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Polysulfone: The Development of a Membrane for Convective Therapies

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Abstract

The polysulfone membrane was developed as a membrane for convective dialysis therapies at the beginning of the 1980s. The target was to produce a higher-permeable membrane on the basis of synthetic polymers, such as polysulfone. The development of a membrane with high permeability went hand in hand with a technology development that finally presented as an essential precondition for the success of the polysulfone membrane. This article describes the development phase of the polysulfone membrane using to-date unpublished extracts of the project report of the polysulfone membrane and commenting these from today's perspective.

Convective renal replacement therapies such as on-line hemodiafiltration (HDF) place high demands on the membranes used – demands that could only be met through the lessons learned during the development of polysulfone membranes.

The history of development of the polysulfone membrane for HDF therapy began with a re-orientation regarding the basic membrane material that, at that time, was predominantly cellulose. The motivation for this new beginning was the need for membranes with a higher permeability in order to support convective hemodialysis processes, coupled with the need to prevent a drop in leukocyte numbers during treatment (leukopenia), neither of which were possible with cellulose membranes. Different synthetic membranes for different applications had already been on the market when first interest in using these synthetic membranes for hemodialysis arose at the end of the 1970s. Examples were polyacrylnitrile (Asahi), polyamide, PMMA (Teijin) and also even a polysulfone

(Amicon). These activities started in different companies that were interested in improving dialysis and that recognized the potential of these new membranes, albeit certainly unaware of all advantages of synthetic membranes at that point of time (e.g. Amicon, Asahi, Gambro, Sartorius). These advantages only developed in the course of use and finally accounted for the later predominance of synthetic membranes. In the beginning, existing knowledge of the production of polysulfone membranes was rudimentary, forming only the basis for the subsequent development of a polysulfone dialysis membrane. The first aim of this development was optimization of the membrane permeability and retention properties for hemodialysis, hemofiltration and HDF applications, together with achievement of good hemocompatibility, stability, high quality and low production costs – all of which together constituted preconditions for a competitive product. Although some predevelopment had already been done, fulfillment of these preconditions required enormous efforts in the field of both product and technology development. For example, it was not possible to buy the necessary process technology in a ready-to-use form; new technological developments were necessary to facilitate creation of an economically successful product with high quality and constant properties. Within this context it was necessary to develop numerous detailed solutions enabling the mass production of dialysis membranes. This allowed scale-up of production from the early experimental process of lab-scale production of polysulfone capillary membranes in very limited qualities. An as yet unpublished report on the development of the polysulfone dialysis membrane provides interesting insight into these times of change, problems that arose and, in many cases, solutions still valid today [K. Heilmann: Project In-House Production of Hollow Fibers, unpubl. data, 1983]:

'1. Initial situation and planning target

Already in 1979, the management board knew about the necessity to develop and produce membranes (hollow fibers) for the dialysis.

Because there was no in-house know-how available about membrane technology, a co-operation with the company Berghof was decided. At the beginning of 1980 a know-how and license agreement was concluded with Berghof.

The advantage of this agreement mainly consisted in the acquirement of basic knowledge, such as spinning recipe and dry-wet spinning technology, as well as in the time saving – the learning process would have taken at least 1 additional year.

The existing basic knowledge was planned to be supplemented by an in-house development in 1980 and a fiber production should be set up. The aim was the production of a capillary hemofilter.

The question for us in St. Wendel was whether to decide for the primitive but quick realization or for the long way leading to better results but probably too late.

In many project phases I decided for the long but better way (often on my own initiative, against resistance and using my complete leeway for decisions).

Emotionally I argue that the whole medical technology area of the company can only survive in case an in-house production of membranes will be successful. This emotion is now supported by the following facts:

– Cellulose membranes are more and more becoming the subject of gossip. We are practically committed to our suppliers' "enthusiasm for innovation".
– Gambro is already producing its own fibers (also for the normal dialysis).
– The Japanese (Asahi, Toray, Teijin) are permanently placing membranes on the market.
– On the one hand filter selling prices are falling and on the other hand fiber costs are increasing.

The planning target has therefore been aimed much higher than at the beginning. It would definitely have been possible to produce a product such as the current Gambro hemofilter one year and a half ago.

But the following specifications were decisive for our development work:
– No momentary successes, but development of basic concepts.
– Learning to spin and no producing.
– Every process step has to be qualified for an economic large-scale production.
– Production has to run fully automatically and continuously (without intermediate handling).
– Minimal manpower requirements.
– No extensive process steps and steps requiring explosion protection.
– The technology also has to be suited for other fibers (normal dialysis).
– It must be possible to quickly boost the production capacity.
– Facilities and equipment will have to be developed and produced by ourselves.

They have to be designed brilliantly simple.

Unfortunately, the last named planning target is a project requirement often being neglected by Fresenius. Many projects broke down in the past because of the estimation that suppliers are running successful complicated developments. It is certainly more comfortable to delegate detailed developments.

If you tax your own brain, it is possible
– to minimize the development risk,
– to design easy systems that are safe for production,
– to save overall, comprehensive but in the end useless specifications and guaranties.

This is certainly only valid for complicated prototype plants.

To sum up, it can be said that we had to reach the high aims with intensive in-house development.'

These development targets definitely include the idea of developing a universal membrane process enabling the production of all dialysis membrane types (low-flux HD, high-flux HD, HF, HDF) only by varying the process parameters. A further key aspect of development was the early orientation to a mass production that is only possible with continuous and fully automatic processes. Remember that, at this time, the volume of today's need for dialysis membranes was unimagined.

Here is a description of the targets for the subsequent realization.

'2. Project realization

At the beginning of 1980, a pilot test stand was set up in self-construction being used for pre-tests until the end of the 80s with the aim to gain a planning basis for the manufacturing plant. No process parameters such as

- dosage of spinning media
- spinneret construction
- rinsing time
- drying time
- temperatures
- spinning speeds

were known and however, a facility had to be constructed in detail at the end of 1980 in order to start production. There was no way to use external know-how because either special firms had been detained by producers of cellulose membranes or no equipment could be offered corresponding to our requirements. In addition to that, we envisioned a completely new continuous process being unique to our knowledge.

Despite verification of some process parameters, we certainly had to rely on our technical instinct in many matters and we had to construct into the dark and commission the facility for about 200,000 DM.

Mid 1980 (after only 6 months) the first fiber ran through the facility and we were able to begin the membrane development. From October 1980 until January 1981, I had to stop all operations in order to start the plasma filter production.

After that, there was an intensive work of 12 months on the membrane structure. About 600 spinning tests were run with different spinning compositions and adjustments.

Test and control techniques were developed. The problem "hydrophobicity" took us about 2 months. All involved persons (also Berghof) were of the opinion that the polysulfone fiber was hydrophilic. The reason for the "bogus hydrophilic properties" was the presence of small quantities of solvents and glycerin. It was only Prof. Klein from USA who helped us with this problem on the occasion of his visit.

When studying patent literature, I again and again had the impression of being unprofessional and at the same time bold. How was it possible at that time to draw level with companies such as Asahi, Cordis, Rhône-Poulenc, Enka, etc.? The compositions about polymer chemistry or the like made by highly specialized scientists had a really frustrating effect on us as beginners. We thought that we would never reach this experience gained during decades. But the fact that these works were always contradictory, that they had hardly any theoretical basic concepts and that they rarely led to practical application made me pause. Prof. Klein confirmed this perception.

It appeared that pioneer work can better be performed in smaller companies and that just within the scope of medical technology quantum leaps are still possible with little effort.

In January 1982, we had a membrane that outclassed all other fibers as to its performance data and characteristics. It only had one disadvantage: it was as inhomogeneous as competitive products; that is to say that it also had the notorious pinholes.

Companies such as Asahi, Amicon, and Gambro solved this problem by strongly glycerinizing the fibers and thus making them airtight. Filters could then be checked with air and that worked most of the time. Reports of the hospitals confirmed this "most

of the time". We then arrived at the point I mentioned at the beginning: We had to decide whether to enhance development or to copy and quickly place the product on the market? It seemed to be practically impossible to reach such homogeneity.

We tried for 3–4 months and did not get ahead. The great breakthrough only came after a capital investment of about 70,000 DM for an electron microscope approved by Mr. Kröner and Dr. Krick. In August 1982 the unit was set up, at the beginning of November the fiber had the current version and was successfully tested in December.

3. Technical specification of the spinning unit

As already mentioned, a process was realized characterized by homogeneity and continuity, that means that the fiber was rinsed residue-free up from the spinneret with 80 degrees distilled water, dried and collected as completed bundles on a reel. That sounds simple but implied the following problems: In order to remove the complete solvent, a rinsing of 10 minutes was needed resulting in a fiber length of over 300 m regarding the current spinning speed (drying included). Considering today's land prices, such a factory length could hardly be realized. But the installation length could drastically be reduced by reiterating changes in vertical direction. But at this point the problem lied on the part of the rinsing field. We could not find any employees with diving qualification and 80-degrees-temperature resistance. How is it possible to get 50 fibers moving continuously 1 m under the surface of the water and all that with 60 direction changes?

We used a principle that might be unique and I do not want to keep record out of confidentiality reasons (as much as many other details). Anyway, the solution of this problem was the key to a continuous process the main advantages of which are:

- There is no need for a cost-intensive intermediate rinsing made by others for the plasma fiber.
- Repeatable quality is only possible with the same basic conditions. The fiber is completed only after about 5 min. An interrupt of the rinsing process leads to strongly varying fiber qualities. The opinion of Enka and other "experts" that synthetic fibers will never show consistent qualities was completely refuted. The fluctuation range of the filtration performance with different raw material lots was smaller than that of cellulose membranes and had nothing on the plasma fiber.
- Fibers with higher porosity and thus better performance data can be spun, because the tensile strength can be kept low.
- It can be worked without interior liquid preventing a fiber collapsing at intermediate levels.
- Stretching and shrinking of the hollow fibers are kept constant.
- Very low manufacturing costs.
- Special treatments such as crimping can be integrated without problems.

No other works are necessary apart from the dropping off of the finished hollow fiber bundle and the preparation of the spinning solution that is necessary twice per week in case of full production activity. At the moment the facility is running without any difficulty with 8 spinnerets for 2 weeks (also at the weekend); there is only one service person that is already bored.

Capacity:

The system is designed for about 150,000 filters F6 (F60). That requires a doubling of the spinning speed – there have already been experimental tests and apart from some

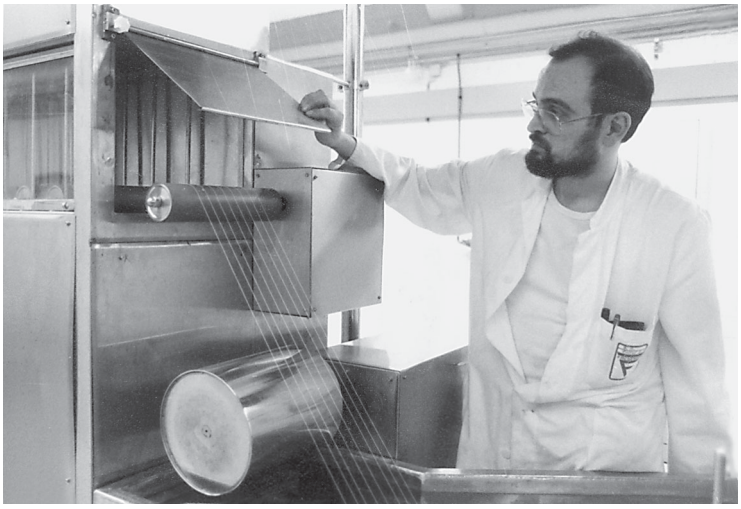

Fig. 1. Elmar Collet produces the first test membranes.

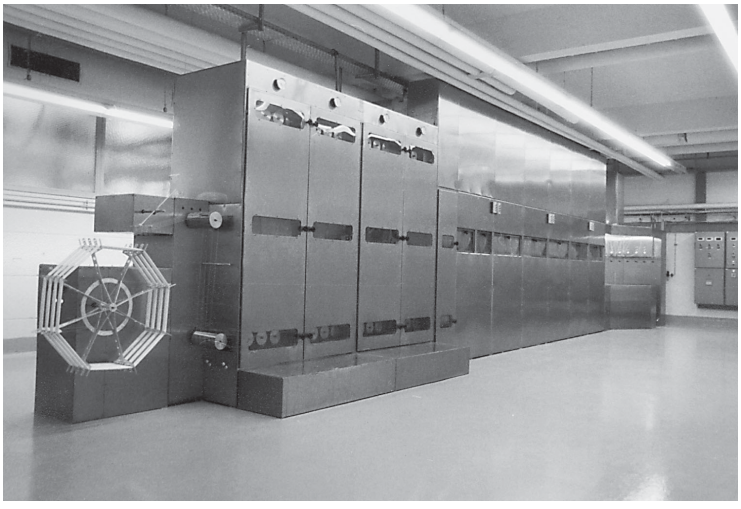

Fig. 2. Fiber spinning pilot test stand mid 1980.

mechanical problems such as roller vibrations because of a too instable bearing no difficulties arose – and an increase of the number of entities from now 8 to 64 spinnerets. This could be realized primitively but quickly by the additional installation of 56 gear pumps (about 25,000 DM). But we want to develop an 8-fold-spinneret (October 1983). However, the problem of a consistent mass distribution means new development effort, but seems answerable to me.

I think that it is necessary to see the systems in order to understand the advantages.

Please find following some pictures that do not reveal details (as shown in figures 1 and 2).'

This section shows that the main focus of innovation was on the technological realization. In the first instance, the process technology engineer was the person being in demand – many detailed solutions had to be found in order to develop a sound, continuous process. Only after implementation of the new solutions where all process conditions were defined and determined as constant in time, was it possible to have a controlled course of the membrane formation mechanism.

'4. Mechanism of membrane formation
Take a polymer (e.g. polysulfone), dissolve it in an appropriate solvent, press this honey-like "spinning pulp" through a hole of about 0.3 mm diameter, in the center of which you can find a small tube with an outside diameter of 0.2 mm and an inside diameter of 0.1 mm, send an appropriate coagulant through the inner small tube and drop this partly coagulated hollow fiber in another coagulant (H_2O) and then you have got a hollow fiber. If you are lucky, you can also find some pores in the fiber wall.

This formula is well known and called "dry-wet spinning process". It is based on the physical process of the fast running phase inversion that means that the fiber freezes at a special solvent-coagulant concentration. The concentration change activating the precipitation procedure is caused by the diffusion of solvents and coagulants running at the same time. Because of the manifold interacting process parameters (temperatures, precipitation speed, spinning speed, concentrations, proportions, molecular masses) these processes are extraordinarily complex even for a textile fiber without pores, hard to handle and can only be gotten under control by empirical tests.

If you want to achieve and maintain a special pore structure and distribution (pore diameter of 10–50 nm), this will be the point at which every theory ends. Then you can only follow your gut instinct.

An example: If we change a concentration theoretically by 2%, we will get a cascade filter instead of a hemofilter. At the same time the spinning speed must be increased because of the slower precipitation. This leads to an increased mass supply. Thereby the concentration at the phase boundary and thus the pore formation change. Therefore the inner liquid also has to be varied – results in an even higher spinning speed – and thus you are deadlocked if you do not additionally vary the air gap height further boosting the complexity.

Today we developed a certain feeling for spinning enabling us to predict certain settings. But the first tests were more than frustrating, so that I realized why Enka had been unrivaled for such a long time.

Today we are also able to spin other polymers under the same procedure. For example, in the meantime, we made a test with our Makrolon (polycarbonate). Surprisingly, we got the same performance data.'

This is a simple description of the dry-wet spinning process for the production of polysulfone membranes. In fact, it is quite easy to produce any membrane based on this formula and one even does not need luck to get some pores. However, it also becomes apparent that it is difficult to achieve specified properties due to complex influences and interrelationships. Today, these influences have been researched better and, based on this knowledge, it is now possible to

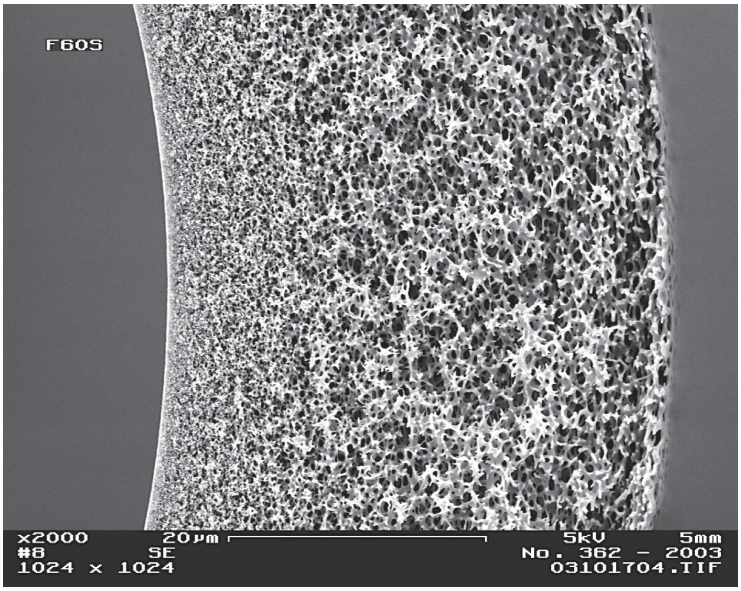

Fig. 3. SEM image of the polysulfone membrane, cross section of the asymmetrical membrane wall. ×2,000.

produce any membrane with any pore size of 1 nm to 1 µm and thus to cover the whole field of blood purification therapies. Pore sizes of 50 nm are well suited for convective therapies as these membranes already retain albumin to a great extent.

'5. Advantages of the hollow fiber "PS 600"

At the beginning of the project the aim was: "Production of a hemofiltration fiber similar to Gambro or Amicon". The mass transport is purely convective with these relatively thick-walled capillaries (80 µ). We were of the opinion that these wall thicknesses strongly limit the diffusive mass transport. Employees of the company Berghof completely excluded diffusive clearance, because then it would be necessary to work with wall thicknesses of 8–12 µ, as with Cuprophan. At a certain project phase, we had the idea to verify this expert opinion. The result with this 35 µ membrane was striking. The purely diffusive clearance for B_{12} was 1.5-fold higher than for the 8 µ membrane of Enka for our "D 6". The reason for this phenomenon seeming to be inexplicable at first sight is the following: The composition of the wall is extremely asymmetrical, that is to say that the smallest and thus limiting pores lie on the internal side of the hollow fiber in a coat being about 0.5 µ thick. The remaining pores are becoming greater and greater from inside to outside and are only forming a supporting layer that is hardly able to resist diffusion because of its high porosity.

However, the Cuprophan membranes (also Cordis, Toray, Teijin, Asahi cellulose) are constructed symmetrically and therefore substances have to "fight" their way through a porous wall of 8–12 µ.

This perception which was new for us completely changed the goal. If we succeeded to outrival the D 6 – accepted as the best hemodiafilter – with our own fibers, this would open an additional market for about 50,000 filters.

The second part of this report documents the advantage of our new type F 60, the high-performance data is reached with only 1.3 m^2 (!) compared to 2.0 m^2 for the D 6 (Cuprophan membrane with a wall thickness of 10 μm).

As already mentioned, a further advantage of the new fiber lies in the absolutely constant structure enabling a bubble point test.

This uniform pore structure has another great advantage. For the range of fluctuation is very small, we could adjust the pore diameter very large without running the risk of the passage of albumin.

This can practically be seen in the steep cut-off almost resembling the human kidney (part 2). The high inulin clearance can also be explained thereby.

Because of the new test method it is also not necessary any more to "cram" the membrane with glycerin. Last year, Asahi set its PAN membrane more open-pored. But therefore they were forced to even more glycerinize – in parts the fiber is almost transparent. The problems with blood leaks followed immediately.

Our "dry" fiber can be stored and processed without any difficulties (not hygroscopic).'

The hemocompatibility aspect of the membranes (which is much better than that of cellulose membranes) remained unmentioned up to this point because this was not known at that time. However, given that the membrane with its 1–2 m^2 represents the greatest artificial material surface in the extracorporeal circuit, hemocompatibility is a very important characteristic of the membrane material. Polysulfone is characterized by a very low activation of the coagulation and complement systems as well as by a lower interaction with blood cells. It is also steam sterilizable, which contributes further to its good hemocompatibility profile. The optimal pore size of a dialysis membrane always presents a compromise between sufficient retention of blood proteins and maximum permeability for toxins. For the retention of albumin and other higher-molecular proteins, it is completely sufficient to arrange a separation layer, consisting of one single layer of small and preferably identical pores that is mechanically supported by a highly-porous substrate layer. Here this was achieved in an almost optimal way: the polysulfone membrane has a separation layer of about 200 nm with a very tight pore size distribution and a substrate layer with a porosity of about 50% so that, in this layer, diffusing molecules barely meet resistance. Because the developed technology enabled an absolutely constant process control and thus a zero-defect membrane with stable properties, a very high cut-off could be chosen when adjusting the membrane. Thus a considerable increase in efficiency was also possible for a hemodialysis membrane with purely diffusive transport. Due to the lack of defects, this was the first synthetic membrane that could be tested using the bubble point test. The diffusive transport could further be improved by the invention of fiber curling: here the concentration gradient as driving force for diffusion was increased by the improved dialysate flow around the fibers.

'6. Post-processing

If there is a disadvantage of the new fiber to Cuprophan at all, it can only theoretically be the less tensile strength of about 25 g (8 µ Cuprophan – 40 g). That means that the fiber cannot be interwoven anymore and our specific product advantage "homogeneous dialysate distribution" would be inapplicable. There were actually big problems to get a good fluid flow. We tried strong crossing at the reel, but the result was not easily repeatable.

Toray spirally wraps two hollow fibers with an additional multiphilic textile fiber – an enormous effort.

We had a better idea. The fibers are slightly crimped with a very simple device (curler) in an inline process.

The results were amazing. Dialysate distribution and thus the clearance were better (!) than that of our hemoflow series that means that by this trick the assumed disadvantage turned out to be an advantage.

At the same time, the very labor intensive spooling could be saved. The bundles will directly be inserted into the housing. However, PU potting has to be executed at a bundle in a centrifuge procedure. The following production steps are the same as those of hemoflow. An additional test console is integrated in the end rinsing.

7. Perspectives and next steps

The version "F 60" will definitely be a fast seller and will result in a positive gross margin by the way. But in 1983, hemofiltration and hemodiafiltration represent an interesting but also limited market of about 150,000 units.

It will indeed be possible to use the "F 60" with our machine 2008 and other machines with a balancing system for the normal dialysis but unfortunately, the vast majority of machines are non-balancing machines.

The system 2008 and "F 60" would nevertheless be the best normal dialysis currently existing (statement of Dr. Streicher). It would definitely be a good idea to merchandise it because this would lead to an enormous increase in machine sales.

Although the future almost certainly belongs to the "open-pored membrane" in combination with machines with a balancing system, the main business is the normal dialysis with low ultrafiltration performance.

Based on this fact, we made some spinning tests in December to get fibers with low UF. The aim was to get similar performance data to the "G 1" Enka fiber having the leading position at the moment. We only changed one spinning parameter and achieved a surprising success. In calendar week 4 we will produce fibers and at the beginning of February we will perform clinical tests with "F 6".

I believe devoutly to the success.'

The high variability of the developed membrane production process also created a reasonable economic basis for successful market penetration. In 1983, the market for hemofiltration and HDF membranes was still very limited. However, the production lines operated at full capacity producing membranes for the evolving high-flux hemodialysis and for low-flux dialysis, which was the standard at that time. Thus, products for convective therapies could also be offered at acceptable prices.

Fig. 4. The polysulfone development team: Rainer Meyer, Walter Guth, Erwin Franiek, Ellen Krug, Elmar Collet, Hans-Gerd Fehr, Ulrich Kramp, Klaus Heilmann, Hans-Josef Lambert (Bernd Nederlof is not in the photo; photograph taken in 2002 at the closure of the pilot plant).

'8. Concluding remark

When taking stock, the reasons of the project success are not to be forgotten. I mean that people are always responsible.

If Dr. Krick had not given me a great leeway for decisions and had not had the courage to take risks, the project would have collapsed at an early stage.

In my opinion, the risk always lies in the perfect solution of details.

At this point I want to present the members of the project team. It goes without saying that they worked more and harder to achieve this pioneer work and that they spent some leisure time. But the key success factor for the project was that they did not realize their work as work, nobody was able to escape the fascination of the project despite some huge setbacks.

Mr. Kramp was the technical project leader and responsible for plant engineering together with Mr. Guth. The plant itself is the best documentation for the quality of their work. Mr. Franiek and Mrs. Krug were responsible for the chemical and physical tests. Without Mr. Franiek's consulting the progress especially in the chemical-physical field would not have been possible.

Even Prof. Klein was impressed by the extraordinary preparation technologies and outstanding fiber pictures being part of the field of responsibility of Mrs. Krug in addition to other tests.

Mr. Collet operated the spinning plant and made all spinning tests. There was no admittance even for me in case susceptible settings were made and sometimes this was definitely a good solution for I am known to set people's nerves on edge.

St. Wendel, 20th January 1983

K. Heilmann'

The fundamentals of polysulfone dialysis membranes were therefore established, but the development proceeded further with aims to improve the product performance and to adjust product quantities to meet increasing demand, thus improving the quality of the membranes and reducing production cost. The controllable lack of defects in polysulfone membranes is a precondition for the absolute retention of endotoxins. A pyrogen-free substitution fluid can be produced at the dialysis machine by filtration through such a membrane. For this purpose, dialysate is filtered through another polysulfone membrane filter and is then available as substitution solution for HDF. Consequently, today the polysulfone membrane also enables on-line HDF.

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