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Nelfilcon A, a New Material for Contact Lenses

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Abstract. The synthesis and the purification of a new photo-crosslinkable poly(vinyl alcohol), Nelfilcon A, is briefly reviewed in this paper. Methods for the attachment of different functional groups to the polymer backbone are described. From the Nelfilcon A macromer, *Focus® Dailies™* contact lenses are produced with a new production technology.

Introduction

For more than 100 years, glass contact lenses have been known, but after poly(methyl methacrylate) (PMMA, trade name *Plexiglas*) was invented in 1936, all 'hard' contact lenses have been made of plastic rather than glass. The more comfortable 'soft' lenses were introduced in the early 1970s. They were invented by the Czech chemist Prof. *Otto Wichterle*, who developed the so called spin-casting process for contact lenses. In this method, a solution of monomers is converted into a hydrogel lens during rotation of the polymerization mould. *Wichterle* is recognized world-wide as the father of soft hydrophilic contact lenses. An other one of his developments was the technology of preparing soft contact lenses from a dry 'xerogel' by a lathing process, followed by swelling in water.

Contact lenses require a regime of daily disinfection and cleaning. Today, there are two main new trends in the contact-lens market which are the daily-disposable and the extended-wear lenses. In both cases there is no cleaning and disinfection of the lens anymore affored. The extended-wear lens stays day and night on the eye. This is possible due to the high oxygen permeability of this kind of contact lenses. With the daily-disposable lens, the patient uses a pair of new and sterile lenses every day. To make this possible, the production process must be simple, reasonably priced and safe, it must produce lenses in high quality and quantity and should offer the opportunity for full automation.

The present paper gives an introduction into the chemistry which led to the new contact-lens material Nelfilcon A, made from poly(vinyl alcohol) (PVA) [1], and to a new production process called the 'Lightstream process'. We started our work about seven years ago, and today our contact lenses *Focus® Dailies™* are produced in Germany and in the USA; they have been on the market for two years.

State of the Art

What is the usual way to fabricate contact lenses? The double-side molding process (DSM) [2] is probably the most common method to produce soft contact lenses in large quantities.

First, we need a pair of UV-transparent molds. The cavity between the front-curve

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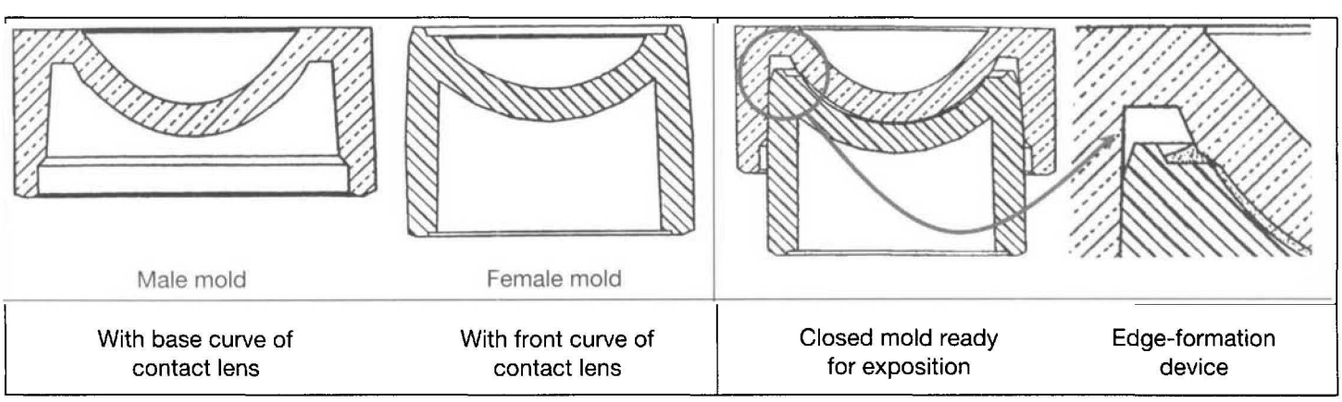


Fig. 1. *Molds for the double-side molding process*

and the base-curve mold determines the desired contact lens geometry. A mixture of polymerizable monomers – a typical compound is 2-hydroxyethyl methacrylate (HEMA) – crosslinker, photoinitiator, and, in some cases, solvents, is dosed into the female mold. After closing the molds, the content is exposed to UV-light. The molds, made by an injection-molding process, must have a sophisticated design to guarantee the optical function and a good edge quality (see *Fig. 1*). The monomer mixture is radical-polymerized to form a crosslinked polymer. The molds are separated and the lens is removed. As the conversion of monomers to a polymer is never 100%, hazardous or even toxic monomers remain in the lens. Therefore, these compounds must be extracted with a suitable solvent or water. In case of a dry lens, *i.e.*, no solvent is used for the polymerization reaction, the lens swells during extraction and gains the final geometry during equilibration in saline. After a final inspection, the contact lens is ready for packaging and sterilization.

There are two time-consuming steps in the DSM process which is not ideal for a simple, fast and low-cost mass production. The production-rate-limiting steps are the photopolymerization reaction and, even more important, the extraction of the lens. What can a chemist do to make the lens-manufacturing process simpler and safer?

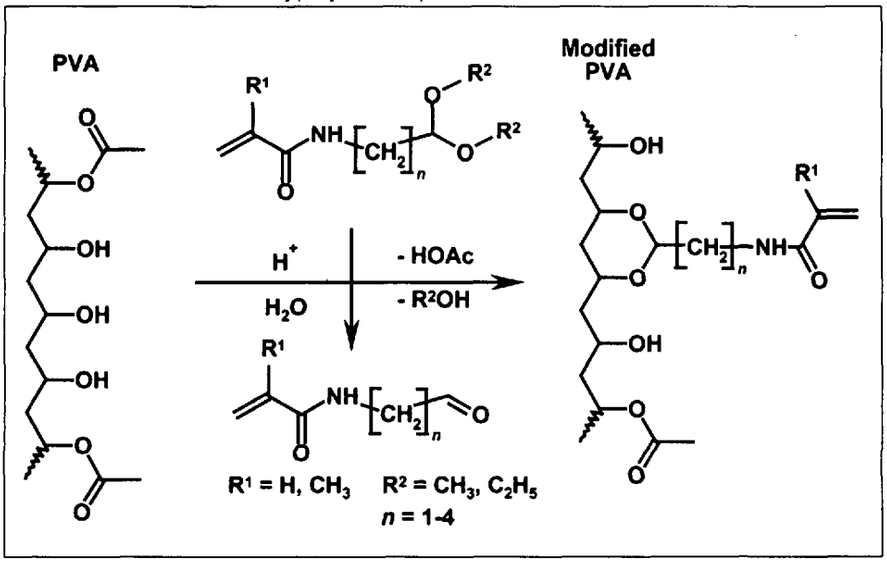
The New System

The DSM process starts with a monomer or a mixture of monomers. The polymerization is time-consuming because the entire polymer backbone and its crosslinks have to be formed. Because of the incompleteness of the reaction and the potentially used solvent, an extraction step is unavoidable. But what about starting with a biocompatible polymer instead of a monomer mixture, and using water as the solvent? In this case, the extraction step of the lens would be obsolete. Water is the ideal solvent because of its compatibility with the ocular environment. Using this approach to make a contact lens, we 'only' have to convert the polymer solution (the sol) into an insoluble polymer network (the gel). The conversion of a polymer into a three-dimensionally crosslinked network can be achieved by a radical-polymerization reaction. To initiate crosslinking, UV-light is ideal. The reactive sol is stable in the dark and can be crosslinked at will by UV-irradiation. Thus, what we finally need is a suitably reactive photopolymer. The crosslinking of a reactive pre-polymer (macromer) is much faster than a polymerization process starting from monomers. Even if not all of the many crosslinking groups on a particular polymer chain will react, this chain is fixed at least through one of the reactive groups to the network and cannot be extracted. Therefore, the conversion of the crosslinking groups does not have to be perfect to ensure complete incorporation of all macromers into the network. Thus, with slightly different chemistry, we can greatly simplify the production process:

- we fully crosslink the existing pre-polymer in a fast reaction
- we use water as solvent
- we do not need to extract the lens.

So we are looking for a water soluble photoreactive pre-polymer. To make a polymer photosensitive, polymerizable units can be attached onto the polymer.

Scheme 1. *Modification of Poly(Vinyl Alcohol)*



Water-Soluble Polymer

Why PVA? PVA is a water-soluble polymer. It is rather well-priced and has many useful properties [3]. Numerous chemical modifications of the backbone are possible and have been reported [4]. PVA is currently available with different molecular weights and with different acetate contents. The molecular weights of commercial PVA spans the range from 14000 up to 200000. PVA is produced in thousands of tons annually. In 1974, the year of the 50th anniversary of PVA, the world-wide production capacity reached 500000 tons per year. Consequently, there should be no problem with the availability of our starting material.

The discovery of PVA was in the pioneer days of macromolecular chemistry, and it is closely connected with the names of Dr. *Alexander Wacker* and Prof. *Hermann Staudinger*. *Staudinger* was Professor at the Swiss Federal Institute of Technology in Zürich/Switzerland and later at the University of Freiburg/Breisgau, Germany. *F. Klatte* had already discovered poly(vinyl acetate) in 1915. But it was not until 1924 that *Herrmann* and *Haehnel* [5] described the first stoichiometric hydrolysis of poly(vinyl acetate) with sodium hydroxide. This work stimulated Prof. *Staudinger* to work on this very interesting polymer. It led to his fundamental insights about the structure of macromolecules and the mechanism of the so-called polymer-analogue reactions. A polymer-analogue reaction gives us the possibility to modify PVA as necessary for the generation of a photo-crosslinkable macromer.

The functional group of PVA is the secondary alcohol, repetitive as polyol in 1,3-position. This 1,3-polyol-structure is ideally suited for the formation of cyclic acetals (*Scheme 1*). This reaction is of great importance in some industrial applications. For example, *Vinylon* fibers are made from acetal-modified PVA. Also, PVA-acetals like polyvinyl formal and polyvinyl butyral are used in paint additives and foams [6]. With a dialdehyde, PVA can be crosslinked. Normally, acetals are formed under acidic conditions in water-free media and are cleaved under aqueous acidic conditions. But PVA can be modified by cyclic-acetal formation in aqueous solution at room temperature nearly quantitative. The reason for this high conversion is the outstanding stability of the (cyclic) acetal.

We combine an aldehyde group with a polymerizable function in one compound. This compound can then be attached to the PVA backbone by cyclic-acetal formation, using the well-established polymer-analogue reaction, thus creating the desired photo-polymerizable macromer with a well-controlled number of reactive groups per macromer chain.

Design of the Crosslinker

The acetalization of PVA is accomplished under aqueous acidic conditions, and therefore, the crosslinking groups have to be designed in a way that they are stable under these conditions. Amides are much more stable than the corresponding esters, and in methacryl- or acrylamide, the double bond additionally stabilizes the amide function against hydrolysis. Another big advantage of the amide is the higher reactivity in polymerization. We used a protected aliphatic amino aldehyde in form of the dialkylacetal. Such compounds can be easily synthesized by reacting the protected amino aldehyde with the acid chloride [7]. They can be purified by extraction and, depending on the molecular size, either by distillation or crystallization.

How to Synthesize the Photopolymer

There are three reactions going on simultaneously during the modification of still partially acetylated PVA in aqueous acid (*Scheme 1*).

The acetal structure of the crosslinker is hydrolyzed to the corresponding aldehyde, the aldehyde reacts with PVA to form the stable cyclic acetal function, and the acetate of the PVA is partially hydrolyzed to form additional OH groups.

The reactions are acid-catalyzed and can be stopped by neutralization at any time. The cyclic acetals of the modified PVA are stable under neutral condition even at autoclaving temperatures.

The acetate content is an important parameter for the rheology of the polymer, and it can be controlled by the reaction time: the longer the reaction time, the lower the acetate content. In case a higher acetate content than provided by the starting material is desired, the reaction has to be carried out in the presence of acetic acid.

The concentration of acetic acid can be calculated by the mass-action law. We found the constant unity as described in the literature [8].

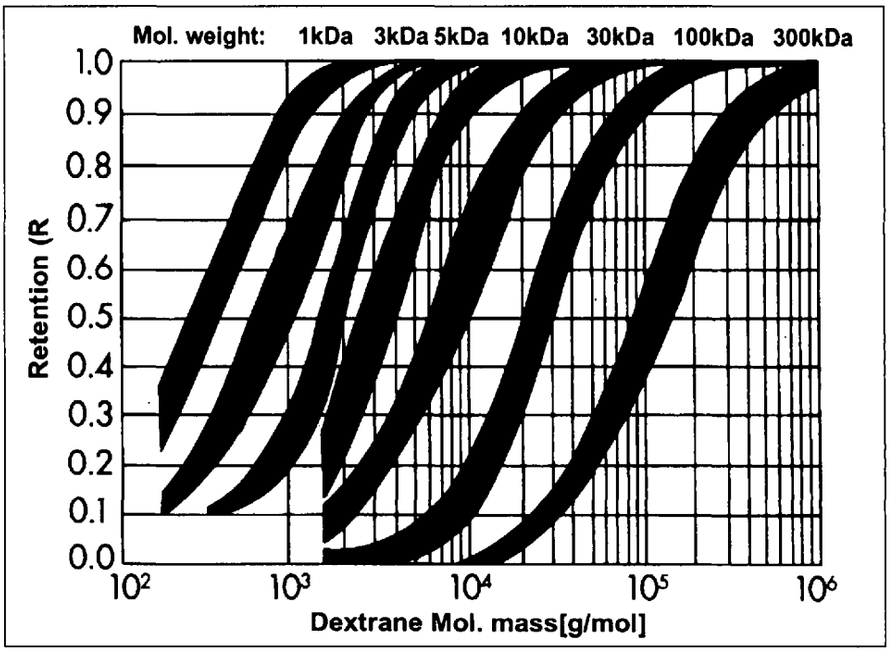
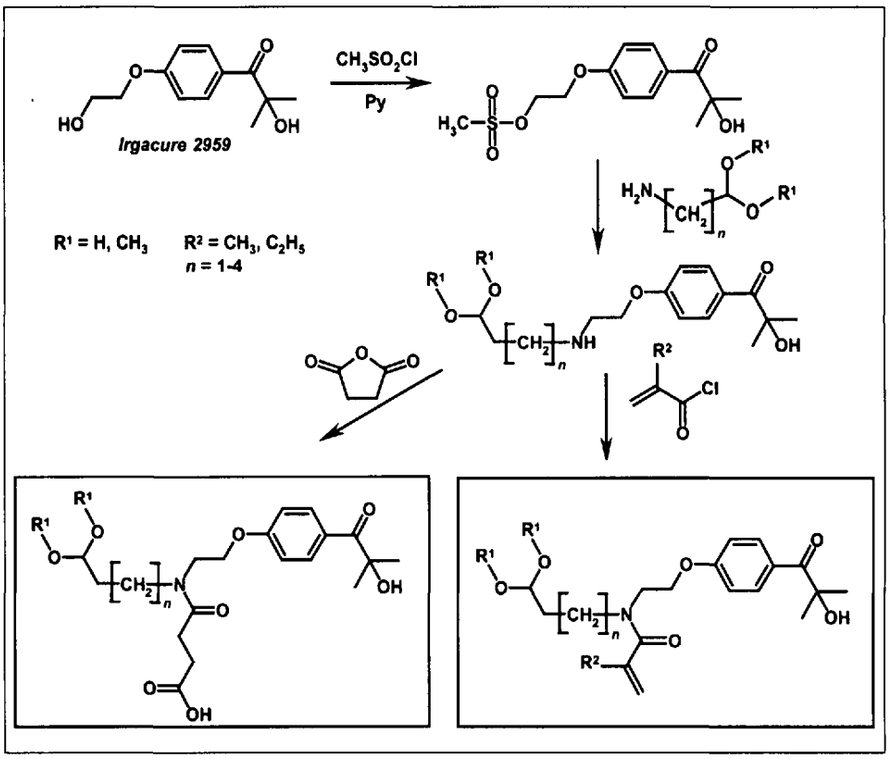


Fig. 2. *Different ultrafiltration membranes*

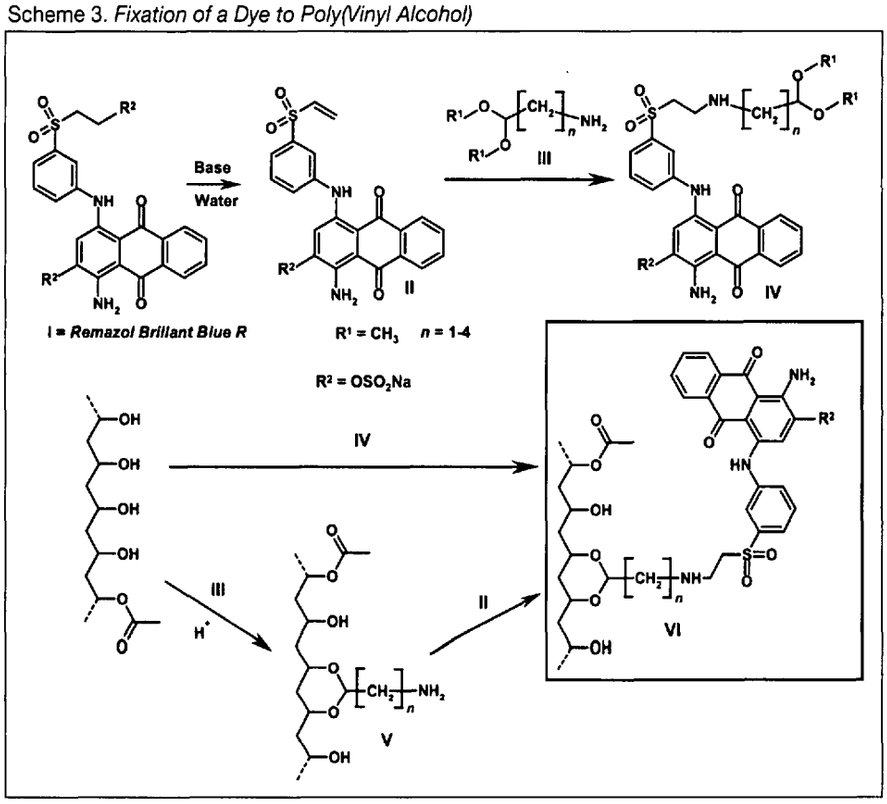
Scheme 2. *Modification of Photoinitator*



As usually technical-grade products are used for the synthesis, an effective purification of the raw product is necessary to remove all traces of hazardous or toxic impurities from the polymer. As explained above, an extremely pure photopolymer is needed to avoid the extraction of the lens. The classical method of polymer precipitation didn't seem to be ideal. Precipitation would have to be repeated several times to achieve the desired purity, and it would require a lot of solvent. The elimination of traces of the solvent from the polymer by drying is difficult, and in the end, we would have to redissolve the polymer in water anyway for the sol formation.

In biochemistry, sensitive products like enzymes are often purified by ultrafiltration in aqueous solution. Ultrafiltration uses special membranes to separate molecules according to their size. Small molecules, like water or salts, permeate through the pores of the membrane, whereas large

Scheme 3. *Fixation of a Dye to Poly(Vinyl Alcohol)*



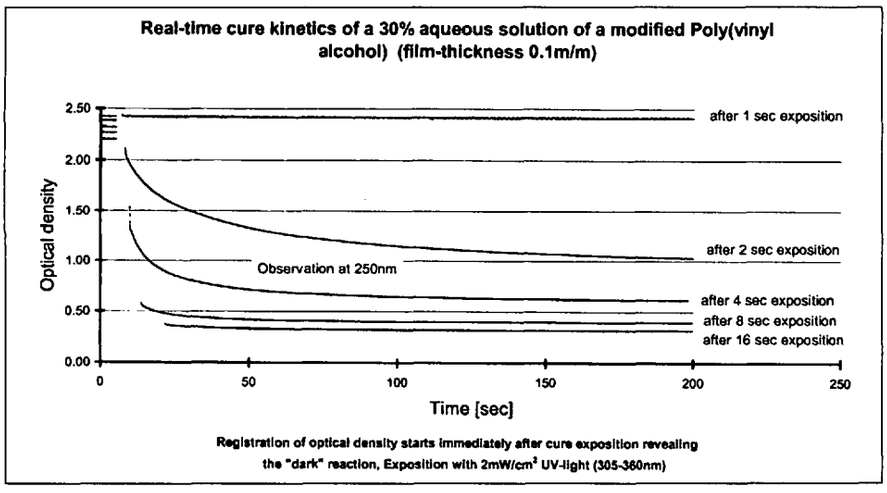


Fig. 3. *Real-time UV-kinetics of the crosslinking reaction*

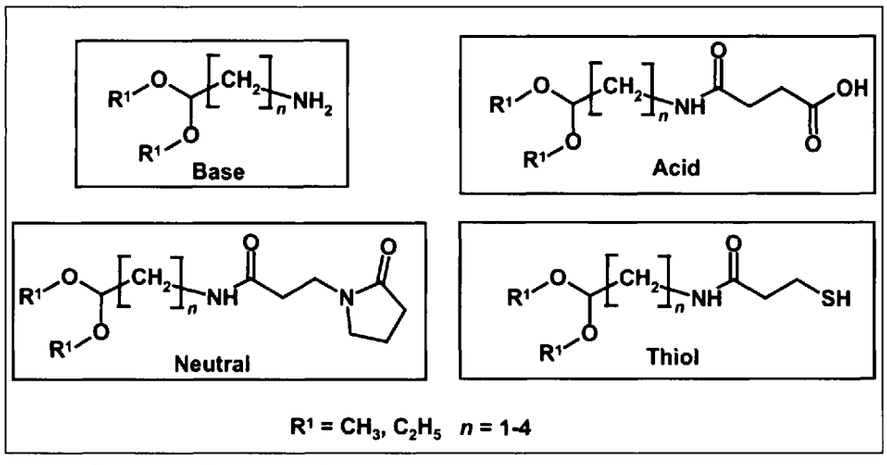


Fig. 4. *Different modifiers for poly(vinyl alcohol)*

molecules – *e.g.*, polymers – cannot permeate due to their size. To give an example: Ultrafiltration [9] of a typical 10 kDa dextran solution through different ultrafiltration membranes would result in retention of *ca.* 60% of the polymer using a 30 kDa membrane, 95% using a 10 kDa membrane and close to 100% employing a 5 kDa membrane (*Fig. 2*).

For our photopolymer, we need a suitable membrane which retains the polymer and allows permeation of the low-molecular-weight impurities and salts.

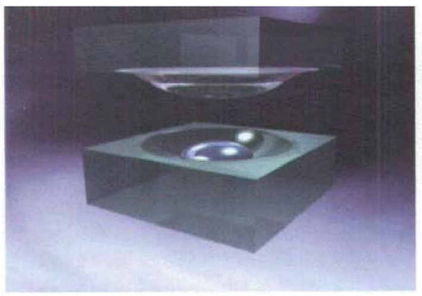
The passing rates of the crosslinker reagent and of sodium chloride were determined. Small organic modules permeate through the membrane with about the same rate as inorganic salts like sodium chloride. The effectiveness of the purification by ultrafiltration can easily be measured by analysis of chloride in the polymer solution or, in case of non-ionic polymers, by conductivity. But ultrafiltration can give us more than the ultrapure polymer. Ultrafiltration allows us to control the concentration of the polymer in the solution. This means, the polymer concentrations for synthesis and crosslinking can be different.

Stabilization

Monomers and reactive polymers normally require a stabilizer to prevent spontaneous polymerization. Our crosslinking reagent also contains a stabilizer, but due to its low molecular weight, it is removed by ultrafiltration. How can we stabilize the acrylamide group of the photopolymer? We can rely on the oxygen in air. We conduct the ultrafiltration in presence of air, taking advantage of the oxygen, which is present anyway in the aqueous solution. Oxygen functions as a stabilizer for the polymer, and this stabilizer is certainly compatible with the eye! In *Fig. 3*, we can see the oxygen inhibition. It needs more than one second exposition time to use up all the oxygen before the crosslinking reaction starts. The polymer solution is sufficiently stable to be heater to 121° in an autoclave without spontaneous crosslinking.

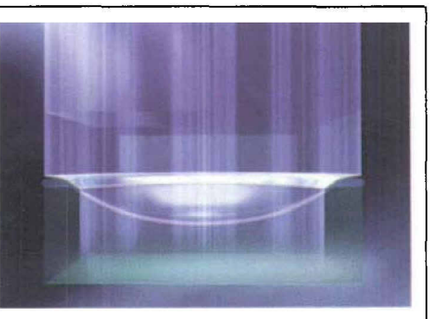
Photoinitiator

Our photopolymer requires a photoinitiator to crosslink. In order to have no extractables in the lens and not even traces of unreacted photoinitiator, the initiator should be linked to the polymer backbone. This can be achieved in a simultaneous

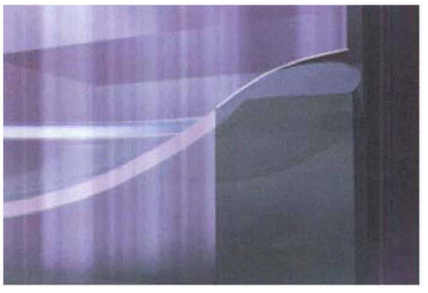


1. Nelfilcon A solution is dosed into a 'female' mold.

2. The male mold is lowered to form the lens. Both molds are separated by the thickness of the lens.

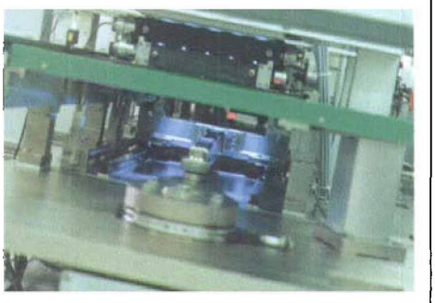


3. A beam of UV-light is passed through the male mold to crosslink the polymer. The lightstream is masked to the size of the mold.



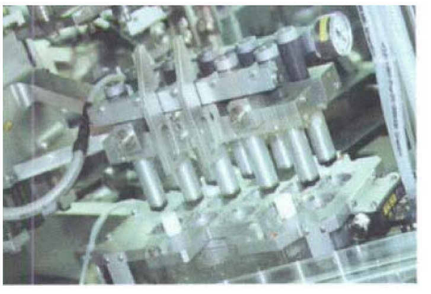
4. The uncrosslinked polymer is later on rinsed off to leave the finished lens. The edge of the lense is formed by positioning of the mask.

5. The reusable quartz molds. The mask which defines the edge is incorporated onto the male mold.

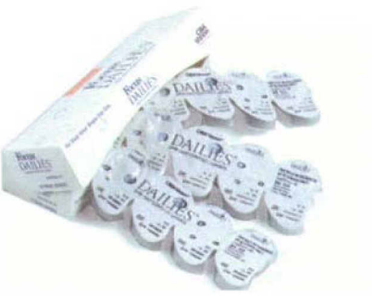


6. The exposition step of the 'Lightstream process'.

8. Vacuum grippers in action.



7. The lens is removed and placed in a blister pack by means of a vacuum gripper.



9. Fifteen days trial pack of *Focus*® *Dailies*™

Fig. 5. *The 'Lightstream process'*

reaction with the linking of the photocrosslinkable moieties, using the same type of acetalization chemistry (*Scheme 2*).

The primary OH group of *Irgacure*® 2959, a commercially available photoinitiator [10], is activated by mesylate and then reacted with the protected amino aldehyde. It can be further transformed into a compound which contains three functions: the aldehyde, the initiator, and the acrylamide function.

Tinting of Poly(Vinyl Alcohol)

To make tinted lenses, one can also fix the dye to the PVA backbone by the same chemistry, using an acetal-modified dyestuff. For example *Remazol Brilliant Blue R*™ (I), a commercially available reactive dye [11], is transformed by a base to the vinyl sulfone II, which reacts with a protected amino aldehyde III to the modified dye IV. Alternatively, PVA can be modified with an amine III, and the formed polymer V reacts with the vinyl sulfone group of the dye II (*Scheme 3*).

Reproducibility

Can we make these polymers in a reproducible manner? The reproducibility relates to the chemical composition (acetate and crosslinker content) as well as the

molecular-weight distribution of the prepolymer. The acetate units can be analyzed by alkaline hydrolysis and titration of the base consumed, the content of acetal by elemental analysis (N) or by double-bond determination and UV-absorption. The residual hydroxy groups are determined by acetalization. As the mild reaction conditions during the synthesis are well-controlled, the contents of the functional groups can easily be kept within narrow margins. These variations are so low that no impact on physical lens parameters can be detected. Gel-permeation chromatgraphy (GPC) and intrinsic viscosity are useful methods to characterize the polymer.

The GPC-analysis in aqueous solution with refractive-index (RI) and UV-detector provides information about the homogeneity of the distribution of the UV-absorbing crosslinker along the polymer chains. No significant variation from batch to batch, nor a significant increase of the molecular weight due to a thermal reaction are observed. Oxygen is indeed a powerful inhibitor! The different batches stay well within the same limits determined by the starting material.

Fast Crosslinking

The crosslinking reaction is initiated by light. UV-light cleaves the photoinitiator, and thereby formed radicals initiate the polymerization. Water is an ideal medium for the radical polymerization. The conversion of the crosslinking reaction can be followed by UV-absorption of the acrylamide groups before and after exposure. Complete conversion corresponds to a saturated system, which was synthesized for comparision.

The crosslinking reaction is fast, the necessary irradiation intensity of 20 mJ/cm^2 for a conversion greater than 93% being very low. The intensity of the UV-source determines the crosslinking time. In *Fig. 3*, we can see the oxygen inhibition and the 'dark' reaction of the radical polymerisation of the acylamides after different exposition times.

Opportunities

The modification of PVA by acetal-formation is polyvalent. We can modify the PVA backbone in different ways, either making it more soluble or less soluble, and we can add acidic or basic groups (*cf. Fig. 4*). We may also use other polymers like copolymers of vinyl acetate and *N*-vinyl pyrrolidone, or different 1,3-diol-containing polymers. Amine-modified polymers can be reacted later on in aqueous solutions with acid chlorides, isocyanates, azlactones or, as we have seen before, with vinyl sulfones. There are many possibilities to modify polymers, which is useful not only for the development of contact lenses.

Conclusion

Our goal was to find a contact-lens material for a simple, safe, and straightforward process.

The problem was solved by the application of water-based polymer synthesis and purification.

- PVA is dissolved in water,
- is reacted with a calculated amount of monomer to give the desired crosslinking density,
- is modified, with respect to the acetate content, with acetic acid according to the mass-action law to prevent rheological problems,
- is then purified and concentrated by ultrafiltration and filtered to sterility in order to obtain the modified PVA without any intermediate isolation step.

The whole procedure is performed in water and thus not harmful to the environment.

In summary: The fast crosslinking reaction and the fact that the extraction step could be avoided led to a new contact-lens production process, called the 'Lightstream process', which was developed by the *Ciba-Vision Nelteg* group in Germany.

The innovations in the 'Lightstream process' (*Fig. 5*) include:

- quartz or glass molds can be used repeatedly,
- fully hydrated lenses with dimensions exactly matching those of the molds without requiring subsequent extraction,
- edges formed by a photolithographic process – the lenses are crosslinked in the molds by controlled exposure to UV-light. An opaque mask is used to prevent crosslinking at the periphery. The non-crosslinked polymer can be washed away.

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