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NEW MATERIALS

MULTIFUNCTIONAL HYDROPHILIC POLYMERS

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ABSTRACT

Different types of multifunctional hydrophilic polymers were synthesized and characterized in view of their possible biomedical application. Several poly(amide)s and poly(ester-amide)s containing oligo(oxyethylene) segments and tartaric or succinic acid residues were prepared by activated polycondensation methods. New functional derivatives of β-cyclodextrin were obtained by reaction with glycidyl ether of protected polyols. The mechanism of β-cyclodextrin polymerization with epichlorohydrine was investigated by ^{13}C-NMR spectroscopy.

INTRODUCTION

In recent years, the increasing use of proteic drugs endowed with high activity, low stability, and significant toxicity, has prompted the development of

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new dosage forms, such as polymeric release systems able to reduce unwanted side effects while improving the drug bioavailability [1].

Following our interest in the synthesis and characterization of biodegradable polymeric systems for biomedical and pharmaceutical applications [2-4] attention has been directed to the preparation of new segmented poly(amide)s derived from tartaric acid and α,ω-diaminooligo(oxyethylene)s. These materials appear to be well suited for the proposed applications due to the presence of natural tartaric acid stereoregular residues and hydrophilic oligo(ethylene glycol) groups, which are known to elicit antiopsonizing effects [5]. Moreover, the large number of amide linkages should guarantee for substantial mechanical properties and eventually for their bioerosion/biodegradation. The simple synthetic procedure developed by Ogata *et al.* [6-9] was adopted for the polymeric preparations. However, the hydrolytic stability of amide bonds may constitute a limitation to their use in applications requiring a facile biodegradation. To overcome this possible flaw, the research was also addressed to the preparation of poly(ester-amide)s containing oxyethylene segments, able to join the features of the above poly(tartaramide)s with the ease of hydrolysis of ester bonds [10].

Parallel to this research line, we have also undertaken the development of new functional cyclodextrin derivatives, both monomeric and polymeric, to be used in the stabilization and complexation of proteic drugs [11-13].

RESULTS AND DISCUSSION

Synthesis and Characterization of Poly(Tartaramide)s

Aliphatic polyamides of AABB type (e.g., nylons m,n) are generally prepared either by direct reaction of diamines and diacids at high temperature to allow for water elimination or by interfacial polycondensation of water soluble diamines and liposoluble diacid dichlorides. Both methods did not appear appropriate for the synthesis of poly(aldaramide)s, since the presence of reactive hydroxy groups might heavily interfere with the polycondensation process.

On the contrary, activation of the carboxyl groups toward aminolysis could promote a chemoselective polycondensation process under mild experimental conditions [14]. Ogata *et al.* showed that the aminolysis of diesters substituted in the α-position with electronegative groups is much faster than that of ordinary esters even at room temperature [9]. Accordingly, polycondensation of α-hetero-diesters and aliphatic diamines was realized in methanolic solution,

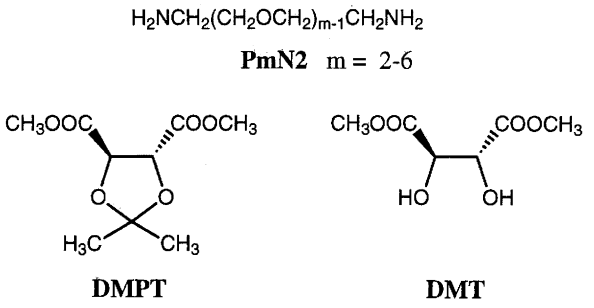

Figure 1. Structures of the monomers used in the synthesis of poly(tartaramide)s.

slightly above room temperature, in the presence of either acid or basic catalysts [6-9].

The commercially available dimethyl (R,R)-2,3-*iso*propilidentartrate (**DMPT**) and dimethyl (R,R)-tartrate (**DMT**) were chosen as diacid monomers (Figure 1). As a consequence, we had to adapt the polycondensation procedure. Indeed, the presence of two chiral centers and of a dioxolane ring in the case of **DMPT**, ruled out the use of strong acid and basic catalysts.

Three monodispersed oligo(oxyethylene) diamines (**P4N2**, **P5N2**, and **P6N2**) were prepared from corresponding glycols having a degree of oligomerization 4-6 either by Williamson etherification of oligo(ethylene glycol) di-*p*-toluenesulfonates with potassium 2-aminoethoxide [15].

A modified Gabriel reaction of oligo(ethylene glycol) dichlorides with potassium phthalimide under phase transfer conditions, followed by hydrazinolysis of the diphthalimido derivatives was also utilized [16, 17]. This latter procedure resulted in better yields and much easier work-up of the crude reaction products than the Williamson synthesis.

The diamines of di(ethylene glycol) (**P2N2**) and tri(ethylene glycol) (**P3N2**) are commercially available.

To select the best experimental conditions, several polymerization experiments of **P3N2** and **DMPT** were performed by using ethanol and 2-methoxyethanol as solvent and triethylamine or 2-hydroxypyridine as catalyst, at temperatures included between 55 and 90°C.

The reactions were monitored within time by end group titration. Kinetic data showed that the polycondensation is autocatalytic in nature, at least for conversions lower than 70%. Under the adopted conditions, racemization of the chiral centers present in the tartaric acid was lower than 10% after 72 hours.

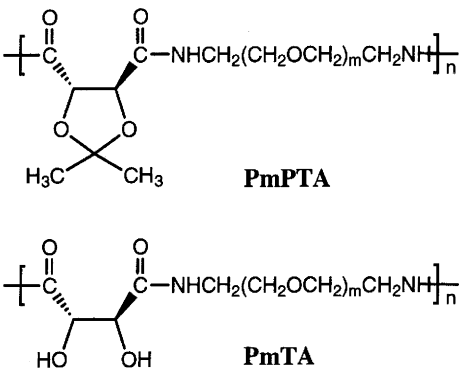

Figure 2. Structures of the prepared poly(tartaramide)s.

Conversions and molecular weights of final polymeric products showed that methanol/triethylamine/55°C was the best combination of experimental parameters.

Two sets of poly(tartaramides) (**PmPTA** and **PmTA**) were prepared by reaction of **PmN2** with **DMPT** and **DMT**, respectively and adopting the indicated experimental conditions (Figure 2). Polycondensation of **DMPT** always proceeded in homogeneous solution, whereas in the case of **DMT** phase separation was observed shortly after the mixing of reagents. Polymers obtained in 60% yield were characterized by FT-IR, ^{1}H-NMR, GPC, TGA, DSC, optical rotation, and solubility measurements (Table 1). All samples resulted soluble in

TABLE 1. Characterization of the Prepared Poly-(tartaramide)s

Sample	Conv. (%)	M_n	M_w/M_n	$[\Phi]$ [a]	T_g (°C)	T_{on} [b] (°C)
P2PTA	56	1300	1.9	-54	48.2	252
P3PTA	56	1500	1.2	-81	13.0	nd
P4PTA	60	1200	1.2	-82	-3.1	210
P5PTA	57	2000	3.2	-91	-10.8	nd
P6PTA	65	1000	3.3	-88	-28.4	250
P2TA	60	800	nd	+152	63.9	183
P3TA	65	800	nd	nd	33.9	197
P5TA	60	1200	nd	+206	1.7	209

a) Molar optical rotation at sodium D line, in degree M^{-1} cm^{-1}, in water at 25 °C.
b) At 1 % thermal decomposition; nd = not determined.

water and, with the sole exception of the most hydrophilic **P2TA** polymer, in polar organic solvents such as chloroform, DMF, and methanol. Solubility in organic solvents increased with the number of oxyethylene groups in the repeating units. All poly(tartaramide)s exhibited a strong optical rotation in water solution thus confirming the absence of a significant racemization of the tartaric acid residues. The dependence of the molar optical rotation on the length of the oligo(oxyethylene) segment demonstrated a contribution to the molecular chirality by the hydrophilic residues. This effect can be tentatively attributed to the presence of a partially ordered secondary structure of the polyether chains.

Thermogravimetric analysis (TGA) indicated that **PmPTA** and **PmTA** were stable up to about 200°C. The larger thermal stability of **PmPTA** as compared to **PmTA** seems to suggest that free hydroxyl groups play a fundamental role in affecting the onset of polymer degradation. DSC analysis of the prepared poly(ether-amide)s highlighted that the T_g values of **PmPTA** are about 10-20 °C lower than those of **PmTA**, as expected from the absence of strongly interacting free hydroxyl groups. In addition, the T_g of **PmPTA** decreased from about 50 to about -30°C on increasing the number of flexible oxyethylene units from 2 to 6. **PmTA** showed a similar behavior. No crystallinity was detected in any of the polymer samples, very likely because of their low molecular weights.

Spectroscopic data were in complete agreement with the expected structure of the prepared polymers. Number average molecular weights included between 800 and 2000, with an average molecular weight distribution of 2-3 were evaluated by GPC analysis and ^{1}H-NMR end group determinations. These values are comparable with those reported in literature for poly(aldaramide)s prepared by a similar procedure.

It has been proposed that in the case of **DMT**, the heterogeneous polycondensation conditions prevent the attainment of high molecular weights [17]. However, low molecular weight products were obtained also in the polycondensation of **PmTA**, that occurs in homogeneous phase. To clarify this point, kinetic investigation of a model reaction was performed. Aminolysis of **DMPT** with 2-methoxy-1-aminoethane in methanol at room temperature was monitored by measuring the 235 nm absorbance within time. The relevant kinetic constants are listed in Table 2 together with comparable data reported for the aminolysis of diethyl galactarate (**DEGA**) and diethyl xylate (**DEXY**) [18, 19].

In agreement with previous reports, these data show that the aminolysis of **DMPT** is an autocatalytic process occurring at a much lower rate as compared to **DEGA** and **DEXY**. The slowness of the polycondensation reaction and the

TABLE 2. Kinetic Constants for the Aminolysis of Aldaric Diesters

Diester	$k_1 \cdot 10^4$ ($M^{-1} \cdot s^{-1}$)	$k_2 \cdot 10^4$ ($M^{-1} \cdot s^{-1}$)	Solvent
DMPT	0.43	1.50	Methanol
DEGA	66.7	–	Dimethylsulfoxyde
DEXY	>250	–	Dimethylsulfoxyde

possible rise of comparable-rate side reactions are very likely responsible of the rather low molecular weight of **PmTA** [20].

Synthesis of Poly(Ester-Amide)s

Poly(ester-amide)s containing oxyethylene segments were prepared by polycondensation of activated esters of oligo(ethylene glycol) monoamines The synthesis of the hydrochlorides of oligo(ethylene glycol) monoamines esterified with succinic anhydride (**PSPmNH**, n = 1-4), in which the poly(ether) segment is constituted by 1-4 oxyethylene units and the carboxylic group is activated by esterification with pentachlorophenol (PcpOH), was performed as outlined in Figure 3.

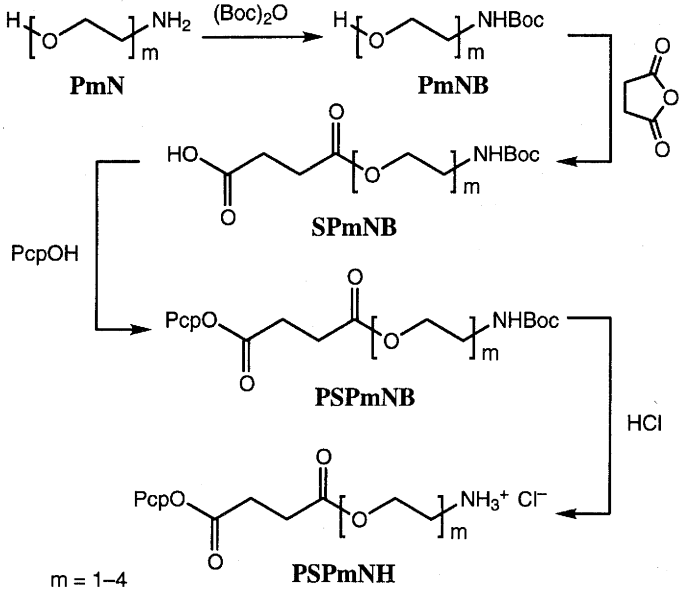

Figure 3. Synthesis of ω-amino oligo(ethylene glycol) pentachlorophenyl succinates.

The monoamine hydrochloride of oligo(ethylene glycol) with degree of oligomerization 3 (**PSP3NH**) was synthesized from the commercially available tri(ethylene glycol) monochloride (**P3C**) by both aminolysis and Gabriel synthesis. The tetra(ethylene glycol) monoamine hydrochloride (**PSP3NH**) was prepared starting from tetra(ethylene glycol). The glycol was first converted to the corresponding monochloride (**P4C**) and monotosylate (**TrP4Ts**). **P4C** was isolated by chromatographic separation of a mixture of mono and difunctional products whereas **TrP4Ts** was directly in pure form by reaction with trityl chloride. Both monofunctional compounds were then converted to the monoamine derivative by aminolysis and in the case of **TrP4Ts** also by Gabriel synthesis (Figure 4).

Conversion of the monoamine hydrochlorides of oligo(ethylene glycol)s to the corresponding amine by reaction with excess triethylamine in anhydrous dichloromethane afforded the activated amino-esters (**PSPmN**) [21, 22]. The monomers were not isolated because under the adopted reaction conditions the free amino group quickly reacted with the activated ester to give a mixture of cyclic (**SPmN**) and linear [**poly(SPmN)**] condensation products (Figure 5). The latter products can be considered as difunctional macromonomers for the preparation of poly(ester-amide)s.

Polymerization experiments were performed at room temperature, both in dichloromethane solution and in bulk, in the presence of a threefold excess of triethylamine. **PSP1NH** and **PSP2NH** monomers resulted insoluble in dichloromethane giving rise to milky suspensions. On addition of triethylamine,

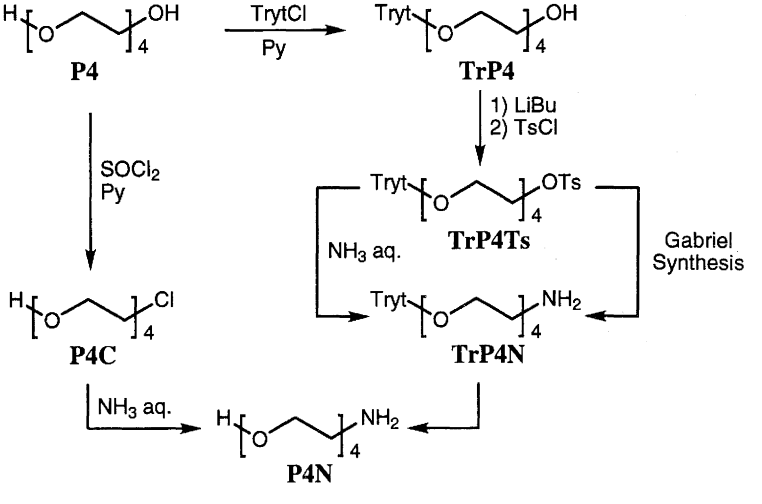

Figure 4. Synthesis of monoamino tetra(ethylene glycol).

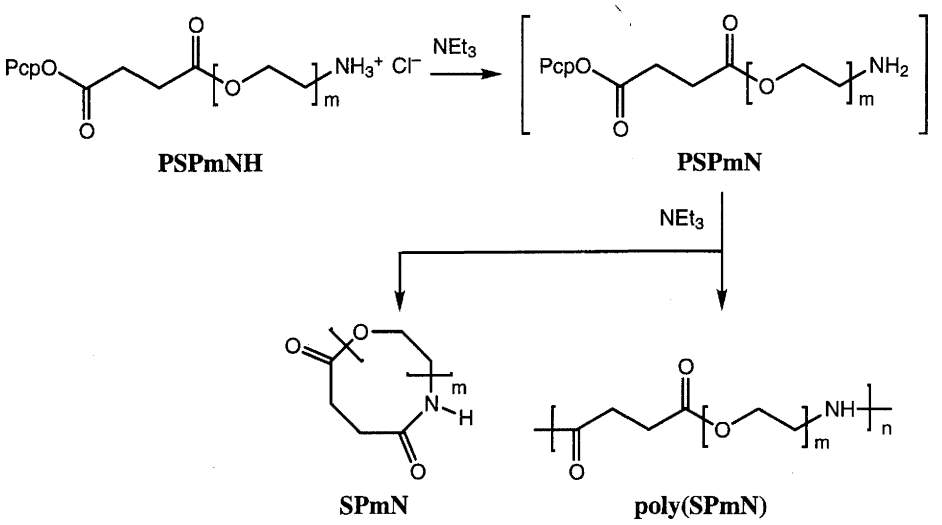

Figure 5. Reaction of **PSPmNH** activated esters with triethylamine.

the suspensions quickly turned clear and after 6 days, 92 and 73% conversions to polycondensation products were observed, respectively. Conversions larger than 70% were recorded when the same reactions were performed in bulk. In all cases the recovered product resulted soluble in DMSO and insoluble in water and in most common organic solvents.

The molecular weight of the polymerization products could not be determined by GPC analysis, due to their insolubility in common GPC solvents. An average degree of oligomerization of about 9 was however computed by ^{1}H-NMR analysis. The observed low degree of polymerization was tentatively attributed to the insolubility of the oligomers in the reaction medium, that prevents a further increase of their molecular weight.

PSP3NH resulted completely soluble in dichloromethane, however only a 1:3 mixture of the intramolecular cyclization product and of low molar oligomers was obtained after addition of triethylamine. When the polymerization was carried out in bulk, a 54% conversion to a poly(ester-amide) soluble in water and in polar organic solvents, such as chloroform, DMS, and methanol, took place. An average number molecular weight of 21 kD and an average polydispersity index of 2.2 was determined by GPC analysis. Also in this case, an appreciable amount of the cyclization product and of low molecular weight oligomers was detected in the polymerization solution.

DSC analysis of the **PSP2NH** and **PSP3NH** polycondensation products evidenced only a well defined glass transition respectively at 7.5°C and -7.0°C,

followed by an endothermic relaxation, in accordance with the amorphous nature of the samples. The **PSP1NH** polymer sample exhibited a melting peak at about 210°C, whereas a glass transition at 17.6°C was observed only after quenching from 200°C to -50°C. In the TGA curves, the onset of the thermal decomposition increased from 220°C to about 270°C on increasing the length of the oligo(oxyethylene) segment.

The different thermal behavior of the investigated poly(ester-amide)s can be related to both the distance among polar amide groups along the polymer backbone and the flexibility of the oxyethylene segments. Kinetic investigation of the polycondensation reaction helped to clarify the reaction mechanism and to establish useful structure-reactivity relationships. Kinetic data were collected by measuring the variation of the UV absorbance of the polycondensation solution due to the formation of the triethylammonium salt of pentachlorophenol. The results showed that even under the assumption of an identical reactivity of all functional groups [23], the **PSPmNH** condensation process is made complex by the occurrence of consecutive as well as parallel reactions.

The reaction of the monomer containing three oxyethylene units (**PSP3NH**) followed a first order kinetic typical of the ring-closure reaction, even at a rather high initial monomer concentration (0.05 M). The polymerization of **PSP2NH** showed a modest deviation from first order kinetics and an optimal fit of the experimental data was obtained only by assuming the occurrence of parallel first and second order reactions. The latter process was attributed to the dimerization reaction and GPC analysis of the reaction product confirmed this hypothesis.

Finally, the reaction of **PSP1NH** obeyed a second order kinetics attributable to the polymerization process and no cyclization product was detected in the polymerization solution. The very steep decrease of the cyclization rate observed in the formation of the 8-membered ring (**SP1N**) as compared to that of 14 (**SP3N**) and 11-membered (**SP2N**) rings can be tentatively attributed to the increasing ring strain [24], in terms of bond angle deformation and bond opposition forces due to eclipsing of atoms (Figure 6).

Accordingly, **PSP1NH** easily polymerized independent of the adopted reaction conditions (concentration and solvent), whereas **PSP2NH** polymerization could be attained only at high monomer concentration. In no case, significant polycondensation of **PSP3NH** was observed in solution, the main reaction product being the cyclic one.

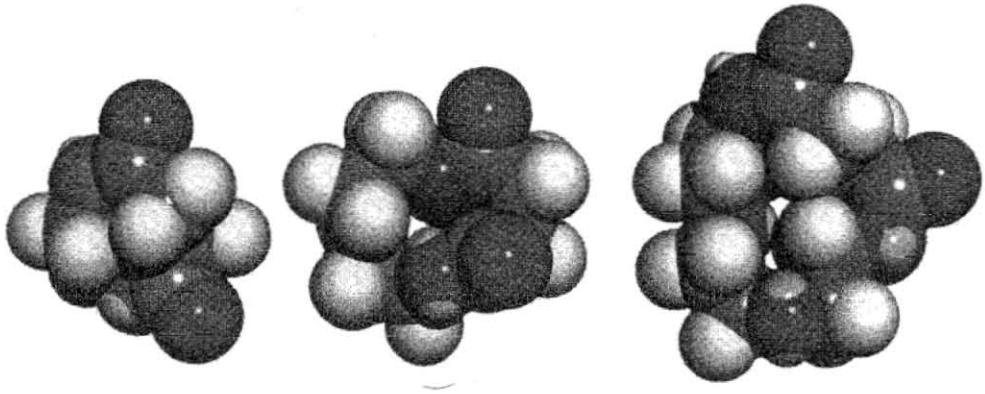

Figure 6. 3D molecular models of **SP1N** (left), **SP2N** (center), and **SP3N** (right) cyclic derivatives.

Functionalization of β-cyclodextrin

A series of monoglycidyl ether of polyols, such as xylitol, trimethylolethane, trimethylolpropane, and D-glucose, in which the free hydroxyl groups are reversibly protected by *iso*propylidene groups, were prepared by reaction of epichlorohydrine (**EPY**) with the protected polyols (Figure 7).

The glycidyl ethers were then reacted with β-cyclodextrin (**βCD**) under alkaline conditions [25]. Precipitation in ether/hexane mixtures made possible to

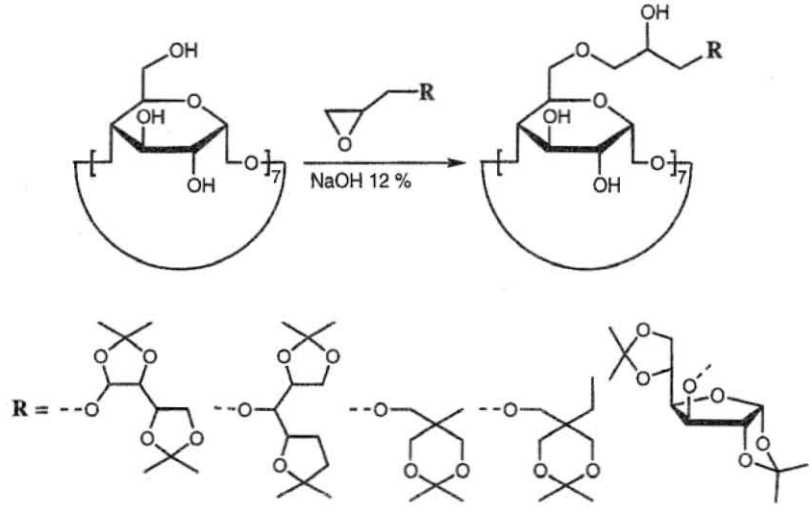

Figure 7. Schematic representation of the functionalization of **βCD** with the glycidyl ethers of protected polyols.

TABLE 3. Solubility of the Functionalized β-cyclodextrin

Glycidyl ether [a]	Degree of substitution [b]	Solubility (g/ml) in water	Solubility (g/ml) in $CHCl_3$
–	0	0.019	–
GDX	0.86	0.114	+
GITP	0.92	0.090	+
GITE	0.86	>1	+
GGD	0.88	0.030	+
GX	0.94	>1	–
GTP	0.92	>1	–
GTE	0.92	>1	–
GGM	0.92	>1	–

[a] **GDX**: 5-O-glycidyl-1,2-3,4-di-O-*iso*propylidenxylitol, **GITP**: glycidyl-O-*iso*propylidentrimethylolpropane, **GITE**: glycidyl-O-*iso*propylidentrimethylolethane, **GGD**: glycidyl-diacetone-D-glucose, **GX**: 5-O-glycidyl-xylitol, **GITP**: glycidyltrimethylolpropane, **GITE**: glycidyltrimethylolethane, **GGM**: glycidyl-monoacetone-D-glucose.

[b] Number of glycidyl ether residues per glucose unit.

collect grafting products having an uniform degree of substitution (0.8-1.1 glycidyl ether residues per glucosyl residue), as determined by ^{1}H-NMR.

All reaction products resulted appreciably soluble in chloroform and much more soluble in water than native **βCD**. Their water solubility was related to the structure of the glycidyl ether, its isomeric composition, and degree of substitution (Table 3).

Removal of side-chain *iso*propylidene groups was carried out either in methanol or in water/methanol mixtures in the presence of an ion-exchange sulfonic resin in the acid form or diluted HCl as catalyst. Under the adopted experimental conditions, no appreciable degradation of the **βCD** heptaglycosydic skeleton occurred, as indicated by NMR analysis. The results of a kinetic investigation allowed for a fine tuning of the reaction conditions, e.g. duration, temperature and pH, to selectively achieve complete or partial removal of *iso*propylidene groups. After deprotection the grafted β-cyclodextrins exhibited a very large water solubility (> 1 g/ml) regardless of glycidyl ether structure and extent of deprotection.

Polymerization of β-cyclodextrin

Native β-cyclodextrin **βCD** was polymerized by reaction with epichlorohydrin in aqueous NaOH at room temperature, according to a literature procedure [26] (Figure 8). Oligomeric, polymeric, and crosslinked products were obtained depending upon stirring speed, NaOH concentration, and **Epy/βCD** molar ratio. Several authors [27, 28] have reported that the upper limit of the molecular weight of the reaction products is about 10^4 and that above this value only swelling gels are obtained. Recently, it has been reported that much higher molecular weight compounds can be reached by stopping the polycondensation reaction just before gelation [26]. This technique requires however, a very accurate reaction control and in most experiments, only low molecular weight polymers or insoluble gels were obtained.

In order to get a better understanding of the polymerization mechanism and possibly to find a better method to obtain high molecular weight **βCD** polymer, a ^{13}C-NMR kinetic investigation of the polymerization reaction was undertaken. Indeed this technique allows us to determine not only the degree of substitution but also to establish the regiochemistry of the reaction [26-29].

βCD grafted with a mixture of isomeric glycidyl*iso*propylidenxylitols resulted as much more soluble than β-cyclodextrin grafted with pure 5-*O*-glycidyl-1,2-3,4-di-*O*-*iso*propylidenxylitol. This behavior can be tentatively attributed to the presence of structural irregularities that weaken the intermolecular forces, transforming the low-solubility crystalline derivative into a much more soluble amorphous one. As expected, the presence of apolar groups negatively affected the water solubility of the β-cyclodextrin derivatives.

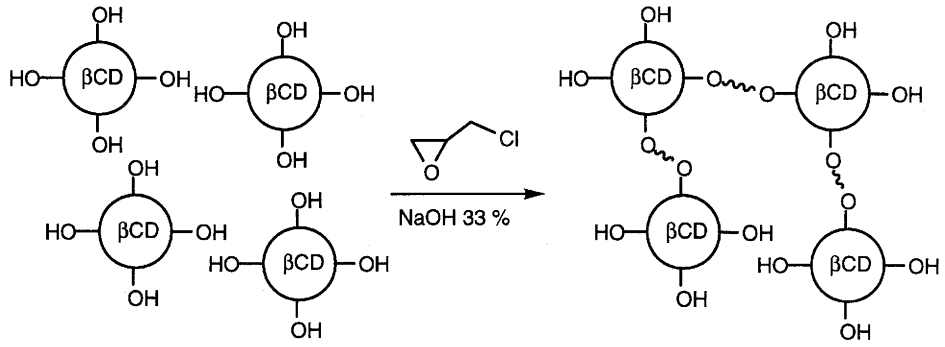

Figure 8. Schematic representation of the polymerization of **βCD** with epichlorohydrine.

Preliminary results so far obtained confirmed that the substitution of βCD C-6 primary hydroxyl was favored at high NaOH concentration, whereas substitution of C-2 and C-3 secondary hydroxyl groups occurred at an appreciably lower rate. The presence of oligo(epichlorohydrine) segments was also evidenced. The variation of the intensity of the different NMR signals during the reaction time, particularly just before and after the gel point, provided valuable information on the reaction progress. In particular, an appreciable increase followed by a rapid decrease of the intensity of the signals of substituted C-2 and C-3 was observed. This information seems to indicate that both polymerization and gelation processes occur mainly by intermolecular reaction of the glycidyl ethers of cyclodextrin secondary hydroxyl groups, whereas the much more abundant C-6 derivatives play only a minor role. Presently, further investigation is in progress to confirm this preliminary result.

CONCLUSION

The results reported in the present contribution attest to the synthetic strategy adopted within the years for the preparation of multifunctional hydrophilic polymeric materials to be used in the formulation of dosage forms viable to the controlled and targeted administration of potent and sensitive active principles, including proteins.

The multifunctional character of the investigated materials should guarantee for their intrinsic properties of bioerosion/biodegradation that can be considered the key parameters in the usage they were designed for. The ever growing interest towards the formulation of smart systems viable to biomedical and pharmaceutical exploitation is sustained and implemented by research activitities based on multidisciplinary strategic approaches.

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REFERENCES

[1] R. Langer, *Science, 249*, 1527 (1990).

[2] E. Chiellini, L. Bemporad, and R. Solaro, *J. Bioact. Compat. Polym., 9,* 152 (1994).

[3] E. Chiellini and R. Solaro, *Adv. Mat., 8,* 305 (1996).

[4] E. Chiellini, S. D'Antone, and R. Solaro, *Macromol. Symp., 123*, 25 (1990).

[5] F. E. Baley and J. V. Koleske, *Poly(ethylene oxide)*, Academic Press, New York, 1976.

[6] N. Ogata, K. Sanui, H. Nakamura, and M. Kuwalara, *J. Polym. Sci., Polym. Chem. Ed., 18*, 939 (1980).

[7] N. Ogata and Y. Hosoda, *J. Polym. Sci., Polym. Chem. Ed., 13*, 1793 (1975).

[8] N. Ogata and Y. Hosoda, *J. Polym. Sci., Polym. Lett. Ed., 12*, 355 (1974).

[9] N. Ogata and Y. Hosoda, *Polym. J., 6*, 412 (1974).

[10] K. Gonsalves, X. Chen, and J. A. Cameron, *J. Appl. Polym. Sci., 50*, 1999 (1993).

[11] T. Loftsson and M. E. Brewster, *J. Pharmac. Sci., 85*, 1017 (1996).

[12] T. Irie and K. Uekama, *J. Pharmac. Sci., 86*, 147 (1997).

[13] K. Uekama, F. Hirayama, and T. Irie, *Chem. Rev., 98*, 2045 (1998).

[14] R. D. Katsarava, D. P. Kharadze, L. M. Avalishvili, and M. M. Zaalishvili, *Makromol. Chem., Rapid Commun., 5*, 585 (1984).

[15] E. Ciuffarin, M. Isola, and P. Leoni, *J. Org. Chem., 46*, 3064 (1981).

[16] W. Kern, S. Iwabuchi, H. Sato, and V. Bohmer, *Makromol. Chem., 180*, 2539 (1979).

[17] D. Landini and F. Rolla, *Synthesis*, 389 (1979).

[18] P. D. Hoagland, *Carbohydr. Res., 98*, 203 (1981).

[19] P. D. Hoagland, H. Pessen, and G. G. McDonald, *J. Carbohydr. Chem., 6*, 495 (1987).

[20] C. G. Overberger and J. Sebenda, *J. Polym. Sci.,* A-1 7, 2875 (1969).

[21] K. Gonsalves and X. Chen, *Polym. Commun., 31*, 312 (1990).

[22] M. Pinilla, M. B. Martinez, and J. A. G. Perez, *Macromolecules, 28*, 3766 (1995).

[23] P. J. Flory, *Polymer Chemistry*, Cornell University Press, Ithaca, New York, 1953.

[24] C. Galli, G. Illuminati, and L. Mandolini, *Macromol. Symp., 95*, 8374 (1978).

[25] R. Solaro, S. D'Antone, L. Bemporad, and E. Chiellini, *J. Bioact. Compat. Polym., 8*, 236 (1993).

[26] E. Renard, A. Deretani, and G. Volet, *Eur. Polym. J., 33*, 49 (1996).

[27] A. Harada, M. Furue, and S. Nozakura, *Polymer J.,13*, 777 (1981).

[28] J. L. Hofman, *J. Macromol. Sci-Chem., A 7*, 1147 (1973).

[29] E. Renard, G. Barnathan, A. Deretani, and B. Sebille, *Macromol. Symp., 122*, 229 (1997).