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2-Hydroxyethyl Methacrylate (HEMA): Chemical Properties and Applications in Biomedical Fields

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1. INTRODUCTION

2-Hydroxyethyl methacrylate is a monomer with numerous applications. More than 1500 publications have been devoted to this product since 1967, 2000 publications or patents mention the corresponding polymer, and a greater number of works involve copolymers incorporating this monomer.

Some factors explain the great interest afforded to 2-hydroxyethyl methacrylate. This monomer, which is commercially available, is prepared in a single step from methyl methacrylate or methacrylic acid and can be easily polymerized as the majority of methacrylic derivatives. A primary alcohol function allows substitution reactions with the monomer or the corresponding polymer. The monomer, which is soluble in water, gives a hydrogel after polymerization whose applications in biomedical fields are important [1].

The first synthesis of 2-hydroxyethyl methacrylate [2] and its polymerization were described in 1936 [3]. The first applications of the polymers as hydrogels were reviewed in 1960 [4], and a more fundamental study of this polymer was made in 1965 [5].

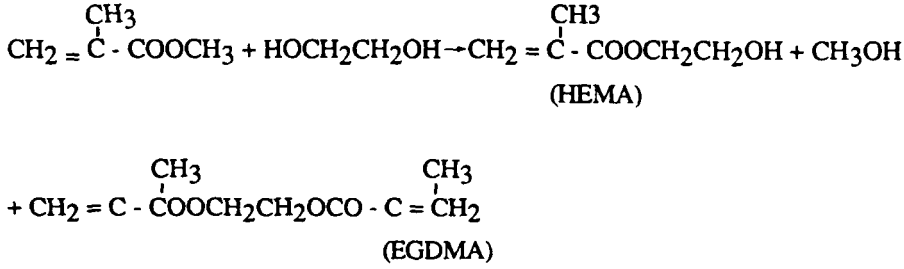
Because 2-hydroxyethyl methacrylate is very important in macromolecular chemistry, it will be useful to review the main properties of the polymers or copolymers prepared from it by summarizing the information published in articles or patents. The following plan is adopted:

Preparation and purification of 2-hydroxyethyl methacrylate
Polymerization and copolymerization of 2-hydroxyethyl methacrylate and physical properties
Chemical modifications of monomer
Chemical modifications of poly-2-hydroxyethyl methacrylate and related copolymers
Grafting reactions of polymer or copolymer
Applications in biomedical fields

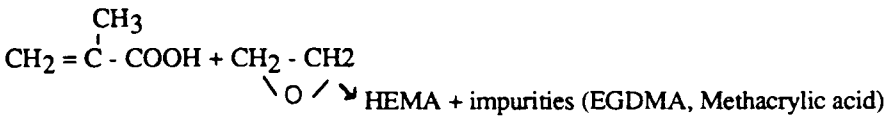
The following abbreviations will be used: HEMA for 2-hydroxyethyl methacrylate (rather than GMA, which is chiefly employed in medical journals) and PHEMA for the corresponding polymers. EGDMA will be used for ethylene glycol dimethacrylate, an impurity synthesized in the preparation of monomer.

2. PREPARATION AND PURIFICATION OF HEMA

HEMA can be synthesized in a single step from methyl methacrylate or methacrylic acid. The first method (Scheme 1) requires the reaction of ethylene glycol (transesterification reaction) [6, 7]. The second



SCHEME 1.



SCHEME 2.

method is the reaction of ethylene oxide and methacrylic acid (Scheme 2) [8–10]. The HEMA prepared by these two methods contains impurities in various percentages: e.g., methacrylic acid results from a hydrolysis reaction of HEMA and EGDMA coming from esterification between methacrylic acid or HEMA and ethylene glycol.

Since HEMA is a commercial product, it seems more useful to summarize the various purification procedures rather than the numerous works about industrial preparations because the commercial product contains EGDMA and methacrylic acid in monomer proportions.

The main procedures use the solubility of HEMA in water or diethyl ether and its nonsolubility in hexane. EGDMA is soluble in hexane. Therefore, HEMA is dissolved in four volumes of water and EGDMA is extracted with hexane. Then the aqueous solution of HEMA is salted to complex methacrylic acid. HEMA is extracted with diethyl ether, the solution is dried, and HEMA is distilled under vacuum [11–14].

The elimination of methacrylic acid can also be carried out by soaking technical HEMA with anhydrous sodium carbonate [15] and extracting EGDMA with hexane. Then HEMA is extracted with diethyl ether and distilled as previously described.

The use of ion-exchange resins (Amberlyst A 21) is a simple method of elimination of methacrylic acid [16–18] but the yield is rather poor. *N,N'*-Dicyclohexylcarbodiimide has also been used for the elimination of methacrylic acid [19], but variations in the quality of the reagent often outweigh the value of the method.

Lastly, extraction of EGDMA with hexane followed by the washing of a dilute solution of HEMA in water with sodium hydroxyde or sodium bicarbonate and the extraction of HEMA with chloroform gives, after drying and evaporation of chloroform, a product of high purity for the preparation of resins for optical microscopy [20, 21].

The purity of the monomer can be checked by using vapor-phase chromatography [22, 24], liquid chromatography [15], or thin layer chromatography [25]. Detailed distillation procedures to avoid polymerization of HEMA have been described [11, 15, 26].

3. POLYMERIZATION OF HEMA, PHYSICAL PROPERTIES OF PHEMA, AND COPOLYMERIZATION OF HEMA

3.1.1. Polymerization

As for the majority of methacrylic derivatives, HEMA can be polymerized by radical initiators or by various methods (γ-rays, UV, and plasma). When the monomer is purified (without EGDMA, which is a crosslinking product), a soluble polymer can be synthesized, but when the monomer contains even a low percentage of EGDMA, the prepared copolymers produce swollen gels in water and in many other solvents [24].

A summary of the main procedures of polymerization is given in Table 1.

Syndiotactic PHEMA has been synthesized by UV catalysis at $-40°C$, and isotactic PHEMA has been prepared through hydrolysis of poly(benzoxyethyl methacrylate) which had been synthesized from the corresponding polymers with dibutyl lithium cuprate as catalyst [52].

3.1.2. Physical Properties of PHEMA

Because PHEMA has numerous applications in biomedicine, its physical properties have been widely studied.

3.1.2.1. Studies of Diffusion. The permeability of PHEMA, used as a membrane for oxygen, has been compared to other macromolecules [53]. The diffusion of water through hydrogels of PHEMA, crosslinked with low percentages of EGDMA, has also been studied [54, 57]. The influence of the degree of crosslinking [58, 60], the diffusion laws, the measurement of the equilibrium constant with water, and a structural study of swollen gels were recently published [61].

3.1.2.2. Mechanical and Viscoelastic Properties. These properties were summarized in two previous reviews [62, 63]. Composites with crosslinked PHEMA have good elastic properties [64, 65]. The influence of aqueous solutions of sodium chloride on the elasticity of PHEMA has also been studied in relation to its use for optical lenses [66].

3.1.2.3. Viscometry, Thermal, and Dielectric Properties, and NMR Characterizations. Because the Mark–Houwink parameters in many solvents are well known, the molecular weights of PHEMA can be measured by viscosity [67, 70]. The thermal properties [71], such as the

TABLE 1

Polymerization of HEMA[a]

Monomer (mol%)	EGDMA (mol%)	Conditions (solvents, initiators)	Refs.
99	1	Various; diisopropylpercarbonate	11
98	2	Bulk; AIBN	6
100	0	γ-Irradiation (−78°)	13
100	0	2 Methoxyethanol; AIBN	12
100	0	γ-Irradiation	26
100	0	Acetylen; γ-irradiation	28–30
96	0.4 + impurities	Redox system	31
100	0	γ-Rays	29–33
100	0	Microwaves	32
99.7	0.3	Methylazoisobutyrate	34
99.7	0.3	γ-Rays	35
100	0	Cellulose; AIBN	36
D		Plasma	37
D		Methyl ethyl ketone; AIBN	38
D		Electropolymerization	39
D		Diallylphthalate pyrolysis	40
D		γ-Rays; biological substances	41
D		Manganese(III) tris (acetylacetonate) acetic acid	42
D		UV + photosensibilizators	43
D		Bulk; azobismethylisobutyrate	44, 45
D		Water or DMSO; plasma	46
D		Water; potassium persulfate	47
99.5	0.5	Water; potassium persulfate	48
D		PHEMA; benzoyl peroxide	49
D		Liquid crystals; UV-rays	50
D		High pressure; radiation	51

[a]AIBN = Azobisisobutyronitrile. D = HEMA has been distilled and the percentages of methacrylic acid and ethylene glycol dimethacrylate are not given.

variations of glass transition temperatures of PHEMA with various tacticities have been studied and a good correlation with the relaxation phenomenon in dielectric properties has been observed [72, 75].

Thermal degradation and determination of volatile fractions by mass spectrometry–vapor-phase chromotography have been carried out [76, 77]. Very few works have been devoted to ^{13}C-NMR studies of swollen gels of PHEMA [78, 79].

Lastly, in order to use the PHEMA in the biomedical field, the purification of polymer gel has been described [80].

3.1.3. Copolymerization Reactions of HEMA

Copolymerization reactions of this monomer have been studied for its fundamental properties (determination of reactivity ratios, Alfrey–Price parameters) [81, 82] and its applications in various fields. The main results are given in Table 2.

Some examples of block copolymerization with styrene [104, 105], 2-phenyl-1,2,3-dioxaphospholane [106], and with macromonomers [107] of polyamine [108] or polyurethane [109] can be cited.

Lastly, fundamental studies on the copolymerization of methyl methacrylate with HEMA [110] and the determination of the composition of its copolymer have been made, and a model of the copolymerization of HEMA and EDGMA was recently published [111].

4. CHEMICAL MODIFICATIONS OF MONOMER

Because HEMA has a primary alcohol function a great number of nucleophilic reactions have been achieved and generally the modified monomer can be polymerized.

A summary of the main chemical modifications is given in Table 3.

5. CHEMICAL MODIFICATIONS OF PHEMA AND RELATED COPOLYMERS

A relatively low number of chemical modifications of PHEMA have been registered because chemical modifications of the corresponding monomer as well as its polymerization are easy to achieve. The listing of these reactions is given in Table 4.

6. GRAFTING REACTIONS OF POLYMER AND COPOLYMER

By using various techniques, the grafting of PHEMA and copolymers prepared with HEMA as a comonomer has been carried out with natural polymers such as cellulose [148], dextran [149], and starch [150].

Synthetic polymers, polyethylene [151], polyurethanes [152], polyvinylic alcohol [153], blends of acrylic networks and polyvinylic alcohol

TABLE 2

Copolymerization of HEMA (M_1) with Various Monomers (M_2)[a]

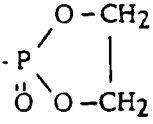
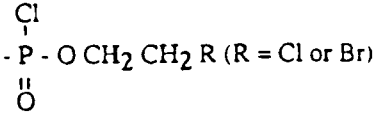
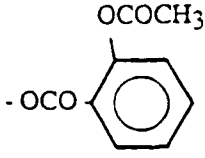
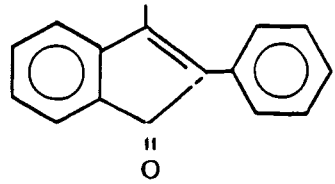
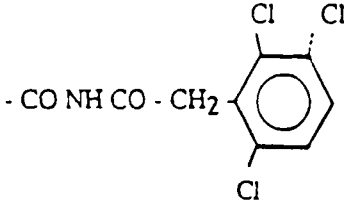
M1	M2	R1	R2	Conditions (solvent, initiator temperature)	Refs.
D	Acrylic acid	0.32	1.02	Bulk; γ-rays; 25°C	83
D	Acrylonitrile	0.632	0.02	DMF; AIBN; 60°C	84
D	Acrylonitrile	1.58	0.03	DMSO; AIBN; 60°C	84
D	Acrylamide	3.98	0.053	DMF; AIBN; 60°C	85, 86
D	Methacrylic acid	1.50	0.67	PEG as a plasticizer; AIBN; 60°C	87, 88
D	Methyl acrylate	7.14	0.012	Bulk; BP; 60°C	89, 90
D	Ethyl acrylate	13.5	0.360	Bulk; BP; 60°C	89, 90
D	*n*-Butyl acrylate	5.4	0.168	Bulk; BP; 60°C	89, 90
D	Methyl methacrylate	1.05	0.296	Bulk; BP; 60°C	90–92
D 1% EGDMA	Methacrolein	0.36	0.77	DMF; AIBN; 60°C	93
D	2-*n*-Vinyl pyrrolidone	4.35	0.06	Methanol; AIBN; 50°C	91–94
D	*n*-Vinyl succinimide	6.6	0.12	Benzene; AIBN; 60°C	95
Pure	Acryloyl methylpentamethyldisiloxane	0.86	0.55	Bulk; 4,4-azobicyanopentanoic acid; 60°C	96

Pure	Methacrylomethylpentamethyldisiloxane	0.97	6.33	Bulk; 4,4-azobicyanopentanoic acid; 60°C	96
D	2-Vinylpyridine	0.58	0.69	DMF; AIBN; 60°C	97
	3-Vinylpyridine	0.74	0.71	DMF; AIBN; 60°C	97
	4-Vinylpyridine	0.66	0.95	DMF; AIBN; 60°C	97
D	Styrene	1.65	0.50	DMF; AIBN	98
D	Tri-*n*-butyltin methacrylate	2.45	0.39	Tetrahydrofuran; AIBN; 60°C	101
D	*n-trans*-4-Stilbenylmethacrylamide	1.82	0.72	DMF; AIBN; 60°C	97
	n-trans-4′-Nitro-4-stilbenyl methacrylamide	1.94	0.84	DMF; AIBN; 60°C	97
D	Methacrylic derivatives of chloramphenicol	1.07–1.7	0	Methoxyethanol; AIBN; 60°C	99, 100
D	Lauryl methacrylate	11.2	0.7	Benzene; AIBN; 60°C	103
	Stearyl methacrylate	3.02	0.76	Benzene; AIBN; 60°C	103
D	2-*p*-Styryl-4,5-bis-tosyloxymethyldioxolanne	0.65	0.44	Benzene; AIBN; 60°C	102

[a]D: HEMA has been distilled and the percentages of methacrylic acid and ethylene glycol dimethacrylate are not given. AIBN: Azobisisobutyronitrile. DMF: Dimethylformamide. DMSO: Dimethylsulfoxide.

TABLE 3

Chemical Modification of HEMA According to the Reaction

Z	Refs.
—CH_3	112
—C_2H_5	112
—$CH_2CH(CH_3)_2$	112
—$Si(CH_3)_3$	113
—$PO(OC_2H_5)_2$	114
	115
	116
	117
	118
—$COC_6H_4CH{=}CHCOC_6H_5$	119
—$COC_6H_4COCH{=}CHC_6H_5$	119
	120

(continued)

TABLE 3 (continued)

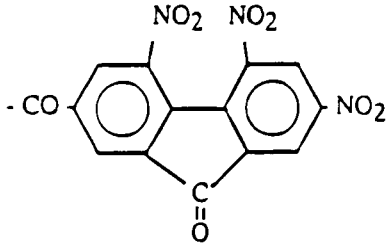
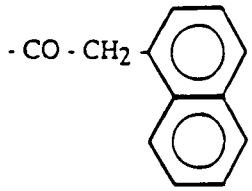
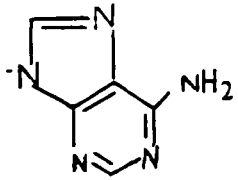
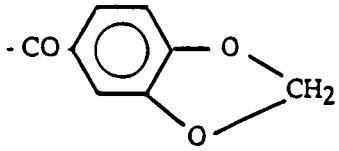
Z	Refs.
—$COC_6H_4N(CH_3)_2$	121
—$CONHC_6H_4CONHCH_2CH_2N(CH_2CH_3)_2$	122
—$CONHC_6H_4SO_2NHCONHC_4H_9$	123
	124
	125
	126
- CO - Ad * (Ad* = Adenine Radical)	127
	128

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TABLE 3 (continued)

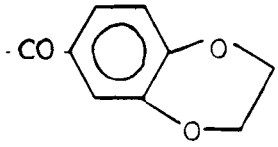
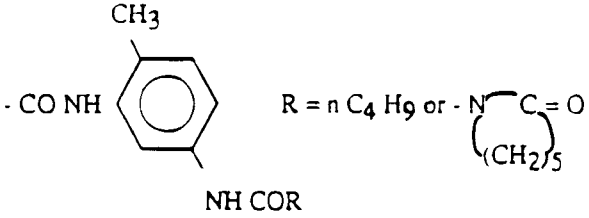
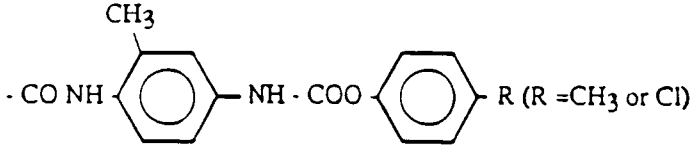
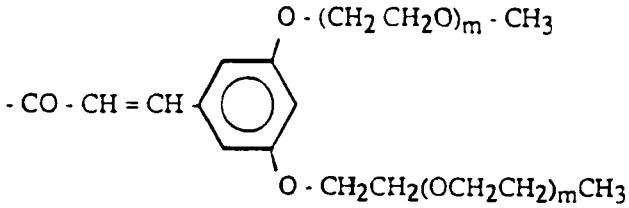
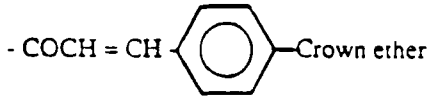
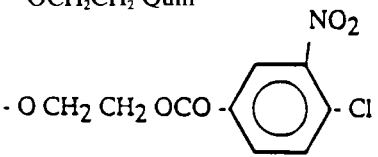
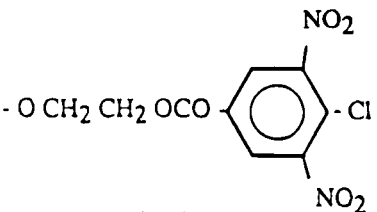
Z	Refs.
	129
	131
	99, 100, 130
	132
	133
	134
Cholecalciferol	135
Cholesterol	136
Cobaltophthalocyanine complex	137
Various lipids	138
Acrylic oligoesterurethane	139

TABLE 4

Chemical Modification of pHEMA or Copolymers Prepared with HEMA monomer

(Co)polymer	Reagent	Product (termination)	Refs.
PHEMA	$SOCl_2$	$—OCH_2CH_2Cl$	140
	$(CH_3CO)_2O$	$—OCOCH_3$	
PHEMA	$p\text{-}(C_6H_5)_3/CCl_4$	$—OCH_2CH_2Cl$	141
	$p\text{-}(C_6H_5)_3/CBr_4$	$—OCH_2CH_2Br$	
PHEMA	1) $SOCl_2$; 2) $N(CH_3)_3$	$—OCH_2CH_2N(CH_3)_3$, Cl	142
PHEMA	1) $COCl_2$; 2) quinine	$—OCH_2CH_2$ Quin[a]	143
PHEMA	4-Chloro-3-nitrobenzoylchloride		144
PHEMA	3,5-Dinitrobenzoylchloride		145
PHEMA	Sterols	$—OCH_2CH_2O$ St[b]	38
Poly(HEMA)*co*-bisglycolacrylate)	5-Fluorouracil	$—OCH_2CH_2$ Fl[c]	146
Poly(HEMA)*co*-trimethylol propane trimethacrylate)	5-Fluorouracil	$—OCH_2CH_2$ Fl[c]	147

[a]Quinine radical.

[b]Sterol radicals (cholesterol, testosterone). These products have also been synthesized from modified monomers.

[c]Fluorouracil radical.

[154, 155], and polyesters [157, 158] also give grafting reactions whose aim is to improve the mechanical and physical properties of the initial products.

7. APPLICATIONS IN BIOMEDICAL FIELDS

Because HEMA can be easily polymerized, possesses a hydrophilic pendant group, and can form hydrogels, an increasing number of applications have been found in various biomedical fields. Although, as previously mentioned, a complete listing of the literature references appears impossible, we have tried to present the main areas of interest for HEMA, either when used alone or in combination with other chemical reagents.

7.1. Irritant and Toxic Effects

First of all, the low toxicity of the monomer is widely accepted but few reports are available on the (potent) irritant effects of HEMA. Intradermal injection of crude HEMA monomer at low concentrations in saline solution (~1%) was found to induce a very mild irritation in the rat, while higher concentrations (up to 20%) were associated with a pronounced reaction. Similar findings were observed with sodium benzoate (an end product of benzoyl peroxide degradation used as a polymerization initiator) emphasizing the irritant role of residues [159]. PHEMA gels implanted into muscles of rats were found to release residual irritant continuously but at a very low rate, thus inducing no cellular reaction [160]. HEMA used at 0.01–1% concentrations was found to alter the fine structure of cultured cells with quantitative video microscopy [161]. On the other hand, numerous clinical trials, listed hereafter within a specific organ description, have found minimal irritant reactions.

7.2. Histological Embedding

The use of HEMA in histological practice (i.e., the study of living tissues and cells at the microscopic level) was proposed by Rosenberg [162] and Wichterle [163]. The hydrophilic properties of the monomer permit it to be used as a combined dehydrating agent for the tissues and as an embedding medium for electron microscopy. However, blocks

of pure PHEMA appeared difficult to section, and they had poor resistance under an electron beam. The quality of commercially available HEMA was reported to vary considerably up to 1965 [164]. Copolymers with *n*-butyl methacrylate [165] or styrene [166] were also found less satisfactory than the epoxy resins. During the last decade, HEMA has found a new interest in light microscopy [167, 168]. An extensive review was made by Bennett et al. [18]. Briefly, HEMA embedding is favored for light microscopy because: 1) The embedding duration is shorter than for classical methods. HEMA was used to embed large and very large specimen [169]. 2) Preservation of tissular and cellular structures is far superior to other classical methods [170]. This is due to the adherence of tissue sections onto the microscopic glass slides and because the resin is not removed prior to staining. (3) Sectioning is easier and semithin sections (i.e., 2 to 3 μm in thickness) can be obtained on conventional microtomes with steel or Ralph's glass knives [171]. Furthermore, once cut, the sections spread on water and do not shrink. (4) Numerous staining methods can be performed on PHEMA sections. Classical stains (excepted those having a hydro-alcoholic vehicle which makes the section swell) have been reported to work well, sometimes after minor modifications [172]. Enzymological studies can readily be done, and large amounts of enzymes are preserved. Calcified tissue enzymes have been demonstrated on undecalcified sections [173].

At the present time, several HEMA-based commercial kits are available (Historesin, JB4, . . .) However, the slow hydrolysis of the resin makes it difficult to obtain regular results; the regenerated methacrylic acid appears to combine with basic stains, and small amounts (1.5% or less) impair correct staining by strongly obscuring the background [16, 18]. Several purification methods specially devoted to histotechnology have been designed [16–21]. Copolymerization with dimethylamino ethyl methacrylate was proposed to complex the carboxylic groups of methacrylic acid [174].

HEMA alone was repeatedly found to be a poor medium for calcified tissues because the size of the molecule makes it difficult to infiltrate such tissues. Combined with methyl methacrylate (MMA) [175] or various types of alkyl methacrylates or acrylates, HEMA was shown to provide suitable embedding media [176]. HEMA is usually polymerized by a redox reaction (benzoyl peroxide and *N*,*N*′-dimethyl aniline), and the method has been used to embed in the cold, thus preserving enzyme activities [169, 173]. Azobisisobutyronitrile has also been proposed [177]. Benzoyl peroxide and UV light were reported to work well, but

they induce staining artifacts [178]. Other initiators have also been proposed (barbiturate cyclo compounds, butazolidine [179]).

PHEMA has been shown to produce better sections when small amounts of crosslinkers are used [171, 180]. We recently showed that HEMA embedding is an inhomogeneous mechanism and that it varies according to the volume of monomer to be bulk polymerized [181].

7.3. Dentistry

Synthetic apatitic calcium phosphate cements were prepared with a PHEMA hydrogel containing tetracalcium phosphate and dicalcium phosphate [182]. PHEMA was found to be a highly biocompatible and resorbable material for primary teeth endodontic filling [183]. However, due to its hydrophilicity, PHEMA appeared more useful in dentistry as a bonding reagent between dentine and other types of restorative resins; varying mixtures of HEMA and glutaraldehyde were investigated [184, 185]. Other bonding complexes using PHEMA have been reported for enamel and dentine [186]. HEMA was found to be a suitable vehicle for dentin self-etching primers (such as acidic monomers) [187]. Other clinical trials have been done with an antiseptic (chlorhexidine) entrapped in a HEMA/MMA copolymer membrane to develop a controlled release delivery system [188]. However, PHEMA was found unsuitable as a permanent soft lining material for covering the oral mucosa in denture-bearing areas [189].

7.4. Immobilization of Molecules and Cells

Immobilization implies the entrapment within a polymeric network of a definite "foreign" compound (i.e., an enzyme, a drug, a cell, . . .), whether it is simply confined or grafted onto the polymeric chains.

7.5. Immobilization of Enzymes

Immobilization of several enzymes on solid supports has found a number of applications in biotechnology because enzyme molecules become reusable and side products are not obtained [190]. In order to preserve enzyme activity, radiation-induced polymerization is often reported: Cellulase was found to be well preserved in HEMA polymerized by γ-radiation (5×10^5 to 5×10^6 rad) at low temperature after salting

out the monomer [191]. Trypsin was found to bind covalently on a composite material made of an alginate copolymerized with HEMA and glycidyl methacrylate. The loss of enzyme activity was only 7% after five successive uses [192]. Glucose oxidase was readily immobilized in PHEMA membranes, but the affinity of the enzyme for its substrate (glucose) was substantially decreased [193]. The activity of lipase was decreased when immobilized in PHEMA due to the hydrophobic character of the enzyme itself [194]. The location of the enzyme within the hydrogel has been studied. The distribution of fluorescein isothiocyanate-labeled glucoamylase was investigated with fluorescence microscopy. The enzyme was found to be located on the interface between the polymer membrane, the pore structures, and partly in the polymer itself [195]. A PHEMA and ethylene dimethacrylate copolymer (Separon HEMA) was used to study the covalent immobilization of various enzymes. The type and concentrations of added salts were found to modify yields [196]. Membranes of PHEMA containing glucose oxidase were found to swell in glucose solutions and may be used for glucose monitoring in artificial pancreases [197].

7.6. Immobilization of Cells

Several types of microbial cells or yeasts known to have biotechnologically interesting enzymes have been entrapped into PHEMA hydrogels (e.g., *Streptomyces phaechromogenes* containing glucose isomerase [198] and *Mortiella vinacea* containing a galactosidase [199]). Pancreatic islets enclosed in a PHEMA hydrogel were found to synthesize and release insuline *in vitro* [200]. The biocompatibility of such pancreatic islets was found to be excellent when implanted into animals [201]. Diffusion chambers made of a PHEMA hydrogel were successfully used *in vivo* after immobilization of rabbit embryos; the chamber was implanted in the peritoneal cavity of male mice and early developmental stages were followed [202]. A hydrogel of pure PHEMA has no effect on spermatozoid motility, but the copolymer of HEMA–methacrylic acid inhibited 100% of spermatozoa after 30 min; the latter might be used as a male contraceptive technique when injected into the *vas deferens* [203].

Composites of alginate and HEMA have been used to prepare microspheres for the microencapsulation of cells [204]. A detailed method for Chinese hamster ovary fibroblast encapsulation was reported [205].

7.7. Immobilization of Drugs

Numerous drugs have been entrapped (or immobilized) in radiation-polymerized HEMA in order to produce drug delivery devices, e.g., ergotamine [14], salicylic acid [206, 207], hormones [208], ... The ability of various drugs to diffuse into polymers may be used in various types of biotechnologies such as membrane separation and drug delivery devices. The prediction of drug solubilities in PHEMA and other polymers has been studied [209]. Immobilization of chloramphenicol in PHEMA hydrogels crosslinked with EGDMA was found to be released upon swelling of the gel in water; the diffusion obeyed Fick's second law [210]. The kinetics of thiamine (vitamin B1) diffusion from previously loaded PHEMA beads was studied at 37.5°C in water [211]. Theophyllin release from an amphiphilic composite made of PHEMA and polyisobutylene was studied from a kinetic point of view [212].

PHEMA membranes are favored as transdermal delivery systems for long-term constant drug delivery [213]. Vidarabine (an antiviral agent) was entrapped to PHEMA membranes and used for transdermal patches: the blood–drug concentrations could be predicted and the permeability coefficient of the membranes could be adjusted by controlling hydration [214, 215]. Similar observations were obtained with progesterone [216]. Nitroglycerin was also entrapped in PHEMA membranes to provide a transdermal delivery system [217].

Synthetic organ substitutes having the capacity to slowly release hormones have been designed: diffusivity of insulin through PHEMA membranes was studied [218]. Because PHEMA hydrogels are hardly degraded *in vivo*, it was found that entrapment of drugs (testosterone) in a blend of PHEMA/albumin resulted in a slowly degraded matrix with continuous release of the drug. Testicular prosthesis releasing testosterone have been done [219, 220].

Anticancer drugs have been extensively entrapped in matrices of PHEMA, thus providing a hard material which can be implanted into the tumor where it delivers higher amounts of drug *in situ* [221]. 5-Fluorouracil was embedded in HEMA/bisglycol acrylate copolymer in 3 mm diameter beads which could be implanted subcutaneously [222]. Methotrexate and 3′,5′-dibromoaminopterin were absorbed on PHEMA and used as local intratumoral implants in Gardner's lymphosarcoma of the C3H mouse [223]. The effect of crosslinking on the swelling of PHEMA gels (and the drug diffusion coefficient through these gels) has been explored [224].

Finally, various substances have been immobilized in PHEMA in order to prepare diagnostic tools. An antiserum-raised methotrexate was entrapped in PHEMA during polymerization. The lyophilized powder was used for radioimmunoassay of this anticancer drug [225]. The entrapment of immunoglobulins has been used for immunochemical studies [226]. The Fc fragment of immunoglobulins has been grafted onto Separon HEMA resins after periodate oxidation, thus providing immuno-affinity sorbents for the isolation of proteins [227]. A dye, Cibracron Blue F3GA, was entrapped within the pores of a nylon/PHEMA gel used for protein purification [228].

7.8. Biocompatibility of HEMA

Biocompatibility of PHEMA has been studied at the cell and tissue levels. Cell cultures on PHEMA-coated slides or on PHEMA hydrogels are used to investigate the intimate mechanisms of cellular compatibility. Implanting pieces of gel in an animal by a surgical procedure allows the study of the adverse reactions of the whole organisms against the resin. Because implantations in the eye or in direct contact with blood induces specific problems, these two aspects of the biocompatibility will be treated separately below.

7.9. Cell Culture

The hydrophilicity of the resin was primarily thought to be favorable for cell culture. Cellular adherence to PHEMA has been recognized since 1975 when myoblasts from chicken embryos were cultured on polysiloxane grafted with PHEMA [229]. Spreading of cells of hamster kidney was found higher on modified PHEMA than on polystyrene due to the hydrophilic properties of the resin [230]. Similar experiments done with endothelial cells of newborn cords have shown that cells first adhere to the hydrophilic substrate, then spread and proliferate [231].

However, pure and unmodified PHEMA appears unable to support attachment and growth of mammalian cells [232]. PHEMA films of increasing thickness decrease cell adhesiveness on culture flasks and alter cell shape [233]. Leukocyte locomotion is suppressed on PHEMA-coated glass plates [234]. When malignant melanoma cells are grown on PHEMA-coated culture dishes, they form aggregates of round cells and generate polykaryons [235]. Adrenal tumor cells grown on PHEMA show decreased steroidogenesis secondary to altered cell shape

caused by the hydrophilicity of the polymer [236]. The time required for rat peritoneal macrophages to adhere to HEMA/ethyl methacrylate copolymers was found to be higher than to hydroxystyrene/styrene copolymers due to the high hydrophilicity of the former [237]. Decreasing rates of adhesion of staphylococci on MMA/HEMA copolymers parallel the increasing HEMA content (i.e., the hydrophilicity) [238].

Simple gels of PHEMA do not permit cell spreading. When ionizable groups are entrapped, cell spreading is no longer inhibited; when collagen is added, cell proliferation occurs [239]. Peritoneal macrophage adherence decreases as a function of increased hydrophilicity of the polymer, and cellular adherence on PHEMA is favored by absorption of proteins of the extracellular milieu: albumin, fibronectine, and immunoglobulines G favor cellular adherence. On the other hand, fibrinogene, elastine, and plasma copolymerized with PHEMA hamper this phenomenon [240]. Alternative modifications of PHEMA allowing cell proliferation have been to incorporate methacrylic acid, diethylaminoethyl methacrylate, or by treating the polymer with concentrated sulfuric acid (creating surface carboxylic groups) [241].

7.10. Implants

PHEMA is a suitable biomaterial for implantation because of its lack of toxicity and high resistance to degradation [242]. Numerous composite biomaterials based on PHEMA and collagen blends have been used [243]. By using various additives, the mechanical properties of PHEMA hydrogels can be adjusted to various biomedical applications [244]. HEMA/methacrylic acid copolymers were found more biocompatible than PHEMA alone which induces a giant cell inflammatory reaction when implanted [245]. When collagen was entrapped in PHEMA gels, their composites were found highly biocompatible when implanted subcutaneously in rats [246]. Composites with a low collagen content were found to be better preserved in long-term implantation studies whereas those containing higher amounts of collagen exhibited calcification in the early stages, followed by full biodegradation [247]. Calcification of a synthetic biomaterial implies poor biocompatibility. Although the chemical composition appears important, the macroscopic structure and surface characters of a PHEMA implant have been shown to play a key role [248]. Extensive calcium accumulation in the mitochondria of cells in close contact with the gels was proposed as the primary mechanism

of calcification [249]; in addition, hydrogels of HEMA and methacrylic acid copolymers were found to pick up large amounts of Ca^{2+} when exposed to aqueous solutions of calcium [250]. This effect was taken into account when porous sponges of PHEMA were compared to demineralized bone for inducing ectopic bone formation [251].

Hydrogels of PHEMA have an excellent biocompatibility but present poor mechanical properties. The mechanical and hydration properties of PHEMA and other polyhydroxyalkyl methacrylate membranes have been studied [252]. Composites of silicone rubber and fine particles of hydrated PHEMA were found to combine both advantages [253]. Radiation grafting of HEMA was done on polyurethane films (with good mechanical properties) and found to increase hydrophilicity and tolerance [254]. HEMA was grafted on polyether urethane area membranes used for hemodialysis; permeability and blood tolerance were improved but tensile strength was reduced [255].

Hemodialysis membranes of PHEMA crosslinked with ethylene dimethacrylate have been prepared [256]. The interaction of urea (the end product of protein catabolism) with PHEMA hydrogels revealed that small amounts of methacrylic acid may dramatically increase the swelling properties of the gel [15, 257].

7.11. Prosthetic Vascular Implants and Blood Compatibility

A very interesting property of PHEMA-based hydrogels is their high hemocompatibility. In the presence of blood, thrombus formation is delayed. Because blood is a complex milieu, in this paragraph we consider all the relationships of PHEMA with blood cells, endothelial cells (i.e., the inner cells of the blood vessels), or/and blood components. Due to the hydrophilicity of PHEMA, films of styrene–butadiene–styrene had a better blood compatibility when grafted with PHEMA [258]. Copolymers of HEMA/styrene or HEMA/dimethyl siloxane suppress platelet adhesion and aggregation (and thus reduce thrombus formation) by the creation of hydrophilic/hydrophobic microdomains [259]. Similar findings were obtained with HEMA/polyethylene oxide and HEMA/polypropylene oxide copolymers [260]. A HEMA–polyamine copolymer was found to induce no blood platelet adherence or activation. Also, this copolymer was used to separate T from B lymphocytes subpopulations via its hydrophilic–hydrophobic microdomain composition [261]. Vascular tubes of polyethylene blended with 14% PHEMA have a very low thrombogeneity due to hydrophilization of the plastic [262].

Radiation grafting of HEMA and *N*-vinyl pyrrolidone on silicone rubber was used to improve the hydrophilicity of artery-to-vein shunts and thus to reduce thrombus formation [263]. A highly antithrombogenic polymer was prepared by immobilizing the fibrinolytic enzyme urokinase in a PHEMA hydrogel [264].

Another important aspect of blood compatibility is the power of a biomaterial to activate the complement system. It is a complex system of plasma proteins activated in cascade and involved in the inflammation process. Intraocular lenses made of PHEMA were found ineffective *in vitro* to activate the serum complement system (C3a, C4a, C5a) [265]. HEMA-grafted polyethylene tubes were not found to inactivate the complement [266]. On the other hand, copolymers of HEMA/ethyl methacrylate were reported to activate the complement when the polymer contained 60% or more HEMA [267].

Low density lipoprotein adsorption on PHEMA was found to be low due to the hydrophilicity of the resin [268]. Particles of PHEMA were used to study the phagocytic processes of macrophages and neutrophils [269, 270].

The hemocompatibility of PHEMA has led to the development of a medical method used to remove endo or exo toxins from blood. Hemoperfusion takes advantage of activated charcoal to bind such toxics (barbiturates, tricyclic antidepressants, ...) [243].

Activated carbon particles have been encapsulated with PHEMA for the construction of hemoperfusion columns; heparinized blood is purified by adsorption of irrelevant toxic molecules onto the entrapped charcoal particles and the cleaned blood is then perfused to the patient [271]. Composites of PHEMA, PEG, and activated carbon were found useful for other blood perfusion applications [272].

Another important application of PHEMA is the occlusion of blood vessels in various organs and principally in tumors (which are always hypervascularized). Spherical particles of PHEMA of regular shape were produced by suspension polymerization. When injected in a vessel close to the tumor, the small beads act as emboli and obliterate the smaller vessels. Thus tumor vascularization is stopped and endovascular embolization is followed by tumoral cell necrosis and size reduction of the tumor. The swelling in water of PHEMA beads makes them suitable to close obliteration of vessels [273]. Detailed procedures have been published for preparing such porous PHEMA beads of regular size suitable as artificial thrombi [274]. Beads can be loaded or coupled with

an x-ray contrasting agent (iodine) which helps radiographic tracing [243].

7.12. Optical Lenses

The main application of PHEMA hydrogels is the preparation of contact and intraocular lenses used after cataract extraction [275, 276].

Black pigmented PHEMA was used to prepare light-occluding lens after opthalmic surgery [277]. Gentamicin-soaked contact lenses made of a 61.4% PHEMA hydrogel were found to retain bactericidal concentrations of the antibiotic up to 3 days of eye contact [278]. Diffusion of oxygen through hydrophilic contact lens is necessary to avoid corneal oedema. With PHEMA lenses, this is obtained with a 33-μm thickness [279]. Deep corneal stromal opacities were seen in PHEMA contact lenses and were related to chronic corneal anoxia [280]. Deposits are sometimes observed within contact lenses. They occur after 12 months of daily lens wear and may be associated with vision decrement [281]. The protein deposits on contact lenses vary according to the copolymer: With HEMA/methacrylic acid copolymers, lenses absorb large amounts of lysosyme, and HEMA/MMA copolymer preferentially adsorbs albumin [282]. Contact lenses of copolymers of HEMA with methacrylic acid or various silanes were found to adsorb less lysosyme than unsilanized lenses [283]. Deposits of calcium in contact lens made of PHEMA have been reported [284].

Intraocular strips of PHEMA hydrogels containing small amounts (1.2–1.4%) of methacrylic acid were found to be favorably tolerated *in vivo* due to the high water and carboxylic group content [285]. PHEMA intraocular lens were found to be better tolerated than conventional amino–polyamide–base implants, but the presence of microvilli on corneal cells suggests the release of impurities from the resin [286]. PHEMA-based intraocular lenses were found to be well preserved after Nd:YAG laser surgery [287].

Various drugs (chloramphenicol, pilocarpine, dexamethasone, ...) were found to have a longer washout period when entrapped in intraocular lenses than in the human lens [288]. The clinicobiological results of PHEMA intraocular lenses were found to be the most favorable, with 92% of implanted patients recovering visual acuity [289]. In a multicenter and international trial, PHEMA intraocular lenses were found to be the most favorable clinically [290].

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