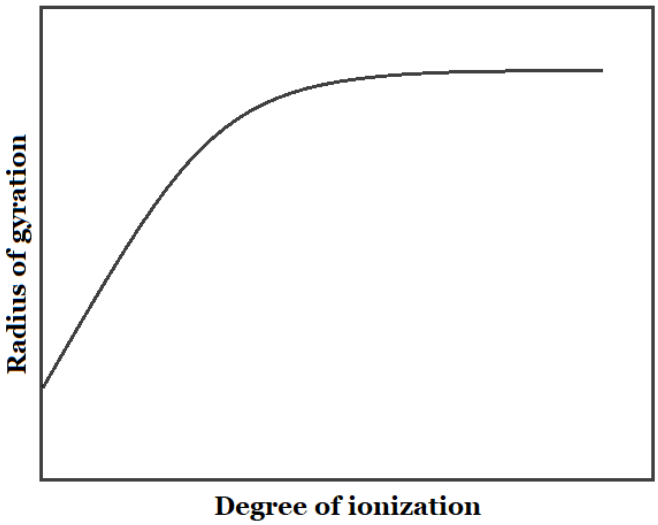
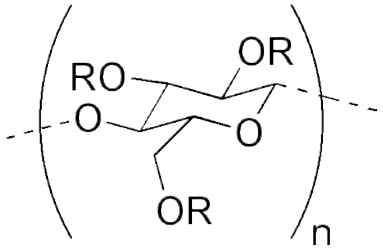


Figure 2.9: Radius of gyration compared to the degree of ionisation as described by Kronberg et al. [19], this is comparable to CMC and its DS.

The carboxymethylation reaction is carried out using chloroacetic acid ($CH_2ClCOOH$) or the corresponding sodium salt in the presence of a base [18]. CMC is used in pharmaceutical applications among others as a thickener, stabiliser, film-former and super disintegrant in tablet formulation. It can also be used in controlled drug release [20]. CMC is also used in food, cosmetics and paper industries [18].

2.6.2.2 Hydroxypropyl Cellulose

The second cellulose ether is hydroxypropyl cellulose (HPC), a type of cellulose hydroxyalkyl ether. The added hydroxypropyl functional group is somewhat hydrophobic and contains a hydroxyl group, making HPC a non-ionic cellulose ether [18, 20]. It is also amphiphilic, meaning it is soluble in both aqueous and polar organic solvents. Commercial HPC is soluble in water below 38 °C [20]. An image of the molecular structure of HPC is shown in Figure 2.10. The properties of HPC depend, as for most polymers, on the molecular weight and DS. Different grades of HPC can be identified both by DS and molar substitution (MS). MS is used because the hydroxyl group on the hydroxypropyl group can react further during synthesis, and another hydroxypropyl group may attach. Commercial HPC usually has a MS between 3 and 4 [20]. The process of making HPC from cellulose involves conversion of alkali-activated cellulose, with epoxides that react with ring opening [18].



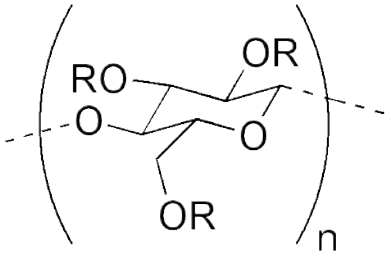
$$R = H \text{ or } CH_2CH(OH)CH_3$$

Figure 2.10: Molecular structure of hydroxypropyl cellulose (HPC).

HPC is typically used as a thickener, stabiliser or coating in for example pharmaceuticals, food and paints. It displays thermoreversible gelation [18] and is thermoplastic, allowing it to undergo melt processing. The thermoplasticity stems from the slightly hydrophobic hydroxypropyl groups. The groups make HPC somewhat surface active. It is also a good film former [20].

2.6.2.3 Hydroxypropyl Methyl Cellulose

The third cellulose ether is hydroxypropyl methyl cellulose (HPMC), which is very similar in structure to HPC. It belongs to the mixed alkyl hydroxyalkyl cellulose ethers [18]. It has the same hydroxypropyl groups as HPC, but there are also methyl groups present, the proportions of both will affect the properties of the polymer [18, 20]. The molecular structure is visualised in Figure 2.11. HPMC is non-ionic and amphiphilic due to the combination of the mostly hydrophilic hydroxypropyl groups and the hydrophobic methyl groups. This gives rise to some surface activity. It is soluble in cold water or in mixtures of water and a solvent like ethanol, as well as in some nonaqueous polar solvents. HPMC is formed from cellulose through a base-catalysed reaction with methyl chloride and propylene oxide. The propylene oxide is the same epoxide as used when making HPC, and the reaction can lead to secondary hydroxyl reactions in the same way, giving a MS that is higher than the DS. Methylation at the secondary hydroxyl is also possible. This gives rise to complex variations in the molecular structure of HPMC [20].



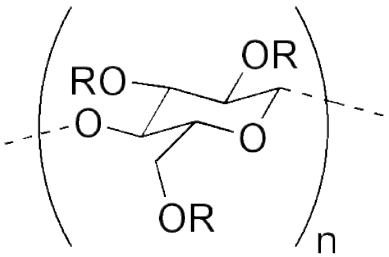
$$R = H \text{ or } CH_3 \text{ or } CH_2CH(OH)CH_3$$

Figure 2.11: Molecular structure of hydroxypropyl methyl cellulose (HPMC).

HPMC is an important food additive, and also has pharmaceutical applications. It is particularly suitable for controlled drug release applications, due to its dissolution properties. When placed in water, HPMC forms a protective gel layer, which slows down further water penetration. This gel layer slowly extends in towards the core, allowing the loaded drug to be gradually released through diffusion [18]. HPMC is also used in pharmaceutics as, for example, a film-coating agent, thickener and tablet binder [20].

2.6.2.4 Hydroxyethyl Cellulose

The fourth cellulose ether, used in this thesis, is hydroxyethyl cellulose (HEC), which is another type of cellulose hydroxyalkyl ether. The substituted functional group is, as evident from the name, a hydroxyethyl group, which contains a hydroxyl group. HEC is therefore a non-ionic cellulose ether. The molecular structure of HEC is visualised in Figure 2.12. Similarly to HPC and HPMC, the modification of cellulose into HEC is carried out by conversion of alkali-activated cellulose with epoxides, that react with ring opening [18].



$$R = H \text{ or } CH_2CH_2OH$$

Figure 2.12: Molecular structure of hydroxyethyl cellulose (HEC).

HEC is typically used as a thickener, stabiliser or coating in, for example, pharmaceuticals, food and paints, similarly to HPC. HEC does not display thermoreversible

gelation, so it can be employed even at elevated temperatures, in contrast to HPC which is thermoreversible in spite of their similar molecular structure [18].

2.6.3 Hyaluronic Acid

Hyaluronic acid (HA), also called hyaluronan, is a biopolymer that is mainly found in animal cartilage. It is found throughout the human body, which makes it highly biocompatible [21]. It was traditionally extracted from rooster combs, but now it is mainly produced through microbial fermentation. The applications of HA depend on its molecular weight, which can be as high as 6 million Da. Microbial fermentation produces a mixture of different molecular weights, which is a current research challenge in the field. HA has a high moisture retention ability which has lead to applications in cosmetics, medicine and food [22].

HA is a linear alternating copolymer, that is also a polysaccharide. It is made up of alternating monosaccharide units of β-D-glucuronic acid and β-N-acetylglucosamine linked together with alternately 1,3- and 1,4-glycosidic bonds [21, 22]. The molecule is a polyelectrolyte, which is the reason it can have such high moisture retention [21]. The structure of the molecule is illustrated in Figure 2.13.

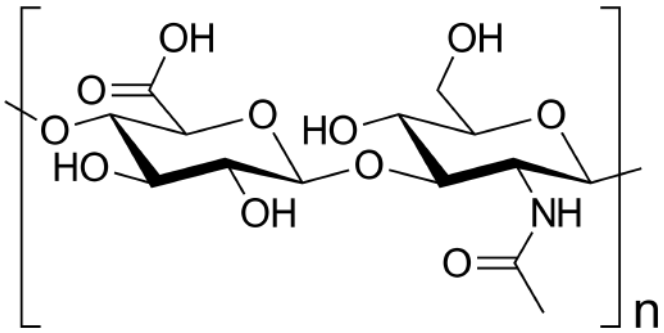
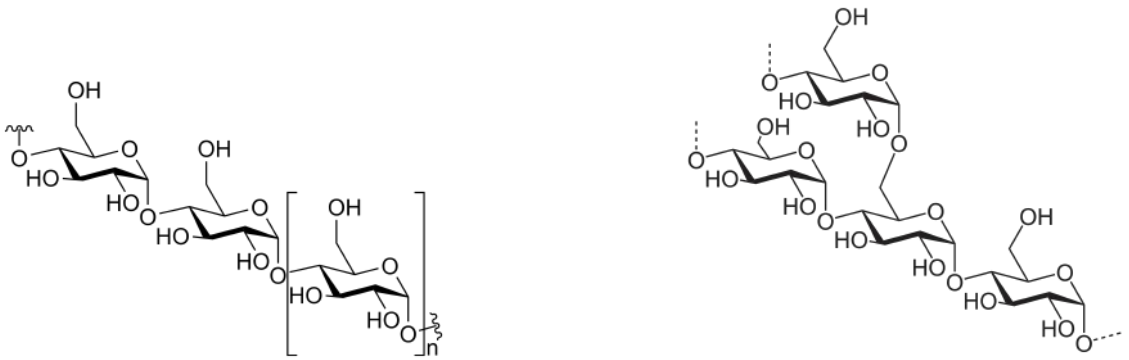


Figure 2.13: Molecular structure of hyaluronic acid.

2.6.4 Starch

Starch is a homopolymer polysaccharide made up of units of α-D-glucose, joined together with 1,4 glycosidic bonds in the main chain, and 1,6 glycosidic bonds to the branches. In nature it is used for energy storage in plants. It is also one of the most abundant and cheap polysaccharides, although it often comes from plants that can also be used for food. In industry, starch is mainly used as a thickening or binding agent in food and pharmaceuticals. Starch is similar in structure to cellulose, but forms a helical structure instead of straight chains. It has two native forms: amylose which is linear, see Figure 2.14a, and amylopectin which is branched, see Figure 2.14b [13, 23, 24].



(a) Amylose. **(b)** Amylopectin.

Figure 2.14: Molecular structures of the two components of starch: amylose and amylopectin.

The proportion of amylose to amylopectin varies depending on the source of starch, for example potato or corn. A starch granule has both amorphous and crystalline regions, which gives it characteristic dissolution properties. During dissolution, starch granules go through three steps: hydration, gelatinisation and retrogradation. First, water is absorbed into the polymeric network (hydration). Secondly, irreversible changes and destruction of the crystalline regions take place after heating (gelatinisation). Finally, a hydrogel network is created after cooling leading to partial recrystallisation (retrogradation) [25].

The properties, such as gelatinisation temperature, swelling and solubility, of starch dictate how it can be used. To tune these properties to fit intended applications, modifications can be made by targeting the three available hydroxyl groups, on each glucose unit of the starch polymers. The four basic types of modifications are: genetic, enzymatic, physical and chemical, with chemical being the most used. Through chemical modification the hydroxyl groups can undergo either oxidation, etherification or esterification [26].

Oxidised starches are generally produced by exposing a starch slurry to an oxidizing agent under controlled conditions. This leads to various changes to the molecular structure of the now oxidised hydroxyl groups, depending on the conditions of the oxidation. For example, aldehyde groups can be introduced to the polymer chain. Oxidised starches have been known to have better film forming and adhesive properties, as well as reduced viscosity and high clarity [26].

Introduction of cationic groups to starch is another major modification, with various applications within water treatment, food and cosmetics industries. The modification is usually carried out in an alkaline solution of starch and an epoxide with an amino or ammonium functional group. The hydroxyl groups are activated by the alkaline solution and attack the epoxy ring of the reactant, which attaches the cationic functional group to the polymer. This forms an ether linkage [27].

2.7 Analytical Techniques

This section will contain the necessary background information, regarding the different analytical methods used in this study.

2.7.1 Viscosity Measurement

One of the most frequently used applications of polymers in solution is as thickening agents, in other words a component to increase viscosity. Polymer coils can, when the concentration is high enough, entangle with each other and create a resistance to the shear force applied to it [19]. After a certain polymer concentration, the increase in viscosity is more rapid, this point is called the overlap concentration (C*), and will cause the solution to thicken. This phenomenon is shown in Figure 2.15 as described by Kronberg et al. [19]. η_{sp} stands for specific viscosity and is a relative measurement, where the absolute viscosity (the fluid internal resistance towards force put upon it), of a known fluid, e.g. water, is used as a ratio measurement for the absolute viscosity of the polymer solution [19].

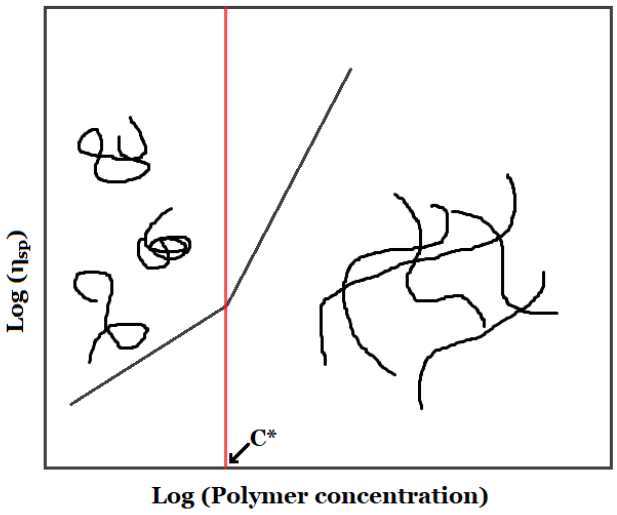


Figure 2.15: Graph showing the drastic increase in the specific viscosity of a polymer solution, η_{sp}, at the concentration C* of a polymer, as described by Kronberg et al. [19]. This is due to entanglements between the different polymer chains.

It is not only via concentration that viscosity of a solution could change. A higher molecular weight of the same polymer, cause a lower C* due to longer chains. Change in viscosity can also be achieved by increasing polymer solubility, via for example temperature change. The temperature above which a polymer is soluble in a specific solution, is called theta temperature. At this temperature the interaction between a solvent molecule and a polymer segment, is the same as between two polymer segments [19]. One of the most commonly used thickeners among the polymers are polyelectrolytes. Thanks to the contribution from their counter ions, they tend to

a larger extent than non-ionic polymer be more extended in the solution. They do this to gain in entropy, and are hence much more ready to form entanglements. However, if more salt is added the polymer coils will contract, since the counter-ions gain less entropy by competing with others in the solution, and achieve the opposite effect, a lowering in viscosity [19].

The fluid viscosity will be measured in this study to gain knowledge about the different coating solutions prepared. More precisely, how the molecular weight, polymer concentration and polymer type can affect the viscosity.

2.7.2 Size Exclusion Chromatography

Size exclusion chromatography (SEC), is a technique to measure molecular weight or molecular weight distribution of polymers. It uses a column packed with gel and separates macromolecules, based on their size or hydrodynamic volume. Smaller molecules, will have increased interactions with the gel stationary phase, getting caught up in the porous structure. Larger molecules, will take the faster route straight out of the column, engaging less with the stationary phase. This gives a separation of polymer samples where larger molecules will exit, or eluate, first. A detector will then count the number of molecules as they exit, and a distribution of molecular weight is obtained. If a reference sample of known molecular weight is analysed in the same column, as a calibration, the molecular weight of an unknown sample can also be identified. This is known as relative SEC. Calibration is also needed to get accurate results for molecular weight distributions [28]. The theory behind this method, is that the ratio between the elution time of a solvent containing a polymer, and the elution time of the pure solvent, should be the same ratio as between the viscosity of a solvent containing that polymer, and the viscosity of the pure solvent. This ratio is called the relative viscosity $\eta_r = \frac{\eta}{\eta_0} = \frac{t}{t_0}$ [19] and is used to obtain the influence of a polymer coil on the viscosity in a specific solvent.

The relationship for viscosity in the solution is dependent on concentration of polymer, c, a shape-dependent factor k, which could either be positive: k' or negative: k". This determines whether the viscosity increases or decreases with higher concentration. The intrinsic viscosity [η] can then be obtained from Huggins equation [29] $\frac{\eta_{sp}}{c} = [\eta] + k[\eta]^2 c$ when $\lim c \to 0$ [30]. In order to retrieve the concentration for the different polymers, the refractive index is measured, since a different polymer concentration in a solvent will refract the light differently. Therefore, it is important to know the relationship between the refractive index (n) and the concentration (c), the dn/dc value. This value is different for different polymers, solvents and temperatures. Once the concentration for the sample is obtained, the [η] can be calculated from Huggins equation and furthermore, the molecular weight can be calculated. Equation 2.1 is called the Mark-Houwink relation and with known values of the constants K and α, the molecular weight M can be obtained. The Mark-Houwink's constants are also dependable on polymer, solvent and temperature, and these are experimentally obtained values from samples with known molecular weight [30].

$$[\eta] = K \cdot M^{\alpha} \tag{2.1}$$

In the universal SEC method, instead of simply running a similar polymer with known molecular weight distribution, and comparing the elution time curve of the unknown polymer to it, a master curve is calibrated and used instead. This takes a known polymer's $[\eta] \cdot M$ and plots it against the elution time, and if this calibration curve is adoptable for the unknown polymer then Equation 2.2 is valid.

$$K_1 \cdot M_1^{\alpha_1} = K_2 \cdot M_2^{\alpha_2} \tag{2.2}$$

Here, subscript 1 and 2 stands for the values for the polymers with unknown and the known molecular weight. Lastly, as shown in Equation 2.3, the molecular weight is obtained by knowing the Mark-Houwink's constants for both polymers, and the molecular weights of the polymer which calibrated the system.

$$logM_1 = \frac{1}{1+\alpha_1} \cdot log\frac{K_2}{K_1} + \frac{1+\alpha_2}{1+\alpha_1} \cdot logM_2 \tag{2.3}$$

In this study SEC was used to try to verify the molecular weights of cellulose ethers, that were candidates for the hydrophilic coating.

2.7.3 Manual Evaluation

In order to quickly evaluate the quality of the coating, a manual evaluation was used in this study, in accordance with Wellspect HealthCare protocol. The properties evaluated were slipperiness and coating release. Both of these properties were evaluated on wetted samples. All assessments in this method are subjective, and made by experts at Wellspect HealthCare. There is an uncertainty in this method, so it was mainly used to give indications about the catheters properties, but it can still provide useful information on which sample groups have the best potential.

2.7.4 Friction Measurement

To investigate how slippery the tested hydrogels in this study were, the coefficient of friction (COF) was measured for the respective coatings. The COF is a dimensionless number, that indicates how easy or hard it is for two surfaces to slide over one another. A low COF means it is easy for the two surfaces to slide, and that the friction between them is low [31].

2.7.5 Water Retention

A measurement of water retention was used in order to analyse how much water, expressed in mg/cm^2, is absorbed in the coating after wetting. This serves as an indication of how much the hydrogel can swell, and for how long it can stay swollen and slippery. This is important to the application, since the users sometimes need some time for insertion. In this case it is desirable that the catheter coating maintains its slippery surface for a few minutes. The retention is known to be affected by both hydrogel thickness and degree of crosslinking.

2.7.6 Contact Angle Measurement

A contact angle measurement can be carried out to find the critical surface tension of a material. It can also be used to see if a surface can be wetted by a particular solvent. In this technique a drop of water is placed on the surface of the sample and the contact angle is measured with a camera. The rate of spreading, or adsorption of the water droplet, can also be determined [32]. In this study the water contact angles of the different hydrogel coatings were measured to learn about their relative hydrophilicity and wettability, directly after the droplet was placed on the coating.

2.7.7 Optical Microscopy

Optical microscopy is used to study the morphology of a sample, yielding a magnified image. The technique is based on the interaction of light with the sample. The magnification usually ranges from x2 to x2000, depending on the instrument. The nature of the sample can also affect the resulting image [32]. In this study optical microscopy was used to study the surface topography of the dry coatings, and to study the swelling behaviour of the coatings when water was added.

2.7.8 Scanning Electron Microscopy

Scanning Electron Microscopy (SEM), is a method for producing high resolution topographical images of the surface of a sample. The depth-of-field tends to be 300-600 times better than optical microscopy, and it is possible to produce 3D images. The magnification usually ranges from x20 to x100 000. In a SEM instrument the surface of the sample is scanned with a fine electron beam. This causes a signal beam of scattered electrons to be emitted from the sample. The detected electrons are split into either secondary electrons or backscattered electrons. In order for this signal to be detected, the sample chamber is kept under vacuum. The sample should be conductive, or sputtered with a thin layer of a conductive material, such as gold [32]. Before analysis a sample usually undergoes extensive sample preparation, to be able to enter the vacuum chamber. In this study SEM was used to study the surface topography of the dry coatings, as a supplement to the optical microscopy.

2.8 Review of the Field

Some research has been made into the improvements of catheter materials in the past. An article by Stripple, Westman and Holm details an LCA of plastic materials commonly used for the tube of hydrophilic catheters at Wellspect HealthCare, which at that time was called Astra Tech AB. This report found that the then new POBE material in a catheter had a lower environmental impact, than the commonly used thermoplastic polyurethane, and about the same environmental impact as polyvinyl chloride, which was also a common material [33]. An assessment, made by IVL in 2021 of the carbon footprint of a POBE catheter, showed much lower carbon dioxide equivalents (CO2e), as compared to polyurethane. It also showed clearly a lower CO2e compared to polyvinyl chloride catheters [34].

Most available research on biobased hydrophilic coatings of catheters is focused on antibacterial coatings and modifications, usually for applications for indwelling catheters. This is useful to prevent biofilm formation, which is a state where adsorbed bacteria are highly stable and difficult to kill. The prevention of biofilm formation can decrease the need for antibiotics, and the risk of catheter related infections. One such article was written by Lalitha et al., on the subject of antimicrobial thin film coatings for hydrophilic catheters made from cardanol, a phenolic lipid found in cashew fruits, and linseed oil [35].

Very little public research could be found on the use of biobased polymers for either uncoated catheters, or hydrophilic catheter coatings. There is although, plenty of research on biobased hydrogels for other medical applications, as well as articles on various biobased extrudable materials.

2.8.1 Alginate Based Hydrogels

Alginate is often used in biomedical applications due to its low cost, biocompatibility and low toxicity. The main advantage is the similarity of alginate hydrogels, to the extracellular matrix of living tissue. This similarity allows for applications in drug delivery, cell transplantation and wound healing [16]. Alginate has found applications in the biomedical field for decades. As a material for accelerated wound healing, alginate hydrogels provide both a moist environment and mechanical support. Alginate hydrogels in particular can accelerate chronic wound healing by, for example, activating macrophages. In recent years alginate has also found applications in scaffold fabrication and stem cell regeneration [36]. Alginate hydrogels can be safely orally ingested, or injected into the body [16].

Alginate hydrogels can be prepared using many different crosslinking techniques, including covalent crosslinking, thermal gelation, ionic crosslinking and photocrosslinking. Covalent crosslinking can give excellent physical and mechanical properties to the gels, but the crosslinking agent used may be toxic, and can remain in the gel if left unreacted. Thermal gelation can be very useful in drug delivery applications, where the gel can be tuned to adjust its swelling in response to temperature changes. This makes it possible to release drugs from the gel manually when needed [16].

Utilizing Ca^{2+} ions for ionic crosslinking is the simplest and most common method. To conduct this gelation, calcium chloride, $CaCl_2$, in an aqueous solution is one of the most frequently used options. This does however, lead to very rapid crosslinking, due to the high solubility of $CaCl_2$ in water [16]. For the application of catheter coating this approach would not be suitable, since the gelation should take place once the catheter is coated in the solution. A more realistic option is to use a slower and more controlled gelation. For this, one could use a buffer containing phosphate, calcium sulphate, $CaSO_4$ or calcium carbonate, $CaCO_3$. The buffer reacts with some of the calcium ions in a $CaCl_2$ aqueous solution, slowing the reaction with alginate. $CaSO_4$ and $CaCO_3$ both have lower solubility than $CaCl_2$ in water. The calcium ions are released more slowly, giving a slower gelation [16]. In the case of $CaCO_3$,

dissolution is not possible in water at neutral pH. By adding an acid, like glucono-δ-lactone, calcium ions are slowly released into the alginate solution, according to the method presented by Crow and Nelson [16, 37]. Glucono-δ-lactone is soluble in water but has a slow hydrolysis, leading to a slow but steady decrease in pH. In this method weak gelation occurs after about 30 minutes [37], giving ample time to coat catheters in the solution before the gel becomes too rigid.

A more uncommon method is to use photocrosslinkable alginate. These hydrogels have a huge potential for biomedical applications, such as scaffolding for tissue engineering. These gels can be used as injectable hydrogels, where gelation can take place inside the body, casting or 3D fabrication. Alginate is not photocrosslinkable in itself, so it needs derivatisation with photocrosslinkable groups. Once these groups are introduced, gelation takes place via free-radical chain reactions initiated by high energy irradiation, such as UV or high blue light. A photoinitiator is usually added for increased efficiency [38, 39]. Smeds and Grinstaff made photocrosslinkable hydrogels from alginate and hyaluronic acid through derivatisation with methacrylic anhydride. Crosslinking was performed using an argon laser, after addition of eosin Y and triethanol amine as the initiators, using water as a solvent [38]. Jongprasitkul et al. used a similar derivatisation of alginate and hyaluronic acid with methacrylic anhydride. They used Igracrue 2959 as the photoinitator, and irradiated the gels with UV light using water as a solvent [39]. The photocrosslinking method results in minimal by-products, but the methacrylation of the polymer comes with practical hazards. It is possible to purchase already methacrylated alginate, but the price is comparably high.

2.8.2 Cellulose Based Hydrogels

Cellulose has been heavily researched as a material for hydrogels in recent years due to its renewability, availability, safety, low cost and biocompatibility [40, 41]. The great variation of cellulose and its derivatives, also make it possible to find applications in many different fields. The application of cellulose-based hydrogels has been studied in biomedical, tissue engineering, agriculture and wastewater applications. It is the presence of various functional groups, such as hydroxyl and carboxyl groups, that can provide hydrophilic character to the cellulose, which makes it a candidate for hydrogels. It is thanks to these groups that crosslinking may take place [40].

Hydrogels may be made from simple cellulose, although there is a problem with dissolution. Cellulose requires a solvent system to be handled and therefore, to avoid the need of complicated solvents, cellulose may be derivatised. For the specific purpose of making hydrogels the cellulose ethers are the most common derivatives, especially the four ethers already mentioned in this chapter: CMC, HPC, HPMC and HEC [40, 41].

The first one, the CMC-based hydrogels, have mostly been used in wound-healing, drug delivery, enzyme immobilisation and adsorbing applications. The addition of nanoparticles to the hydrogel can impart anti-bacterial activity. It has also been

used as a crosslinking agent in other hydrogels. CMC hydrogels have a high swelling capacity, due to the entropic gains from the release of its counter ions, when water is absorbed. The second, which is the HPC-based hydrogels have been studied for medical and pharmaceutical applications, such as wound-healing. HPC is very easy to prepare into hydrogels. The third, HPMC-based hydrogels are mainly used for medical applications such as scaffolds, membranes and films. HPMC can form transparent, colourless gels with good stability and viscosity. The last on is HEC-based hydrogels, and are also used in medical applications, mainly for controlled release of encapsulated drugs. This release can be controlled, and related to the diffusion of water through the hydrogel [41]. The properties of the formed hydrogels will depend heavily on the DP and DS, of all of the derivatives, as well as the degree of crosslinking. It is also possible to combine these derivatives in the same gel, to further tune the properties of the hydrogel.

To construct hydrogels from cellulose some type of crosslinking reaction must take place. These usually fall under the category of either physical or chemical crosslinking, as previously mentioned [40, 41]. Some of the most common crosslinking methods for cellulose-based hydrogels include photoinitiation, radiation and reaction with crosslinking chemicals such as citric acid, glutaraldehyde or epichlorohydrin [41].

In the photoinitiated hydrogels the irradiation is done by high energy light. This light should start the formation of radicals in the cellulose molecules, which in turn, leads to chain reactions and eventual network formation. The addition of a photoinitiator can increase the efficiency of this technique. For medical applications the safety of the chosen photoinitiator should be considered, as it can remain in the hydrogel. The degree of crosslinking can be controlled by adjusting the dose of irradiation or the concentration of photoinitiator [41].

Radiation-induced crosslinking uses a source of gamma radiation, or an electron beam to, similarly to photoinitiation, start a free radical reaction between the polymer chains. There is however, no need for extra chemicals or initiators, and is termed as a fast, cheap and environmentally friendly method of crosslinking hydrogels. The degree of crosslinking is easily adjusted with the dose of radiation [41]. Fei et al. utilised radiation crosslinking in their study to create CMC-based hydrogels for wound dressing applications. It was found that a higher DS, and a higher concentration of the aqueous CMC solution, both lead to a higher crosslinking density. Attempts to crosslink CMC in its solid state were also carried out, but this resulted in degradation of CMC instead of crosslinking [42]. Other derivatives such as HPC can also be made into hydrogels with the same method [43].

By crosslinking through a reaction with a chemical called a crosslinker, this chemical becomes incorporated into the gel structure. There is always a risk that some of the crosslinker will remain unreacted in the hydrogel after synthesis, so depending on the application the safety of the crosslinker is of highest importance. If a dangerous or toxic crosslinker must be used, the gel may need to undergo washing and dialysis after synthesis.

Citric acid crosslinks to cellulose via an ester reaction between the hydroxyl groups at the cellulose chain, and one of the three carboxyl groups in the citric acid molecule, see Figure 2.16 for the molecular structure of citric acid. It is an inexpensive, non-toxic and hydrophilic chemical. In a hydrogel it can improve water swelling, thermal stability and tensile strength. Demitri et al. used citric acid to make crosslinked hydrogel films from the cellulose derivatives of pure CMC and HEC, as well as a 3:1 mixture of CMC and HEC [44].

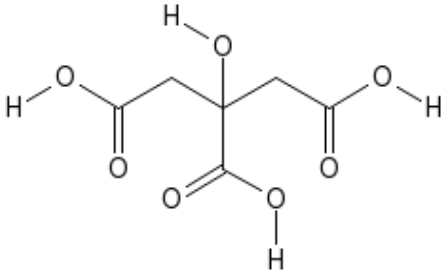


Figure 2.16: Molecular structure of citric acid.

The combination of CMC and HEC is motivated by Anbergen and Opperman. They studied the comparative crosslinking efficiency, swelling behaviour and gel strength of hydrogels made from CMC, HEC and combinations of CMC and HEC. They used divinyl sulphone as a crosslinker, which reacts similarly with cellulose ethers as citric acid. They found that HEC had a higher crosslinking efficiency than CMC, forming stronger gels from the same amount of crosslinker. The mixtures of the two derivatives fell in between the two pure derivatives, in terms of crosslinking efficiency [45].

Their theory as to why this happened is, firstly, that in CMC more of the C6 hydroxyl groups, on the cellulose chains, are substituted than on HEC. The C6 groups are the most reactive on the cellulose chains. If less of these reactive groups are available for the crosslinking reaction, it is possible that this, could cause lower crosslinking efficiency. In HEC there is also hydroxyl groups on the substituting hydroxyethyl groups. These hydroxyl groups, which get added to the cellulose chains, may even be more reactive due to lower steric hinderance. Secondly, is that the electric charges present on CMC molecules give rise to electrostatic repulsion between chains, which hinders intermolecular contact and crosslinking. It is therefore believed, that the presence of HEC would help favour intermolecular, instead of intramolecular crosslinking. However, as discussed in Section 2.6.2.1, this is probably due to the counter-ion effect, rather than actual repulsion between the carboxylic acid substituents. The benefit of using CMC is the swelling capacity. The study by Anbergen and Opperman found that CMC had better swelling behaviour than HEC, and that the mixtures of the two had swelling capacities in between the two. CMC is believed to induce hydrogel swelling since it is a polyelectrolyte. The ionic strength will greatly influence the swelling, due to the entropy gain of the release of counter-ions. The need for a hydrogel with a balance of gel strength and swelling

properties, is the motivation behind using a mixture of CMC and HEC. The ratio of 3:1 between CMC and HEC gave the most optimal combination of properties [45].

The crosslinking with citric acid which Demitri et al. performed, was carried out in a heat activated reaction at 80 °C, using water as a solvent. Different concentrations of citric acid were tested, ranging from 1.75 % to 20 % w/w polymer (meaning a weight percentage of the total polymer weight in the solution), to find an optimal amount to maximise swelling of the gel. It was found that, in the hydrogels with a composition of mixed derivates, a lower concentration of citric acid resulted in the highest degree of swelling for this application [44]. Dharmalingam and Anandalakshmi used a very similar crosslinking method as Demitri et al., with the same heat activated reaction at 80 °C using water as a solvent. The difference was that Dharmalingam and Anandalakshmi studied hydrogels made from a 3:1 mixture of CMC and HPMC. In this case HPMC plays the role of promoting intermolecular crosslinking, similarly to HEC. The concentration of citric acid was varied in this study as well, here between 5 % and 20 % w/w polymer. It was found that the higher concentrations of citric acid, led to lower degrees of swelling, and decreased water contact angles of the hydrogel films [46].

Both articles present the same possible reaction mechanism, which is displayed in Figure 2.17. Here citric acid, with supplied heat, forms a cyclic anhydride, through an intramolecular condensation reaction between two of its carboxyl groups. The ester bond is then formed between a hydroxyl group in the cellulose and the anhydride group. After the ester bond is formed, the two remaining carboxyl groups can form another cyclic anhydride under heating, which can then create a second ester bond, forming a crosslink between two cellulose chains [44, 46].

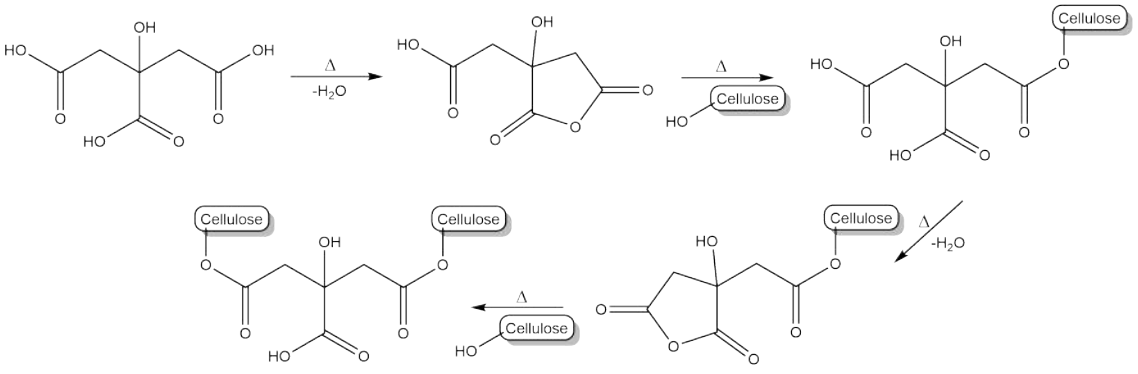


Figure 2.17: A possible crosslinking reaction of citric acid and cellulose as described by Demetri et al. [44] and Dharmalingam and Anandalakshmi [46].

Glutaraldehyde also crosslinks to the hydroxyl groups of the cellulose chain. It has two formyl functional groups, which connect cellulose chains together. It is widely applied due to its low cost, high reactivity and efficiency. In a hydrogel it improves water swelling and viscosity. Epichlorohydrin also crosslinks to the hydroxyl groups. It has one epoxide group and one chloride group. In a hydrogel

it helps with the pore size distribution, chemical stability and water retention [41]. For medical applications such as CIC it is worth noting that both glutaraldehyde and epichlorohydrin are toxic chemicals, and any hydrogel synthesised with either of them would need to be purified of the unreacted crosslinker, before being safe to use.

2.8.3 Hyaluronic Acid Based Hydrogels

Hyaluronic acid (HA) has been used in biomedical applications for many decades. Due to the fact that HA can be found in the human body, it is highly biocompatible. Some common applications for HA hydrogels include cell therapy, scaffolding for tissue repair and drug delivery of growth factors. It is possible to modify HA by targeting three functional groups: carboxylic acid groups, hydroxyl groups and acetyl groups. Some of these modifications make it possible to make hydrogels from HA by introducing crosslinks. Some of the most common modifications of the carboxylic acid groups are carbodiimide-mediated reactions, amidation and esterification. To modify the hydroxyl groups etherification, esterification, bis-epoxide crosslinking and divinyl sulfone crosslinking are most common [21].

Yang et al. created HA hydrogels using 1,4-butanedioldiglycidyl ether (BDDE) as a crosslinking agent. The crosslinking was carried out in a heat activated reaction at 40 °C, using water with 1 % NaOH as a solvent. After crosslinking, the gel had to undergo dialysis to remove the residual BDDE, as it can be toxic. The purpose was to make injectable scaffolds for tissue regeneration [47].

Both Smeds and Grinstaff and Jongprasitkul et al. made photocrosslinkable HA hydrogels, as mentioned in Section 2.8.1. The two methods both used methacrylic anhydride to modify the HA to make it possible to crosslink it with a free radical reaction initiated by irradiation [38, 39]. As previously mentioned, methacrylation of a polymer brings some practical hazards. It is possible to purchase already methacrylated HA, but at an elevated price point.

2.8.4 Starch Based Hydrogels

Starch based hydrogels are not mainly used for biomedical applications. Some of the most prominent applications are in sorption of dyes, agriculture and metal capture from wastewater. Starch hydrogels are however biocompatible, non-toxic and have a low cost, and so have found some uses in the biomedical field. Some examples are personal care products, like diapers, scaffolding for tissue engineering and drug delivery. Starch is of course also widely used in the food industry. For applications other than food, starch often needs to be modified, typically to change the dissolution or viscosity properties. For some derivatives this will increase the swelling capacity, if they are formed into a hydrogel, by making the starch more hydrophilic [25].

To make a hydrogel from starch the hydroxyl groups are usually targeted through etherification or grafting. Etherification can for example produce sodium carboxymethyl starch, with the same derivatisation groups as CMC. Etherification as a

direct crosslinking reaction is also possible using polyfunctional compounds, such as glycerol or citric acid. The method with citric acid uses the same mechanism as Demitri et al. [44] and Dharmalingam and Anandalakshmi [46], as described in Section 2.8.2.

Grafting is usually done with vinyl monomers, which act as crosslinking agents between the starch chains. The crosslinking typically needs an initiator, and is a free radical reaction [25]. One such grafting method was used in the article by Zhai et al. In this method starch from corn and hydrolysed polyvinyl alcohol (PVA), were used in an aqueous solution, and the free radical reaction was initiated by radiation with gamma and electron beam. This article found that the amylose of starch was the main component that took part in the crosslinking, and impacted the properties of the formed hydrogels. In the method more PVA than starch was used to form the hydrogels, calling the renewability of the gels into question [24].

2.8.5 Biobased Extrudable Materials

Starch can be made into a bioplastic with the addition of plasticiser [13]. The addition of plasticiser is needed because native starch has a higher glass transition and melting temperature than its degradation temperature. In order to make starch that can be processed via for example extrusion, it is pre-treated with plasticiser, which turns it into thermoplastic starch (TPS) [48]. Some examples of plasticisers that work well with starch are water, glycerol and sorbitol [13, 48]. A TPS with sufficient flexibility could be a potential biobased alternative to POBE.

3

Materials and Methods

This chapter contains information about the materials and methods used in this study. What kind of chemicals and materials were used and studied will be described first. Then the literature study process, of finding what to examine and the selection of probable candidates will be presented. The chapter will briefly touch upon the extrusion method used, and then give a thorough explanation of how the screening process was conducted. Towards the end, the methods of preparing the hydrogels, and the coating procedure are explained. Lastly, the description of each characterisation method for the different samples: viscometry, SEC, manual evaluation, friction, water retention, contact angle, optical microscope and SEM.

3.1 Chemicals and Materials

For making the different cellulose derivative hydrogels, two types of Ashland's carboxymethyl cellulose (CMC) (Blanose™7LPEP) were used with molecular weights of 95 kDa and 395 kDa, and a degree of substitution (DS) of 0.7. In addition to that hydroxypropyl cellulose (HPC) (Klucel™LF), with a molecular weight of approximately 75 kDa, hydroxypropyl methyl cellulose (HPMC) (Benecel™K15M) with a molecular weight of about 500-600 kDa and lastly hydroxyethyl cellulose (HEC) (Natrosol™250 HHX) with a molecular weight around 1300 kDa, all obtained from Ashland, were used in the hydrogels. Citric acid was obtained from VWR Chemicals. Milli-Q water was used as the solvent. A reference sample and a TPS sample were made using the PVP solution produced at Wellspect HealthCare.

For the screening tests sodium alginate from Fisher Chemical, D-(+)-gluconic acid δ-lactone (glucono-δ-lactone) from Sigma-Aldrich and calcium carbonate ($CaCO_3$) from Sigma-Aldrich were used. Lastly two types of starch were used in the screening tests from Avebe: Amylofax™, a cationic modified starch and Perfectamyl™, an oxidised starch. In addition to these poly(vinyl alcohol) (PVA) hydrolysed with a molecular weight of about 30-70 kDa was purchased from Sigma-Aldrich. The thermoplastic starch, which was extruded, was Solanyl C1201 from Rodenburg. Wellspect HealthCare standard uncoated catheters in POBE material were used for the biobased coatings.

3.2 Literature Studies and Selections

The first step in the project was the selection of which biobased hydrogels should be studied. Therefore, a literature study was conducted, the result of which can be found in Section 2.8. The literature study focused on non-animalic biopolymer sources, and therefore polysaccharides such as chitin and chitosan, originating from crabs and other shellfish, were left out. The main materials researched as hydrogel candidates were alginate, the cellulose ethers CMC, HPC, HPMC and HEC, modified starches and microbial hyaluronic acid. The solvent, crosslinking method and other chemicals required in the synthesis, as well as the toxicity and hazards involved in the method, were evaluated and used to eliminate some of the alternative materials and methods. The choice of TPS as the biobased substrate was based on previous studies done at Wellspect HealthCare.

3.3 Extrusion of Biobased Substrate

In order to test the potential biobased substrate material, melt extrusion was carried out using a lab extruder (Stand-alone Extruder KE 19 from Brabender) at the Department of Industrial and Materials Science at Chalmers University of Technology. TPS was extruded into tubes with similar dimensions as tubing used for uncoated catheters. At this stage, the surface properties were the most interesting, as the coating properties of the material were to be investigated. The softness and flexibility of the TPS, was not tuned to be appropriate for the application at this point.

3.4 Screening of Potential Hydrogels

In the screening stage for the hydrogel materials, the selected methods were all tested to see if a hydrogel could indeed be made in the laboratory, and if the resulting hydrogels had promising properties for the application, mainly slipperiness. In addition to this a very brief assessment of whether the methods were plausible for scale-up. The candidates and crosslinking methods evaluated in the screening were the following: ionically crosslinked alginate (Crow and Nelson [37]), grafting of PVA and starch with radiation from electron beam (Zhai et al. [24]) and cellulose ethers crosslinked with radiation from electron beam (Fei et al. [42]). An attempt was also made to crosslink starch with radiation from electron beam according to the method proposed by Fei et al. [42]. The final candidates were cellulose ethers as well as starch crosslinked with citric acid (Demitri et al. [44] and Dharmalingam and Anandalakshmi [46]). An overview of all the tested hydrogel candidates is presented in Table 3.1.

Table 3.1: The tested combinations of crosslinking technique and polymers from the screening of potential hydrogels.

Crosslinking	**Polymer(s)**
Ionic	Alginate
Radiation	Oxidised starch
	Cationic starch
	CMC
	HPC
	Oxidised starch/PVA
	Cationic starch/PVA
Citric Acid	CMC
	HPC/CMC
	HPMC
	HPMC/CMC
	HEC
	HEC/CMC
	Cationic starch
	Cationic starch/CMC

3.4.1 Alginate Crosslinked with Ions

Ionic crosslinking of alginate using calcium carbonate ($CaCO_3$) and glucono-δ-lactone was first tested in a glass petri dish, to verify the formation of a hydrogel, and then by dipping an uncoated catheter into the solution, to investigate the coating properties. The tests were carried out using a 1 wt% sodium alginate solution in water. $CaCO_3$ was added first to a concentration of 15 mM, to a beaker of alginate solution while stirring. Glucono-δ-lactone was added to a concentration of 30 mM. Upon the addition of glucono-δ-lactone the viscosity slowly began to increase, as the ionic crosslinking began. In the first test a thin layer of the solution was poured into a glass petri dish and allowed to set. After gel formation, the slipperiness of the gel was manually evaluated, and the sample was dried in a 90 °C oven. Drying was carried out as intermittent catheters are usually packaged and stored dry. After drying the ability of the gel to rehydrate was evaluated. In the second test an uncoated catheter was dipped into the same solution at appropriate viscosities, to investigate if the solution could wet and coat the surface.

3.4.2 Cellulose and Starch Crosslinked with Radiation

Radiation-induced crosslinking of starch and cellulose derivatives was tested using electron beam radiation. The electron beam was also used to test the grafting of starch with hydrolysed PVA. All options were tested both as solutions in a sealed container, and as dried films on an uncoated catheter.

Both oxidised and cationic starch, were tested to see if they would crosslink in the election beam. Solutions of 1.75 wt% were prepared by gently heating the solution

until all starch was dissolved. The radiation-induced crosslinking of CMC and HPC was also tested in the electron beam. Solutions of these two were mixed at 1 wt%. To test the grafting reaction of starch and PVA, both oxidised and cationic starch were used. Due to the different viscosities of the oxidised and cationic starch in aqueous solutions with PVA, different total concentrations were used for these two. For the oxidised starch a solution with 5.75 wt% PVA and 1.76 wt% starch was prepared. For the cationic starch 2.87 wt% PVA and 0.86 wt% starch was used to prepare the solution. At these concentrations, appropriate viscosities for dipping with an uncoated catheter were achieved.

The solutions were poured into plastic containers, that were safe to use in the electron beam, and could be sealed tightly. Uncoated catheters were also dipped into the solution, and dried in an oven, before being exposed to the electron beam. All samples were run through the electron beam at process doses of 46 kGy. Samples were exposed to one, three or four consecutive irradiations at 46 kGy, resulting in total doses of 46, 138 or 184 kGy. After this the samples were studied to see if crosslinking had occurred, and if so, how slippery the hydrogels were.

3.4.3 Cellulose and Starch Crosslinked with Citric Acid

Chemical crosslinking of cellulose ethers and modified starch using citric acid was tested using different combinations of CMC with HEC, HPC, HPMC and cationic starch, as well as using only one polymer. An overview of the combinations used is presented in Table 3.1, and detailed information regarding the methods is given below. Aqueous solutions were mixed with the polymers, and citric acid was added. The amount of citric acid added is denoted as % w/w polymer of citric acid, meaning a weight percentage of the total polymer weight in the solution. To test the crosslinking and slipperiness thin layers of the solutions were poured into glass petri dishes and crosslinked in a 90 °C oven until a film formed. The films were wetted, and the success of the crosslinking and degree of slipperiness were evaluated manually. For some of the polymers that passed the first test, a dip with an uncoated catheter was carried out to see if the solution could wet and coat the surface, if no conclusion could be drawn from previous tests.

CMC crosslinked by citric acid was tested in a solution of 2 wt% polymer with 20 % w/w polymer of citric acid, similarly to what was used by Demitri et al. [44]. This solution was tested by pouring a thin layer onto a glass petri dish, and crosslinking in a 90 °C oven for 1 hour.

HPC was tested with citric acid and CMC. A solution of in total 2 wt% polymer was prepared with 20 % w/w polymer of citric acid. The solution had a composition of 3 parts CMC to 1 part HPC, based on weight, the same ratio that was motivated by Anbergen and Opperman [45]. This solution was tested on a glass petri dish in a 90 °C oven for 1 hour. A coating test on an uncoated catheter was also carried out.

HPMC was tested with citric acid both on its own and with CMC. For the test with

only HPMC and citric acid a solution of 1 wt% HPMC was prepared, to which 10 % w/w polymer of citric acid was added. For the test with both HPMC and CMC, a solution of in total 2 wt% polymer was prepared, with a composition of 3 parts CMC to 1 part HPMC, based on weight. To the solution 5 % w/w polymer of citric acid was added. For the first test thin layers of both solutions were poured into glass petri dishes and put into a 90 °C oven to crosslink for 4 hours. At this point the HPMC/CMC solution moved on to the second test of coating an uncoated catheter. For this test a solution of 1 wt% polymer was used to give it an appropriate viscosity for dipping, and 20 % w/w polymer of citric acid was added to make the crosslinking more efficient.

HEC was tested with citric acid, both on its own, and with CMC. Both solutions had a total polymer concentration of 1 wt% with 20 % w/w polymer of citric acid. In the solution with both HEC and CMC, the composition was 3 parts CMC to 1 part HEC, based on weight. To test them both, thin layers of the solutions were poured into glass petri dishes and put into a 90 °C oven to crosslink. After 1.5 hours the petri dishes were removed. The coating ability of the solutions was also tested on an uncoated catheter.

Cationic starch was tested with citric acid both on its own and with CMC. Both solutions had a total polymer concentration of 1.75 wt% with 20 % w/w polymer of citric acid. In the solution with both starch and CMC, the composition was 3 parts CMC to 1 part starch, based on weight. To test the crosslinking, both solutions were poured into glass petri dishes and put into a 90 °C oven to crosslink. At this point the coating ability of the solution with starch, CMC and citric acid was tested with an uncoated catheter, this time with a solution of 2 wt% polymer and 20 % w/w polymer of citric acid.

3.4.3.1 Adjustment of Parameters

In the initial screening, only a few of the cellulose ether hydrogels crosslinked with citric acid, were deemed suitable to move into the final round of testing. Before this round, however, some of the parameters involved in the crosslinking were adjusted, for the hydrogel to work better as a coating on the uncoated catheters. These parameters were total polymer concentration, concentration of citric acid and time in the oven. The polymer concentration was adjusted to get a better thickness of the coating, and the concentration of citric acid and time in the oven, were adjusted to improve the amount of crosslinking, and by extension the swelling capacity of the hydrogels. This step was not a complete optimisation, for that a more thorough study would be needed.

The hydrogels with cellulose ethers that showed potential as coatings were CMC, HPC/CMC, HPMC/CMC and HEC/CMC. The gel with CMC needed increased crosslinking, so the oven time was increased. The HPC/CMC gel needed both a higher degree of crosslinking, and a thinner coating to work well in the application. The HPMC/CMC gel needed to be thinner, and the crosslinking needed to be faster than 4 hours to be a plausible candidate. The HEC/CMC gel needed to be thicker,

and the degree of crosslinking needed to be decreased. The variations of tested parameters are displayed in Table 3.2. After this trial the combinations of parameters that gave the best coating properties were carried into the next step of the study.

Table 3.2: Variations of parameters tested to improve the coating properties.

	CMC	**HPC/CMC**	**HPMC/CMC**	**HEC/CMC**
Total concentration [wt%]	2	1, 1.5, 2	1, 2	2
Citric acid concentration [% w/w]	20	5, 20	10, 20	5, 7.5, 10
Time in oven at 90°C [h]	1.5, 2, 3	1.5, 2	1.5, 2, 3	1.5

3.5 Preparation of Final Samples

In this section the methods for preparing the aqueous hydrogel solutions are described, as well as the method for manually coating the POBE catheters.

3.5.1 Preparation of Solutions for Hydrogels

The four different types of cellulose ether hydrogels were prepared by adding one of the cellulose ethers HPC, HPMC or HEC together with CMC, and one with only CMC to a water solution with Milli-Q water. Citric acid was added in various amounts, depending on the outcome from the screening test. The parameters used are presented in Table 3.3

Table 3.3: The four different cellulose derivative hydrogels used in this study, CMC, HPC/CMC, HPMC/CMC and HEC/CMC. Their different polymer concentration, citric acid concentration and time to crosslink in the oven are presented below.

	CMC	**HPC/CMC**	**HPMC/CMC**	**HEC/CMC**
Total concentration [wt%]	2	1.5	1	2
Citric acid concentration [% w/w]	20	20	20	5
Time in oven at 90°C [h]	3	2	2	1.5

The method was as follows. For the hydrogel only containing CMC, a 2 wt% polymer solution by water weight was prepared. Two types of CMC, one of high molecular weight (395 kDa) and one of low molecular weight (95 kDa) were mixed together in the solutions. This was due to shortage of just one, and interest in possible properties of this mix. The ratio of these different molecular weights was 1:1 corresponding to weight. The CMC was fully dissolved by stirring in distilled water at room

temperature overnight, showing a drastic increase in viscosity. Lastly the crosslinker citric acid was added, and the screening had shown that a concentration of 20 % w/w polymer of citric acid would ensure a crosslinking reaction.

The hydrogels containing more than one type of polymer followed almost the same method but with different parameters, see Table 3.3, all decided through the screening tests. All of them contained the same mixture of high and low molecular weight CMC. The HPC/CMC hydrogel was a 1.5 wt% polymer solution by water weight and the polymer mix was a 1:3 ratio. First HPC was added to distilled water and was stirred until dissolved, after that CMC was added and the mixture was left stirring overnight to dissolve. Citric acid was added lastly with a 20 % w/w polymer here as well.

The HPMC/CMC hydrogel was prepared as a 1 wt% polymer solution by water weight, the polymer ratio the same as the last one, 1:3 based on weight. Here HPMC was also added first, but the solution needed to be heated to approximately 90°C, while stirring in order for the HPMC to get dispersed in the water, to then be cooled down to room temperature while stirring, in order to dissolve. Then, when cooled CMC was added and left to stir overnight. The same concentration of citric acid 20 % w/w polymer was added to the solution.

The final hydrogel with HEC/CMC was prepared as a 2 wt% polymer solution by water weight. Once again, the polymer ratio was 1:3 based on weight and HEC was added to the distilled water first and stirred until dissolved. CMC was then added to the solution to be left stirring overnight in order to dissolve. A citric acid concentration of 5 % w/w polymer, decided by the screening test, was added.

3.5.2 Manual Coating Procedure

In order to investigate biobased options to the POBE uncoated catheter and PVP coating, a lab scale setup of the LoFric® production process was made, manually dipping uncoated catheters in different coating solutions.

The reference sample was created from a POBE catheter coated with PVP in a method in accordance to Figure 2.3, with two layers and a drying and curing step between each one. The TPS substrate was produced with the same PVP coating method on a TPS catheter.

The samples for the four different cellulose ether hydrogel solutions were all made from POBE catheters coated with their respective solution. All of them were put in the oven at 90°C but for different amounts of time in order for the hydrogel to crosslink, see Table 3.3.

3.6 Analytical Methods

This section will give a brief overview of how the different analytical methods were performed. It is worth noting, that for all the following analytical techniques, all of them were carried out on non-sterile catheters. This is not according to standard, where all the techniques are supposed to analyse sterile products. The coatings were analysed both in their dry and wet states, depending on the method.

3.6.1 Viscosity of the Cellulose Ether Solutions

The fluid viscosities of the four different cellulose ether solutions, described in Section 3.5, were measured in this study. This was done to learn about how the viscosities were affected by molecular weight and concentration, as well as to see if the viscosities would be appropriate for a large-scale dip coating production. To measure the viscosities the Brookfield AMETEK DV2T Viscometer was used. 6.7 ml from each of the solutions were put inside a water bath of 25.6 °C and left for 30 minutes in order for the sample to reach the temperature of 25 °C. The spindle that was used was SC4-18. The obtained values from the instruments are the rotational velocity (rpm), the torque (%) which should be between 10-90 % to validate the measurement, and lastly viscosity in centipoise (cP), where 1 cP is equal to 1 mPas.

3.6.2 Size Exclusion Chromatography

Size Exclusion Chromatography (SEC) was carried out to verify the molecular weights of the cellulose ethers used to make hydrogels. For this analysis an Agilent Technologies 1260 Infinity system was used, with a PL aquagel-OH MIXED 8 µm, 7.5 x 300 mm column. The mobile phase used was an aqueous solution of 0.1 M sodium nitrate ($NaNO_3$) with 0.02 % sodium azide (NaN_3). The standard used for calibration was a solution of polyethylene glycol with a molecular weight of 117 kDa. The cellulose ethers analysed were the two types of CMC (Blanose™7LPED), the HPC Klucel™LF, the HPMC Benecel™K15M, and the HEC Natrosol™250 HHX. All five cellulose ether samples were dissolved with mobile phase to a concentration of 0.5 mg/ml and analysed in the SEC setup. The analysis was done at 40° C. The detector used was refractive index, making this a relative SEC. The software of the system was used to integrate and calibrate the resulting peaks. This was used to attempt to find values for weight average molecular weight as well as a polydispersity index and a dispersion curve.

3.6.3 Manual Evaluation

Manual evaluation was done to get a quick and simple first evaluation of the produced coatings. This was by an expert on the coatings produced at Wellspect HealthCare. Only one of each sample was tested at the time of screening, and this method provided the biggest impact on what type of sample would move on beyond the screening, as well as differentiating between the cellulose ether samples from the adjustment of parameters. For the final samples one sample of each type was tested.

The analysed sample was wetted with water for 10 seconds, to then be left to dry at room temperature for 90 seconds. It was then evaluated manually with the fingers sliding over the coating repeated times and points were given on slipperiness and coating release, on a five point scale. For slipperiness a value of four or over was a passing grade, and for the coating release the target was a value of four, with both too low and too high values being undesirable. This method is subjective and is therefore only performed by a few people at Wellspect HealthCare who are well versed in it.

3.6.4 Friction Measurement

To investigate how slippery the coatings were, the coefficients of friction (COF) of the hydrogel surfaces were measured, using the FTS 6000 Friction Test System from Harland. The COF was measured for all the selected final samples, using five replicates of each sample type. The coated sample was wetted for 30 seconds and left to dry at room temperature for 90 seconds in accordance with Wellspect HealthCare protocol. The sample was mounted inside a clamp which pressed with a clamp force of 200 g while the sample was pulled and the resulting pull force was registered and used to calculate the COF. The same length of 5 cm was analysed in 5 consecutive strokes. A mean value and standard deviation for the sample's COF was calculated.

3.6.5 Water Retention

Water retention was measured in order to learn how much water the coatings can absorb and for how long they stay wet, as it is important to the application that the catheter stays slippery for some time to help with insertion. Water retention was measured for all the cellulose ether samples, the TPS sample and the reference sample.

First the dimensions of the samples' coatings were measured in order to retrieve the surface area which could uptake water. After that the sample was weighed when dry, and the coating was soaked in water for 30 seconds. It was left to dry at room temperature for 1 minute to then be weighed in order to retrieve the first retention value. The sample was then left for a total of 6 minutes to then be weighed a second time. The use of 1 minute and 6 minutes as drying times is a standard at Wellspect HealthCare. Two values measured in mg/cm^2 were retrieved for each sample, and 5 replicas of each type of sample were measured. A target value for the water retention after 1 minute is 10 mg/cm^2, with 8 mg/cm^2 being the lowest acceptable. It is not desirable to have a water retention that is much higher than 10 mg/cm^2, as this often leads to a lot of the coating releasing from the catheter. In addition to this, the TPS material was also tested without any coating, this to eliminate the possibility of the surface material retaining water and causing unrealistic high values.

3.6.6 Contact Angle

The contact angle measurements were carried out to learn about the hydrophilicity of the different coatings. There is no benchmark value of contact angle for this appli-

cation. The instrument Drop Shape Analyser Krüss DSA100 was used to determine the contact angle of all the produced coated sample types along with the reference. The initial touch of the water droplet was measured and photographed and repeated a total of three times on each sample in order to be able to make a good comparison of the different samples. The average values and standard deviations of the contact angles were then calculated.

3.6.7 Optical Microscope

Optical microscopy was carried out in this study to analyse the surface topography of the hydrogel coatings, to see if the surface was smooth or rough and if it had any cracks. It was also used to study the swelling behaviour of the coating when water was added.

The optical microscopy was performed using Nikon Upright motorised Microscope ECLIPSE, with the NIS-Elements software. One of each sample group was investigated, except the TPS surface since the material does not transmit light. The dry surface and the dry and wet cross-section were of interest. The cutting was done with a razor blade, to make the cross-section as thin as possible. A thin cross-section was needed to get adequate focus on the coating. For the surface pictures a 4x magnification was used, while 40x magnification was used for the cross-section. Furthermore, both the cross-section of the dry and the wet coating were studied. The wetting of the coating was achieved by using a micropipette to carefully put a drop of water close to the coating of the cross-section. In order to try to better spot the ends of the coatings, the contrast was edited after a picture was captured. The thickness of the dry and wet coating was measured in the cross-section images.

3.6.8 Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) was used in this study as a complement to the optical microscope, to study the surface topography of the coatings. It was also possible to study the TPS coated with PVP with this technique, which was not possible with optical microscopy.

The Scanning Electron Microscope Hitachi SU5000 was used to capture images of the surface of the different samples, using the secondary electron mode. A cross-sectional image was only possible for the TPS sample, as the TPS tube was brittle enough to be snapped in a clean break. The samples with the POBE tube were not able to be snapped, and when cutting was attempted the coating smeared too much to get clear images of the cross-section. Low vacuum was used, since the polymers used in this study weren't conductive materials, and sputtering is a time-consuming preparation method.

4

Results and Discussion

This chapter contains the results from the cellulose ether hydrogels, as well as the PVP coated TPS catheter. Followed by the results from the screening process, and the analytical techniques utilized to evaluate the catheter samples with different coatings. The analytical techniques are presented in the same order as in Chapters 2 and 3: Viscometry, SEC, Manual evaluation, Friction, Water retention, Contact angle, Optical microscope and SEM. Each section concludes with a subsequent discussion of the presented results.

4.1 Literature Studies and Selection

In the literature-based selection, all methods of making hydrogels that included chemicals that were considered hazardous were eliminated. Subsequently, methods which included derivatisation by methacrylation were disregarded due to containing potentially toxic reagents that could reside inside the hydrogel if not properly washed through. It was possible to purchase already methacrylated polysaccharides, but they were too expensive to be applicable in a large-scale process. This eliminated the routes of photocrosslinkable methacrylated alginate and hyaluronic acid as proposed by Smeds and Grinstaff [38] and Jongprasitkul et al. [39]. For similar reasons of toxic reagents potentially remaining in the hydrogel, the method using BDDE proposed by Yang et al. [47] was also disregarded from the selection. Hydrogels based on hyaluronic acid were also discarded due to the high cost of pharmaceutical grade microbial hyaluronic acid, as this option would not be suitable for a large-scale process. The methods of crosslinking cellulose derivatives with glutaraldehyde or epichlorohydrin were also both eliminated due to toxicity.

After the selection based on literature, the candidates for hydrogel materials included ionically crosslinked alginate (Crow and Nelson [37]), grafting of PVA and starch with radiation from electron beam (Zhai et al. [24]) and cellulose ethers crosslinked with radiation from electron beam (Fei et al. [42]). An attempt was also made to crosslink starch with radiation from electron beam according to the method proposed by Fei et al. [42]. The final candidates were cellulose ethers and starch crosslinked with citric acid (Demitri et al. [44] and Dharmalingam and Anandalakshmi [46]). All these were carried on into the screening phase, see also Table 3.1.

4.2 Screening of Potential Hydrogels

The results of the screening of hydrogel candidates were that only some of the cellulose ether options, crosslinked with citric acid, showed sufficient properties to be moved on to the next round of testing, with a good level of crosslinking, able to create a coherent and sufficiently thick coating and good slipperiness. The rest of the samples were eliminated because they lacked some or all of these properties. An overview of the candidates that passed or were eliminated is presented in Table 4.1. More detailed descriptions follow below.

Table 4.1: The results of the screening of the potential hydrogels.

Crosslinking	**Polymer(s)**	**Result**
Ionic	Alginate	Eliminated
Radiation	Oxidised starch	Eliminated
	Cationic starch	Eliminated
	CMC	Eliminated
	HPC	Eliminated
	Oxidised starch/PVA	Eliminated
	Cationic starch/PVA	Eliminated
Citric Acid	CMC	Passed
	HPC/CMC	Passed
	HPMC	Eliminated
	HPMC/CMC	Passed
	HEC	Eliminated
	HEC/CMC	Passed
	Cationic starch	Eliminated
	Cationic starch/CMC	Eliminated

4.2.1 Alginate Crosslinked with Ions

Ionically crosslinked alginate was discarded as a candidate for a hydrogel coating as it was found that the gel was not very slippery when tested in the glass petri dish. The solution did not wet the uncoated catheter at all and so could not form a coating. It was also reasoned that the nature of the solution of having an increasing viscosity with time after the release of Ca^{2+} would not lend itself well to a large-scale production.

4.2.2 Cellulose and Starch Crosslinked with Radiation

Electron beam radiation was tested on CMC, HPC and starch as both dried coatings and as solutions. The cationic starch at first showed promise, as it had some slipperiness after one dose of radiation as a dried coating on the POBE catheter. It was however judged that it was not slippery enough, and that the coating was too thin. It did not crosslink at all when placed as a solution in the plastic container. The oxidised starch did not form a gel as a solution or as a dried coating. The same

was true for the CMC samples. The HPC underwent some minor crosslinking as a solution, forming clumps of gel, but no crosslinking as a dried coating. The sample of cationic starch and PVA formed clumps of gel as a solution, but these clumps were not very slippery. As a dried coating it provided a little bit of slipperiness. The sample of oxidised starch and PVA formed a complete gel as a solution, but not a very slippery one. As a dried coating it was not very slippery. As the two samples with PVA did not have sufficient slipperiness, and because they had a relatively low percentage renewable polymer, they were both eliminated. In the end, all methods that used the electron beam for crosslinking were eliminated.

4.2.3 Cellulose and Starch Crosslinked with Citric Acid

The methods that were judged to be plausible candidates for a hydrogel coating were CMC with citric acid, HPC with CMC and citric acid, HPMC with CMC and citric acid and HEC with CMC and citric acid. All of these formed a cohesive hydrogel, were sufficiently slippery and coated the POBE catheter well.

The ones that were eliminated were HEC with citric acid, due to very low swelling and slipperiness, and HPMC with citric acid, due to lack of crosslinking. Both combinations of cationic starch with citric acid only and cationic starch with CMC and citric acid were also all eliminated. The solution of cationic starch with citric acid did not crosslink, and the solution of cationic starch with CMC and citric acid did crosslink but had poor coating properties. HPC with citric acid was not tested, since testing of HEC and HPMC with only citric acid had already been carried out at that point, with disappointing results. It was therefore judged that CMC was a vital component in order to get sufficient swelling, and slipperiness, of the hydrogel.

4.2.3.1 Adjustment of Parameters

The best combinations of the parameters total polymer concentration, citric acid concentration and time in the oven for the hydrogels made from cellulose ethers are presented in Table 3.3. These were the parameters used to make the final hydrogel samples, which were later analysed with various techniques. For the CMC hydrogel it was found that the best oven time was 3 hours, in combination with 2 wt% polymer solution and 20 % w/w citric acid. The full 3 hours were needed due to low crosslinking efficiency in the hydrogel with only CMC. For the HPC/CMC hydrogel it was found that the best combination of parameters was 1.5 wt% polymer solution, 20 % w/w citric acid and 2 hours in the oven. For the HPMC/CMC hydrogel it was found that the best combination of parameters was 1 wt% polymer solution, 20 % w/w citric acid and 2 hours in the oven. All higher polymer concentrations failed to crosslink. Finally, for the HEC/CMC hydrogel it was found that the best combination of parameters was 2 wt% polymer solution, 5 % w/w citric acid and 1.5 hours in the oven. This hydrogel had very efficient crosslinking and needed much lower citric acid concentration and time in the oven than the other hydrogels.

4.3 Results from the Analytical Techniques

In this section the results from the various analytical techniques used on the final samples are presented and discussed.

4.3.1 Viscosity of the Cellulose Ether Solutions

The measured viscosities of the cellulose ether aqueous solutions used as hydrogel coatings are presented in Table 4.2 below. The viscosities are presented in centipoise (cP). The rotational velocity in revolutions per minute (rpm) used for the measurements and the torque in % that resulted from the measurements are also presented. To put the viscosities into context the Table also has values for total polymer concentrations in wt% in the measured solutions, as well as the average molecular weights in kDa of the different polymers used in the solutions as stated by the suppliers, since the viscosity is dependent on these parameters.

Table 4.2: Viscosities of the cellulose ether solutions used to make hydrogels, as well as rotational velocities, torques, total polymer concentrations and molecular weights.

	CMC	**HPC /CMC**	**HPMC /CMC**	**HEC /CMC**
Viscosity [cP]	275	80	104	2 833
Rotational velocity [rpm]	9	30	23	1
Torque [%]	83	80	80	85
Total polymer concentration [wt%]	2.0	1.5	1.0	2.0
Molecular weights [kDa]	95 (CMC), 395 (CMC)	75 (HPC), 95 (CMC), 395 (CMC)	500-600 (HPMC), 95 (CMC), 395 (CMC)	1 300 (HEC), 95 (CMC), 395 (CMC)

As evident from Table 4.2 there is a great difference between the viscosities of the four cellulose ether solutions. These viscosities were not adapted for manual coating. They were instead the result of using a solution with as high polymer concentration as possible while still being able to perform crosslinking on the POBE tube. For example, the HPMC/CMC solution would not crosslink at higher concentrations than 1 wt%.

As stated in Section 2.7.1 the viscosity of a polymer solution can be impacted by both the concentration and the molecular weight, with the presence of polymer entanglements in the solution being a key to high viscosity. It is also affected by the solubility of the polymer, and how it is oriented in solution. A polymer in a good

solvent can be stretched out, making entangling much easier, while a polymer in a bad solvent is more coiled up in itself.

This analysis makes it possible to get an overview of these relationships, between viscosity, concentration and molecular weight, for the cellulose ethers used to make hydrogels. All of these parameters do affect the hydrogels in some way, and it is not possible to say which of the parameters affect the viscosity the most only from this analysis. In a future large-scale process application, viscosity is an important parameter. It should be appropriate for dipping, so it should not be too high nor too low, but it is difficult to say any exact value that is appropriate. It is therefore not possible to say which polymer solution is best suited to a process application at this stage, as the solution parameters are not optimised.

The HEC/CMC solution has a much higher viscosity than any of the others. This is because the HEC used in the solution is of a very high molecular weight. The HEC/CMC solution also has a relatively high concentration. The HEC/CMC solution can be compared to the CMC solution, which has the same concentration, but no component with such high molecular weight. The viscosities of these two are very different, with the HEC/CMC solution having more than 10 times as high viscosity. The higher viscosity can also cause a thicker layer of solution to coat the POBE catheter in the manual coating. This could give a thicker coating, but it should also be noted that this high viscosity results in dripping after dip coating and is not a suitable viscosity for a coating process.

The HPMC/CMC solution has a lower viscosity than the solution with only CMC. The HPMC used has a higher molecular weight than the two kinds of CMC used, but the concentration is lower. The lower concentration is likely the reason for the lower viscosity. HPMC is also not as hydrophilic as HEC and might coil up more in solution, decreasing the number of polymer entanglements. However, the molecular weight of HPMC is much lower than the one for HEC, which makes comparison between the solutions a bit difficult.

The HPC/CMC solution has both a lower concentration than the CMC solution and a low molecular weight component. It is no surprise that the viscosity of this solution is low. HPC may also have a low hydrophilicity, depending on the MS, which may result in a lower R_G. This would decrease the amount of polymer entanglements in the solution. The low molecular weight and low concentration would also contribute to a low number of entanglements.

4.3.2 Size Exclusion Chromatography

The measurements made with Size Exclusion Chromatography (SEC) were not conclusive. Due to a lack of literature parameters (dn/dc and Mark-Houwink constants) the accuracy of the molecular weight calculations was not satisfactory. The measurement of the HPC sample was not detectable at all, likely due to precipitation as the sample reached its cloud point during analysis, as the temperature went above 35

°C. The analysis did however give information about the relative molecular weight distributions of the remaining four cellulose ethers.

The plot of retention time against refractive index is presented in Figure 4.1. In accordance with the principles of SEC, the larger molecules eluate first, so in the plot the peaks farther to the left have a higher average molecular weight. According to the plot, when the measured cellulose ethers are compared, HEC has the highest molecular weight, HPMC and the high molecular weight CMC have fairly similar molecular weights, and the CMC with the lower molecular weight has the lowest weight of the four cellulose ethers. The data for HPC can be seen in the graph, but no peak resulted from the measurement. All measured cellulose ethers have quite regular (although wide) distributions, with one single clear peak.

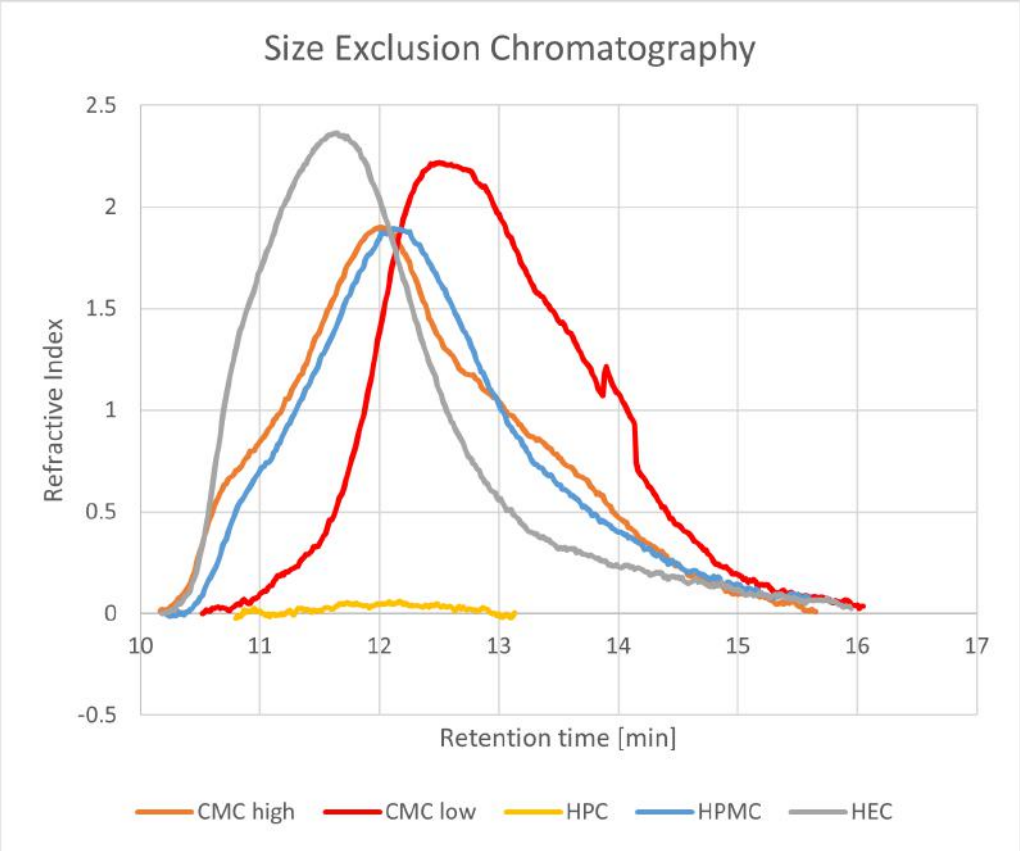


Figure 4.1: Plot showing the results from the SEC measurement, with retention time plotted against the refractive index.

The distribution of the measured peaks lines up quite well to the reported values for molecular weight from the producers of the cellulose ethers. The main inconsistency is the closeness of the peaks for HPMC and the CMC with high molecular weight. The HPMC should be the larger one, but according to the measurement the CMC eluates first. It is possible that these issues are due to some interaction between the column material and the cellulose ethers, as it is selected for analysing PVP. Since CMC is charged it could have some interaction, attractive or repulsive. It is also

possible that, because the mobile phase had ions, the hydrodynamic volume of the CMC was affected in some way that the other cellulose ethers were not. Another unexpected result from the SEC measurement was the big overlap in the peaks for the different polymers. This indicates a very large dispersity in the polymers.

4.3.3 Manual Evaluation

The first method to be used in the assessment of a new coating was manual evaluation. Here the coating was graded on a five point scale, and was either passed or not. For slipperiness a passing grade was four and above. For coating release a passing grade was as close to four as possible, with both higher and lower values being undesirable. In this section the manual evaluation results of the final cellulose ether, TPS and reference samples are presented.

Slipperiness is similar to a manual version of the friction test. Here both PVP coated surfaces, the reference and TPS, scored the highest value 5. HPMC/CMC scored second best, with 4.5. While some areas of the HPC/CMC coating scored 4.5 other areas of the same surface were not as slippery and it was deemed a 4. HEC/CMC also scored a 4, probably due to the sample being overly crosslinked. And lastly the surface coated with only CMC scored the worst at 3.5. A slipperiness grade of 4 or below is considered as too low, i.e. the CMC coating did not pass this evaluation.

The second parameter that was evaluated was coating release. The target was to have some coating slip away from the surface, but not too much, as some coating release is beneficial, to further decrease the friction. The coating release is dependent on both the crosslinking density, and on the thickness of the coating. The reference scored a 4, which is a benchmark. Both HPC/CMC and HEC/CMC scored a 4.5, releasing less than the reference. HPMC/CMC released even less and scored 4.75. The CMC sample was not assessed in this category, since it failed in the slipperiness test. The TPS sample with PVP was worst with a score of 3.75, and released too much coating to pass.

Overall, the coating that performed best in the manual evaluation were the HPMC-/CMC, due to its slipperiness and low coating release. Nevertheless, it did not perform as well as the reference with PVP coating. All of the cellulose ether hydrogels, with the exception of the pure CMC one, performed well, indicating that a sufficient hydrogel had been formed. This also indicates that the hydrogel needs a combination of CMC together with another cellulose ether, in order to coat the catheter sufficiently and consistently enough. Surprisingly, the HEC/CMC hydrogel was deemed overly crosslinked, despite it having the lowest concentration of citric acid and shortest time in the oven. This combination would probably need a lower concentration of citric acid in order to receive a better score in the manual evaluation of slipperiness. The TPS catheter with PVP coating scored badly with coating release, propably due to insufficient chemical bonding between the hydrogel and TPS surface.

This analysis method is highly subjective and is as told before only done by a certain experts at Wellspect HealthCare. In one way this method relies on the experience and knowledge of the expert, but it is impossible to avoid the possibility of two persons doing a different evaluation of the same samples. Fortunately, even though the assessments might differ, it will still give a a good indication of the potential of a new coating.

4.3.4 Friction Measurement

The mean values of the coefficients of friction (COFs) for each sample type, for each of the five strokes, along with standard deviations are presented in Figure 4.2. The calculated COF values for each stroke and sample are presented in Table A.1 in Appendix A.

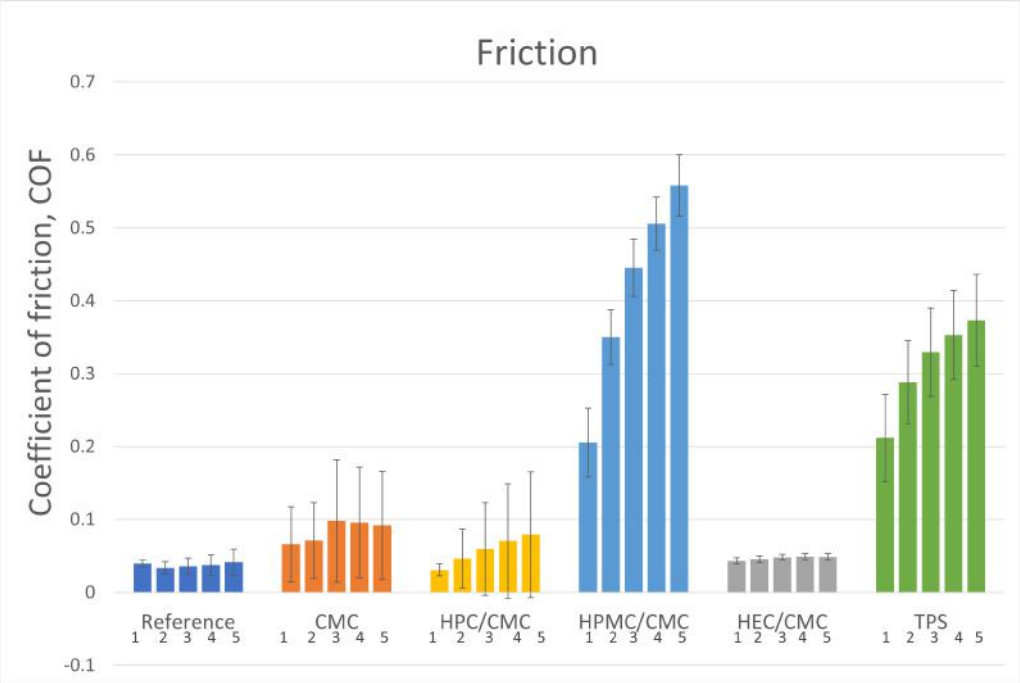


Figure 4.2: Chart showing the mean values and standard deviations for coefficient of friction, COF, measured for all sample types. Five strokes for each sample are shown as 1, 2, 3, 4, 5.

The HEC/CMC hydrogel got values closest to the reference with the PVP coating, with little deviation between the samples. This despite that the HEC/CMC hydrogel wasn't assessed as very slippery in the manual evaluation. This could be a case of the hydrogel being overly crosslinked, and while this could result in good friction values, as has been known to happen in the past at Wellspect HealthCare, the overall assessment of slipperiness by hand is not the same.

Both CMC and HPC/CMC received low mean values but large standard deviations. Of the five CMC samples, two of them received values for COF that were 10 times

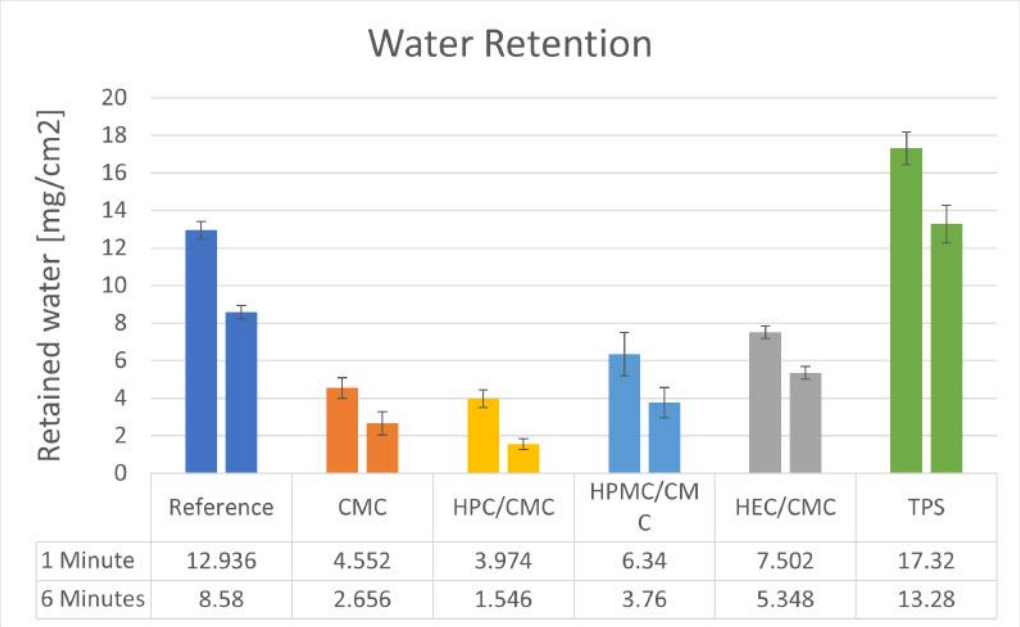
higher than the other three. This is probably due to dry spots on the catheter, that for some reason had not been coated, or had a very thin coating. This variation of the coating was also observed in the manual evaluation of slipperiness. These outlier values were kept in order to show the inconsistency of the CMC-hydrogel's ability to successfully coat the surface, due to some unknown factor. A similar issue occurred to one of the five analysed HPC/CMC samples, where the COF's values became 10 times higher due to a presumably non-coated spot at the POBE catheter. This resulted in the standard deviation being greater than the mean value in the three last strokes.

HPMC/CMC received high COF values despite being the one which performed best at the manual evaluation. A second test was performed, on samples manually coated at a different date, to exclude the possibility of a bad batch, caused by the manually done coating process. However, these HPMC/CMC coated catheters showed the same pattern. The values could maybe be explained by a bad drying process, resulting in droplets forming and roughening the coated surface, which affected the friction measurement, however this is debatable. The PVP coated TPS samples had no noticeable non-coated or dry spots, but simply scored high values for COF. A possible explaination for this, is that the coating, due to not being fully attached to the TPS catheter, was scraped of during the test.

This is a result is based on five samples of each hydrogel, which did give some variation in the measurements, with the HPC/CMC and CMC coatings, but it would probably need more replicas in order to do make a definite conclusion. Another aspect is that the friction measurement method is customised for the PVP coating, with regards to wetting and drying times. There is a possibility that the cellulose ether hydrogels might absorb water faster and do not need the extra seconds that are required for PVP. Furthermore, the waiting time could result in the cellulose ether hydrogels drying out more than necessary, and thereby receiving a higher COF value.

4.3.5 Water Retention

The mean values of the water retention measurements of each sample type are presented in Figure 4.3, with the standard deviations of the measurements presented as error bars. Two values are presented for each sample type, representing the two different drying times of 1 minute and 6 minutes. The target value for the water retention after 1 minute is 10 mg/cm^2, with 8 mg/cm^2 being the lowest acceptable. The two sample types coated with PVP, reference and TPS, scored the highest, while the CMC and HPC/CMC samples scored the lowest. The reference sample has a retention that is a bit high, and the TPS sample has a much too high value. None of the cellulose ether coatings reach the benchmark of 8 mg/cm^2.



	Reference	CMC	HPC/CMC	HPMC/CMC	HEC/CMC	TPS
1 Minute	12.936	4.552	3.974	6.34	7.502	17.32
6 Minutes	8.58	2.656	1.546	3.76	5.348	13.28

Figure 4.3: Chart and table showing the mean values and standard deviations for the water retention measurement. Values were measured in mg/cm^2 after drying for 1 and 6 minutes.

This method of measuring water retention is adapted to analysis of PVP hydrogels. Because of that it is not certain whether the times for wetting and drying are optimal for cellulose ether hydrogels. The measurements were made on five samples from each sample type, and the distribution of values are similar for all samples. This makes the analysis reliable. The most likely source of error is the length measurements by hand that were taken before analysis. There could be some slight errors in the measurements of the length of the coatings on the samples, which could cause errors in the calculations of water retention.

The two samples coated with PVP, the reference and the TPS, should have similar water retentions. However, TPS has a much higher value. Through testing it was established that this is not due to any water absorption by the TPS material. The higher water retention could be a result of either a thicker coating or a lower degree of crosslinking, or a combination of the two. If the coating is thicker, then there is more PVP available to absorb water. If the degree of crosslinking is different between the TPS sample and the reference sample, then that could affect the value of water retention since the degree of crosslinking and swelling capacity are connected. This correlation between crosslinking and swelling is described in Section 2.5. The higher coating release observed in the manual assessment also indicated lower crosslinking of the PVP on the TPS catheter.

In theory, CMC is the cellulose ether that should contribute most to the swelling, due to the counter ion effect. In the hydrogel coating with only CMC, however, the water retention is comparatively low. This is likely due to poor crosslinking, which

can also decrease the swelling capacity of a gel. As stated in Section 2.8.2, CMC on its own has low crosslinking efficiency. This was also made clear in the hydrogel crosslinking process, where this gel needed the most time in the oven to crosslink. It is clear that the water retention is better when an additional cellulose ether like HEC or HPMC is added, which improves the crosslinking efficiency.

All four cellulose ether samples had fairly similar water retention values, and none of them passed the benchmark. This in likely due to the coating being too thin, and is a property that could probably be improved. It would seem that the cellulose ether sample that absorbed the most water was the HEC/CMC sample. This sample was deemed to be overly crosslinked in the manual evaluation. If this is true, then a better tuning of the crosslinking could lead to an even higher water retention in future, since the swelling could be improved by a decrease in crosslinking. The reason for the HEC/CMC hydrogel having the highest water retention could be that HEC is more hydrophilic, or have a higher molecular weight than HPMC and HPC.

It seems that the HPC/CMC sample dries out faster than the other cellulose ether samples. It loses more than half of its retained water after 6 minutes compared to after 1 minute. The other three cellulose ether coatings seem to retain a larger amount of their water after 6 minutes of drying time. None of the cellulose ether hydrogels appear to dry out completely after 6 minutes, which is a good sign that they can be useful in this application.

The thickness of the hydrogel also affects the water retention and the different cellulose ethers could have different coating thickness. The solutions used when making the coatings did not have the same viscosities and concentrations due to variations in molecular weights, and both these parameters are known to influence the coating thickness. The PVP coating was most likely thicker than the cellulose ether hydrogels since it was made in two coating layers.

4.3.6 Contact Angle

The images and recorded water contact angles of the different sample types are presented in Appendix A in Figures A.1 to A.6. The average values of the contact angles for each coating are presented in Figure 4.4, with the standard deviations as error bars. The two PVP coated samples, reference and TPS, have the two highest contact angles, and the CMC hydrogel has the lowest contact angle. Among the cellulose ether hydrogels there are large differences in contact angles. There is no set benchmark value for contact angle in this application.

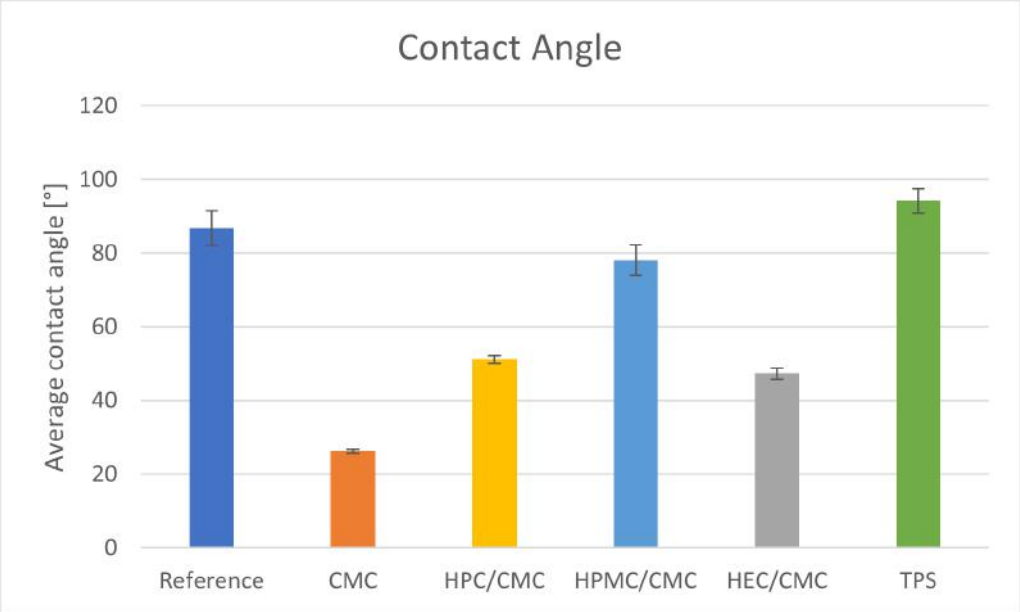


Figure 4.4: Chart of the average values of the measured water contact angles of all sample types, with standard deviations.

This method of measuring contact angles is widely used and reliable, but mostly on materials which don't absorb water and swell. What might affect the results in this study is that for each sample type only one sample was used in this measurement and taken to be representative of the whole sample group. There were also only three measurements taken on each surface. This slightly decreases the reliability of the data since any irregularities or bumps in the coating can affect the recorded contact angle. On the whole, however, this is judged to be a reliable method.

From Figure 4.4 it is clear that the PVP coated samples have higher contact angles than the cellulose ether coated ones. This is likely due to the fact that a PVP hydrogel needs some time to absorb water, possibly because the hydrophobic part of the PVP molecule becomes oriented toward the surface during drying. PVP is not instantly wettable by water in the same way that the cellulose ether hydrogels seem to be.

There is a large variation of contact angles within the cellulose ether samples. This is likely due to either the difference in hydrophilicity between the ethers, or to differences in degree of crosslinking. It is known that HEC is more hydrophilic than HPMC and HPC. This holds true as the HEC/CMC sample has a slightly lower contact angle than the HPMC/CMC and HPC/CMC samples. The sample with only CMC has a much lower contact angle than the others, and it is also more hydrophilic, since it is a polyelectrolyte. The concentration of citric acid, and by extension the degree of crosslinking can also affect the contact angle, as demonstrated by Dharmalingam and Anandalakshmi [46]. In their report the contact angle decreased with higher concentrations of citric acid. In this case, however, it is most likely that the difference in contact angles stems from the differing hydrophilicity of the cellulose

ethers. It is not possible to say which of the cellulose ethers had the preferable contact angle, as there is no such value for this application.

4.3.7 Optical Microscope

Optical microscope pictures were taken with 4x enlargement for the surfaces and 40x enlargement for the cross-sections. All the different samples surfaces were examined except TPS (since this material cannot transmit light). In addition to this, only one measurement of each sample, both surface and cross-section, is presented, except for the reference sample. A correct thickness of the coating is hard to assess due to the variation of the dry coating and of swelling layer of the hydrogel, and the lack of contrast in the images. Therefore, these values should be read as an indication more than an absolute.

In Figure 4.5 the uncoated POBE catheter is presented. The surface is rough and uneven, the structure of which would not be visible under a sufficiently thick coating layer.

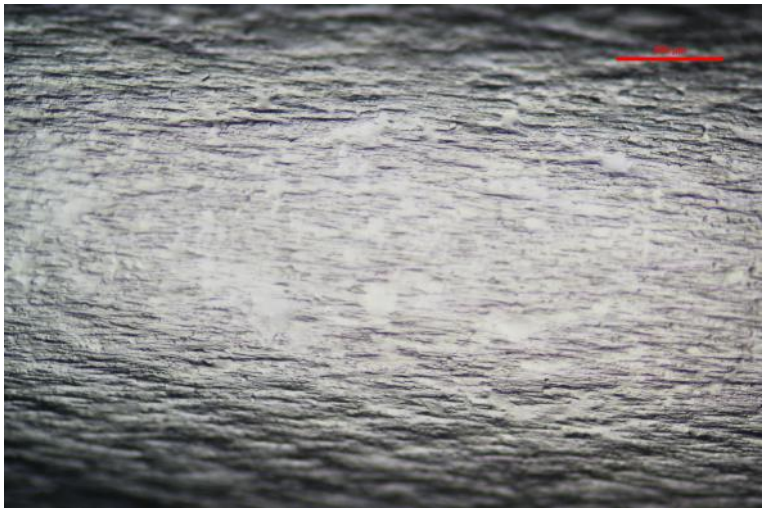


Figure 4.5: Optical microscope picture of the uncoated POBE catheter, red bar showing a scale of 500 µm.

In Figure 4.6 an image of the reference surface with the current PVP coating is shown. As can be seen in the picture, there is a large crack in the coating. This crack is present throughout the whole surface. Overall, there is a lot of minor cracks and the surface looks wobbly but uniformly coated and one can barely make out the rough surface underneath.

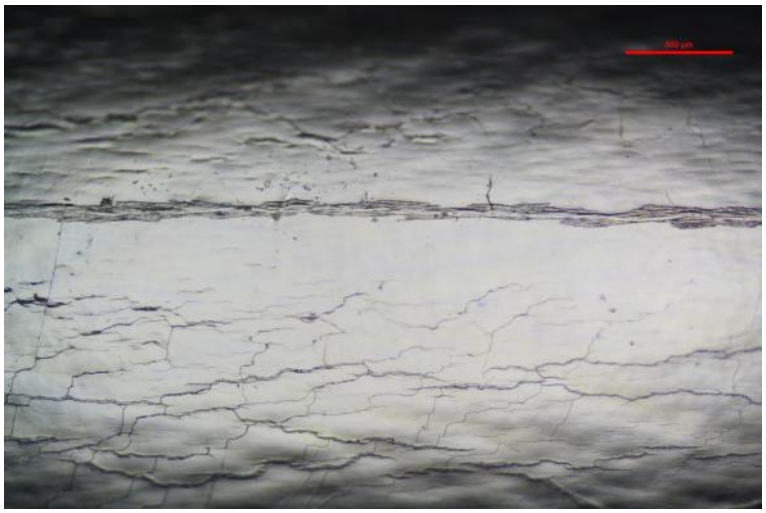


Figure 4.6: Optical microscope picture of the reference surface, with a double layer of PVP coating, red bar at upper right corner of each picture, shows a scale of 500 µm.

Figure 4.7 shows a cross-section of the PVP coated reference. In these images the cross-section of the catheter is visible in the upper right-hand corner, with the coating visible as a darker line. On the left the sample is dry and has a thickness of about 7 µm while the wet sample is shown to the right and has a thickness of about 62 µm resulting in roughly a 9 times increase.

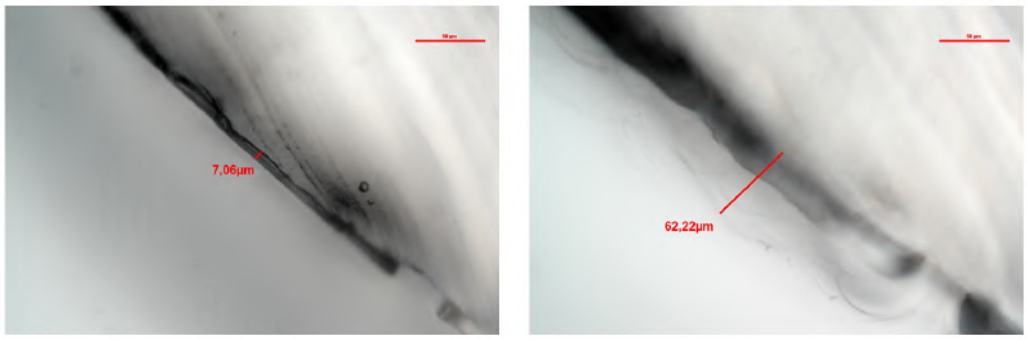
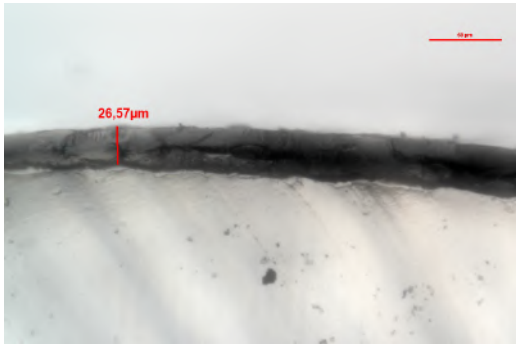


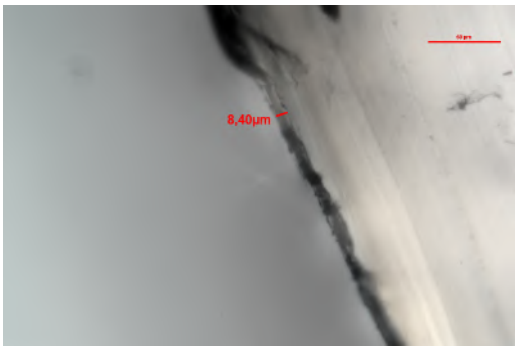
Figure 4.7: Optical microscope picture of the cross-section of PVP coated reference surface, left showing a dry sample with a layer thickness of about 7 µm, and the right showing a wet sample with a thickness of about 62 µm. Red scale bar in the upper right corner, shows a distance of 50 µm

This pair of images show the comparison between the dry and wet coating well, but the thickness of the dry coating may be misleading, and not representative. In Figure 4.8 there are images presented of other sites on the dry cross-section of the reference sample, showing other thicknesses. Figure 4.8a shows a coating thickness

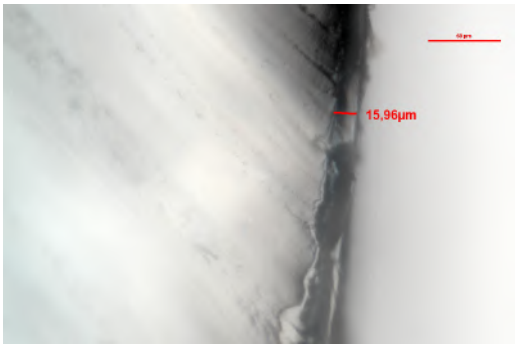
of about 27 µm, Figure 4.8b a thickness of about 8 µm and Figure 4.8c a thickness of about 16 µm. This displays a great variation in coating thickness for the PVP reference sample.



(a) Optical microscope picture of the dry cross-section of PVP coated reference surface, with a coating thickness of about 27 µm. The catheter is visible in the lower half of the image.



(b) Optical microscope picture of the dry cross-section of PVP coated reference surface, with a coating thickness of about 8 µm. The catheter is visible in the right side of the image.



(c) Optical microscope picture of the dry cross-section of PVP coated reference surface, with a coating thickness of about 16 µm. The catheter is visible in the left side of the image.

Figure 4.8: Optical microscope pictures of the dry cross-section of PVP coated reference surface, all showing different coating thicknesses. Red scale bar in the upper right corner, shows a distance of 50 µm

The different cellulose ether coated surfaces are presented in Figures 4.9 to 4.15. They all share common traits, where the most prominent is the structure of the underlying surface compared to the reference coating, indicating a thin coating. The different cellulose ether coatings do not appear to provide as thick of a one layer coating as the double layer PVP coating, since this roughness can show through.

In Figure 4.9 the coating only containing CMC is shown. The coating appeared to be unevenly spread across the area and additional pictures of this are found in

Appendix A in Figures A.7 to A.9. The picture shows an area where the surface appears to be less coated on the left side of the image and more coated on the right side.

Figure 4.9: Optical microscope picture of CMC (2 wt%) coated POBE catheter, red bar showing a scale of 500 µm.

The cross-section for the CMC sample is shown in Figure 4.10 below. In these images the cross-section of the catheter is visible in the upper right-hand corner, with the coating visible as a darker line. The picture to the left shows the dry sample, and a coating thickness of about 7 µm, the right the wet coating with an increased thickness of about 41 µm. This results in an almost 6 times enlargement.

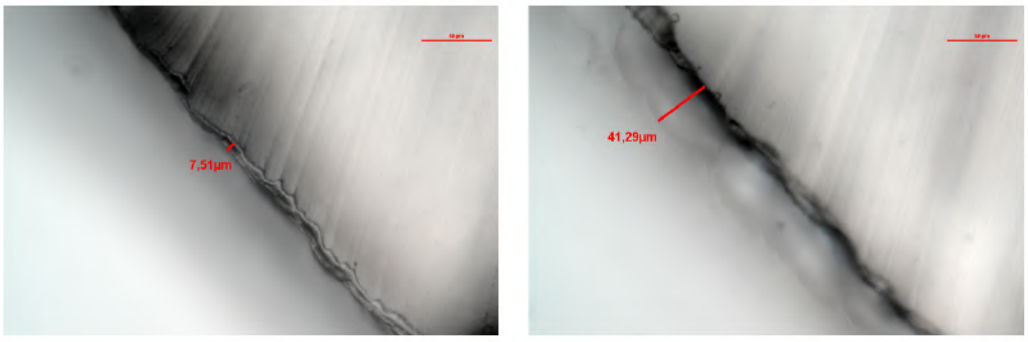


Figure 4.10: Optical microscope picture of the cross-section of CMC (2 wt%) coated POBE catheter, left showing a dry sample with a layer thickness of about 7 µm, and the right showing a wet sample with a thickness of about 41 µm. Red scale bar in the upper right corner, shows a distance of 50 µm

In Figure 4.11 the surface with HPC/CMC is presented. The coating appeared very

thin, based on the roughness of the underlying POBE catheter, and cracked in thin lines diagonally across the area, during the sample preparation for the microscope study.

Figure 4.11: Optical microscope picture of HPC/CMC (1.5 wt%) coated POBE catheter, red bar showing a scale of 500 µm.

The cross-section of the HPC/CMC coating is shown in Figure 4.12. In these images the cross-section of the catheter is visible on the right-hand side, with the coating visible as a slightly lighter line. The dry sample on the left has a coating thickness of about 6 µm and a wet coating thickness of about 20 µm shown on the right. This results in an increase of above 3 times.

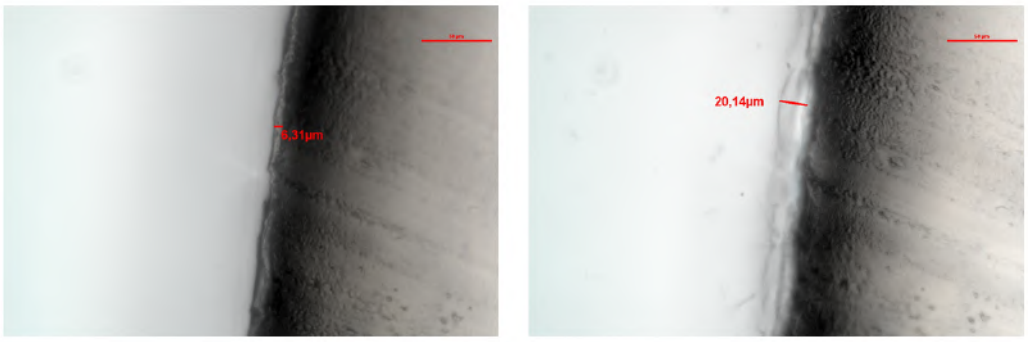


Figure 4.12: Optical microscope picture of the cross-section of HPC/CMC (1.5 wt%) coated POBE catheter, left showing a dry sample with a layer thickness of about 6 µm, and the right showing a wet sample with a thickness of about 20 µm. Red scale bar in the upper right corner, shows a distance of 50 µm

The coating containing HPMC/CMC is shown in Figure 4.13. The coating seems to be, like the other cellulose based hydrogels, thinner than PVP, based on the

roughness of the underlying POBE catheter, although no cracks were visible from the cutting.

Figure 4.13: Optical microscope picture of HPMC/CMC (1 wt%) coated POBE catheter, red bar showing a scale of 500 µm.

In Figure 4.14 the cross-section for the HPMC/CMC sample is shown. In these images the cross-section of the catheter is visible on the right-hand side, with the coating visible as a darker line. This sample showed a very small increase in size when wetted, from 4 µm when dry to 15 µm. This results in an increase of a little more than 3 times.

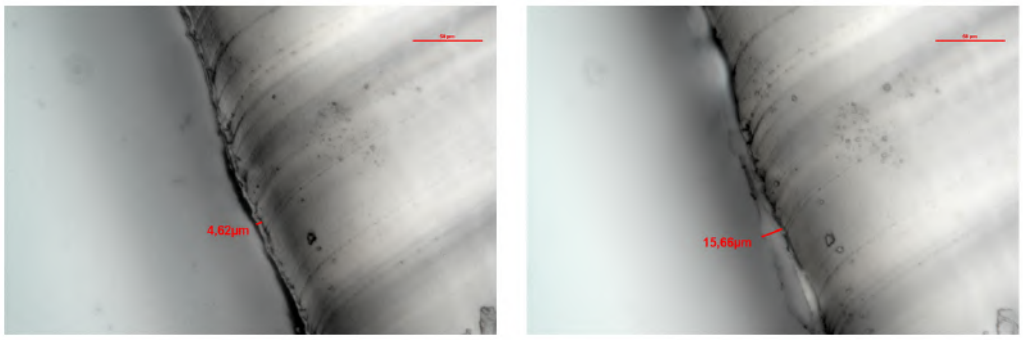


Figure 4.14: Optical microscope picture of the cross-section of HPMC/CMC (1 wt%) coated POBE catheter, left showing a dry sample with a layer thickness of about 4 µm, and the right showing a wet sample with a thickness of about 15 µm. Red scale bar in the upper right corner, shows a distance of 50 µm

Figure 4.15 shows the coating of HEC/CMC. Here small vertical markings are visi-

ble. These might have appeared as the sample was bended. Otherwise, the shadows might indicate a thicker coating than the other cellulose ether coatings, and more depth in the photo.

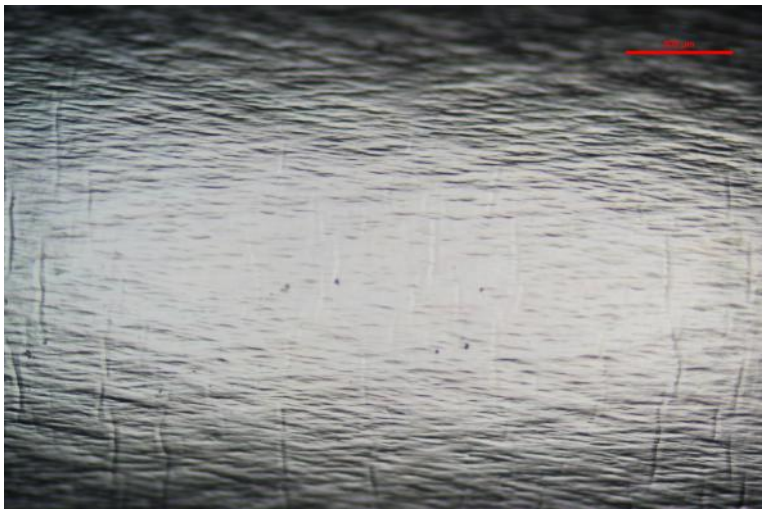


Figure 4.15: Optical microscope picture of HEC/CMC (2 wt%) coated POBE catheter, red bar showing a scale of 500 µm.

Lastly in Figure 4.16 the cross-section for the HEC/CMC sample is shown. In these images the cross-section of the catheter is visible in the upper right-hand corner, with the coating visible as a slightly darker line. The dry coating had a thickness of about 5 µm and the wet 28 µm. This results in an increase of almost 6 times.

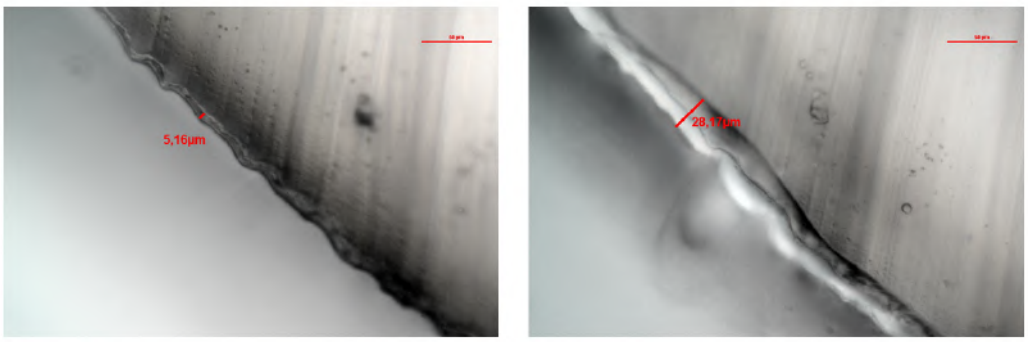


Figure 4.16: Optical microscope picture of the cross-section of HEC/CMC (2 wt%) coated POBE catheter, left showing a dry sample with a layer thickness of about 5 µm, and the right showing a wet sample with a thickness of about 28 µm. Red scale bar in the upper right corner, shows a distance of 50 µm

From the surface pictures, there is an obvious indication that the cellulose ether coatings are thin, because of the rough structure from the POBE catheter that is

clearly seen on every sample but the reference. An additional explanation for this, is that the reference catheters are double coated, in accordance with the LoFric® products. The extra coating could possibly explain the smoother surface, and also the higher thickness and swelling ability.

The cross-section pictures are interesting, but assessing their reliability is quite hard. The edges of the coating will always be up to a subjective estimation, and factors as the thickness of the catheter cut-out piece, contrast of the microscope and focus is of importance when judging the thickness of the coating. The cut can also make some of the coating smear over the edge, which could lead to the coating thickness appearing larger than it actually is. The main issue, as seen with the reference sample, is that the coating may be uneven and thicker in some places and thinner in others. It is very difficult to know whether the images captured with the optical microscope are representative. These images cannot give a conclusive result of the coating thicknesses of these samples, but they give a good indication of the difference in thickness between the dry and wet coatings.

One thing that might explain the results is the POBE catheter. There is a slight difference in the surface structure on the cross-section pictures, just at the edge of the catheter. Between the reference PVP coated POBE and the cellulose ether coated POBE, there appears to have happened something with the catheter. The cellulose ethers POBE catheter appears to be more uneven and rugged. Since the cellulose ether POBE catheters were put in the oven at 90 °C for 1.5 to 3 hours, depending on the hydrogel, this might have caused the POBE catheter to shrink and change its surface structure. In turn, this might affect how the cellulose ether catheters feels when manually assessed, and looks, when assessing the coating through the microscope.

Compared to the water retention result in Section 4.3.5, these results regarding coating swelling don't align with each other. The reference is, once again, better at swelling than the cellulose ether hydrogels, but it appears as though CMC is the hydrogel that swell the most in this analysis. Despite this, it wasn't assessed as the cellulose hydrogel that retained the most water, it was second to last. The reason for this could be explained by the results in Section 4.3.6. Here the results from the contact angle measurement shows that the CMC hydrogel has the lowest contact angle. The CMC hydrogel might be better at water uptake, at first contact with water, but not so good at retaining it after 1 or 6 min, as tested in the water retention method.

There are sources of error for these results, and as previously discussed, they are the subjective estimation of the coating's edges as well as few replicas. For the surface pictures, only one catheter was used. While a few cut-outs where studied when taking the cross-section pictures, these were taken from the same catheter sample. To get more reliable measurements, there has to be a lot more samples studied. There is also a question, on how the cross-section cut should be performed, in order to retrieve a clean and clear sections of catheter and hydrogel, to study

in the optical microscope. While the method is fast and doesn't require the same amount of sample preparation as SEM, the cutting technique is of essence in order to receive good cut-outs. In addition to this, it requires a good knowledge, and experience, with optical microscopy in order to be certain of settings, contrast and shadows, to be able to tell what is there and what isn't. It would also seem that the coating is not always uniform, so a lot of images would need to be taken to get accurate results.

4.3.8 Scanning Electron Microscopy

In this section, the images from the SEM analysis are presented. For all samples, images were taken of the coated POBE catheter as seen from above, to see any cracks or abnormalities. For the TPS sample, images could also be taken of the cross-section of the coated TPS catheter, to see the thickness of the PVP coating. An image was also taken of the surface structure of the uncoated POBE catheter, see Figure 4.17, to compare to the coated surfaces. The image shows a rough and structured surface, in the direction of the tube length.

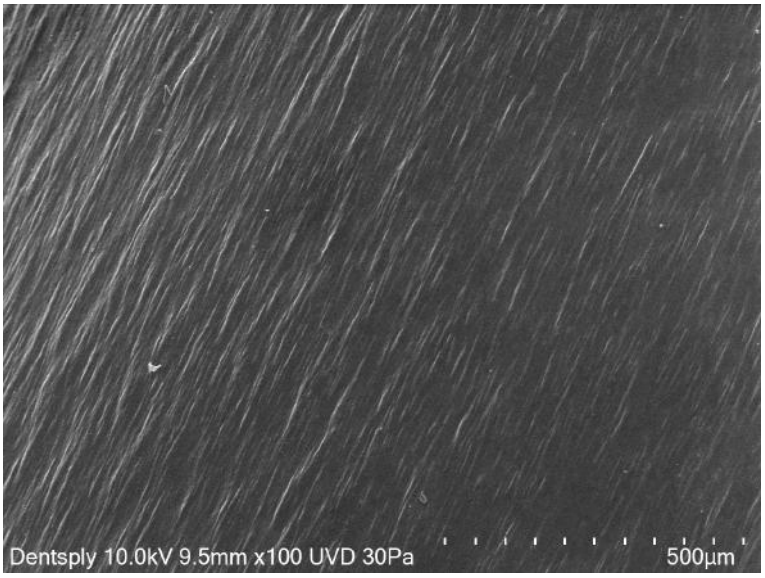
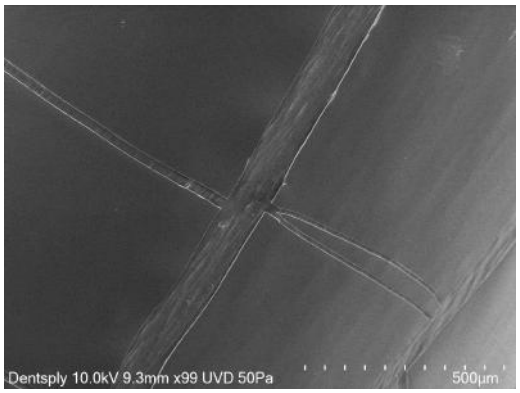
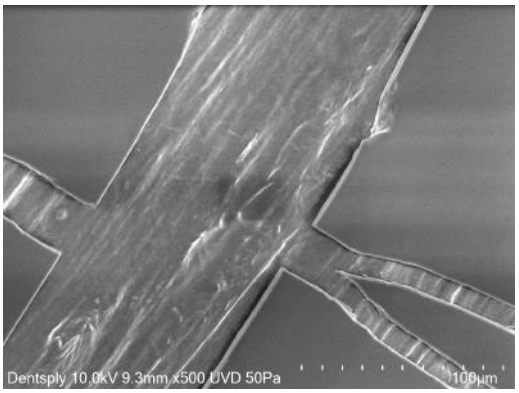


Figure 4.17: SEM image of the structure of the uncoated POBE catheter from above.

Figure 4.18 shows the reference sample, which is the POBE catheter coated with PVP. In Figure 4.18a an overview of the coating can be seen, along with several cracks. The coating appears smooth and thick, with no hint of the roughness of the POBE catheter showing through. In Figure 4.18b a close up of a crack is displayed, where the rough outline of the uncoated POBE catheter can be seen in the crack.



(a) SEM image of the reference PVP coating as seen from above.



(b) A close up SEM image of a crack in the PVP coating in the reference sample.

Figure 4.18: SEM images of the reference sample coated with PVP.

Figure 4.19 shows the image of the CMC coated sample. There are a few fine lines or cracks visible, and the roughness of the underlying POBE catheter can be seen through the coating.

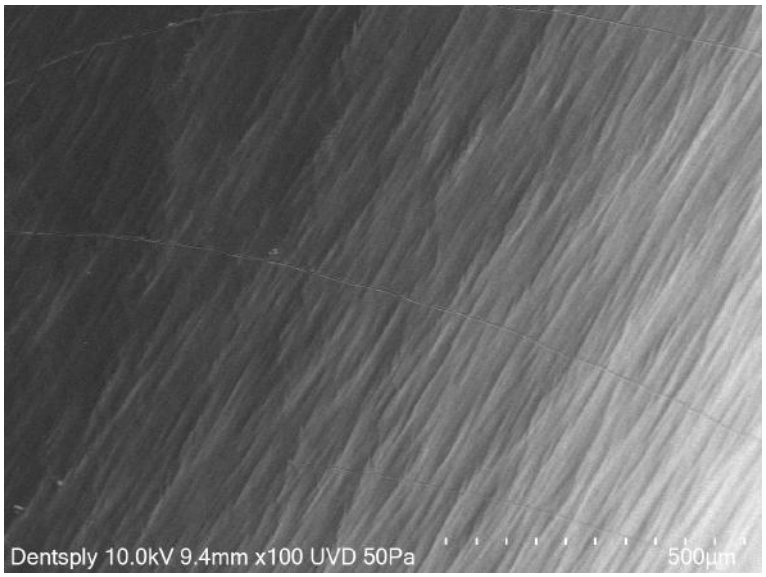


Figure 4.19: SEM image of the sample coated with CMC (2 wt%) as seen from above.

In Figure 4.20 the image of the sample coated with the HPC/CMC mixture is presented. The image shows the coated surface, with a few very fine lines and clear roughness from the underlying POBE catheter.

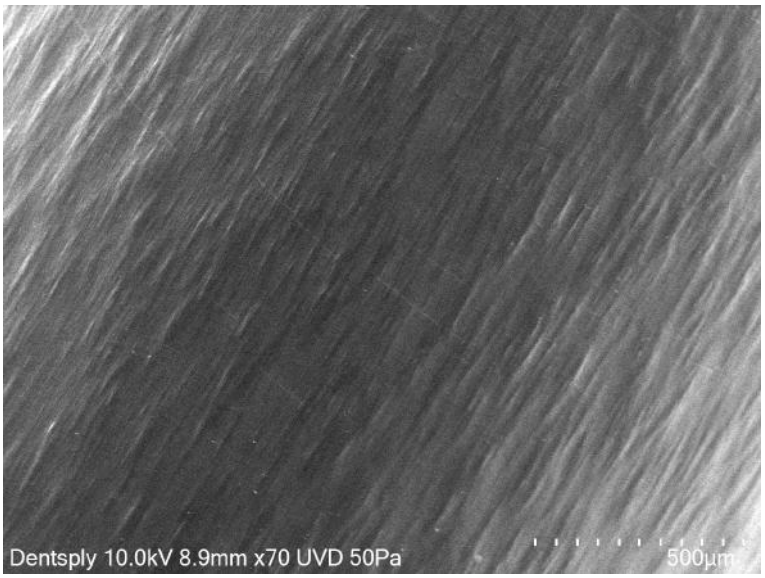


Figure 4.20: SEM image of the sample coated with the mixture of HPC/CMC (1.5 wt%) as seen from above.

The image of the sample coated with the mixture of HPMC/CMC is shown in Figure 4.21. The figure shows the coated surface. There are no clear lines or cracks, but a clear roughness from the POBE catheter below the coating.

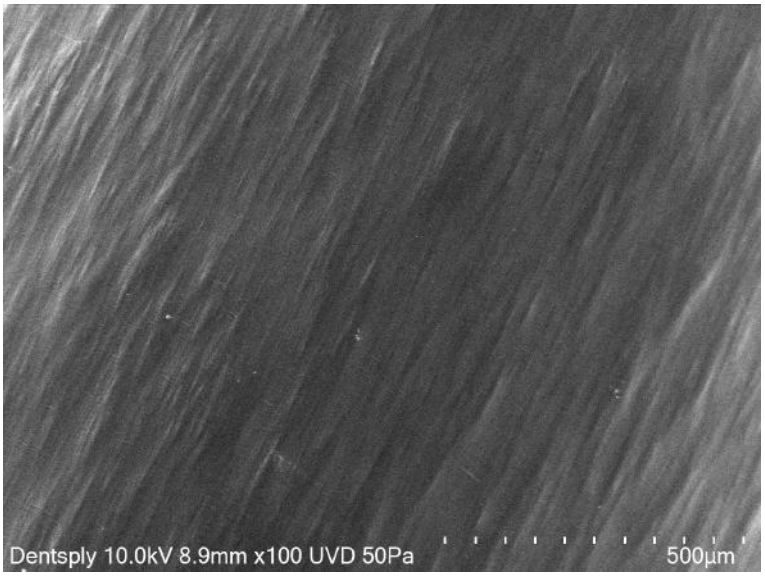


Figure 4.21: SEM image of the sample coated with the mixture of HPMC/CMC (1 wt%) as seen from above.

In Figure 4.22 the image of the sample coated with the mixture of HEC/CMC is presented. There is one clear crack running down the surface. There is also a bit of roughness showing in the coating from the POBE catheter below.

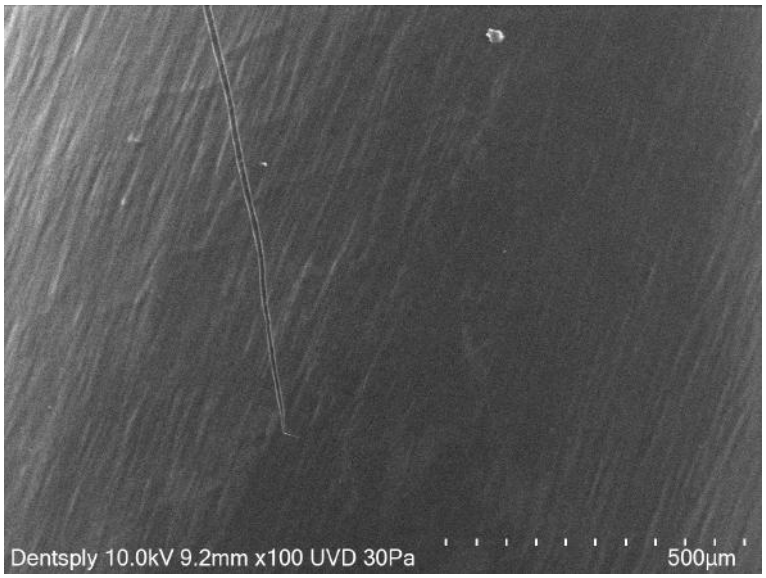
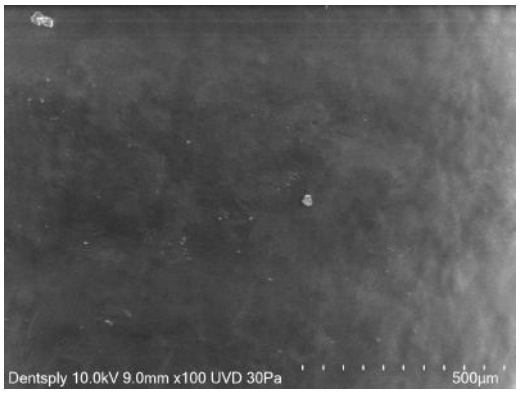
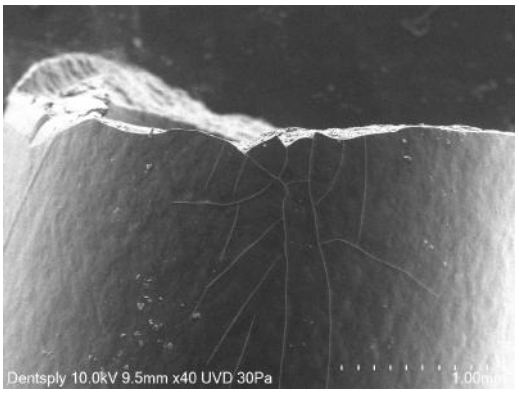


Figure 4.22: SEM image of the sample coated with the mixture of HEC/CMC (2 wt%) as seen from above.

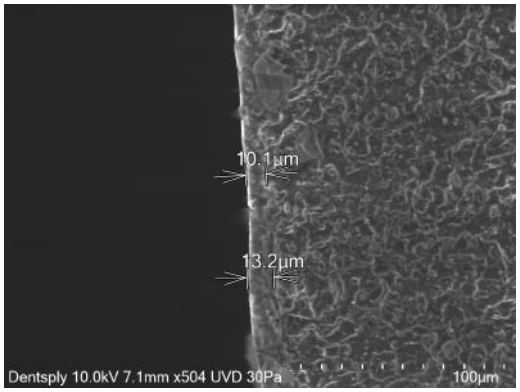
The images in Figure 4.23 show the sample of TPS coated with PVP. Figure 4.23a shows the coated surface from above. There are no cracks visible. Some structure is present in the coating, as well as some tiny granules of TPS which became stuck to the coated surface as the sample was cut into smaller pieces. Figure 4.23b shows some cracking in the PVP coating at the site where the sample was cut, as well as more of the TPS granules. Figures 4.23c and 4.23d both show cross-sectional images of the sample. In the images, measurements have been taken of the thickness of the PVP coating, indicating a thickness between 6 and 13 µm.



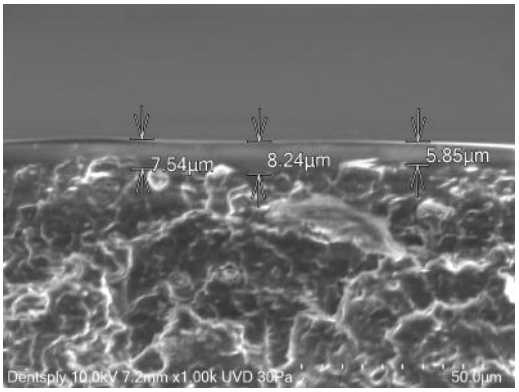
(a) SEM image of the coated TPS sample as seen from above.



(b) SEM image of the coated TPS sample as seen from above, at the site of the cut.



(c) SEM image of a cross-section of the coated TPS sample, with measurements. The catheter is visible on the right side of the image.



(d) SEM image of a cross-section of the coated TPS sample, with measurements. The catheter is visible on the lower half of the image.

Figure 4.23: SEM images of the TPS sample coated with PVP.

The SEM images of the surfaces as seen from above are very similar to the ones taken with the optical microscope. The uncoated POBE catheter had the same rough surface as seen in the optical microscope, and the reference sample looked smooth with prominent cracks in the same way. The images of the cellulose ether coatings showing the same roughness from the underlying POBE catheter. The HEC/CMC sample again showed slightly less structure than the other cellulose ether samples, which may be due to a thicker coating. This was also the sample with the highest water retention of the cellulose ethers.

The big difference in the two different microscope techniques is that in SEM, the TPS sample could be studied. This sample could also be imaged as a cross-section, since it could be snapped and had a clean break. The measured thickness of the coating showed great variation depending on where the measurement was taken. This could be due to an uneven coating or to an uneven TPS surface. It could also be due to the difficulty of determining exactly where the coating began. The measurements

were in the same size range as the measured thickness of the PVP coating on the reference sample from the optical microscope. This spread in thickness observed in SEM could possibly also be present in the other coatings measured in the optical microscopy images above, however only few samples were evaluated.

Clear cross-sectional images could not be taken of the reference or cellulose ether samples because the coating smeared when it was cut, making it very difficult to see where the coating ended and began. From this analysis it is not possible to make any conclusions of the thickness of the cellulose ether coatings. For this a clean cross-section would be needed. This could perhaps be attained with better cutting or some type of etching. There was an attempt made to ion etch the cross-sections, but this was not successful.

5

General Discussion

This chapter contains the overall discussion of the study. Firstly, there will be a discussion about the outcome of the study, and what factors might have been a key factor for the end-result, as well as important factors to consider if this method was to be turned in to a full-scale process. Secondly, there will be a discussion on the unresolved matters in this study. What questions are still unanswered, and what parameters are of interest? Lastly, there will be a discussion concerning sustainability.

5.1 Discussion of the Outcome

From the results in this study, there isn't an obvious answer to whether the PVP coating could be replaced with a biobased one or not. The assessments and values received from the tests showed that the cellulose ethers have potential as coatings, and provided some clarity in what to focus further research on. Arguably the hydrogel containing HEC/CMC and HPMC/CMC performed best in an overall judgement.

HEC/CMC was assessed to possibly be overly crosslinked in the manual evaluation. This, despite it being the hydrogel with the least amount of the crosslinker, citric acid, in its solution, only 5 % w/w compared to HPMC/CMC with 20 % w/w. A reason for this could be the high molecular weight of the HEC, where only a few crosslinks on the chain would reduce the mobility, and thereby the assessed slipperiness. The friction and water retention measurements provided results that showed the hydrogel's potential, with lowest COF and the most retained water out of the cellulose ether hydrogels. The HEC/CMC solution coated the catheter surface well, and no dry spots with uncoated POBE were found on the samples. However, the solution was very viscous, and in the coating process a lot of coating was applied to the catheter, to then drip off in the oven.

HPMC/CMC was deemed as the best in the manual evaluation test. It felt more slippery than HEC/CMC and had not over-crosslinked. The HPMC/CMC hydrogel's result in retaining water was good, arguably on par with the HEC/CMC coating. Nevertheless, the high COF value measured is a mystery. It could be due to drips of coating, dripping over already dried coating, and thereby creating an uneven

and sort of rough surface. A new type of drying and crosslinking set-up would be interesting to investigate.

A possible reason why the HEC/CMC hydrogel performed the best, stems from the molecular structure of HEC and CMC, and the crosslinking reaction. The hydroxyethyl substituent in HEC will provide hydrophilicity, compared to the rather hydrophobic methyl group of HPMC, or similiarly in HPC with its the high MS value, as discussed in Section 2.6.2.2. Furthermore, if HEC is put in an aqueous solution, and dissolves well, its radius of gyration expands, and it can be easier to find other polymers in the solution and form entanglements. In addition to this, since HEC is, as well as all the other cellulose ether but CMC, non-ionic, it does not have any counterions. The HEC used in this study is supposed to have a very high molecular weight, about 1300 kDa, which also helps to create an entanglement of polymers. This provides many opportunities between the polymers to crosslink. HPMC also provides a good crosslinker companion to CMC, by not having any counterions interrupting. The one used in this study, also had a rather high molecular weight of approximately 500-600 kDa. However, HPMC is only soluble in water at low temperatures. It is therefore a possibility that the transition of temperature in the oven might influence the coating.

To evaluate whether these methods and hydrogels are applicable in a large-scale setting, as the one at Wellspect HealthCare, there are other factors to keep in mind. Firstly, HPMC is a surface-active molecule, which means that it would, unless prohibited, create a lot of foam in a process. In this lab-scale method, the foaming of the HPMC/CMC solution was a problem, every time the solution had to be poured into a different container or even when air bubbles appeared when the catheters were coated. It might be a costly feature for a larger set-up. Secondly, the solvent used in this study is water. Water is a safe and relatively sustainable solvent, however, when working with medical products it is of the utmost importance that the products are sterile, and that bacteria and such don't grow in the factory. Water that is kept stationary might start to grow algae. Furthermore, water also needs a lot of energy in order to evaporate. In the citric acid crosslinking technique, water is not needed for the reaction, but simply as a solvent. The first energy barrier for the crosslinking reaction is simply to evaporate all the water. So, there are advantages to replace the water, however if this will work as well is a question for further studies.

5.2 Discussion of Unresolved Matters

This master thesis work, was an investigative study from the beginning, meaning that the outcome of the possible biobased alternatives was unknown. Therefore, there still is a lot more to be learned about the applicability of the biobased hydrogels to the LoFric® products.

Firstly, an important aspect is that the osmolality of the hydrogel must be correct, in order for it to be a realistic candidate. There are different osmotically active small molecules, one of which is ions. CMC has a lot of ions in its structure with

the retained water. Anbergen et al. have found that an increase in the salt concentration, will reduce the swelling of a hydrogel containing CMC [45]. There could therefore be complications if additional ions were added to the coating, or solutes used when the catheter is wetted. For that reason, another osmotically active small molecule should be used, rather than salt.

Secondly, there are many parameters that could affect the end results of the hydrogels. The molecular weight, DS, viscosity of the solution, citric acid concentration, polymer concentration, the temperature of the oven, the time in the oven and the coating procedure to name a few. It would be interesting to invest in this further, to understand which of these factors has the most impact on the result. One of the key aspects to get a good functioning hydrogel, is to build intermolecular bonds, i.e. between different polymer chains, and not just intramolecular links, i.e. within the same polymer chain. This is achieved by having a good polymer solution mixture. The concentration must be high enough for the physical entanglement to occur between the chains, that is C* must be reached, explained in Section 2.7.1.

Lastly, the selection method of this study might have impacted the outcome negatively. Since all the hydrogels that were tested in the screening part were only tested on a POBE catheter, their elimination from further study was based on only one catheter material. There could be a possible candidate, amongst the ones that got eliminated, which works with another type of catheter material. There are many ways to construct a hydrogel with biobased materials, and these cellulose ether hydrogels are in no way the sole way forward for this type of application.

5.3 Discussion Regarding Sustainability

When it comes to improving the sustainability of a medical device it is important to not compromise on functionality or safety. If you make a material switch in a product, but at the same time make it less functional than the original, a user will most likely still prefer the old product with better properties. So, before a biobased coating or biobased substrate can be introduced into a catheter it has to live up to the standard of the original product.

It is also important to be realistic about how much of an impact that can be made by such a material switch. If the PVP coating in the LoFric® catheter was to be switched to a biobased coating, it would only be a small percentage of the total catheter material weight. But intermittent catheters are a single-use product, so the used volume is large, and every little bit helps when trying to improve sustainability.

The sustainability of cellulose as a raw material can be debated, assuming it originates from wood. The environmental impact will come down to the forestry practices and pulping processing used to extract cellulose from wood. It can be a resource intensive process, especially since high purity cellulose is needed for derivatisation. However, pulp as a raw material has a significantly lower carbon footprint as compared to fossil based polymers.

The derivatisation of cellulose is also a key factor in the sustainability of the cellulose ether hydrogels discussed in this report. As mentioned in Sections 2.6.2.1 trough 2.6.2.4 the derivatisation reactions require epoxides and/or molecules containing chlorine. These molecules are usually not from renewable sources and may require resource intensive synthesis steps of their own. The result is that cellulose derivatives are not fully biobased and have some percentage of their carbons originating from fossil sources. The degree of how renewable they can be considered depends on their DS, and the type of processing they undergo. For one type of cellulose ether a renewable content of 32 % was given by the supplier. The information on carbon footprint in kg CO2e for the cellulose ethers was not available from the suppliers. But, as mentioned above, every little bit helps. There are most likely biobased polymers out there which can be considered more sustainable, but cellulose ethers were what was found to be functional in this study. It would also, most likely, not be possible to make a hydrogel with the same functionality and ease with native cellulose. Another factor to consider is the energy demanded by the coating process of the cellulose ether hydrogels, in particular the energy demanded by the several hours of oven time.

The choice of TPS as a substrate material can also be debated. Using starch as a bioplastic has some negative aspects. Starch is a biomass which can also be used as food. Diverting too much of the starch production towards technical materials will affect global food prices, as well as using up crops that could feed humans. It is, however, possible to utilise starch side streams for materials such as this, which could not have been used for food anyway. Starch also needs various additives and/or mixtures with other polymers to become TPS, which can come from both biobased and fossil sources.

In the end, sustainability is not as simple as just switching to biobased materials. To make sure a switch is truly sustainable a complete LCA would need to be conducted.

6

Conclusions

The results of this study show that there are possible biobased candidates that could replace the PVP coating or the POBE catheter in the future. This study concludes, according to the method used, that the best possibility to compete with the PVP, is by using a cellulose ether hydrogel based on a 1:3 ratio of HEC/CMC or HPMC/CMC, crosslinked by citric acid. The study has created a stable hydrogel using a relatively simple process, with non-hazardous reagents and solvent. No clear conclusion can be drawn about the use of TPS to replace POBE, but it has not been ruled out as a possible future replacement. Furthermore, there is need for a LCA in order to fully conclude whether this sort of change in a product truly can be considered sustainable.

7

Future Outlook

To further evaluate the possibility of replacing PVP with cellulose ethers, a number of further studies must be conducted. One of the most urgent is to evaluate the sterilisation of the hydrogel and how it will affect the product. There is interest in making the coating thicker, and to possibly use other solvents than water. It would also be interesting to investigate how well the coating ages, and if its function stands the test of time. Furthermore, an optimisation of the parameters determining the outcome of the hydrogel, polymer- and citric acid concentration, oven-temperature and time and so forth, should be done in order to fully understand what will affect the finished hydrogel. It would also have been interesting to evaluate whether or not a cellulose-based hydrogel could be implemented on a biobased catheter, and what sort of new difficulties and questions would arise with such a product. Finally, a LCA study should be conducted on a product such as this, in order to evaluate whether or not it could be a more sustainable alternative than the current product made today.

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A

Appendix

In this appendix the mean values of the COFs from the friction measurements will be presented first. Then the images from the contact angle will be presented. Lastly some supplemental images from the optical microscopy will be presented.

A.1 Friction Mean Values

In Table A.1 the data for the chart in Figure 4.2 are presented. The Table displays the mean values of the COF for the different samples types, split into the five strokes or pulls over the surface. The mean values come from five replicas.

Table A.1: Mean values of COF for the different surface samples.

Sample/Pull No.	**1**	**2**	**3**	**4**	**5**
Reference	0.040	0.034	0.036	0.038	0.041
CMC	0.066	0.071	0.098	0.096	0.092
HPC/CMC	0.031	0.047	0.059	0.071	0.079
HPMC/CMC	0.206	0.350	0.445	0.506	0.558
HEC/CMC	0.043	0.046	0.048	0.049	0.049
TPS	0.212	0.288	0.329	0.353	0.373

A.2 Contact Angle Images

The images from the contact angle measurements for each sample type are presented below in Figures A.1 to A.6. For each sample three images are presented, each representing a water droplet placed on a different location on the sample. These recorded contact angles were used to calculate the average values and standard deviations for the chart in Figure 4.4. The measurements were made, and a total of 6 angles were used to calculate the mean value. The measurement was made directly after the droplets impact on the coating.

The contact angle images for the reference sample, the POBE catheter coated with PVP, are presented in Figure A.1. They show an average contact angle of 87 °.

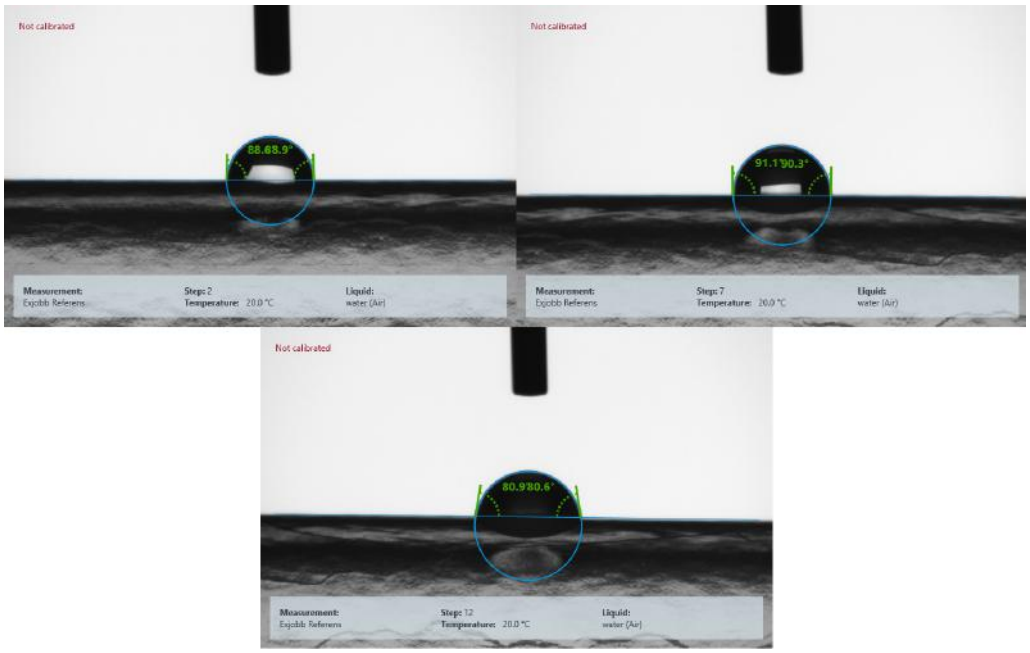

Figure A.1: Contact angles of three water droplets placed in different locations on the reference sample, a POBE catheter coated with PVP.

The contact angle images for the CMC coated sample are presented in Figure A.2. They show an average contact angle of 26 °.

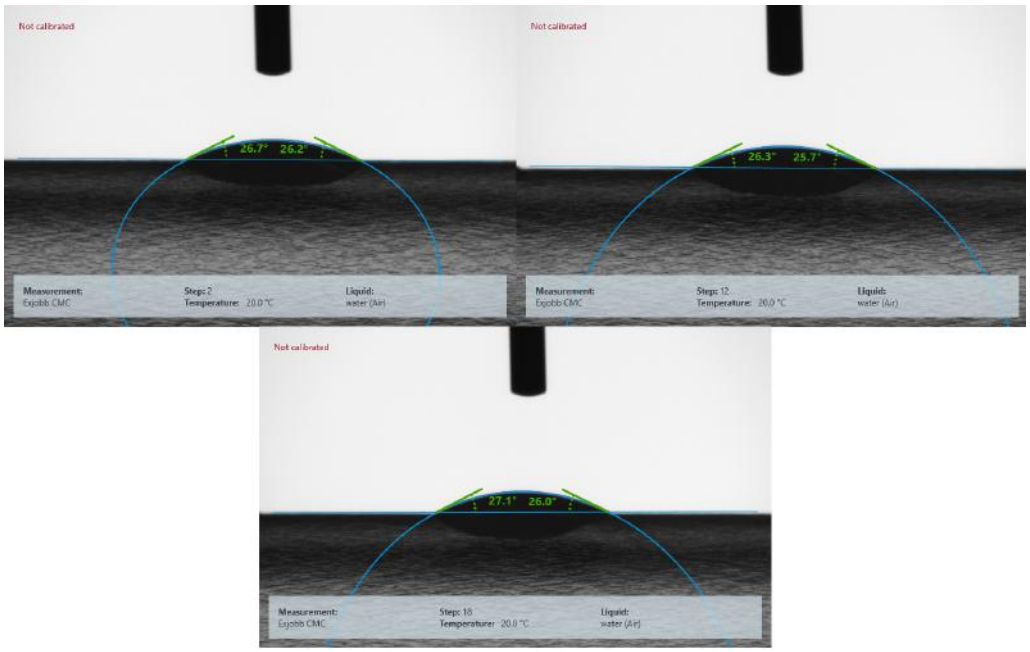

Figure A.2: Contact angles of three water droplets placed in different locations on a POBE catheter coated with CMC.

The contact angle images for the HPC/CMC coated sample are presented in Figure A.3. They show an average contact angle of 51 °.

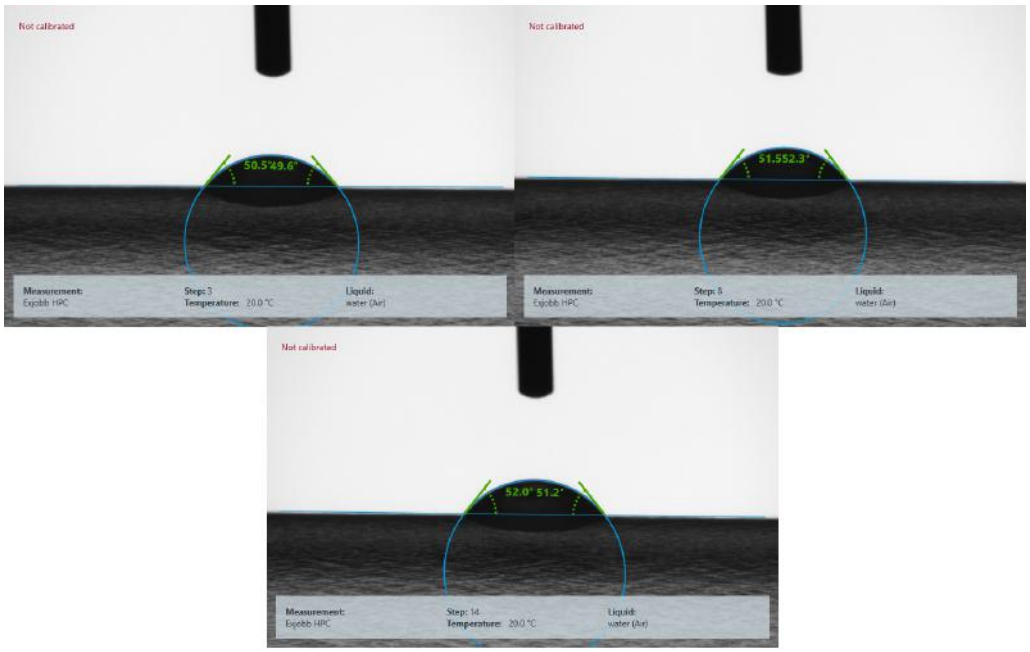

Figure A.3: Contact angles of three water droplets placed in different locations on a POBE catheter coated with HPC/CMC.

The contact angle images for the HPMC/CMC coated sample are presented in Figure A.4. They show an average contact angle of 78 °.

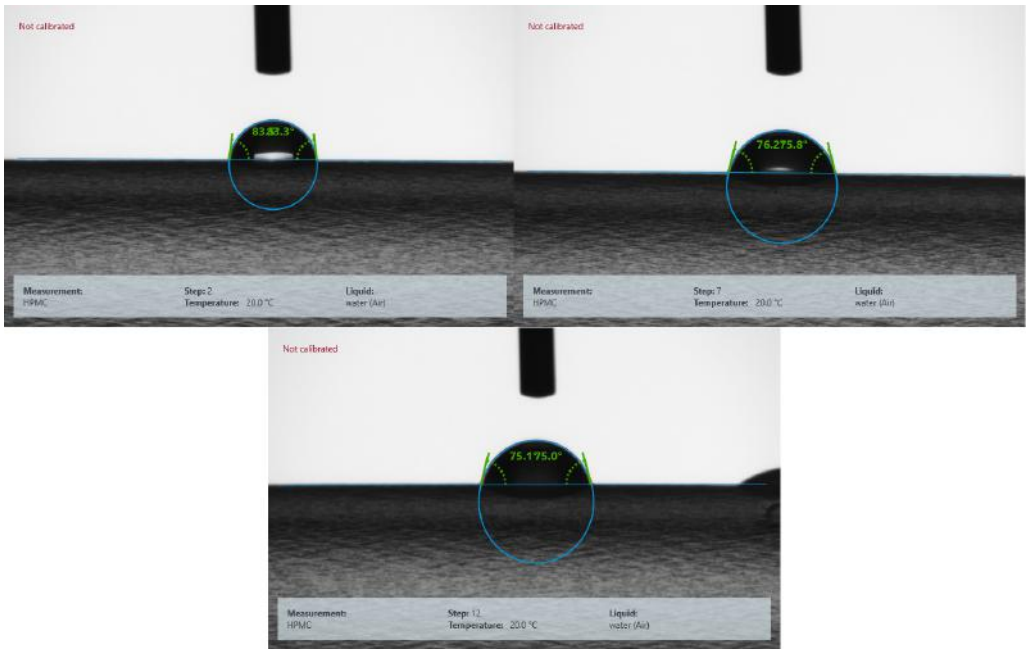

Figure A.4: Contact angles of three water droplets placed in different locations on a POBE catheter coated with HPMC/CMC.

The contact angle images for the HEC/CMC coated sample are presented in Figure A.5. They show an average contact angle of 47 °.

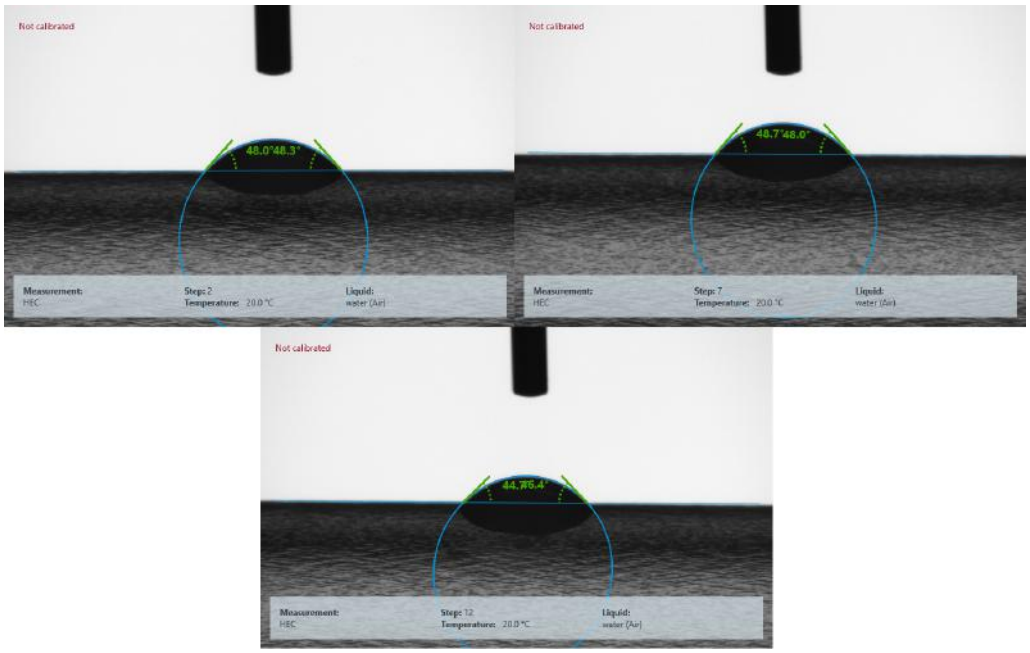

Figure A.5: Contact angles of three water droplets placed in different locations on a POBE catheter coated with HEC/CMC.

The contact angle images for the TPS sample coated with PVP are presented in Figure A.6. They show an average contact angle of 94 °.

Figure A.6: Contact angles of three water droplets placed in different locations on a TPS surface coated with PVP.

A.3 Optical Microscopy Supplementary Images

The supplementary images from the optical microscope analysis of the CMC coating are presented in Figures A.7, A.8 and A.9. They show how the coating appears to be unevenly spread across the surface.

Figure A.7: Optical microscope picture of the CMC coated POBE catheter, an area in which the uncoated surface structure is clearly visable, red bar at upper right corner of each picture, shows a scale of 500 µm..

Figure A.8: Optical microscope picture of the CMC coated POBE catheter, following the surface in Figure A.7 a transition of a smoother area is visible in the middle of the picture, red bar at upper right corner of each picture, shows a scale of 500 µm.

Figure A.9: Optical microscope picture of a different area of the CMC coated POBE catheter compared to Figure A.7 and A.8. Here the coating covers the surface more smoothly, red bar at upper right corner of each picture, shows a scale of 500 µm.

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