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True Story of Poly(2-Hydroxyethyl Methacrylate)-Based Contact Lenses: How Did It Really Happen

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Abstract. Soft hydrogel contact lenses represent the most famous and commercially successful application of poly(2-hydroxyethyl methacrylate). The scarcely crosslinked network of this hydrophilic polymer finds its use also in many other fields, be it in (bio)medicine or technology. Moreover, the polymer itself and its crosslinked forms, discovered more or less serendipitously in the early fifties by a group of Czech chemists, is extremely interesting due to its exceptional properties: it readily swells in water, is optically clear, soft, biologically compatible, sufficiently strong, stable, gas-permeable, cheap, and easy to produce. Looking for its as-yet undiscovered qualities and possible utilization still continues. The story of the invention of hydrogel contact lenses was referred to many times in various literary sources which, however, contain numerous errors and misinterpretations. In the present article, we put these records straight and present the correct chronology of the hydrogel contact lenses development including the dramatic patent litigation. A brief overview of the chemical nature, properties, and applications of the constitutive substance of the lenses, i.e., the hydrophilic methacrylate, is also given.

Keywords: hydrogels, contact lenses, intraocular lenses, poly(2-hydroxyethyl methacrylate), Otto Wichterle.

1. INTRODUCTION

Modern hydrogels are usually tailor-made for the given purpose and application, be they synthesized by radical-initiated or stepwise processes, performed in a standard way, or by 3D printing. Since the times of the invention of the first hydrophilic plastic “swellable Perspex”, prepared by O. Wichterle’s group in the 1960s using the radical polymerization of 2-hydroxyethyl methacrylate (HEMA),[1] much effort has been devoted to a detailed study of this polymer. This was due both to its use for pioneering hydrogel contact lenses (the so-called “swelling plastic”) and to its interesting properties. Poly(2-hydroxyethyl methacrylate) (PHEMA) is distinguished by a good swellability (primarily in hydrophilic and partially also in hydrophobic media) and by a very good compatibility with living tissues. Even after swelling in aqueous media it keeps its mechanical strength and flexibility and is stable in time. That is why this material has found so many applications. Besides the medicinal use in the fields of ophthalmology, implants, or systems for drug transport and releasing, there are less known but no less successful uses for sorbents with a large intrinsic surface or separation monoliths in chromatography.[2-4] Thus, PHEMA remains a subject of lively scientific interest, as indicated by the number of papers with this keyword, published every year. At the same time, it represents an important model polymer both for the scientific research of synthetic hydrogels and for biomedicinal applications, including testing experiments of tissue engineering.

This paper brings information on the history of the research and applications of this unique monomer and its polymers, with special regard to hydrophilic contact lenses. It is the authors' ambition to put some erroneous historical data straight. Moreover, we consider it useful to briefly outline also the classification and history of the whole phenomenon of contact lenses.

2. EXCITING HISTORY OF CONTACT LENSES IN GENERAL

What is the contact lens? The basic definition reads: *Contact lens is a small optical system placed directly on the cornea.* All the issues and problems related to the contact lenses follow therefrom.

Contact lenses can be categorized in various ways. However, according to M. F. Refojo,[5] the fundamental division is based on the nature of the material. Most simply, contact lenses could be distinguished into rigid ones and soft ones, the latter then into hydrophobic and hydrophilic. Further categorization, necessary in connection with the development of new materials for contact lenses, is given in more detail in the Appendix (Tab. I). In current sources, this division is, regrettably, often oversimplified.

The idea of contact lenses is very old, reaching back as far as the 16th century and Leonardo da Vinci concepts, and its implementation is closely connected with the development of material science. Various inventors tried to use a broad spectrum of materials for contact lenses.

For example, when poly(methyl methacrylate) (PMMA) was introduced into the market (1933) and its relatively good biocompatibility was discovered, a way was opened for new medicinal applications of this plastic. Thanks to its optical properties, PMMA found its main use in ophthalmology (as a material for contact lenses, later for intraocular lenses, spectacles, etc.). This was the beginning of the era of polymers or covalent polymer networks in contactology, a brief history of which is presented in a tabulated form in the Appendix (Tab. II).[6-9]

After PMMA had been tested and finally abandoned, the following development of contact lenses was carried out to improve the properties of the lenses, namely, their permeability for gases (primarily oxygen) and also for water-soluble substances and ions. Although both of these requirements were met excellently by hydrogels studied by Wichterle and Lím,[1] another branch of the research continued towards the silicone elastomers (1965) which offered a high permeability for gases and showed good softness but were hydrophobic. These properties were then responsible for problems met when removing these lenses from the eye, namely, mechanical damage to a testing person's cornea. As a consequence of this, contact lenses based purely on silicone hydrophobic elastomers are no more accessible in the common market.[10]

Still another route of the development resulted in rigid gas-permeable (RGP) materials (1974), usually copolymers of alkyl methacrylates and siloxane methacrylates (possibly also fluoroalkyl methacrylates) which guarantee a high permeability for oxygen[11] but are hydrophobic and do not allow the transport of water-soluble substances.

Diverse variants of high-swelling hydrogels for contact lenses have continuously been being developed which had, in dependence on the equilibrium water content, a higher permeability for both water-soluble substances and gases. In addition to the basic sparsely crosslinked PHEMA, other glycol methacrylates were used, such as diethylene glycol methacrylate, triethylene glycol methacrylate, dihydroxyalkyl methacrylates (e.g., glycerol methacrylate), acrylamide, and, for ionogenic materials, also methacrylic acid sodium salt. Besides the acrylic acid derivatives, also 1-vinyl-2-pyrrolidone and polyvinylalcohol found their use as materials for high-swelling hydrogel contact lenses.[12]

Thus, in the sixties and seventies, the development headed toward soft contact lenses based on PHEMA or similar hydrophilic methacrylates, as will be discussed below. Later, however, silicone hydrogel lenses of the first generation were developed and introduced (1998-1999, according to the territory) and became an important milestone. Based on the first experience, the second generation arrived in 2004 and soon after (2006) even the third one. Interestingly, the first relevant patent dates back to 1979.[13]

3. TRUE STORY OF SOFT PHEMA-BASED CONTACT LENSES

3.1. Origins of the idea

The story of the origin of PHEMA-based contact lenses from the primal idea to the invention itself and its putting into practice seems to be generally known. The discovery of the synthetic hydrogel based on sparsely crosslinked PHEMA and its successful application as a biomimetic material for soft contact lenses are often mentioned in introductory parts of scientific papers. Similarly, the pioneering article by Wichterle and Lím[1] on the unexpected hydrophilic behavior of certain plastics and future possibilities of their biological applications, as well as the corresponding patents (see, e.g.,[14]) are frequently cited, too. However, although the history of the development of PHEMA, its polymerization, and properties, as well as hydrogel lenses based on it, has been published many times in various literary sources, the interpretations very often digress from reality. Hence, the following chapter aims to bring a systematic survey of events that led to the worldwide known invention and to the subsequent global development of soft contact lenses. The text is based on reviewed sources, Otto Wichterle's book of memoirs,[15] and a personal experience of the first author, i.e., his collaboration with the famous inventor for fifteen years.

The primary impulse arose from a fortuitous meeting of Prof. Wichterle with Dr. Pur, the secretary of a certain committee for the application of plastics in medicine at the Czechoslovak Ministry of Health Care. By coincidence, in 1953, they traveled together by train and looked through an ophthalmological journal with an advertisement for a tantalum prosthesis to substitute the eyeball. As he later mentioned in his memoirs,[15] Wichterle had expressed an opinion that it would be more suitable to prepare such implants from biocompatible polymers and suggested an idea of three-dimensional sparsely crosslinked hydrophilic gels.

This idea attracted Wichterle's attention so much that he started to put it immediately into practice in the Department of Plastics at the then Czech Technical University in Prague, together with his younger colleagues, especially Drahoslav Lím. At that time, research on methacryloyl derivatives of oligoethylene glycol was already running with the aim to get new plastics for future biomedical applications. The first hydrogel prepared and identified by D. Lím was crosslinked triethylene monomethacrylate, as described in a paper by J. Kopeček.[16] Later, as mentioned in another paper by Kopeček *et al.*,[17] in 1953 D. Lím succeeded in synthesizing the first hydrogels by the copolymerization of HEMA with ethylene dimethacrylate. In the same year Wichterle, as the only inventor, submitted a patent application for an invention, in which he claimed the whole class of sparsely crosslinked hydrophilic polymers including a description of many potential uses including even contact lenses unless he (or whoever else) had prepared this material.[15, 18] Of course, this was a pure fantasy at that time but, as it turned out later, also a realistic prophecy. Later on, this application was withdrawn and substituted by another one[19], which finally led to a patent entitled "The way of preparation of hydrophilic gels".[20] In the meantime, however, patents were granted to translated versions of the applications with differing delays in various territories. For example, in Great Britain and the then Federal Republic of Germany, it was granted still to the earlier application from 1953, while in other countries already to the one from 1955. That is why various literary sources differ in dating the origin of hydrogel lenses.

Since 1956 the contact lenses have been being prepared in Wichterle's lab in Prague but their ridges were of poor quality so testing persons were able to tolerate them on their eyes only for a few minutes at most. In the meantime, however, part of the applied research was transferred under the supervision of the Ministry of Health (Dental Laboratory, Prague). Several good lenses could have eventually been selected from the production of this laboratory where they were being prepared in polystyrene molds (1957).

The tests on patients (performed in the 2nd Ophthalmology Clinic at the General University Hospital in Prague, Mr. Dreifus, M. D.) proved that the soft hydrophilic lenses, prepared on a lab-scale but using ground glass molds, can ensure a very good correction of vision and are excellently tolerated (1959).

We quote here from the paper cited above (entitled „Hydrophilic Gels for Biomedical Use"):[1] "Promising results have also been obtained in experiments in other cases, for example, in manufacturing contact lenses, arteries, etc." That is why some sources proclaim 1960 as the year of the origin of soft hydrophilic lenses. Till today, this publication has been cited almost 1100 times.

However, most authors consider 1961 to be a true year of the origin of the hydrogel lenses. At the end of December 1961, prof. Wichterle, using a Czech-made children's toy building set *Merkur* (similar to the well-known *Erector Kit*), assembled at his home a device for the spin casting of contact lenses and named it (with his typical sense of humor) the "lens-machine" (Fig. 1, left). The principle of the spin casting consists in that the starting liquid polymerization mixture, dropped into a mold with a precise inner shape, is rotated by fine-tuned

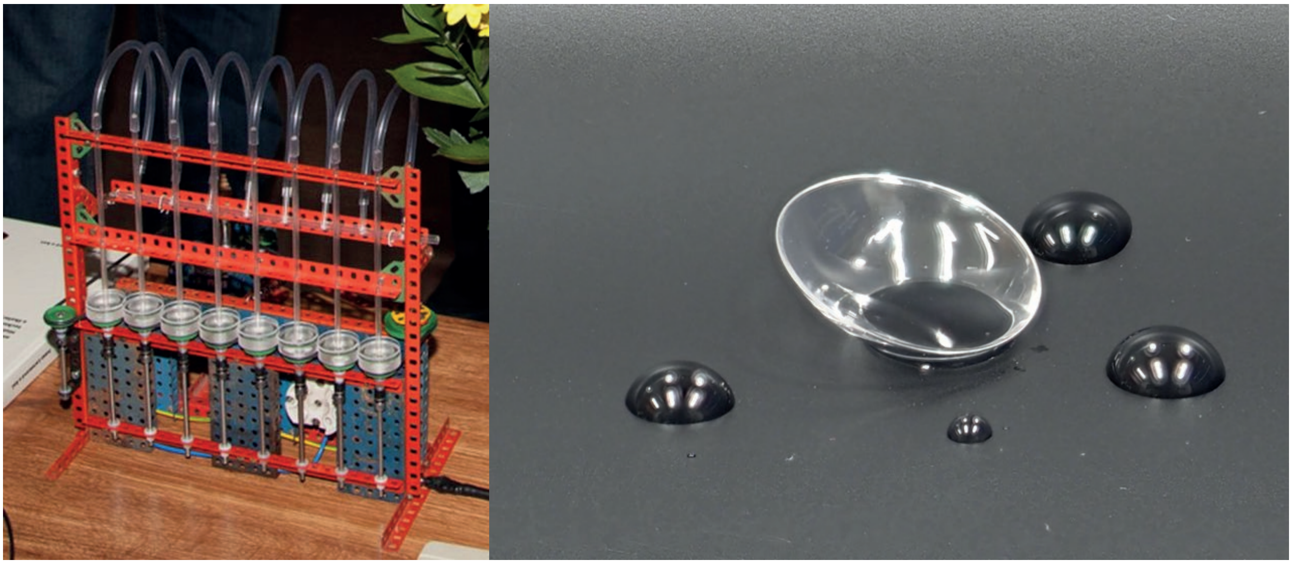

Figure 1. Replica of the building set *Merkur* (improvised lens-machine) for spin-casting (left), an example of a soft hydrophilic PHEMA-based contact lens (right).

number rpm. Due to a combination of the mold shape, the centrifugal force, and the surface tension, a proper lens shape is formed and, after the polymerization is finished, the solid contact lens acquires also the desired optical properties. With this improvised pilot-plant device, the first hydrogel contact lenses were produced (Fig. 1, right).

Later on, but still before the end of the same year, Wichterle patented a method to produce contact lenses.[21] In this way, the patents protecting the material for contact lenses were complemented by those describing the production method and the foretold use of synthetic hydrogels for contact lenses came into existence. A typical appearance of a contact lens is in Fig. 1.

A meeting with G. Nissel, a British producer of lathes and facilities for lathe-cutting of hard contact lenses, inspired Prof. Wichterle to submit another patent application of the invention to produce soft hydrogel lenses by turning from xerogel blocks, i.e., from prefabricated parts constituted by hydrogel in a dry state (Fig. 2), followed by fine polishing and swelling the lathed lenses.[22]

In 1964 Prof. Wichterle met his license partners-to-be from the National Patent Development Corporation (NPDC, USA). During the negotiations, he took out a lens from his eye, put it down to the ground, trampled it, then picked it up, removed the dirt from it first by fingers and then in his mouth, and finally put it back on his eye. This impressed his guests enormously. In 1965, the first license deal was signed between the then Czechoslovak Academy of Sciences and NPDC. Later on, in 1966, NPDC transferred the sub-license for soft contact lenses to Bausch & Lomb Co. which started to produce them in the USA, to prepare the distribution network and the marketing support, while waiting for approval of the production from the Food and Drug Administration (FDA). This was granted as late as 1972 but thanks to thorough preparation, Bausch & Lomb quickly penetrated the market and met a considerable demand for lenses.

3.2. Fascinating lawsuit on the patent priority

Already at the beginning of the seventies, infringements of Wichterle's patents by some producers appeared and even the Bausch & Lomb Co. took part in the litigations to save money for license fees. They used a tactic of denying the validity of Wichterle's patents with an argument of alleged pre-publication of some results and an absence of clinical tests. After NPDC had requested Wichterle's personal participation and testimony in American courts, the lawsuits began. To make the long story short, we set aside complications and obstacles laid by Czech communist authorities to block Wichterle's travel to the USA. Fortunately, he was allowed to testify in the end.

These legal disputes stretched till the beginning of the 80ies, although, thanks particularly to Wichterle's unambiguous replies to questions, became increasingly obvious that the validity of the patents will be confirmed.

By the end of 1976, despite this promising course, the Czech side acceded to an out-of-court settlement,

Figure 2. Special lathe for contact lens manufacturing (left) and the lathing of the contact lens from xeroblock.

and, for receiving an amount equal to the license income for one year, the Czechoslovak Academy of Sciences, controlled by the communist regime, stupidly opted out of the contractual liability for the participation in the patent lawsuits. In this way, the Czech side forfeited not only the license contracts but also the share of the proceeds of the lawsuit.

In 1980, a radical turnaround happened in the lawsuit which meant a full victory because all disputed issues were explained and Dr. Dreifus, who had been apparently manipulated by the infringers, was convicted of false testimony.

Still, it had taken two years of thrilling waiting before the final verdict was delivered (1982). In the meantime, still in 1981, NPDC made, probably as an expression of gratefulness to O. Wichterle for his contribution to the victory at the Court, a new license contract regarding the preparation of contact lenses by a photopolymerization initiated by UV radiation.[20-22] License fees from this contract have been coming to the Czech Republic till 2000.

3.3. Further development

Simultaneously with improving the quality of the contact lenses, also the means of maintenance of them had to be adapted to the newly developed materials. Thus, the physiological solution, used in the beginning, was substituted by multipurpose solutions containing, e.g., a disinfection or conservation component, a buffer system, detergents, wetting agents, and auxiliary substances, such as those with chelating effects. Similarly, the regime of wearing the lenses, as well as the planning replacement of them (rate), have been developing. In this way, the development resulted in disposable lenses.

In the nineties (1993) a one-time non-recurring contract was made with South Korean partners who took over a new lens-making machine (“lens machine”) of the carousel type with an electronic-pneumatic control of functions and documentation for innovative technological processes including a new version of the software (Fig. 3).

Although the Koreans paid for a corresponding part of the charges, they never started to produce so the fees derived from the number of pieces produced were never received by the Czech side.

Prof. Wichterle’s decease in 1998 symbolically closed the era of the early development of PHEMA-based hydrogel contact lenses. In the same year, the first “silicone hydrogels”, constituted partly of polysiloxane chains, were introduced into the market. The polysiloxane structure, hydrophobic by nature, is made sufficiently hydrophilic by the covalent attaching of methacryloylated segments and other hydro-

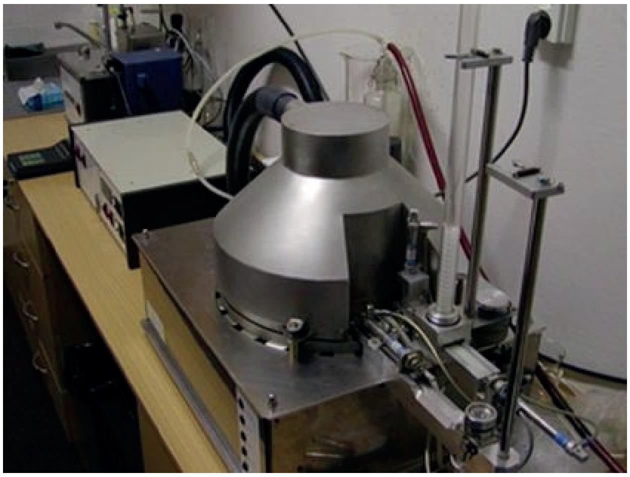

Figure 3. Lens machine for spin casting, the carousel type from the nineties.

philic vinylic polymers. [23] Silicone hydrogel contact lenses arrived at their 3rd generation and the "tricks" of attaining hydrophilicity differ from generation to generation. The type Dailies Total One, which was introduced on the market in 2012, represents a unique type of lens with a swelling gradient. However, hydrogels based on polymethacrylates or poly(vinyl alcohol) still constitute a substantial part of the world's production of contact lenses. Supposedly, for some clients, they will remain a suitable variant of the ocular refraction defect correction. Innovations still appear, for instance, the product called Hypergel from Bausch & Lomb, which is a bio-inspired hydrogel material containing 78% of water and showing an increased oxygen permeability (Dk = 42 barrer). This multicomponent polymer formulated on the basis of HEMA, *N*-vinylpyrrolidone, and 2-hydroxy-4-*tert*.butyl-cyclohexyl methacrylate, and crosslinked by ethylene dimethacrylate and allyl methacrylate, contains also a UV stabilizer based on benzotriazole and incorporated in the chain by a methacryloyl substituent. Undesirable drying of the lens surface made of a highly swelling material is prevented by a block copolymer formed by two outer blocks of poly(ethylene oxide) and a central block of poly(propylene oxide). The copolymer is terminated on both ends by two methacrylate groups, through which it is incorporated into the structure of the whole polymer network. Contact lenses made from it were introduced in the market under the trademark Biotrue ONEday in 2014.

4. HEMA AND ITS POLYMERS

4.1. History of HEMA and PHEMA

The first notices on HEMA and its polymers date back to the Thirties, namely in the US patent No. 2,129,722 entitled *Esters of Methacrylic Acid* and registered on September 13, 1938, for John C. Woodhouse as the inventor and DuPont de Nemours Co. as the applicant.[24] In several claims (1-4), esters of methacrylic acid and a series of aliphatic diols, triols or pentaerythritol, etc. are generally presented; among these alcohols, also ethylene glycol is mentioned. Claim 8 is devoted solely to polymeric monomethacrylate prepared by heating the monomeric ester to 60-100 °C in the presence of dibenzoyl peroxide. Although the monomer, the polymer, and their preparations were thus described, a real utilization of them came as late as during the systematic study of the hydrophilic structures performed by Wichterle and Lím.[1,15]

4.2. Nomenclature, structure, and properties of the HEMA monomer

The most frequently used, non-systematic but the deep-rooted name is 2-hydroxyethyl methacrylate (usually acronymed as HEMA), sometimes also glycol methacrylate. Names like glycol monomethacrylate, hydroxyethyl methacrylate, ethylene glycol methacrylate, or 2-(methacryloyloxy)ethanol are also used. According to IUPAC, the systematic name is 2-hydroxyethyl-2-methylprop-2-enoate. To preserve intelligibility and to comply with the scientific community's common usage, the name 2-hydroxyethyl methacrylate (HEMA) is used throughout the text; similarly, ethylene glycol will be used instead of the systematic 1,2-ethanediol.

The structure of the monomer is presented in Fig. 4 together with its basic physical properties. If not stated otherwise, the values correspond to standard conditions, i.e., 25 °C and 101.325 kPa.[25]

4.3. Preparation of the HEMA monomer

Of the procedures to produce HEMA, two have been used on a larger scale. The Czechoslovak patent was based on the reesterification of methyl methacrylate by glycol.[26] This process led to a product with a relatively high content of diester (ethylene dimethacrylate causing a crosslinking during the polymerization), the concentration of which had to be decreased by subsequent purification procedures. In addition to that, the prod-

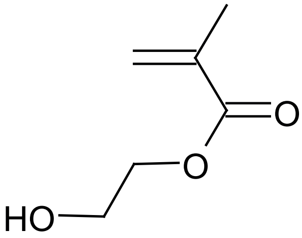

Figure 4. The schematic formula of 2hydroxyethyl methacrylate (properties: colorless liquid, density 1.07 g·cm^{-3}, melting point 99 °C, boiling point 213 °C, vapor pressure 0.08 hPa).

uct contained traces of diethylene glycol methacrylate and diethylene glycol dimethacrylate (the latter being a crosslinking agent, too) but was free of methacrylic acid.

Nowadays HEMA is commonly produced by a reaction of ethylene oxide with methacrylic acid. The resulting product contains a low level of the crosslinking agent and traces of methacrylic acid (see, e.g.,[27]).

4.4. Polymerization of HEMA

The double bond of 2-hydroxyethyl methacrylate reacts readily under normal pressure in bulk or in a solution, similarly to other methacrylates. The temperature range of the radical polymerization of HEMA has its upper limit at ca. 160 °C; at this and higher temperatures, depolymerization of the polymer chain takes place. Practically, the lower limit corresponds to the solidification (vitrification) temperature of the polymerizing system; however, it is possible to perform a redox-initiated polymerization under the condition of the so-called cryogelation, i.e., at sub-zero temperatures, e.g. around -20 °C and in presence of a diluent, when interesting macroporous structures are formed in the resulting gel thanks to freezing of the diluent (typically aqueous) off the system.[28] A living anionic polymerization of HEMA with a protected hydroxyl group has also been reported, [29,30] proceeding at much lower temperatures (40 to 80 °C) and yielding an isotactic polymer. In the latest decade, papers have been published reporting on the possibility to control the HEMA polymerization by the RAFT (reversible addition-fragmentation chain transfer)[31] or ATRP (atom transfer radical polymerization)[32] methods. It is the aim of these controlled radical polymerizations to get a polymer with the distribution of molar mass narrower than that obtained by standard (uncontrolled) free radical polymerization and to possibly attach certain functional groups onto the chain ends.

Interestingly, the sparsely crosslinked PHEMA (i.e., with the level of the crosslinker below ca. 1 mol.%) significantly swells in water attaining swelling equilibrium at approx. 36-38 wt.% of water at room temperature.[33] The swelling behavior of the PHEMA macromolecular network is very interesting and shows a certain "swelling anomaly": the equilibrium swelling degree does not depend much on the crosslink density which is also true for a linear PHEMA of a high degree of polymerization. PHEMA belongs to the UCST-LCST[1] system exerting swelling minimum at 55°C.[34]

4.5. Physical prerequisites for making the perfect contact lens

The PHEMA-based hydrogel suitable for lenses (PHEMA prepared with 38–40 wt.% of water and ca. 1 mol.% crosslinker) is characterized by some key properties such as the equilibrium content of water (approx. 38 wt.%), the oxygen permeability (8-12 x 10^{-11} barrer), and modulus of elasticity (typically 0.5-0.6 MPa).[8,28] However, these parameters strongly depend on the starting conditions and exact way of hydrogel preparation, especially on the concentration of the crosslinking agent and diluent (water) at polymerization. Here we focus solely on the microstructure and porosity. The PHEMA hydrogels can be prepared either as macroscopically homogeneous (optically transparent) or, inversely, as a heterogeneous substance, showing a loss of transparency and a formation of opalescence, thus indicating refraction of light on microscopic interphases due to the formation of pores. At this point, our report deserves a more detailed explanation of the PHEMA hydrogel optical clarity. In the early studies, when Wichterle and his coworkers observed the first crosslinked PHEMA gels, the pieces of water-swollen material were rather transparent and colorless. Their observations were truly serendipitous as the material resembled clear glass and provided an index of refractivity very close to that of the biological cornea, so the ideas about a gel-based soft contact lens could be explored ever since. But it soon became evident that not always the free radical crosslinking of the HEMA-based system leads to an optically clear material and that there are critical limits of composition beyond which the resulting material turns irreversibly hazy, or completely non-transparent – and thus not useful for an optical lens. These "clarity limits" for HEMA-based systems were subjected to thorough experimental studies in the Institute of Macromolecular Chemistry in Prague in the 1970s. It was found that when the content of water as a diluent in the polym-

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[1] UCST – upper critical solution temperature, LCST – lower critical solution temperature

erizing system exceeds ca. 50 vol.%, an opaque or white, or even porous heterogeneous material is obtained. Indeed, the limits also correlated with the amount of crosslinker. The reasons for the existence of the limits were in the meantime explained by K. Dušek who put forward the analysis of the formation of thermodynamic phases leading to the porosity of the crosslinking system styrene-divinylbenzene investigated for ion exchange resins.[35] Deeper studies of PHEMA and its solution and gel properties continued in the seventies.[36] Dušek derived a generalized thermodynamic treatment for phase separation in a three-dimensional polymer system based on the analysis of the Flory-Huggins swelling equation and he coined the term microsyneresis (or syneresis). This term denotes a separation of phases in the so-called quasi binary system where the phase of the swollen gel separates from that of the diluent, the latter, however, possibly containing residua such as a soluble monomer or its oligomers. This separation is a consequence of the change of miscibility within the polymerizing system with conversion, so-called c-syneresis, and/or is induced by increasing crosslink density, so-called n-syneresis.[37] Whereas HEMA monomer is unlimitedly miscible with water (starting state), the growing chains only have limited solubility in the water-HEMA mixture and limited entropy of chain arrangements (crosslinked state). Microsyneresis in water-HEMA crosslinking system proceeds through the mechanism of the nucleation and growth which leads to a typical structure of mutually connected microscopic spheres providing a heterogeneous gel well visible in Fig. 5. These gels, when swollen to equilibrium volume in water, macroscopically appear white or opaque – far from the perfectly transparent appearance necessary for a contact lens. Interestingly enough, even standard hydrogel of composition used for contact lenses showed, already during polymerization, the formation of nanosized inhomogeneities, supposedly pores, of several typical dimensions between 1 and 10 nm.[28] Such inhomogeneities do not deteriorate the optical clarity of the final product but can enhance the transport of water, oxygen, and small ions. [38]

Microsyneresis provides an interesting and well-explored way nowadays leading to a formation of porous systems, predominantly with communicating pores having their size in the range of 10^0-10^1 μm. It is a system-specific thermodynamic phenomenon that can be predicted, is perfectly reproducible, and is inevitable within a certain compositional range.

As mentioned above, the HEMA monomer always contains a little amount of bis-methacrylic units (ethylene dimethacrylate, EDMA). During the polymerization, EDMA is gradually incorporated through its two vinyl groups into the polymer chains so that the branching and, at higher degrees of conversion, also crosslinking inevitably takes place.

During the development, various methods have been used to achieve the porosity of PHEMA:[40] besides the thermodynamic demixing, also introducing washable microparticles (porogen) into the gel matrix. In this way, interesting porous structures based on PHEMA have been prepared, including (nano)fibers.[41] Also composites of PHEMA, e.g. with bacterial cellulose, [42] or interpenetrating networks,[43] as well as materials with dual porosity[44] have been described.

5. PHEMA − APPLICATIONS OTHER THAN CONTACT LENSES

5.1. Medicinal applications

Since the seventies, within the group of younger Wichterle's colleagues, there existed a lively activity in the field of biological application of PHEMA materials other than ophthalmology.[45]

Due to its good compatibility with living tissue, PHEMA was predetermined for medicinal applications. During its decades-long history, this biocompatibility was proved beyond any doubt by its long-term use in this field. Some later studies then confirmed that not only the high-molar-mass polymer of HEMA but also its very short chains (oligomers) are well biocompatible.[46]

In fact, PHEMA has become a material of the first choice for biomedicinal applications, in particular for pilot experiments; subsequently, the material can be modified in many ways according to the needs of the particular application. Thanks to their transparency, homogeneous HEMA polymers found their first medicinal applications in ophthalmology. In addition to the already discussed soft hydrophilic contact lenses which aroused a global response, PHEMA has its history too as a material for intraocular lenses implanted into the eye during cataract surgery,[47] artificial vitreous body, [48] etc. Wichterle himself proposed many medicinal applications of PHEMA which were put in practice more or less successfully.

Of the other applications, known are implants for otorhinolaryngology,[49,50] plastic or general surgery,[51] gynecology,[52] urology,[53] and neurology,[54] as well as carriers for cell cultivation for dermal wounds healing, burns, or bedsores.[55,56] Polymers of HEMA are still used to prepare ointments/salves[57] and various gel preparations,[58] drug carriers,[59] tissue expanders,[60] synthetic emboli[61], or hemoperfusion detoxicating columns.[62] 3D microstructured carriers for cell cultivation, known as

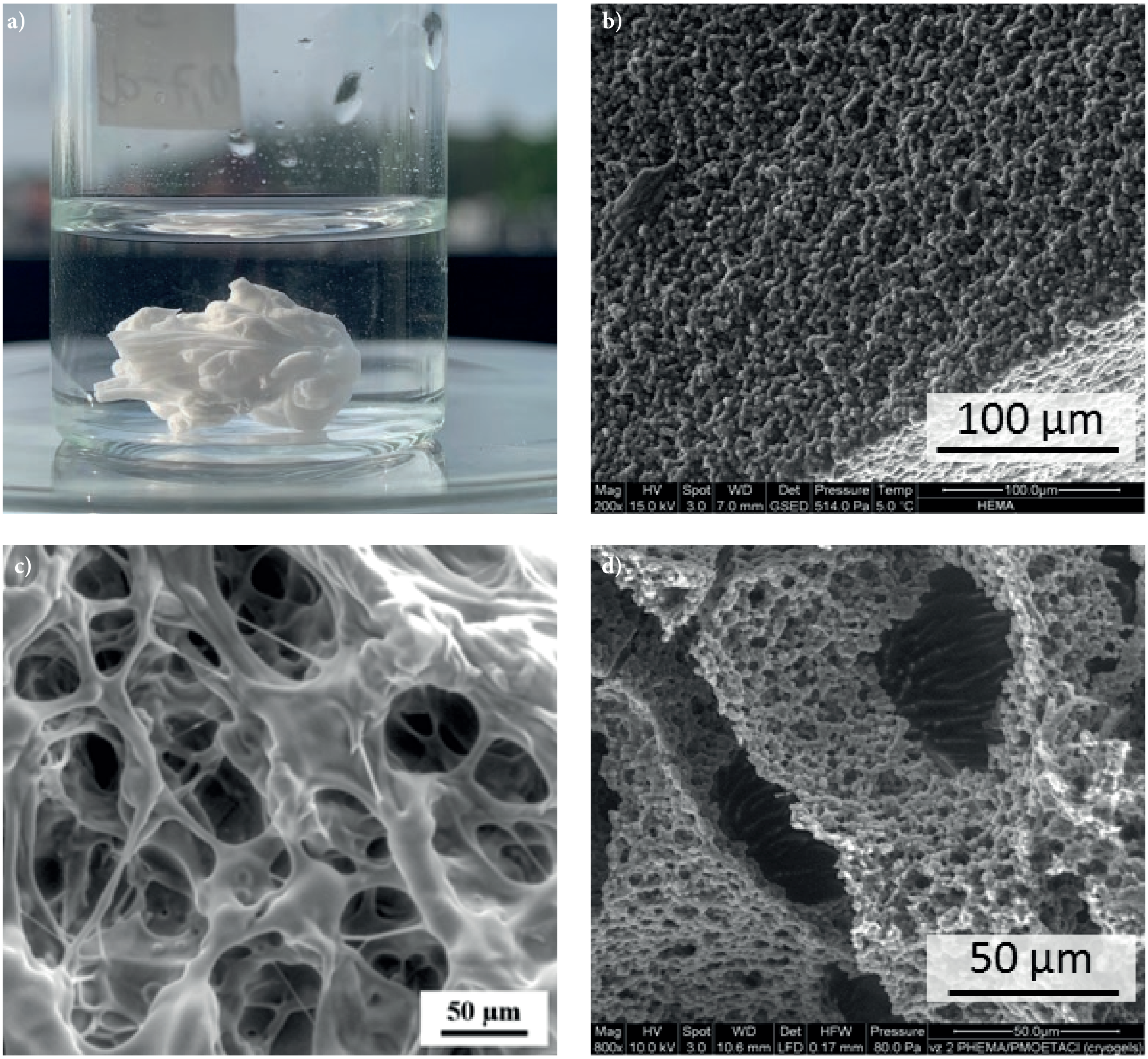

Figure 5. Porous hydrogels prepared from poly(2hydroxyethyl methacrylate) and visualized by the methods of scanning electron microscopy. (a) Macroscopic view; (b) PHEMA hydrogel showing after the microsyneresis a structure of connected spheres, (c) PHEMA hydrogel prepared from poly(HEMA-*stat*-MA) (fractionated NaCl was used as a porogen; after washing out the porogen, the gel was visualized by the AquaSEM method); (d) microscopic structure of a cryogel of HEMA showing the dual size of pores. Figs 5b and 5d were obtained by the so-called environmental SEM.[39]

scaffolds, have since recently been used. Thus, PHEMA has become a successful reference material also in the fields of cell therapy and tissue engineering.

Recently, with the development of additive manufacturing methods, HEMA finds its use as a photopolymerizing monomer in the resin compositions in stereolithographic 3D printing and 3D writing methods. It was used to constitute photopolymerizable ink for direct writing of 3D microarrays as scaffolds for neuronal cultures.[63]

5.2. Technical applications

To this category belong, e.g., (meth)acrylate coatings. PHEMA of technical grade is being used as a part of single-component dispersion coatings (together with

Figure 6. Historical cup restored using a preparation based on PHEMA. (a) an example of gluing glass on a base, (b) a detail of an attached substitutive bottom.

butyl acrylate or butyl methacrylate). As a comonomer, HEMA carries the functional reactive OH group into the polyol component of the two-component curable and highly resistant polyurethane coatings.[64] Another proven application, though not yet published, was the preparation of heterogeneous membranes with incorporated ion exchangers. The high adhesivity of PHEMA to other materials, as well as its transparency, enabled such technical applications as gluing of methacrylates or their layers. As an example, until now unpublished results of the tests (performed in 1982 and based on stress-strain curves) enabled one to assess the strength of the link formed by polymerization of 2-hydroxyethyl methacrylate in between two specimens, the latter being constituted by a common mineral glass, an organic glass, a polyamide, and steel of class 11. In all cases, very firm joints were obtained, resisting stress of about 2 MPa. The results, suitable especially for gluing glass, led to the testing of polymers based on PHEMA, to prepare permanent microscopic preparations, mechanically resistant layered glass or antifire layered glass, or to restore various historical glass objects (Fig. 6).

In an interesting application, water confined in certain hydrogels (semi-interpenetrating PHEMA/polyvinylpyrrolidone networks) was used to gently remove dirt from the surface of water-sensitive cultural artifacts.[38] Similarly, complex cleaning fluids confined in these hydrogels were used to remove aged varnishes.[65]

A highly diluted solution of PHEMA was tested by O. Wichterle as an "anti-spray" coating to prevent the creation of graffiti. Regrettably, to the best of our knowledge, this method has been neither patented nor published. Its advantage lies in that that the coating is cheap and can easily be removed by excess water.

6. CONCLUSIONS

It follows from the facts presented that the history of the origin, development, and applications of 2-hydroxyethyl methacrylate and its polymers is extremely interesting, varied, edifying, and sometimes even exciting. In this review, the development of the famous application of hydrogel based on poly(2-hydroxyethyl methacrylate) for contact lenses is presented. Inventors' effort was idea-driven rather than serendipitous: Otto Wichterle and his co-workers not only arrived at a technically useful product but also showed the general importance of hydrogels. The dispute over the validity of the corresponding patents became a subject of a thrilling lawsuit that ended with the victory of the inventors. The eventual success was possible thanks to inventors' endurance and ability to overcome the obstacles, both technical and political. The whole process from idea to final product took twenty years. When inspected in more detail, the present state of the art in the field suggests a possibility of further and deeper studies and even broad projects on the subject. In this way, some new properties, behavior, and applications of poly(2-hydroxyethyl methacrylate) hydrogels, so far unexplored, could be discovered.

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APPENDIX

Table I. Categorization of contact lenses from the material point of view. How it changed in time

Original division	hard			
	soft	hydrophobic		
		hydrophilic		
Recent division	hard	impermeable	glass, PMMA	
		gas permeable	rigid gas permeable (RGP)	
	soft	hydrophobic	silicone elastomers	
		hydrophilic	standard hydrogels	PHEMA
			high swelling hydrogels	
			hybrid hydrogels	silicone hydrogels
Present day division	rigid gas permeable (RGP)			
	hydrogels			
	silicone hydrogels			

Table II. Important dates in global contactology (from the viewpoint of polymer materials and manufacturing methods)

1933	Rohm and Hass Co. introduced transparent polymethyl methacrylate (PMMA) into the market.
1936	William Feinbloom described a scleral lens composed of a central clear part (glass) and an opaque edge (PMMA). Soon after that, rigid lenses have been produced by turning solely from PMMA.
1948	By mistake in turning, Kevin Tuohy prepared a very small size lens of PMMA and found that it was better tolerated than that of the original size. Afterward, he patented hard corneal lenses of PMMA.
1953	D. Lím successfully prepared the first hydrogel following the idea of Otto Wichterle; application of the first O. Wichterle's patent.
1956	The first hydrogel contact lens was prepared in Wichterle's Prague laboratory.
1959	Tests on volunteers showed good correction of *visus* and excellent tolerance of hydrogel contact lenses.
1960	Wichterle and Lím published an article in *Nature*, entitled "Hydrophilic Gels for Biomedical Use" where they described PHEMA gels.
1961	Priority of spin casting method of hydrogel contact lens fabrication (Wichterle)
1963	Priority of lathe cutting method of lens fabrication from xerogel blocks (Wichterle)
1965	Hydrophobic soft contact lenses made of silicone elastomers
1972	Hydrophilic (hydrogel) soft contact lenses were introduced to the global market.
1974	RGP – rigid gas permeable lenses
1988	Lenses with regular replacement (cast molding technology began to prevail)
1994	Disposable lenses (regular replacement after one day)
1998	Silicone hydrogels, 1st generation
2004	Silicone hydrogels, 2nd generation
2006	Silicone hydrogels, 3rd generation (till present day)
2014	New highly swollen hydrogel contact lenses (Biotrue ONEday) were introduced on the global market. Their material (Hypergel™) contains in equilibrium 78% of water.