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Effect of functional crosslinking agents on preparation and swelling properties of dextran hydrogels

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Abstract

Crosslinking reactions of Dextran (Dx) (M_n of 2.0×10^6 g mol^{-1}) with some selective *Cl*-, and *P*-containing functional monomers such as epichlorohydrin (ECH) and phosphorus oxychloride ($POC1_3$) were carried out in the basic aqueous solutions (2.8 N NaOH) at 40 °C. The optimum conditions of the effective swelling and crosslinking for the each system studied were found in nickel ($NiCl_2\cdot6H_2O$) solution. The percent swelling, equilibrium swelling, initial rate of swelling, swelling rate of constant, equilibrium water content, and diffusion type and constant values were evaluated for Dx/crosslinker (CL) systems at 1 mg/100 ml nickel ($NiCl_2\cdot6H_2O$) solution. A substantial difference of these parameters observed for the various Dx/CL systems was explained by the effect of nature of crosslinking agents on the mechanism of crosslinking and swelling processes. It was shown that S_{eq} values increase depending on the nature of CLs in the following order: ECH < $POCl_3$. General scheme and proposed mechanism of crosslinking reactions in the Dx/CL systems were also described.

Keywords: Dextran hydrogels; Crosslinking; Epichlorohydrin; Phosphorus oxychloride; Equilibrium swelling

1. Introduction

Hydrogel is a material, when placed in excess water, able to swell rapidly and retains large volumes of water in its swollen three-dimensional structure without dissolution. Hydrogels may be sensitive to their environment and their structure may change according to the conditions around them (Hoffman, 2002). The interaction of polymers with blood and body fluids is of interest because of their high potential in the production of biomaterials. Many hydrogels obtained from synthetic polymers display good biocompatibility that can be used for drug delivery systems (Hovgaard & Bronsted, 1995; Livney et al.,2001). Dextran is a bacterial polysaccharide, consisting essentially of a α-1,6 linked D-glucopyranese residues with a few percent of α-1,2-, α-1,3- or α-1,4-linked side chains. The low molecular weight fractions of dextran are used as a plasma expander. Furthermore, dextran is widely under investigation as a polymeric carrier in novel drug delivery systems. Because of its good biocompatibility, dextran is also a suitable polymer to be used for the preparation of hydrogels, which are becoming increasingly important in the biomedical, pharmaceutical, biotechnological and environmental fields Dextran hydrogels can be obtained by several different approaches. Dextran hydrogels have received increased attention due to their variety of biotechnological and biomedical applications. Owing to their low tissue toxicity and high enzymatic degradability at desired sites, dextran hydrogels have been frequently considered as a potential matrix system for colon-specific delivery and/or controlled release of bioactive agents (Cadée et al., 2000). Dextran hydrogels can be obtained by several different approaches. Edman et al. synthesized dextran hydrogels by chemical incorporation of glycidyl acrylate into dextran in aqueous phase, followed by free radical polymerization of the dextran derivatives in the presence of *N*,*N*′-methylenebisacrylamide as an additional crosslinker (Edman, Ekman, & Sjoholm, 1980). Bronsted and Hovgaard prepared hydrogels

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from cross-linking of dextran with 1,6-hexanediisocyanate in DMSO (Brondsted, Anderson, & Hovgaard, 1998). Kim et al. also reported the synthesis of methacrylated and acrylated dextrans by reacting dextran with methacrylic anhydride, and with bromoacetyl bromide and sodium acrylate, respectively. Preparation of dextran hydrogels was then carried out by UV irradiation of MA-dextrans (Kim, Won, & Chu, 1999a,b). Van Dijk-Wolthuis et al. introduced vinyl group into dextran in a full control manner of the degree of conjugation by transesterification of glydicyl methacrylate (GMA) with dextran molecules in DMSO at ambient temperature (De Smedt et al., 1995; Van Dijk-Wolthuis et al., 1995). Polyvalent metal cation modified dextran hydrogels combine characteristic properties of dextran/epichlorohydrin crosslinked materials as well as dextran/metal cation complexes (Spychai & Bartkowiak, 1998). The porous structure, forming from dextran macromolecules crosslinking with epichlorohydrin, forces the immobilization of oxygen groups of the polymer gel matrix. Phosphate diesters of waxy maize starch were prepared by cross-bonding reaction using various concentration of phosphorus oxychloride (Bartkowiak, Jezierska, & Spychai, 1998). Crosslinked dextran is applied as a packing material for gel filtration columns. The swelling properties, enzymatic degradability and release behavior of dextran hydrogels have also been extensively studied by Hennink, Franssen, van Dijk-Wolthuis, and Talsma (1997).

In this study, the functional polymer hydrogels forming from the crosslinkable Dextran (Dx/(ECH) and Dextran (Dx)/($POC1_3$) systems have been synthesized. The percent swelling, equilibrium swelling, initial rate of swelling, swelling rate of constant, equilibrium water content, and diffusion type and constant values were evaluated for Dx/crosslinker (CL) systems at 0.001 g/100 ml nickel ($NiCl_2\cdot 6H_2O$) solution. General scheme and proposed mechanism of crosslinking reactions in the Dx/CL systems were also described.

2. Experimental and methods

2.1. Materials

The initial dextrans with nominal molecular weight of 5.0×10^5 and 2.0×10^6 g mol^{-1} used in this study were supplied by Pharmacia Fine Chemicals AB (Uppsala, Sweden). Inorganic salt ($NiCl_2\cdot 6H_2O$), (BDH) was used without further purification. The initial crosslinking agents, such as ECH (Sigma) and $POC1_3$ (Fluka) purified by distillation, have the following characteristics: ECH: b.p. 116.5 °C, $d_4^{20}=1.180$, $n_D^{20}=1.4380$; $POCl_3$: b.p. 105–109 °C, $d_4^{25}=1.6750$, $n_D^{20}=1.4610$.

2.2. Synthesis of hydrogels

Synthesis of polymeric hydrogels from Dx/crosslinker (CL) mixtures is carried out by intermolecular side-chain reaction of dextran hydroxyl groups with monomeric crosslinking agents in aqueous solutions at 40 °C in the presence of NaOH. Bidistillated and deionized water is used as a solvent. Reaction conditions: [Dx] = constant = 1.4 base-mol/l, molar ratio of [Dx]/[NaOH] = constant = 0.5 and [NaOH = constant = 2.8 mol/l]; molar ratios of [CL]/[NaOH] = 0.33 (for Dx/ECH system; the molecular weight of 2.0×10^6 g mol^{-1}) and 0.17 (for Dx/$POCl_3$ system; the molecular weight of 5.0×10^5 and 2.0×10^6 g mol^{-1}).

2.3. Swelling studies

Crosslinked Dx samples have been obtained in long cylindrical shapes cut in to pieces 0.5 cm long. Hydrogels prepared were firstly immersed in bidistillated water for a week to remove uncrosslinked polymers dried to constant weight in vacuum at 40 °C before swelling experiment. Hydrogels were left for swelling in water at 25 °C to determined swelling; then they were removed from the water bath, dried, weighted and placed in the same bath. The swelling degree of crosslinked Dx/CL systems was determined gravimetrically by the following equation:

$$S(\%) = [(M_t - M_0)/M_0] \times 100 \qquad (1)$$

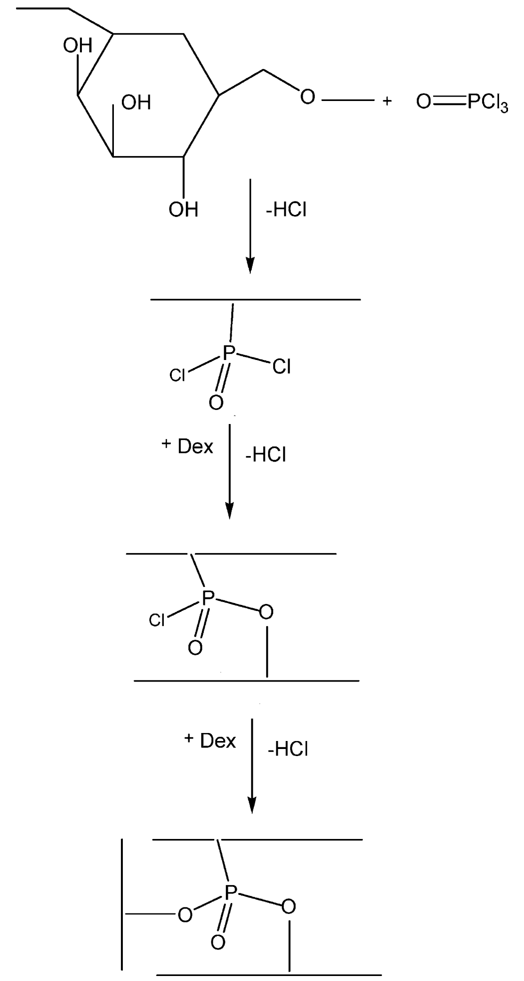
where M_0 is the dry/initial weight of hydrogel, M_t is the weight of swollen gel at given time (t) in water.

3. Results and discussion

3.1. Effect of crosslinkers type on swelling

A fundamental relationship exists between the swelling of a crosslinked polymer in a solvent and the nature of polymer, solvent and crosslinker (Chiu, Lin, & Hsu, 2002; Kaplan & Güner, 2000a). It is well known that reaction of ECH with ether polyols (ethylene glycol and polyethylene glycols) in the base-aqueous medium is the basic for most epoxy resin production. This reaction proceeds in the presence of NaOH, which is acceptor for HCl-product of dehydrochlorination of chlorohydrine. In the Dx/ECH/NaOH systems Dx used as a polyether polyol and general scheme of crosslinking reactions corresponded to known reaction of ECH with polyols (Güner, Akman, & Rzaev, 2001). Probably, the addition of ECH to Dx's macromolecules in the base-aqueous medium is a molecular reaction passing via the side-chain alkoholate (Dx-ONa) formation stage (Krentsel et al., 1997). The chlorohydrine fragments formed can easily transform to epoxy group by dehydrochlorination in the presence of NaOH (Aubert, Mauzac, & Jozefonvicz, 1987).

In accordance with this well known macromolecular reactions of functional polymer with reactive organic compounds; there can be proposed the following general



Scheme 1. Representation of crosslinking reaction of dextran with $POCl_3$.

scheme of the crosslinking reactions in the Dx/POC1$_3$ systems in the chosen conditions. The reaction proceeds in Dx/$POCl_3$ system which is also accompanied by step-by-step elimination of HCl and formation of the network structure (Scheme 1). It is known that $POCl_3$ is a reagent used for preparation of polysaccharide phosphates which are useful as cation-exchange resin in ion-exchange chromatography of proteins. Probably, reaction of Dx with $POCl_3$ also can be proceeded in the strong basic medium through formation of Dx–O–P(ONa)$_2$ fragment in side-chain macromolecules. Then, this fragment is easily reacted with HCl-product of immediately hydrolysis of POC1$_3$. The –O–P(ONa)$_2$ groups formed can also be influenced on swelling and crosslinking processes in Dx/$POCl_3$/NaOH system.

Swelling of the three dimensional network structure in a chosen/suitable solvent is the most important parameter especially one of the most important parameter in mass swelling for studies of swelling process (Brannon-Peppas & Peppas, 1991; Kaplan & Güner, 2000b). The intake of initially dry Dx hydrogels was followed for a long period of time. In the present work, the swelling process of Dx with certain molecular weight in the presence of various types of organic (ECH) functional monomer and inorganic substance ($POCl_3$) in aqueous nickel solutions are investigated in detail. The kinetic curves of swelling in the Dx/CLs obtained are illustrated in Fig. 1. It can be clearly seen that the swelling capabilities of all Dx/CL hydrogels formed are increased by time, but after a certain period they show constant swelling behavior, and the process is transformed to equilibrium swelling state. Comparative analysis of these results obtained showed that the higher swelling degree took placed in the Dx/$POCl_3$ system, but swelling process in this system proceeded slowly as compared with Dx/ECH systems. As shown in these curves, the swelling capabilities of Dx/$POCl_3$ and Dx/ECH hydrogels vary in the range 7200 and 1390% for M_n 2.0×10^6 g mol^{-1} in nickel solutions, respectively. The swelling capabilities of Dx/$POCl_3$ for the M_n 5.0×10^5 g mol^{-1} was determined as 4065% (Dx/CL:3:1) and 3195% (Dx:CL:5:1). It can be understood that as the crosslinking reagent ratio increases in the gel content, swelling percentage of the gel decreases (Zhang, Won, & Chu, 1999). In order to make a better comparison, the determined equilibrium swelling percentages are given in Table 1. It can be clearly seen that the highest swelling percentages are observed in the Dx/$POCl_3$ hydrogel system for the M_n 2.0×10^6 g mol^{-1}. For the high molecular weight of the dextran molecules; the swelling percentage of the gel has higher swelling capability at the same Dx/CL ratio. Before explanation of the swelling of hydrogels in the presence of metal ion solution, it is better to discuss the effect of additives on the structure of water and interactions

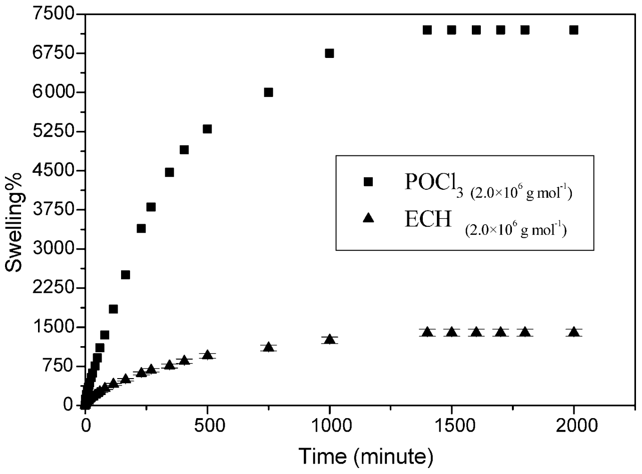


Fig. 1. Swelling %–time curves of the Dextran/$POCl_3$ and Dextran/ECH hydrogels at room temperature.

Table 1
Equilibrium Swelling (%) of dextran/CLs hydrogels in nickel (II) solutions (1 mg/100 ml $NiCl_2\cdot6H_2O$)

Dextran/CLs hydrogels	Equilibrium swelling (%)
Dextran/$POCl_3$ (2.0×10^6 g mol^{-1})	7200
Dextran/$POCl_3$ (5.0×10^5 g mol^{-1})	4065
Dextran/ECH (2.0×10^6 g mol^{-1})	1390

between polymer and solvent molecules. In the presence of $POCl_3$ as a crosslinker, the crosslink density of the gel is decreasing (Kaplan Can, Kırcı, Kavlak, & Güner, 2003b). It is obvious that the additives can change and/or disturb the hydrogen-bonded structure of water and the molecular association of the water-soluble polymer in aqueous media, as well as the swelling behavior of crosslinked dextran chains. In the presence of metal ion solution, swelling of hydrogels can easily follow the change of the hydrogen-bonded structure of water and polymer-solvent interaction. Because of the higher swelling value of the dextran gel in the metal solution, these types of the gels can be used in the purification of the environmental aims.

3.2. Diffusion

The swelling curves of $Dx/POCl_3$ and Dx/ECH hydrogels in aqueous nickel solution were used for the calculation of a certain diffusion characteristics. The following equation was used to determine the nature of diffusion of metal solution into dextran hydrogels (Kaplan Can, Kavlak, Kırcı, & Güner, 2003a)

$$F = M_t/M_\infty = kt^n \quad (2)$$

where M_t/M_∞ denote the amount of solvent diffused into the gel at time, t, and infinite time (at equilibrium), respectively, k is a constant related to the structure of the network, and the exponent n is a numerical value to determine the type of diffusion. For a cylindrical shapes, $n \leq 0.50$ and corresponds to Fickian diffusion, whereas $0.50 < n < 1.00$ indicates that diffusion is non-Fickian Eq. (2) was applied to various stages of swelling and plots of ln F against ln t yielded straight lines from which the exponents n and k were calculated from the slope and intercept of the lines listed in Table 2 at 1 mg/100 ml aqueous nickel solutions. It can be clearly seen from the Table 2 that the values of the diffusion exponent range between 0.655 and 0.432. For dextran/$POCl_3$ hydrogel system was taken as non-Fickian character. Hence, the diffusion of nickel solutions into dextran/ECH hydrogel was assumed to be Fickian in character. It can also be noticed from Table 2 that in dextran/ECH hydrogel, i.e. the higher the crosslinking density, the more the transport of metal solution into the hydrogel becomes Fickian. For extensive swelling of dextran hydrogels in metal solution the following equation can be used (Kaplan Can et al., 2003a),

$$t/S = A + Bt \quad (3)$$

Table 2

Fick coefficients (n and k) of the dextran/CLs hydrogels in nickel solutions (1 mg/100 ml $NiCl_2 \cdot 6H_2O$)

Dextran/CLs hydrogels	Fick coefficients	
	n	k
Dextran/$POCl_3$ (2.0×10^6 g mol^{-1})	0.655	0.0097
Dextran/ECH (2.0×10^6 g mol^{-1})	0.432	0.0399

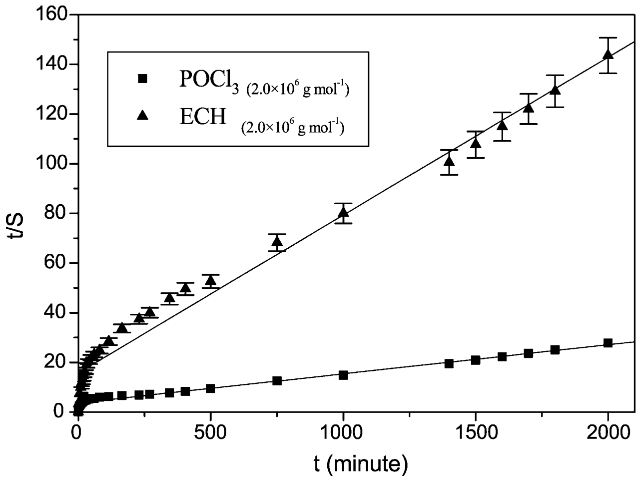


Fig. 2. t/S vs. t graph plotted for Dextran/$POCl_3$ and Dextran/ECH hydrogels systems at room temperature.

where $B = 1/S_{eq}$ is the reciprocal of the maximum or equilibrium swelling, $A = 1/(k_s S_{eq}^2)$ is the reciprocal of the initial swelling rate of the gel, and k_s is the swelling rate constant. This relation represents second order kinetics (Kaplan and Güner, 2000a). Fig. 2 exhibits the linear regression of the swelling curves obtained by means of Eq. (3) for dextran hydrogels in 1 mg/100 ml nickel solution. The initial rate of swelling (r_i), swelling rate constant, and equilibrium swelling (or as commonly used, theoretical equilibrium swelling) of dextran hydrogels are calculated from the slope and intersection of the lines given in Table 3 both for hydrogel systems in 0.1 g/100 ml nickel solutions. The values of theoretical equilibrium swelling of the hydrogels are in good agreement with the results of equilibrium swelling of dextran hydrogels (Fig. 1). Swelling process of dextran/$POCl_3$ hydrogels is quicker than the swelling rate of dextran/ECH hydrogels. It is well known that swelling is directly related to the structure of the crosslinked polymer and/or the density of the hydrogel (Stenekes & Hennink, 1999; Kaplan & Güner, 2000a).

The study of diffusion phenomenon in hydrogel and solvent is of importance as it clarifies the polymer behavior. The short-time approximation method is used for the calculation of diffusion coefficients of hydrogels. This method is used for the first 60% of swelling of cross-linked polymers in a chosen solvent. Commonly, the diffusion coefficient of cylindrical hydrogel is determined by the following equation

Table 3

Calculated r_i {g water/g gel)/min}, k_s {g gel/g water)/min}, and S_{eq} {(g water/g gel)} Dextran/CLs hydrogels in nickel solutions (1 mg/100 ml $NiCl_2 \cdot 6H_2O$)

Dextran/CLs hydrogels	Swelling coefficients		
	r_i	$k_s \times 10^{-4}$	S_{eq}
Dextran/$POCl_3$	0.010	0.25	98.0
Dextran/ECH	7.505	23.3	7.57

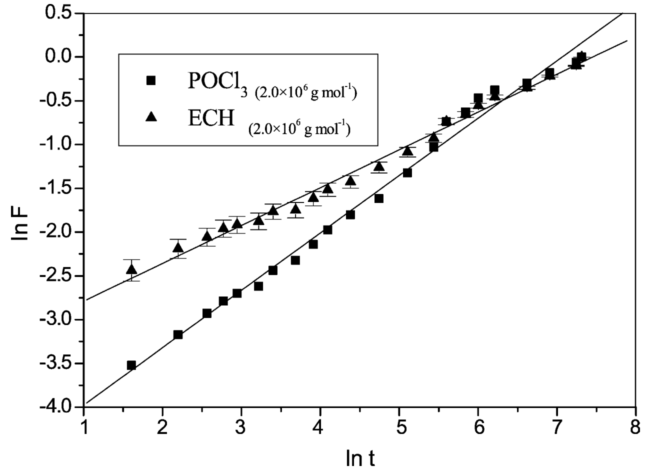


Fig. 3. ln F vs. ln t graph plotted for Dextran/$POCl_3$ and Dextran/ECH hydrogels systems at room temperature.

$$F = M_t/M_\infty = 4[Dt/\pi r^2]^{1/2} - \pi[Dt/\pi r^2] - \pi/3[Dt/\pi r^2]^{3/2} + \cdots \quad (4)$$

where D is the diffusion coefficient ($cm^2\ min^{-1}$), t is the time (min), and r is the radius (cm) of cylindrical polymer samples. The graphical comparison of Eqs. (2) and (4) show the semi-empirical Eq. (2) with $n=0.50$ and $k=4[Dt/(r^2]^{1/2}$. The diffusion coefficients of dextran hydrogels were also calculated from the slope of the lines of F against $t^{1/2}$ from the graph in nickel solution (Figs. 3 and 4). The results are listed in Table 4 for hydrogel systems. It can be seen from the table that the values of the diffusion coefficients dextran/$POCl_3$ and dextran/ECH hydrogel system in 1 mg/100 ml aqueous metal solution change between the ranges 1.86×10^{-5} and 2.05×10^{-5} $cm^2\ min^{-1}$, respectively.

Table 4
Diffusion coefficients of dextran/CLs hydrogels in nickel solutions (1 mg/100 ml $NiCl_2\cdot 6H_2O$)

Dextran/CLs hydrogels	Diffusion coefficient [$D\times 10^5$ (cm^2/min)]
Dextran/$POCl_3$ (2.0×10^6 g mol^{-1})	1.86
Dextran/ECH (2.0×10^6 g mol^{-1})	2.05

Table 5
Equilibrium nickel content (ENC) % of dextran/CLs hydrogels in nickel solutions (1 mg/100 ml $NiCl_2\cdot 6H_2O$)

Dextran/CLs hydrogels	Equilibrium nickel content (ENC) %
Dextran/$POCl_3$ (2.0×10^6 g mol^{-1})	98.63
Dextran/ECH (2.0×10^6 g mol^{-1})	93.30

3.3. Equilibrium nickel content % (ENC)

Equilibrium nickel content of the dextran/$POCl_3$ and dextran/ECH hydrogels have been calculated from (Kaplan & Güner, 2000b), Eq. (5)

$$ENC(\%) = [(W_{eq} - W_{dry})/W_{dry}]100 \quad (5)$$

where W_{eq} is the nickel content diffused into the gel at equilibrium state and W_{dry} is the weight of initially dried gel. The determined ENC values are presented in Table 5. Along with the type of the crosslinker, the equilibrium nickel content is decreased for hydrogel systems in the order of $POCl_3 > ECH$. Equilibrium nickel content, as well as the swelling behavior of hydrogel, mainly depends on the nature of network structure, that is, hydrophilicity, crosslinking density, and the average molecular weight between two consecutive crosslinks. When these three different hydrogel systems are compared, it is clearly seen that the values of ENC of dextran/$POCl_3$ hydrogels in 1 mg/100 ml aqueous nickel solution are higher than the values of ENC for dextran/$POCl_3$ hydrogels in the same solutions. This observation is also in good agreement with the swelling results of these hydrogel systems and with that of equilibrium swelling and initial swelling rate values mentioned previously.

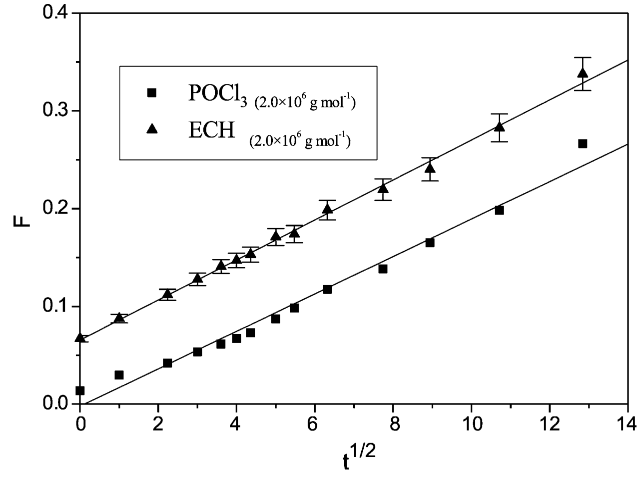


Fig. 4. F vs. t graph plotted for Dextran/$POCl_3$ and Dextran/ECH hydrogels systems at room temperature.

4. Conclusions

1. New type of *Cl*- and *P*- containing functionalized dextran hydrogels are synthesized and swelling properties are determined.
2. It was experimentally demonstrated that Dx macromolecules easily undergo to crosslinking by ECH and $POCl_3$ in the presence of NaOH.
3. The optimum conditions of the effective swelling and crosslinking for the each system studied were found in nickel ($NiCl_2\cdot 6H_2O$) solution.
4. The percent swelling, equilibrium swelling, initial rate of swelling, swelling rate of constant, equilibrium water content, and diffusion type and constant values were evaluated for Dx/crosslinker (CL) systems at 1 mg/100 ml nickel ($NiCl_2\cdot 6H_2O$) solution.

5. According to the crosslinking characteristics the following order obtained in the increasing order of ECH < $POCl_3$.
6. The diffusion of nickel solutions into dextran/$POCl_3$ hydrogels was assumed to be non-Fickian in character.
7. Proposed general crosslinking reaction scheme of the dextran with $POCl_3$ is described. In the presence of $POCl_3$, the uptake capacity of gel system is increased. Penetration of nickel solution into dextran/$POCl_3$ hydrogels is the most efficient, implying that aqueous solution of nickel facilitates and consequently increases the diffusion process compared to that in water. Because of the high adsorption capacity of the hydrogels, they can be used as waste-water treatment. The results obtained allow to simply reflecting the possibility of the formation of network structure with different type and functionality in the Dx/CL hydrogel systems. As a conclusion, it may be said that the dextran hydrogels, which have high swelling capacities, have shown wide application areas, such as environmental, biotechnology, etc.

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