PVNO—DVB Hydrogels: Synthesis and Characterization

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Synopsis

Hydrogels with various degrees of crosslinking were synthesized from 2-vinylpyridine and divinylbenzene/ethylbenzene monomers using gamma irradiation. The influence of the solvent solubility parameter, ionic strength, and temperature on swelling and gel density were studied. Adsorption of water vapor on these gels was determined, and the data were used in the calculation of free energy changes involved in the process. Finally the drug release behavior–crosslink content relation was investigated. It was found that increase in crosslinking agent content adversely influenced swelling, gel density, and water vapor adsorption. The solvent solubility parameter was found to influence swelling more than ionic strength. Contrary to what was expected, it was not possible to classify the drug release behavior as first order.

INTRODUCTION

Hydrogels are three-dimensional networks of hydrophilic polymers produced not as byproducts of polymerization or monomer distillation, but as products of carefully designed experiments to satisfy certain biomedical requirements. Their controllable swelling, density as well as absence of toxic ingredients enabled hydrogels to have various uses as biomaterials. Crosslinks can be introduced into the polymers by the formation of active sites followed by binding or by using bifunctional monomers. In the first case, random modification of the side chains of the polymer takes place. The second process takes place in fewer steps and enables one to prepare a hydrogel with more controlled composition.

In this work, we chose to use bifunctional monomers because of the above mentioned advantages and synthesized hydrogels from 2-vinylpyridine and divinylbenzene monomers. Divinylbenzene served both as a crosslinking agent and as the hydrophobic ingredient. 2-Vinylpyridine was, after incorporation into the gel, oxidized and acted as the hydrophilic ingredient. Thus, we were able to control the ratio of hydrophilic and hydrophobic groups as well as the crosslinking agent content. Polymerization initiation could only be effected by gamma irradiation. After synthesis, swelling, water vapor adsorption, and drug release behavior were studied.

EXPERIMENTAL

Synthesis of the Gels

Gels with different compositions were synthesized from fresh vacuum distilled 2-vinylpyridine and divinylbenzene (containing 45% ethylvinylbenzene) according to Table I by irradiation under nitrogen atmosphere for 22 h by ^{60}Co

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TABLE I
Composition of Mixtures for Preparation of PVNO—DVB Gels

Gel no.	2-VP (mL)	DVB—EVB (mL)
G 69	1.0	—
G 70	1.0	0.1
G 72	4.0	0.1
G 73	2.0	0.1
G 74	1.0	0.2
G 75	1.0	0.5
G 76	1.0	1.0

γ-rays with an exposure rate of 1.56×10^5 rad/h. After polymerization, the gels were stored in chloroform for 2 days for the extraction of monomers or homopolymers. The gels were then oxidized with hydrogen peroxide[1] in order to convert vinylpyridine to vinylpyridine *N*-oxide. The gels were then subjected to several washes with water.

Solvent Content (wt %), Swelling Ratio (Q) and Volume of Adsorbed Solvent (VAS) Determination

The gels were equilibrated for 4 days in solvents with different solubility parameters (δ), ionic strength (μ), and in water at different temperatures. Weights were determined in the swollen and vacuum-dried states. The method of calculation of wt %, Q, and VAS were presented in a previous paper.[2]

Gel Density Determination

Gel density was determined according to a modified pycnometric method after equilibration for 10 days in water.[2–4]

Water Vapor Adsorption

Gels were brought to constant weight after drying under vacuum for 3 days at 40°C. The gels were then brought in contact with air-containing water vapor at various relative humidities and water vapor adsorbed on gels was determined by weighing.[2,5,6]

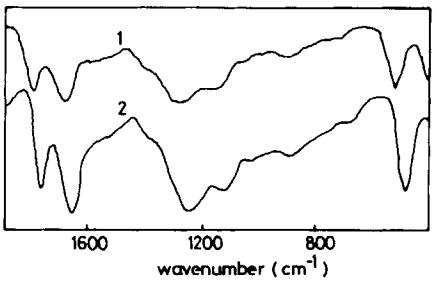

Fig. 1. Infrared spectra of PVNO(1) and G 73(2) (KBr pellets).

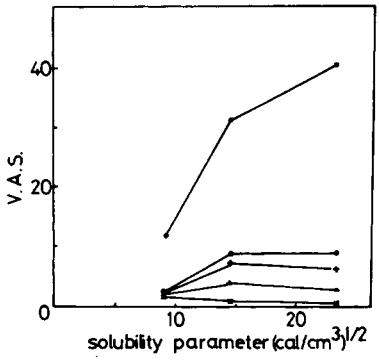

Fig. 2. Volume of adsorbed solvent vs. solubility parameter: (○—) G 72; (●—) G 73; (+—) G 70; (△—) G 74; (×—) G 75.

Drug Release

The release of methyl red from the gels was tested. Methyl red solution (100 mL, 1 mM) was added to the swollen gel that corresponded to a dry weight of 1.0 g and the gel was equilibrated there for 6 days at room temperature. The gel was then placed into an isotonic phosphate buffer (8 mL, pH 7.4) that was replaced every 24 h. The amount of methyl red released was determined spectrophotometrically at 433 nm.

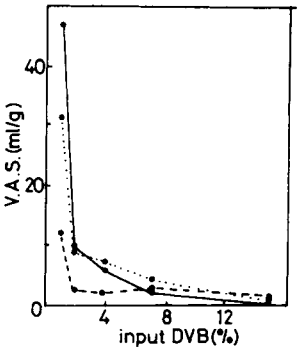

Fig. 3. Relation of volume of adsorbed solvent and input DVB (%): (●—) Water; (● ····) methanol; (● - - -) chloroform.

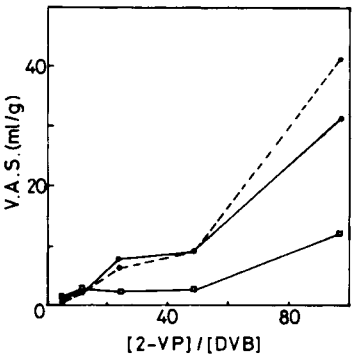

Fig. 4. Volume of adsorbed solvent vs. concentration ratios of 2-VP and DVB: (○ - - -) Water; (●—) methanol; (□—) chloroform.

RESULTS AND DISCUSSION

Synthesis of Gels

All the preparations (except G 69) formed gels after irradiation. G 69 was found to have become viscous indicating a high degree of polymerization. It can be concluded from these that gamma radiation caused the initiation of polymerization by opening the double bonds of the vinyl groups rather than by causing radicals randomly, and thus the major source of crosslinks is the bifunctional monomer, divinylbenzene. This can further be supported by the almost identical appearance of the IR spectra of PVNO and PVNO—DVB gel (Fig. 1).

When azo-bis-isobutyronitrile was used instead of radiation to initiate polymerization, gelation could not be observed in any of the preparations during an equal period of time. This was possibly because of the inactivation of the second vinyl group of divinylbenzene upon the incorporation of the first into the polymer.[7] Radiation proved to be effective in causing the inactive vinyl group to take part in polymerization and cause gelation.

Effect of Solubility Parameter on Swelling

It is known that for a polymer to dissolve in a particular solvent solubility parameters (δ) of both must be close. For gels, δ is known to be equal to that of the solvent (or solvent mixture) in which maximum swelling is observed.[8] It was observed that δ of G 72 and G 73 were closer to that of water than they were to that of methanol and chloroform (Fig. 2). G 70 and G 74 had δ much similar to that of methanol and G 75 to that of chloroform. When the effect of the input PVNO/DVB or input DVB (%) on swelling was examined, it was observed that increasing the DVB content decreased swelling (Fig. 3). This can be explained by the nonpolar nature of DVB and EVB. Another observed effect of DVB was that swelling in any solvent (regardless of δ) was decreased due to greater crosslinking in gels with high DVB content (Fig. 4).

Effect of Solvent Ionic Strength on Swelling of G 73

When the swelling characteristic of G 73 was investigated in various saline solutions, it was observed that sodium chloride and potassium chloride do not have any significant detrimental effect on swelling in the concentration range of the test (Fig. 5). In the same range, however, it was observed that magnesium chloride reduces the swelling ability of the gel. Magnesium chloride thus had a "salting out" effect on the gel. When the change in the mean activity coefficient of magnesium chloride is considered (Fig. 6), the abrupt decrease in swelling that is followed by an almost undetectable change is understandable. Since the decrease in mean activity coefficients for sodium and potassium chloride is not as large, the effect of ionic strength on swelling was quite small.

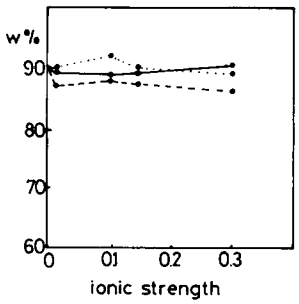

Fig. 5. Water at equilibrium swelling (%) vs. ionic strength: (●—) Sodium chloride; (● · · · ·) potassium chloride; (● – – –) magnesium chloride.

Effect of Temperature on Swelling in Water

It is known that the effect of temperature increase is decrease in intra- and intermolecular attractions and that this causes a poor solvent to become a better solvent. It is shown in Figure 7 that temperature increase leads to an insignificant swelling decrease. This unexpected observation can be explained by the counteracting effects of increase in solubility of DVB and EVB (for which water is a poor solvent) and decrease in solubility of PVNO (for which solvation is probably an exothermic process[2]).

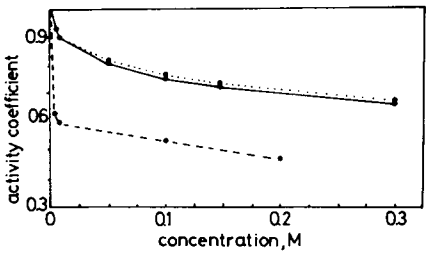

Fig. 6. Mean activity coefficient vs. salt concentration: (●—) Potassium chloride; (● · · · ·) sodium chloride; (● – – –) magnesium chloride.

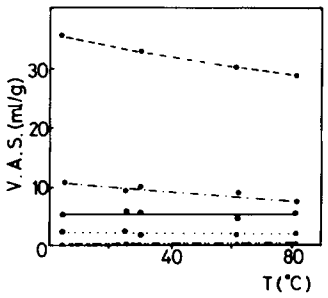

Fig. 7. Effect of temperature on the volume of adsorbed solvent: (● – – –) G 72; (●– · – · – ·) G 73; (●—) G 70; (● · · · ·) G 74; (● · · – · · –) G 75.

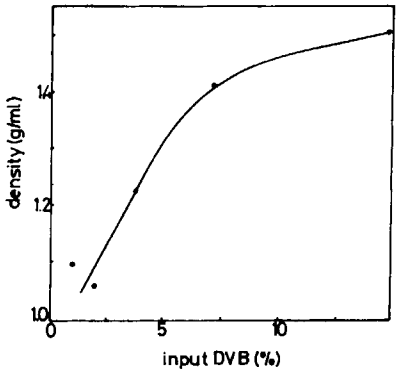

Fig. 8. Density vs. input DVB (%) relation for the hydrogels.

Gel Density and the Effect of Crosslinking Agent Content

Density of a gel is a function of its swelling ability, which in turn is a function of solubility of the polymer in a solvent (or their solubility parameters) and the crosslinking density. The solubility parameter of the gel is influenced by all the monomers whereas the crosslinking density is a function of only the DVB content. In Figure 8 it is observed that as input DVB (%) is increased, the density of the gel in water increased. This is in accordance with the expectation that high crosslinking agent concentration should lead to low degree of swelling. When Figures 2 and 3 are studied, one observes that using methanol instead of water as solvent does not lead to substantial changes in the swelling of the gels (except G 72), even though the solubility parameters are quite different. It can thus be concluded that the major factor influencing the density (or swelling) is the crosslink density.

Another important observation is that gels with high swelling ratios have densities that are very close to that of water. One would expect them to be more biocompatible[9] than denser gels because soft tissues are also thought to have about the same density.

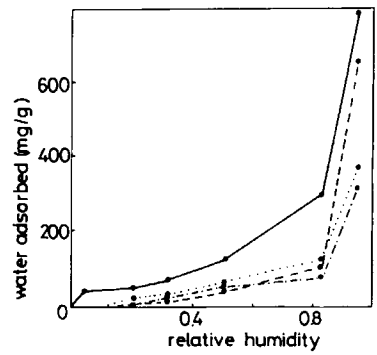

Fig. 9. The relation between the amount of vapor adsorbed and relative humidity of the medium: (●—) G 72; (● – – –) G 73; (● · · · ·) G 70; (● · – · –) G 74.

Water Vapor Adsorption on Gels

Water vapor adsorption on hydrogels is controlled by the number hydrophilic sites on the gel. The higher the number of sites, the greater the interaction with water molecules leading to higher water adsorption. In Figure 9, it is observed that less crosslinked gels (the ones which reveal a higher number of hydrophilic sites) adsorb more water than the highly crosslinked ones. The free energy decrease (for calculation procedure, see Ref. 10) is greatest for the gel with the highest PVNO content (G 72) and the least in G 75 (the lowest PVNO content) (Fig. 10). Another observation is that in G 72 and G 70 the ΔG vs. p/p_0 plots do not reach a plateau, indicating that there still is a great driving force behind the hydration of the gels. These results imply that the above mentioned gels bind water molecules and swell extensively, exposing new sites for further water binding. In G 75, however, a plateau is reached at about $p/p_0 = 0.5$. The high crosslinking agent and the low hydrophilic site content of G 75 prevents the resultant changes from being as great as that observed in the other two gels.

Release of Solutes from Gels

In order to test the suitability of the gels as drug depots, a highly chromogenic substance was required for ease of detection, and sodium salt of methyl red was chosen to simulate the drug to be released from the gel.

Although in the equilibration of the gels 100 mL of 1-mM methyl red solution was used for every gram of dry gel, Table II indicates that different amounts of drug have been retained in different gels. This can be explained by the fact that some gels contain much more water in swollen form than others and (after removal of drug solution) retain more of the drug. In Table II we also observe that the concentration of drug in the gels has values higher than that of the medium (here the drug concentrations were calculated by taking the amount of water in the gels into account), and the higher the crosslinking, the more the concentration effect (e.g., G 72). This might be explained by physical and/or chemical adsorption of the drug on the gel matrix. In Figure 11 we see that highly crosslinked gels (e.g., G 74) release more of their drug content within the first day, supporting the fact that physical adsorption is taking place. One cannot then expect the release of drugs from these gels to be a first order process. Inability to observe a linear $\ln[d_0/d_0 - x]$ vs. t plot (where d_0 and x are the initial and released drug concentrations, respectively, and t is time) (Figure 12) supports this conclusion.

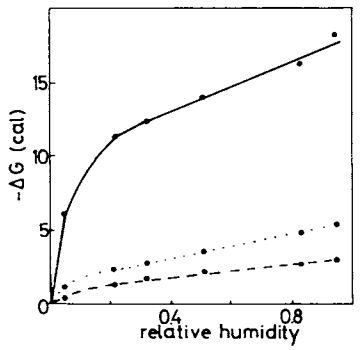

Fig. 10. Free energy change vs. relative humidity: (●—) G 72; (● ···) G 70; (● – – –) G 75.

TABLE II
Concentration of Methyl Red in Drug Release

Gel no.	G 70	G 72	G 73	G 74
Initial methyl red content of gel				
(a) calculated (mM)	0.943	0.710	0.916	0.975
(b) observed (mM)	3.727	0.905	3.612	6.970
(c) observed (μmol)	1.2	2.8	8.6	2.3
Methyl red released (%) in time (days)				
1	68.7	34.0	17.2	48.7
2	10.3	9.5	6.4	20.7
3	1.7	2.5	2.4	11.8
4	0.9	0.7	0.9	5.8
5	0.3	0.5	0.4	3.3
6	0.1	0.1	0.2	2.0

Thus the expected first-order release of drug from the gel is complicated by the fact that a certain fraction of the drug contained in the gel is chemically or physically adsorbed.

In conclusion, it can be stated that it is possible to prepare gels of 2-vinylpyridine and divinylbenzene with desired hydrophilicity, swelling properties, and density to satisfy the requirements of a specific biomedical problem.

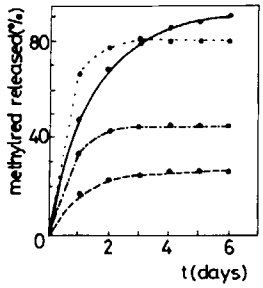

Fig. 11. The amount of drug released (%) vs. time relation: (●—) G 74; (● ····) G 70; (● – · – · –) G 72; (● – – –) G 73.

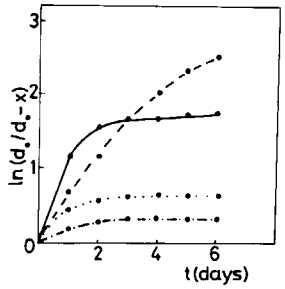

Fig. 12. $\ln(d_0/d_0 - x)$ vs. time relation: (● – – –) G 74; (●—) G 70; (● ····) G 72; (● – · – · –) G 73.

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