Structure and Applications of Poly(vinyl alcohol) Hydrogels Produced by Conventional Crosslinking or by Freezing/Thawing Methods

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Poly(vinyl alcohol) (PVA) is a polymer of great interest because of its many desirable characteristics specifically for various pharmaceutical and biomedical applications. The crystalline nature of PVA has been of specific interest particularly for physically cross-linked hydrogels prepared by repeated cycles of freezing and thawing. This review includes details on the structure and properties of PVA, the synthesis of its hydrogels, the crystallization of PVA, as well as its applications. An analysis of previous work in the development of freezing and thawing processes is presented focusing on the implications of such materials for a variety of applications. PVA blends that have been developed with enhanced properties for specific applications will also be discussed briefly. Finally, the future directions involving the further development of freeze/thawed PVA hydrogels are addressed.

Keywords. Poly(vinyl alcohol), Hydrogels, Freezing/thawing, Crystallinity, Biomedical applications, Crosslinking, Crystallites

1
Structure and Properties of Poly(vinyl alcohol) (PVA)

Poly(vinyl alcohol) (PVA) has a relatively simple chemical structure with a pendant hydroxyl group. The monomer, vinyl alcohol, does not exist in a stable form rearranging to its tautomer, acetaldehyde. Therefore, PVA is produced by the polymerization of vinyl acetate to poly(vinyl acetate) (PVAc), followed by hydrolysis of PVAc to PVA. The hydrolysis reaction does not go to completion resulting in polymers with a certain degree of hydrolysis that depends on the extent of reaction. In essence, PVA is always a copolymer of PVA and PVAc. Commercial PVA grades are available with high degrees of hydrolysis (above 98.5%). The degree of hydrolysis, or the content of acetate groups in the polymer, has an overall effect on its chemical properties, solubility, and the crystallizability of PVA [1].

The degrees of hydrolysis and polymerization affect the solubility of PVA in water [2]. It has been shown that PVA grades with high degrees of hydrolysis have low solubility in water. Figure 1 shows the solubility of a PVA sample with a number average molecular weight of $\overline{M}_n$=77,000 as a function of the degree of hydrolysis at dissolution temperatures of 20 and 40 °C. Residual hydrophobic acetate groups weaken the intra- and intermolecular hydrogen bonding of adjoining hydroxyl groups. The temperature must be raised well above 70 °C for dissolution to occur. The presence of acetate groups also affects the ability of PVA to crystallize upon heat treatment. PVA grades containing high degrees of hydrolysis are more difficult to crystallize.
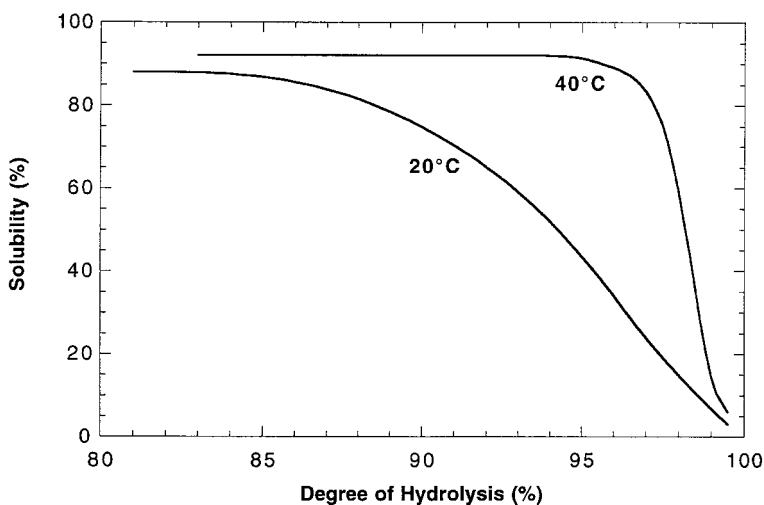

Fig. 1. Solubility as a function of degree of hydrolysis at dissolution temperatures of 20 and 40 °C

PVA is produced by free radical polymerization and subsequent hydrolysis, resulting in a fairly wide molecular weight distribution. A polydispersity index of 2 to 2.5 is common for most commercial grades. However, polydispersity indices of 5 are not uncommon. The molecular weight distribution is an important characteristic of PVA because it affects many of its properties including crystallizability, adhesion, mechanical strength, and diffusivity.

2
Synthesis and Properties of PVA Hydrogels

PVA must be crosslinked in order to be useful for a wide variety of applications, specifically in the areas of medicine and pharmaceutical sciences. A hydrogel can be described as a hydrophilic, crosslinked polymer (network) which swells when placed in water or biological fluids [3]. However, it remains insoluble in solution due to the presence of crosslinks.

PVA can be crosslinked through the use of difunctional crosslinking agents [4]. Some of the common crosslinking agents that have been used for PVA hydrogel preparation include: glutaraldehyde, acetaldehyde, formaldehyde, and other monoaldehydes. When these crosslinking agents are used in the presence of sulfuric acid, acetic acid, or methanol, acetal bridges form between the pendant hydroxyl groups of the PVA chains. As with any crosslinking agent, however, residual amounts are present in the ensuing PVA gel. It becomes extremely undesirable to perform time-consuming extraction procedures in order to remove this residue. If the residue is not removed, the gel will not be acceptable for biomedical or pharmaceutical applications. If the gel were to be used in biomedical applications, the release of this toxic residue would have obvious undesirable effects. For pharmaceutical applications, especially when PVA is used as a carrier in drug delivery, the toxic agent could alter the biological activity or degrade the biologically active agent being released. There are also other toxic residual components associated with chemical crosslinking such as initiators, chain transfer agents, and stabilizers.

Other methods of chemical crosslinking include the use of electron beam or γ-irradiation. These methods have advantages over the use of chemical crosslinking agents as they do not leave behind toxic, elutable agents. Danno [5] discussed the quantitative and qualitative effects of irradiation by γ-rays (from ^{60}Co sources) to produce hydrogels from aqueous PVA solutions. He found that the minimum gelation dose depended on the degree of polymerization and the concentration of the polymer in solution. Further studies by Saito [6] and Dieu and Desreux [7] showed that when no impurities are present, the intrinsic viscosity and the viscosity-average molecular weight of irradiated aqueous solutions of PVA increase with radiation dose.

Sakurada and Mori [8] and Peppas and Merrill [9] investigated the effects of γ-irradiation by ^{60}Co on the physical properties of PVA fibers, hydrogels, and films irradiated in water. The effect of the irradiation dose on the molecular weight between crosslinks is more closely represented in Fig. 2 for aqu-
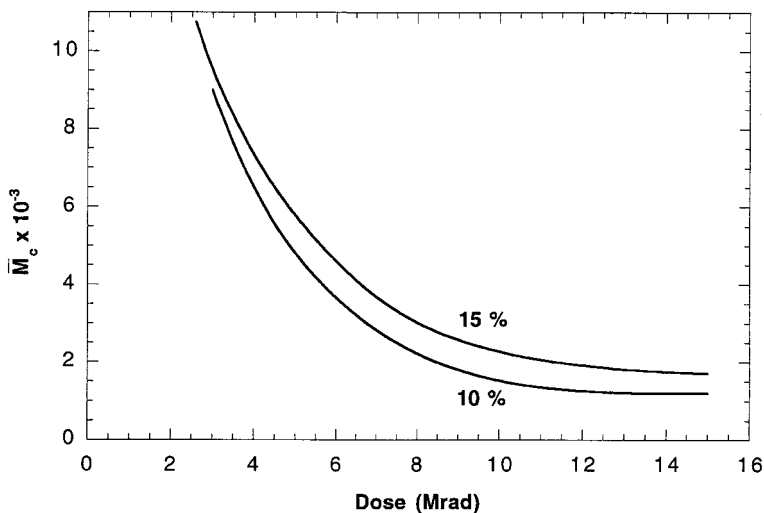
Fig. 2. Effect of concentration and irradiation dose on the molecular weight between crosslinks $\overline{M}_c$

eous PVA solutions of 10 and 15 wt %. Significant differences in swollen films were observed between irradiation under vacuum and in air. However, when the concentration of the aqueous solution was significantly high, little difference was observed. One problem observed in this technique of crosslinking was bubble formation. This problem was also encountered by other researchers [5, 10] with little success in solving the problem. A proposed solution was to pre-cool the aqueous solution for a certain amount of time to yield homogeneous hydrogels. This, however, is not a desirable procedure to carry out with PVA.

The mechanical strength of crosslinked, partially crystalline PVA hydrogels has already been examined [11]. In particular, efforts were made to enhance the mechanical strength of crosslinked PVA networks that were prepared initially by electron beam irradiation of aqueous PVA solutions. Peppas and Merrill [9, 12] examined the phenomenon of partial crystallization by a process of dehydration and annealing. Resulting materials contained crystallites in addition to crosslinks. The crystalline regions essentially served as additional crosslinks to redistribute external stresses. The degree of crystallinity of samples annealed at 120 °C for 30 min is shown as a function of the crosslinking density in Fig. 3.

A third mechanism of hydrogel preparation involves "physical" crosslinking due to crystallite formation [13]. This method addresses toxicity issues because it does not require the presence of a crosslinking agent. Such physically crosslinked materials also exhibit higher mechanical strength than PVA gels crosslinked by chemical or irradiative techniques because the mechanical load can be distributed along the crystallites of the three-dimensional struc-
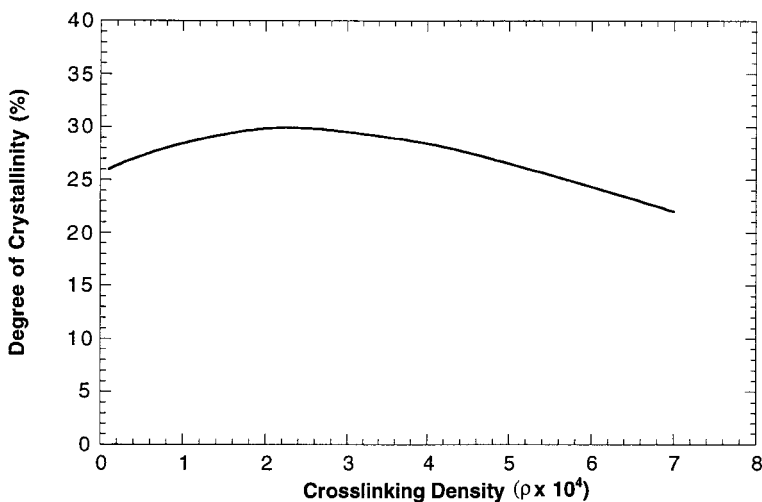
Fig. 3. Degree of crystallinity as a function of crosslinking density of PVA gels swollen to equilibrium in water at 37 °C

ture. Aqueous PVA solutions have the unusual characteristic of crystallite formation upon repeated freezing and thawing cycles. The number and stability of these crystallites are increased as the number of freezing/thawing cycles is increased. Some characteristics of these "physically" crosslinked PVA gels include a high degree of swelling in water, a rubbery and elastic nature, and high mechanical strength. In addition, the properties of the gel may depend on the molecular weight of the polymer, the concentration of the aqueous PVA solution, the temperature and time of freezing and thawing, and the number of freezing/thawing cycles. The development of this technique and its ensuing materials will be discussed in more detail in Sect. 4.

3
Crystallization of PVA Hydrogels

The crystalline structure of PVA has been discussed in detail by Bunn [14]. On a molecular level, the crystallites of PVA can be described as a layered structure [15, 16]. A double layer of molecules is held together by hydroxyl bonds while weaker van der Waals forces operate between the double layers. A folded chain structure of PVA chains leads to small ordered regions (crystallites) scattered in an unordered, amorphous polymer matrix. Values representative of the crystallinity and thermal properties of PVA have been reported [4]. The crystalline melting range of PVA is between 220 and 240 °C. The glass transition temperature of dry PVA films has been reported at 85 °C. In the presence of water (and other solvents), the glass transition temperature decreases significantly [2].

Usually, there is a minimum PVA chain length necessary to crystallize PVA. Mandelkern [17] reported that as the molecular weight of the polymer increased, the size of crystallites also increased. However, the character and appearance of the crystallites did not change over a molecular weight range. The stereoregularity of PVA has also been shown to influence the crystallizability of PVA. Harris et al. [18] examined these effects by determining dissolution temperatures as a function of crystallization temperatures for PVA samples of varying tacticity. In addition, degrees of crystallinity were also determined for PVA samples of varying tacticity that were prepared by solution-crystallization techniques. Overall, the stereoregularity was found to significantly affect the crystallizability. However, PVA of increasing stereoregularity did not increase the crystallizability. In particular, isotactic PVA resulted in less crystalline samples than syndiotactic PVA due to increased intramolecular hydrogen bonding and, thus, reduced intermolecular forces. Fujii [19] has further shown that stereoregular structures do not favor crystallizability. In fact, he reported that atactic PVA is the most crystallizable form, with syndiotactic somewhat less crystallizable, with the isotactic form showing poor crystallinity.

Different methods have been investigated for the crystallization of PVA. Most of these methods involve heat treatment to introduce crystallites. The degree of crystallinity, as well as the size of crystallites, depends on the drying conditions. One method involves slow-drying rate dehydration at room temperature under different relative humidities [20–22]. In this process, the amount of polymer in the system is increased and crystallization actually begins late in the process. The effect of drying time on the degree of crystallinity is shown in Fig. 4 where dehydration of the samples was performed with
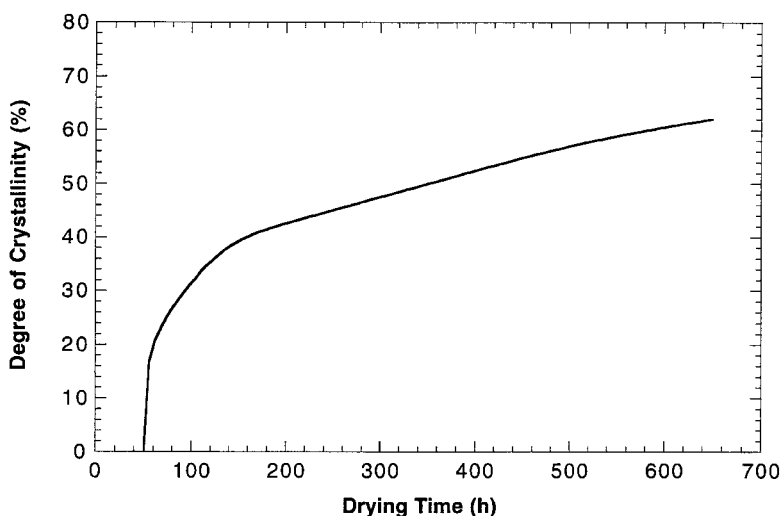

Fig. 4. Degree of crystallinity of dehydrated PVA gels as a function of drying time

Ca(NO$_3$)$_2$ as the drying agent. Fast-drying rate processes, such as annealing, usually result in the rapid formation of crystallites. One such method involves annealing PVA films at a constant temperature that is between the glass transition temperature and the melting point of the polymer [23]. Under these conditions, macromolecular chains have enough mobility to align themselves and fold to form crystallites. Gels produced by such techniques involving these annealing conditions have been further characterized recently in terms of their structure and dissolution behavior in water [24].

Yamaura et al. [25–27] examined PVA gels that had been prepared in the presence of various solvents including dimethylformamide, ethylene glycol, and phenol. The thermal and mechanical properties of these gels and dried gel films were studied. Additionally, gel spinning was implemented with solutions of PVA, phenol, and water to produce filaments with very high dynamic moduli (up to 45 GPa).

It has also been shown that crystallization takes place in PVA gels due to aging [28]. A decrease in the swelling ratio in water is indicative of this phenomenon which has been confirmed by X-ray analysis. Tanigami et al. [29] have more closely characterized aged PVA gels. Such gels were prepared in a mixed solvent of dimethyl sulfoxide (DMSO) and water. PVA films were aged in water for several months at 10 °C, then dried, and drawn at 200 °C. The aging process significantly affected the tensile strength and modulus of the drawn films. Specifically, the low temperature of 10 °C was necessary to allow for crystallites at low melting temperature to grow within the aged gel. Additional work by Tanigami et al. [30] more closely examined the swelling of PVA gels that had been dried and annealed. The swelling agent was a mixed solvent of DMSO and water. They characterized the relaxation and swelling rates of such gels in relation to the solvent composition and degree of crystallinity. Anomalous swelling was attributed to the low relaxation rate of PVA that compared with the diffusion coefficient of the penetrant. Another key observation was that the degree of crystallinity played an important role in controlling the relaxation rate. Further work by Tanigami et al. [31] also characterized the aging of PVA gels prepared by freezing and thawing techniques and will be discussed in Sect. 4.

Semicrystalline PVA is characterized by its degree of crystallinity which is defined as the ratio of the volume of PVA crystallites to the total volume of PVA. Density measurements, calorimetric methods, spectroscopic methods, X-ray analysis, and other methods such as NMR spectroscopy have been used to determine degrees of crystallinity of PVA hydrogels [32]. Using such methods, degrees of crystallinity were determined for PVA samples ($\overline{M}_c$=4770) that were prepared under varying annealing conditions (Table 1).

Density measurements can be used for PVA hydrogels without the presence of voids or other imperfections. The calculation of the degree of crystallinity uses the principle of additivity of volumes and the densities of 100% crystalline and amorphous PVA [15]. These values have been reported in the literature by Sakurada et al. [34] as ρ_c=1.345 g/cm^3 for 100% crystalline PVA and

Table 1. Crystallinity as a function of preparation conditions as determined from various techniques

Annealing conditions		Degree of crystallinity (%)		
Temp (°C)	Time (min)	From density	From DSC	From IR spectra
90	30	30.0	35.6	31.1
105	60	45.0	46.8	44.5
120	30	50.8	50.1	52.3
120	90	64.7	71.1	62.7

ρ_a=1.269 g/cm^3 for 100% amorphous PVA. The degree of crystallinity, X, of PVA on a dry basis is:

$$\frac{1}{\rho_g} = \frac{X}{\rho_c} + \frac{1-X}{\rho_a} \tag{1}$$

where ρ_g is the density of the sample. This can be modified for PVA hydrogels where the additivity of the volumes of PVA and water is assumed:

$$\frac{1}{\rho_h} = \frac{1-W_{PVA}}{\rho_{H_2O}} + \frac{W_{PVA}}{\rho_g} \tag{2}$$

Here, ρ_h is the density of the hydrogel, W_{PVA} is the weight percentage of PVA in the sample, and ρ_{H2O} is the density of water.

Calorimetric methods can also be used to determine the crystallinity of PVA films. They include differential thermal analysis, differential scanning calorimetry (DSC), and thermogravimetric analysis. Typically, the heat of crystallization of a PVA sample, ΔH, is compared to the heat of crystallization of 100% crystalline PVA, ΔH_c. The degree of crystallinity is expressed as:

$$X = \frac{\Delta H}{\Delta H_c} \tag{3}$$

The melting of PVA occurs over a range of temperatures because the crystallites range in size. Therefore, calorimetric methods can also be used to calculate crystallite size distributions.

Of the spectroscopic methods, infrared (IR) spectroscopy is the most widely used. The intensity of the peak at 1141 cm^{-1} in the IR spectrum of PVA depends on the degree of crystallinity. It has been proposed that the band arises from a C–C stretching mode and increases with an increase in the degree of crystallinity [34]. A method for determining degrees of crystallinity from ATR-FTIR spectra has been further discussed by Peppas [35]. The height of the peak at 1141 cm^{-1} is analyzed in terms of the height of the peak at 1425 cm^{-1} which remains constant.

X-ray analysis has also been used for films and fibers of PVA. X-ray diffraction methods are used to determine the percentage of crystalline PVA by comparing the scattering of a sample to that of a completely amorphous one. How-

ever, in the case of swollen PVA films, results are difficult to analyze due to the existence of the pattern of water. Sakurada et al. [33] analyzed the crystallinity of swollen PVA films, showing that swelling does not change ("melt out") the crystalline regions of PVA.

4
Hydrogels by Freezing and Thawing of Aqueous PVA Solutions

To avoid crosslinking processes which potentially lead to the release of toxic agents, a physical method of gelation and solidification of some polymers, particularly PVA, has been developed. This freezing and thawing process of PVA gel preparation has been summarized recently by various researchers [36, 37]. In particular, the impact of various preparation conditions on the overall properties of such materials has been addressed. Here, a thorough analysis of previous work in this area will be presented. In particular, the implications of such materials prepared by freezing and thawing processes for various applications will be described.

The preparation of pure PVA hydrogels using freezing and thawing techniques was first reported by Peppas [38] in 1975. In this work, aqueous solutions of between 2.5 and 15 wt % PVA were frozen at –20 °C and thawed back to room temperature resulting in the formation of crystallites. The crystallites were characterized using measurements of the change in turbidity of the PVA samples. The formation of crystallites in the samples was found to be related to the concentration of PVA in solution, the freezing time, and the thawing time. The transmittance of visible light through samples prepared with vary-
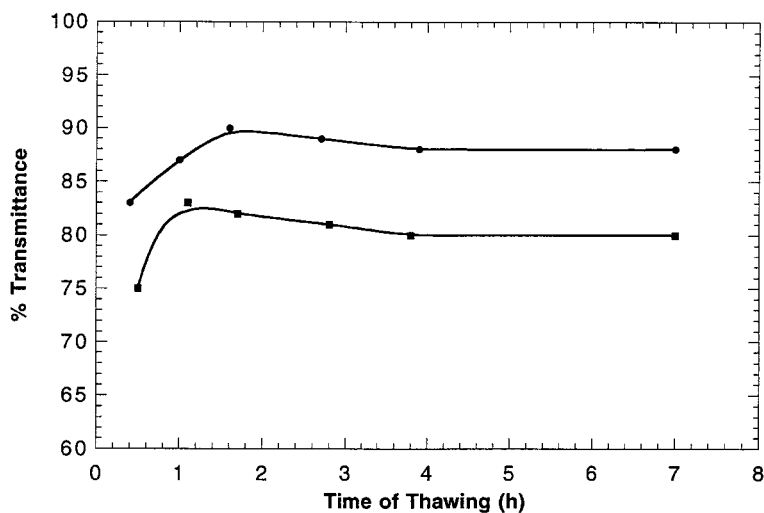

Fig. 5. Transmittance of visible light as a function of thawing time for samples prepared from 10 (●) and 15% (■) aqueous PVA solutions

ing aqueous PVA concentrations is shown as a function of thawing time in Fig. 5. Overall, the crystallinity was found to increase with increasing freezing time. During the thawing process, the size of the crystallites initially increased and then decreased. This was attributed to the breakdown of the crystalline structure. The degree of crystallinity was found to increase with increasing PVA solution concentration.

Since this pioneering discovery, much research has been conducted on the freezing and thawing process as well as on the characterization of such gels produced with these techniques. The research of Nambu [39] introduced the potential use of pure PVA gels produced by freezing and thawing processes for biomedical applications. His freeze-drying technique consisted of cooling a PVA solution to below –3 °C followed by the vacuum evaporation of water. Further work by Nambu and collaborators [40] examined the mechanical properties of gels prepared with this freeze-drying process. Simple extension experiments were performed to analyze the force-extension relationship at large deformations. It was determined that an increase in the evacuation (evaporation of water) time resulted in an increase in the tensile force. This was attributed to the strengthening of the gel by decreasing the number of imperfections which may not have been attached to the network structure. More recently, Nambu and collaborators [41] have also examined PVA gels prepared by freezing and thawing techniques for use as a phantom in magnetic resonance imaging due to its close resemblance to human soft tissue.

Yokoyama et al. [42] further examined gels that had been prepared by Nambu's method of repeated freezing and thawing cycles. Using X-ray diffraction, scanning electron microscopy (SEM), light-optical microscopy, and tension experiments, the structure was described as one consisting of three phases: a water phase of low PVA concentration, an amorphous phase, and a crystalline phase that restricts some of the motion of the amorphous PVA chains.

Watase and Nishinari [43] further characterized freeze/thawed gels through the analysis of DSC endotherm peaks and X-ray diffraction. They also performed an extensive analysis concerning the effect of the degree of hydrolysis on various properties of PVA gels prepared by freezing and thawing [44]. They reported that the presence of bulky acetate groups can inhibit the formation of a gel. Additionally, slight differences in the degree of hydrolysis can significantly impact the thermal behavior of the gels.

In preparing such PVA gels by freezing and thawing techniques, the addition of solvents has also been investigated. Hyon and Ikada [45] prepared porous and transparent hydrated gels from a PVA solution in a mixed solvent of water and water-miscible organic solvents. The concentration of PVA in solution was between 2 and 50 wt %. The organic solvents examined included dimethyl sulfoxide, glycerine, ethylene glycol, propylene glycol, and ethyl alcohol. The method consisted of cooling the solution to below 0 °C for the crystallization of PVA followed by the subsequent exchange of the organic solvent in the gel with water. This process resulted in the formation of a hydrated gel of PVA with high tensile strength, high water content, and high light transmit-

tance. High light transmittance was an important property of the material, especially when considering the material for contact lens applications. Explanations were offered concerning the mechanism for gel formation as well as increased light transmittance. As the temperature of the homogeneous solution was lowered, there was a restriction in the molecular motion. The intermolecular interaction of PVA, likely due to hydrogen bonding, was promoted to yield small crystalline nuclei. Crystallization could proceed further as the solution remained at low temperatures for longer times. The crystallites served as crosslinks to hold the three-dimensional structure together. The addition of the organic solvent served to prevent the PVA solution from freezing even below 0 °C. This allowed for PVA crystallization to proceed without significant volume expansion. Therefore, the ensuing gel contained pores of less than 3 µm, resulting in a transparent gel. Additional work by Hyon et al. [46] further examined the preparation of such PVA gels due to crystallization at low temperatures.

Other contributions have been made concerning the characterization of PVA gels prepared by freezing and thawing techniques in the presence of other solvents. In particular, Berghmans and Stoks [47] described a two-step mechanism for the gelation of PVA gels in the presence of ethylene glycol. The first step involves a liquid-liquid phase separation that occurs as the gel turns opaque. Then during the second step, crystallization occurs in the more concentrated phase.

Lozinsky and collaborators [48, 49] characterized various aspects of cryogels, or gels prepared by freezing and thawing processes. Initial work showed that upon exposing aqueous PVA to one cycle of freezing and thawing, no destruction or covalent crosslinking of macromolecules of PVA was noted. An extensive investigation of freeze/thawed PVA gels involved the introduction of a filler that could model microbial cells. The filler that was used consisted of spherical particles of a crosslinked dextran gel. Such gels were characterized in terms of their rheological and thermal properties. Additional work in this group [50, 51] examined various properties of freeze/thawed gels prepared in the presence of other components. The influence of both polyols and low molecular weight electrolytes was investigated. The addition of triethylene glycols and higher oligomers of ethylene glycol was found to increase the strength and thermal stability of the gels. Freezing and thawing in the presence of electrolytes was also found to impact the gelation process and subsequent swelling characteristics.

PVA hydrogels prepared by freezing and thawing techniques were further characterized by Urushizaki et al. [52, 53], and it was determined that many properties of these gels were closely related. They found a good correlation between tack and viscoelasticity which was useful for predicting the properties of the material for pressure-sensitive adhesives in transdermal drug-delivery systems. Additionally, the amount of unincorporated PVA, the density of the PVA gel, viscoelasticity, and swelling behavior were also closely related. The rate of swelling of the gels was found to increase linearly with the square

root of time immersed in water. In addition, the water uptake upon swelling in water increased with increasing temperature. In studying the mechanical properties, the viscoelasticity showed little change between 15 and 50 °C but changed significantly above 50 °C as there was an irreversible physical change from gel to sol.

Further research by Ohkura et al. [54] focused on the use of dimethyl sulfoxide/water solutions. They reported interesting features of PVA gels that were formed from solutions of mixtures of DMSO and water. Gels that were prepared by freezing below 0 °C were transparent and exhibited high elasticity. Higher gelation rates were observed when compared with aqueous solutions of only PVA in water. Specifically, the properties were dependent on the ratio of dimethyl sulfoxide to water. It was also observed that gelation from the mixture occurred without phase separation below –20 °C. However, above this temperature, phase separation plays an important role for the gelation process. This research emphasized that the structure of the gels was not well understood from microscopic viewpoints leading to a sparked interest in studying the gels by wide- and small-angle neutron scattering. Additional work by this group [55] determined the gelation rate as a function of polymer concentration, quenching temperature, and degree of polymerization.

In this continued work [56–58], it was confirmed by wide-angle neutron scattering that crosslinking, or points of junction, in the gels were indeed crystallites. Furthermore, small-angle neutron scattering experiments showed that the surface of the crystallites had a clear boundary. The average size of the crystallites was approximately 70 Å and the average distance between crystallites was approximately 150 to 200 Å

The thermal properties of gels prepared by freezing and thawing techniques were further examined by Hatakeyama et al. [59]. They classified the water contained within the gels as non-freezing, restrained, and free water. In addition, the work showed that the rate of freezing affected the size of ice crystals formed and, therefore, the number of crosslinks formed.

Cha et al. [60] further examined the microstructure of PVA gels with differential scanning calorimetry. They also classified the water in PVA hydrogels as free, intermediate, or bound water. PVA gels were prepared by three different techniques: chemical crosslinking with glutaraldehyde, annealing of dried films, and crystallization at low temperatures. Gels prepared by low temperature crystallization contained less bound water with the concentration increasing as the degree of polymerization of PVA was increased. This was likely attributed to the fact that the concentration of free PVA chains, which did not participate in the crystallite formation process, increased with the increasing degree of polymerization. It was determined that low temperature crystallization resulted in larger free space between crystallites and larger size of crystallites than annealing.

Significant changes in the crystalline structure of freeze/thawed gels over time was examined by Murase et al. [61]. They studied the synersis, or volumetric shrinkage (i.e. solvent exclusion), of gels prepared from PVA solutions

in a mixed solvent of DMSO and water. They attributed increased crystallinity over time to be due to the interaction between DMSO and water which isolated PVA hydroxyl groups. Further work by this group [31] studied the structure of aged PVA gels and the associated syneresis. The gels were prepared from PVA solutions in a mixed solvent of DMSO and water by freezing at –34 °C for one day. The gels were aged for up to 500 days at 30 °C to allow for the growth of crystallites. The aged gel was found to have an increased modulus as well as solvent exclusion. This was again attributed to a densification of the structure caused by phase separation. The crystallization produced three components which were detected in the form of a multi-peak endotherm using differential scanning calorimetry.

Trieu and Qutubuddin [62] further examined the structure of freeze/thawed PVA gels prepared from aqueous DMSO solutions. In particular, they characterized the gels using freeze-etching and critical point drying SEM techniques. A higher porosity was observed at the surface than within the bulk of the gel. Tazaki et al. [63] also examined the porous nature of freeze/thawed PVA gels through SEM techniques. They confirmed the presence of fairly large pores within the structure. They further examined such gels for the separation of a water/ethanol mixture by pervaporation.

The porous structure of freeze/thawed PVA gels has been further characterized by Suzuki et al. [64, 65]. Gels containing poly(acrylic acid) and poly(allyl amine) have porous structures that result in the fast exchange of solvents. The relationship between the mechanical properties and porosity was more closely examined. A substantial increase in the modulus was observed with increasing cycles of freezing and thawing for up to ten cycles. Above ten cycles, the modulus still increased but not as significantly. Additional work focused on cryo-SEM techniques and X-ray analysis to characterize the porous structure of amphoteric PVA gels. The influence of the cooling rate and the number of freezing and thawing cycles was further examined.

There have also been applications of such freeze/thawed materials in the biomedical field. Bao and Higham [66] reported the use of such materials as intervertabrate disc nuclei. Specifically, the hydrogels prepared had a water content of 30% or higher and a compressive strength of 4 MPa or higher. They discussed the combination of various pieces of the hydrogel to obtain an overall conformation of the natural disc nucleus.

Recently, the use of freeze/thawed PVA hydrogels for particular drug-release applications has been investigated. Takamura and collaborators [67–69] examined the use of PVA gels prepared by freezing/thawing processes for various applications including controlled drug release. Early work [67] first addressed the preparation of strong, freeze/thawed PVA gels. They reported that it was necessary for the grade of PVA to have a degree of polymerization of over 1000 and a concentration of PVA of over 6% to obtain adequate strength. In particular, the strength was found to increase with the first three cycles of freezing and thawing and then level off. They also characterized the drug release of PVA gels prepared from emulsions [68]. Release of both hydrophobic and hy-

drophilic drugs was found to be zero-order. Such a system was examined for use as a suppository. Additional work by this group [69] focused on studying the effects of additives on the release and physicochemical properties of the gel. The additives used were sodium alginate and Pluronic L-62. The physical strength of the gels was found to increase with increasing sodium alginate concentration. The addition of Pluronic L-62 had no effect on the overall strength. However, drug release from the gel was found to decrease with an increase in the content of sodium alginate or Pluronic L-52.

PVA gels prepared with a mixed solvent of water and DMSO were also characterized in terms of artificial articular cartilage applications [70]. The solutions were cooled to below room temperature to allow for gelation. The gels were then exposed to annealing at various temperatures. Such preparation techniques produced PVA gels with increased tensile strength and dynamic modulus which are important when considering the wear properties of the polymer.

Significant contributions to the development of PVA gels prepared by freezing and thawing techniques have been made in our own laboratory. Some of the parameters that have been investigated include the concentration of aqueous PVA, the molecular weight of PVA, the number of freezing and thawing cycles, the time of freezing, and the time thawing. Specifically, the gels investigated have been characterized in terms of swelling behavior, degree of crystallinity, the transport and release of drugs and proteins, mechanical strength, and adhesive and mucoadhesive characteristics. Some of the most recent characterizations have been described by Peppas [71] and addressed in terms of potential applications.

Stauffer and Peppas [13] investigated the preparation and properties of such materials. Aqueous solutions of 10 to 15 wt % PVA were frozen at –20 °C for between 1 and 24 h and then thawed at 23 °C for up to 24 h for five cycles. It was found that 15 wt % solutions produced strong thermoreversible gels with mechanical integrity. Specifically, gels that were frozen for 24 h for five cycles and thawed for any period of time were the strongest. Swelling experiments as a function of thawing time and freezing cycles indicated that denser structures were observed after five cycles (Fig. 6). This was indicative that the physical crosslinking, due to the presence of crystallites, increased with an increasing number of freeze/thaw cycles.

Peppas and Scott [72] investigated such PVA gels in terms of controlled release applications. PVA hydrogels were prepared by freezing aqueous solutions of 15 wt % PVA at –20 °C for 18 h and thawing at room temperature for 6 h for three, four, and five cycles. The samples with the highest PVA molecular weight and the highest number of freeze/thaw cycles led to the densest gel structure. These gels were also observed to be the strongest and most rigid. Swelling studies in conjunction with DSC experiments indicated that there was an initial decrease in the degree of crystallinity due to the melting out of smaller crystallites. This stage was followed by an increase in the crystallinity at long times which was attributed to additional crystallite formation due to
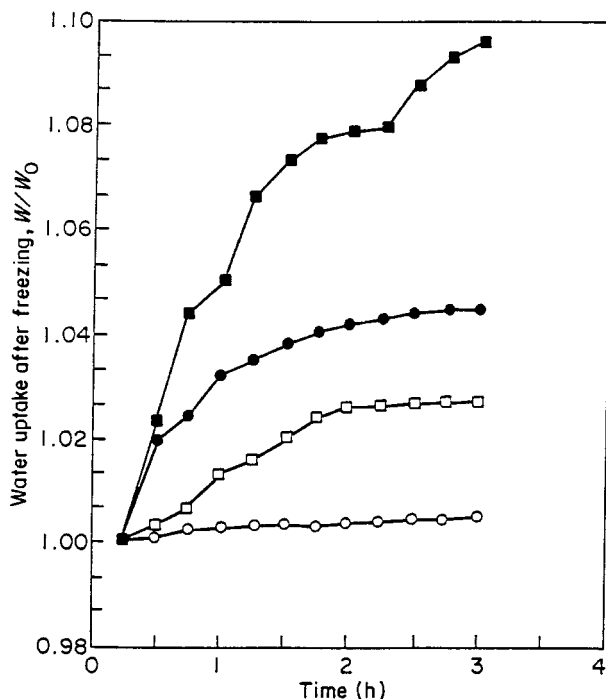
Fig. 6. Swelling in water at 23 °C for freeze/thawed gels prepared with two (■), three (●), four (□), and five (○) cycles of freezing and thawing

aging. The melting out of crystallites as well as secondary crystallization have proved to be important issues when considering the overall stability of this system. Release studies were also conducted with bovine serum albumin which was incorporated into the gel prior to freezing and thawing. The release profile was examined over a period of 19 days and determined to be Fickian. Therefore, bovine serum albumin release was controlled by diffusion with changes in crystallinity having little effect on the release mechanism.

Ficek and Peppas [73, 74] further examined controlled drug delivery from ultrapure PVA gels with the preparation of microparticles. PVA microparticles with diameter ranging from 150 to greater than 1400 µm were prepared by freezing and thawing processes. An aqueous solution of PVA was dispersed in corn oil with 1.25 wt % sodium lauryl sulfate as the surfactant. The suspended droplets of PVA solution were solidified upon exposure to several freezing/thawing cycles. Important parameters which were investigated in this work were the oil to PVA ratio, the amount of surfactant added, and the reagitation of particles after the oil had been partially frozen. The microparticles were investigated for bovine serum albumin release. High release rates were initially observed followed by a constant period of release over longer times (7 days).
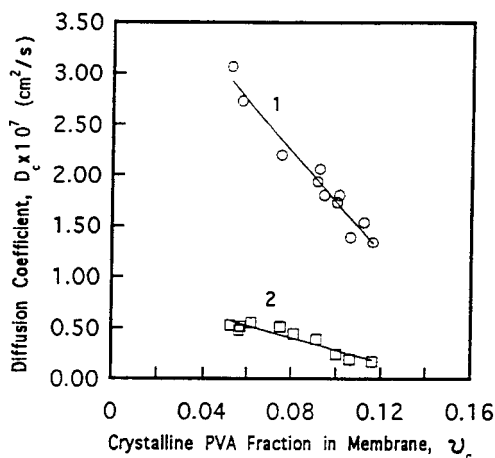
Fig. 7. Diffusion coefficients through freeze/thawed PVA gels as a function of the crystalline PVA volume fraction for theophylline (*curve 1*) and FITC-dextran (*curve 2*)

The diffusive characteristics of PVA gels prepared by freezing/thawing techniques were examined more closely by Hickey and Peppas [75]. Semicrystalline PVA membranes were prepared by freezing and thawing aqueous solutions of PVA for up to ten cycles under the conditions previously described. It was determined that the PVA crystalline fraction was a function of the number of cycles as well as the duration of each cycle. The volume-based crystalline fraction of PVA on a wet basis ranged from 0.052 to 0.116. The equilibrium volume swelling ratio also varied from 4.48 to 9.58 with decreasing degree of crystallinity. The focus of this work concerned diffusion studies. The permeation of theophylline and FITC-dextran was investigated with PVA membranes to determine size exclusion characteristics. It was determined that the diffusion coefficient could be approximated by a linear relation with the crystalline PVA volume fraction as shown in Fig. 7. It was also found that the transport of theophylline in semicrystalline PVA membranes produced by heat treatment was an order of magnitude higher than transport in the membranes under investigation. Overall, solute transport was a function of the crystalline fraction of PVA and the mesh size. Figure 8 shows in more detail the three-dimensional network structure of swollen, freeze/thawed PVA gels that was proposed in this work. The mesh size is shown between the crystalline regions that serve as the physical crosslinks. Overall, a size exclusion phenomenon was demonstrated by these permeation studies which was attributed to the crystallites that created the physical network.

The mucoadhesive characteristics of ultrapure PVA gels were examined in detail by Peppas and Mongia [76]. PVA hydrogels were prepared by exposing 15 to 20 wt % aqueous solutions of PVA to repeated cycles of freezing for 6 or 12 h at −20 °C and thawing for 2 h at 25 °C. The average degree of crystallinity for the 20 wt % solution was 19.3% on a dry basis. Adhesion studies showed
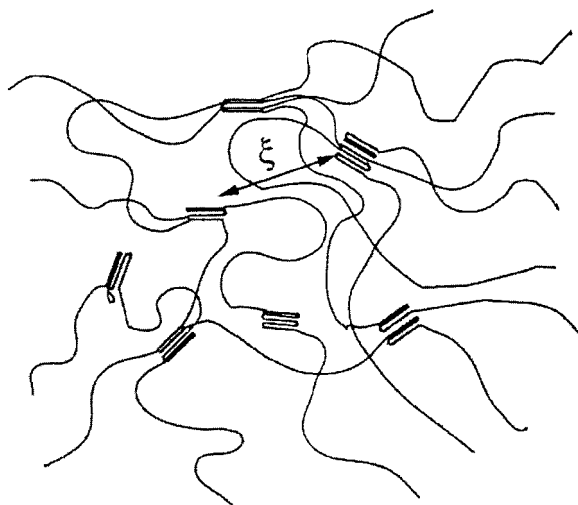
Fig. 8. Three-dimensional network structure of freeze/thawed PVA gels

that the work of fracture, or detachment, decreased with an increasing number of freezing/thawing cycles due to the increase in PVA degree of crystallinity. Maximum adhesion was achieved after two cycles. So, although increasing the number of freezing and thawing cycles likely contributed to the stability of the network, the adhesive characteristics decreased. Oxprenolol and theophylline were used in drug-release studies. Drug release was affected by the number of freezing/thawing cycles. Their results indicated that the mucoadhesive characteristics and drug release could be optimized for a certain mucoadhesive controlled release application by controlling freezing and thawing conditions.

Such bioadhesive materials were also examined for the controlled release of growth factors and other proteins [77–82]. Of particular interest was the investigation of mucoadhesive PVA gels for use in epidermal bioadhesive systems for the controlled release of epidermal growth factor or ketanserin to accelerate wound healing [78]. Such systems were examined not only for their drug-release properties but also for their strength and adhesive characteristics.

The most recent work on PVA gels prepared by freezing and thawing techniques [83–85] has focused on the effect of preparation conditions on the structure, morphology, and stability over long time periods. Parameters involved in the preparation of the PVA gels included the number of freezing and thawing cycles, the concentration of the aqueous solution, and the molecular weight of PVA. When considering the stability, several issues were addressed including the possible dissolution of PVA, melting out of crystalline regions, and additional crystallization during swelling at long times. In addition, structure and stability have been related to the use of such materials as carriers for drug delivery [85].

Although the work of Mallapragada and Peppas [24, 86] did not involve pure PVA gels prepared by freezing and thawing techniques, the analysis and results obtained are quite applicable to the current research. They examined the dissolution of semicrystalline PVA in water. These materials, however, were crystallized by annealing at 90, 110, and 120 °C for 30 min. The samples were partially dissolved in deionized water at 25, 35, and 45 °C. The samples were analyzed during the dissolution process using DSC, FTIR, and IR spectral analysis in order to determine the changes in the degree of crystallinity and lamellar thickness distribution. It was determined that an initial drastic decrease occurred in the degree of crystallinity due to the unfolding of most of the smaller crystallites when placed in water. The initial decrease was followed by a constant degree of crystallinity during which the unfolding of larger crystals took place. This continued until complete unfolding and subsequent dissolution of the gel in water. Some important findings were that an increase in the molecular weight of PVA resulted in a smaller number of crystallites, but larger lamellar thicknesses. So although there were fewer crystals in such a system, the crystals formed were more stable. This analysis can be applied to the issue of stability when considering other semicrystalline PVA systems such as freeze/thawed hydrogels.

A mathematical model was also proposed by Mallapragada and Peppas [87] to describe the dissolution of semicrystalline polymers. The development of this model was based on free energy changes during the crystal unfolding and disentanglement process in order to predict the overall dissolution kinetics. In addition, further work [88] examined controlled release systems based on semicrystalline polymers that exhibit such dissolution behavior in the presence of a solvent. Drug release was found to be controlled by the rate of crystal dissolution in a solvent (water or a biological fluid). A model was also developed to predict the drug release from such a device. The new system was described as a crystal dissolution-controlled system, a type of phase-erosion polymeric system.

In addition, such semicrystalline materials of PVA were further examined in some rather unique ways by Mallapragada et al. [89, 90]. Specifically, the crystal dissolution-controlled system described was investigated for the controlled release of metronidazole [89]. The crystalline phase of this system was also characterized more closely in terms of modifications of drug-release profiles [90].

Narasimhan et al. [91, 92] also examined the dissolution of PVA in water using magnetic resonance imaging to detect changes in the microstructure and molecular mobility. In this work, however, PVA samples were prepared by a quenching technique that yielded samples with degrees of crystallinity less than 5%. Such imaging techniques gave information as to solvent concentration profiles and the spatial variation of the water self-diffusion coefficient. This analysis shows promise for assisting in the development of drug-delivery systems based on polymer dissolution.

5
PVA Blends by Conventional and Freezing/Thawing Techniques

There has been a considerable amount of research which has investigated the addition of other components, notably other polymers, with poly(vinyl alcohol) to create a material with desirable characteristics and properties. This section will discuss the work involving pH-sensitive polymeric systems containing PVA and poly(acrylic acid) (PAA). The addition of poly(ethylene glycol) (PEG) into a poly(vinyl alcohol) system to reduce protein adsorption will also be discussed.

pH-sensitive membranes of interpenetrating polymer networks of PVA and PAA were investigated by Gudeman and Peppas [93, 94]. Membranes were prepared by chemical crosslinking techniques to contain varying degrees of crosslinking and ionic content. The molecular weight between crosslinks was found to vary from 270 to 40,000 from equilibrium swelling studies. The mesh size, upon swelling, varied from 19 to 710 Å as shown in Fig. 9. The oscillatory swelling behavior of the system was investigated over the pH range 3–6. An increase of 13–86% in the mesh size was observed when going from pH 3 to 6. The swelling ratio was also found to increase with a decrease in the ionic strength of the swelling environment. Swelling and syneresis occurred more abruptly with more loosely crosslinked membranes. Permeation studies indicated that solute separation was greatly affected by size exclusion and ionic interactions. These results showed that desired separation and selectivity characteristics can be obtained by appropriately designing the gel.

The diffusion of solutes in composite membranes of PVA and PAA was studied by Hickey and Peppas [95, 96]. These membranes were prepared by the freezing and thawing of aqueous solutions of the two components. The membranes were found to be strong and swelled to equilibrium within a few hours
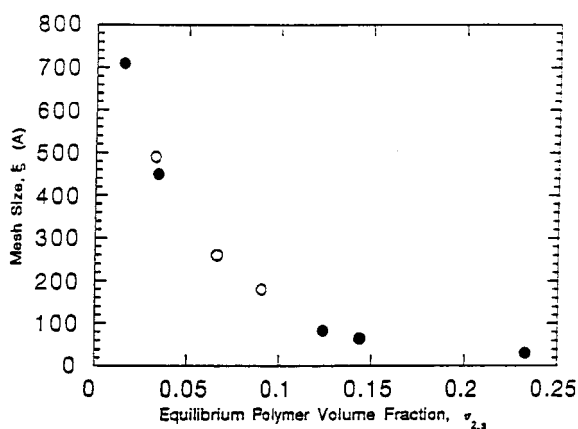

Fig. 9. Mesh size, ξ, as a function of the equilibrium polymer volume fraction, $\upsilon_{2,s}$, for PVA/PAA IPN membranes with PAA content of 50 (●) and 60 mol % (○)

at 25 °C. As the PAA content increased, the membrane swelling ratio increased due to the ionization of the carboxylic groups of PAA. In general, it was observed that the equilibrium mesh size was larger than that of PVA membranes prepared by the same techniques due to the ionic nature of PAA. Results from permeation studies with theophylline and FITC-dextran indicated that solute transport through such PVA/PAA membranes produced by freezing/thawing techniques is considerably slower than through chemically crosslinked membranes. A size exclusion phenomenon was observed and attributed to the physical network created by the formation of crystallites.

Solute transport in PVA/PAA interpenetrating networks was further investigated by Peppas and Wright [97–99] to address the possible binding of solutes during the transport process. Chemical crosslinking was implemented in the preparation of such networks. The diffusion of theophylline, vitamin B_{12}, and myoglobin was analyzed under varying pH conditions of 3 and 6. ATR-FTIR spectroscopy was used to qualitatively analyze the interactions between the ionized membranes and ionized solutes. It was found that solute binding occurred only for hydrogels in the ionized state.

Argade and Peppas [100] examined copolymers of PVA and PAA for their superabsorbent properties. A functionalized PVA was copolymerized with acrylic acid to prepare such materials. Additionally, the degradation of the PVA links between PAA chains was examined to determine the possible biodegradation to lower molecular weight polyacrylates.

A temperature- and pH-sensitive PVA/PAA interpenetrating polymer network was investigated by Shin et al. [101]. The release of the model drug, indomethacin, was studied under varying environmental conditions. The amount of drug released increased as the temperature was increased due to the dissociation of hydrogen bonding and resulting increase in swelling. However, a more significant change in drug release was observed when alternating the pH of the environment. This was attributed to the ionization created within the network. Overall, it was concluded that the release rate of a drug could be optimized in such a system by controlling the degree of swelling/deswelling as a function of pH and/or temperature. Further work by this group [102] examined the permeation of non-ionic and ionic solutes through interpenetrating polymer networks of PVA and PAA. Non-ionic solutes showed permeation results corresponding with the swelling in response to changes in the environment. However, with the permeation of ionic solutes, different trends were observed due to the attraction or repulsion between ionized groups in the gel and ionized electrolytes in solution.

Of additional interest is the incorporation of poly(ethylene glycol) (PEG) onto a poly(vinyl alcohol) hydrogel in order to decrease the adsorption of proteins and deposition of cells. Llanos and Sefton [103] examined the immobilization of PEG onto a PVA hydrogel using acetal or urethane linkages. Two mechanisms were investigated to accomplish this. In the first mechanism, the hydroxyl terminus of PEG was oxidized to an aldehyde. In the second mechanism, PEG was modified with a diisocyanate to produce an isocyanate end

group. Upon completion of either mechanism, the modified PEG was grafted through a reaction with the hydroxyl groups of PVA. These grafted gels were characterized by various spectroscopic techniques. It was suggested that the immobilization was limited by the degree of mixing of PVA and PEG, not by the reactivity of the PEG end groups. Both mechanisms, therefore, were equally satisfactory resulting in a maximum oxyethylene content of between 70 and 75%. The findings were significant in that as the molecular weight of PEG was increased, it was expected to have fewer PEG molecules covalently bound to the surface. Thus, the biological properties of the surface would be adversely affected.

To gain a better understanding of the preparation of blends containing both PVA and PEG, there has been extensive work to further characterize polymer–polymer interactions. Sawatari [104] examined blends of PVA and poly(ethylene oxide) (PEO). In particular, different preparation conditions were investigated including the ratio of PVA to PEO, solvent concentration, and temperature. An increase in the amount of solvent resulted in a decrease in the crystallinity of the resulting films of the PVA/PEO blend. Inamura [105] more accurately described the phase separation of a system containing PVA, PEG, and water. It was found that the PEG molecular weight was a key issue in both phase separation and gelation. Further work by Inamura et al. [106] utilized viscometry to study interactions of the PVA-PEG-water system particularly between PVA and PEG. This work showed that there are repulsive interactions between the polymers and considerable incompatibility.

Recently, Masaro and Zhu [107] studied the diffusion of PEG in PVA solutions using pulsed-gradient NMR spectroscopy. In fact, the self-diffusion coefficients of ethylene glycol, its oligomers, and polymers were determined in aqueous solutions and gels of PVA. A diffusion model was proposed to describe the effect of diffusant size, polymer concentration, and temperature. Continued work in this area is focusing on more accurately predicting the effect of the diffusant shape and molecular interactions.

6
Biomedical and Pharmaceutical Applications of PVA

PVA hydrogels have been used for numerous biomedical and pharmaceutical applications [32]. PVA hydrogels have certain advantages that make them excellent candidates for biomaterials. Some of these advantages include their non-toxic, non-carcinogenic, and bioadhesive characteristics, as well as their associated ease of processing. PVA has an uncomplicated chemical structure and modifications are possible by simple chemical reactions. In addition, PVA gels exhibit a high degree of swelling in water (or biological fluids) and a rubbery and elastic nature. Because of these properties, PVA is capable of simulating natural tissue and can be readily accepted into the body. PVA gels have been used for contact lenses, the lining for artificial hearts, and drug-

delivery applications. In addition, they have been shown to have potential applications for soft tissue replacements, articular cartilage, catheters, artificial skin, artificial pancreas, and hemodialysis membranes. Some specific applications of PVA will be discussed here.

Peppas and Merrill [108, 109] conducted some of the earliest work in considering PVA hydrogels as biomaterials. PVA gels were examined for their use in applications where blood compatibility was a major issue. The physical and surface properties of the gels were examined. In particular, the heparinization of PVA to provide for biocompatibility was examined. In addition, the elastic nature of such PVA gels was investigated and recognized for its importance in various biomedical applications. Based on such observations, PVA hydrogels were investigated for the possible reconstruction of vocal cords [110, 111]. Crosslinked PVA hydrogels have also been considered as candidates for biomembranes in artificial kidney applications [112].

Much research has focused on biocompatibility issues to more accurately ascertain information as to the use of such PVA gels for biomedical or pharmaceutical applications. Tamura et al. [113] examined the use of PVA gels prepared by freezing/thawing processes as a material for medical use. The gel had a water content of 80 to 90% by weight, high mechanical strength, and rubberlike elasticity. The characteristics of the gel, which resembled those of natural tissue, did not change after long-term implantation. In addition, gel samples that were implanted subcutaneously or intramuscularly into rabbits showed good bioinertness. No adhesion to surrounding tissue was found. Although there was some infiltration of inflammatory cells initially, it disappeared during the second week after implantation. They concluded that the material would be useful for clinical applications.

Further biocompatibility issues of PVA were addressed by Fujimoto et al. [114]. This work focused on PVA gels that had been annealed in the presence of glycerol. When such materials were examined for their interactions with blood components, reduced adsorption and platelet adhesion were observed due to the addition of glycerol. Glycerol essentially altered the surface of the PVA gel. They described the mechanism as being due to increased tethered PVA chains on the surface which served to decrease the direct contact of blood components with the surface.

There has been a great deal of work focusing on the use of hydrogel materials for the development of articular cartilage. Oka et al. [115] investigated PVA hydrogels for such applications. They reported on the biocompatibility as well as the mechanical properties of PVA gels in relation to their usefulness as artificial articular cartilage. They examined such aspects as lubrication, load bearing, biocompatibility, and attachment of the material to the bone to look at the overall biomechanics of the material. Problems that were encountered with the use of PVA for such applications included its wear resistance properties. However, continued work has examined the use of higher molecular weight PVA along with a new annealing process to enhance the mechanical properties.

With the continuation of this work by Noguchi et al. [116], the new manufacturing process was found to increase the tensile strength to 17 MPa, which resembles that of normal human articular cartilage. However, it was necessary to investigate the biocompatibility of the improved PVA hydrogel. A series of in vivo tests was performed in an intra-articular environment. It was found that upon implantation of the material into the rabbit knee joint, there was only slight to mild inflammation initially. This new material was found to have excellent biocompatibility and physical properties for use as artificial articular cartilage. They did, however, report some issues that needed to be addressed such as degradation in vivo, the reaction of tissue to wear particles, and methods for shaping the material.

In considering such applications, the mechanical and wear properties of the material of interest are critical. Cha et al. [117] made additional contributions in preparing PVA gels with increased mechanical strength and hardness. The method involved the preparation and characterization of gels of low water content by low temperature crystallization of PVA in a mixed solvent of dimethyl sulfoxide (DMSO) and water.

Further biomedical applications of PVA were examined by Scotchford et al. [118]. In this work, blends of collagen and PVA were cast into films and used as substrates for the culture of osteoblasts. They investigated the ratio of collagen to PVA as well as the crosslinking technique. The crosslinking technique of interest, dehydrothermal treatment, involved two dehydration steps followed by a crosslinking step by annealing. This method was found to be favored over chemical crosslinking (through the use of glutaraldehyde) due to increased biological stability. Overall, this work showed the potential of PVA for orthopedic applications.

PVA gels have also been closely investigated in terms of their diffusive characteristics. The diffusion of macromolecules through crosslinked PVA networks was studied by Sorensen and Peppas [119]. Such an analysis was important particularly when considering such materials for potential drug-delivery applications. Further research by Peppas and collaborators [120, 121] more closely analyzed drug and protein diffusion in such PVA materials. Specifically, the release of a water-soluble drug, theophylline, was investigated from matrices of crosslinked PVA. The effect of the molecular weight between crosslinks, $\overline{M}_c$, on the diffusion of bovine serum albumin (BSA) was also examined as shown in Fig. 10. The diffusion coefficient of BSA was normalized with respect to its diffusion coefficient in pure water at 37 °C. Additional work by Gander et al. [122–124] further demonstrated the appropriateness of crosslinked PVA for various pharmaceutical applications. Kim and Lee [125] also investigated PVA gels for oral drug-delivery applications. They prepared spherical PVA beads by suspension polymerization techniques. The effect of the crosslinking density on the overall swelling and drug-release behavior was examined.

Additional drug-release applications have been investigated which employ the bioadhesive nature of PVA gels. Morimoto et al. [126, 127] examined the
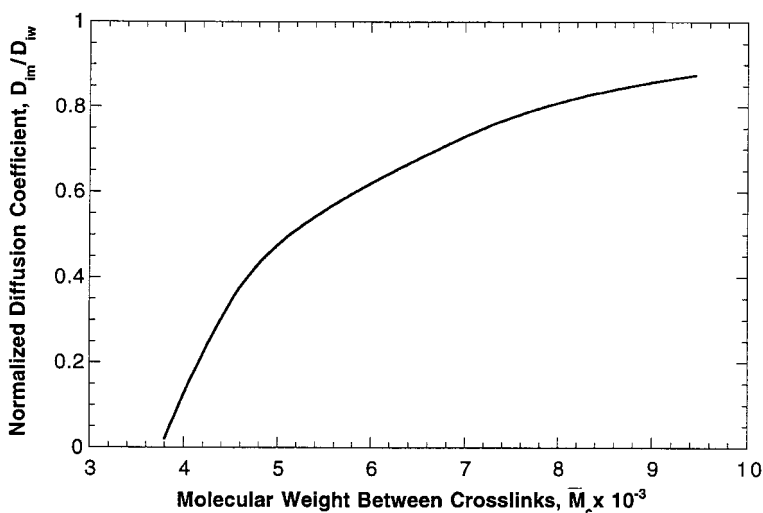
Fig. 10. Normalized diffusion coefficient of bovine serum albumin as a function of molecular weight between crosslinks for PVA hydrogels swollen to equilibrium

controlled release of several drugs from crosslinked PVA gel carriers for rectal administration. Of specific interest was the transrectal delivery of drugs for the treatment of hypertension. Buccal delivery systems of PVA hydrogels were also examined by Tsutsumi et al. [128] for the release of ergotamine tartrate for the treatment of migraine headaches. Recently, there has been considerable work in our own laboratory with the use of freeze/thawed PVA gels for various bioadhesive applications [76–82]. This work will be discussed in more detail in the following section.

PVA gels have shown promise for use as a soft contact lens material. Peppas and Yang [129] investigated the transport of oxygen through crosslinked and pure PVA materials. In particular, the permeation of oxygen was related to the overall polymer structure. Cha et al. [130] performed preliminary studies with transparent PVA gels that were prepared using low temperature crystallization from PVA solutions in a mixed solvent of water and DMSO. Such gels showed the potential for contact lens applications due to a decrease in protein adsorption. Hyon et al. [131] further developed such materials with certain enhanced properties for contact lens applications using low temperature crystallization with a water-miscible organic solvent. Such a technique allowed for the preparation of a transparent gel with high mechanical strength and high water content. This material was further investigated as a soft contact lens material through numerous experiments. It was determined that the gel had five times the tensile strength of poly(2-hydroxyethyl methacrylate), the most widely used soft lens material today. In addition, the adsorption of proteins to the PVA material was half to one thirtieth of the adsorption to conventional lens

materials. Additional studies showed that the corneal epithelium of rabbit eyes was not affected by wearing the lens material.

Kuriaki et al. [132] also examined PVA gels with potential contact lens applications. They reported a process for preparing transparent PVA gels with high tensile strength. PVA solutions of 20 wt % were freeze-dried at –4 °C. Dried PVA gels were then swollen in an ethanol and water solution followed by the exchange of water. The resulting transparent gels had high tensile strength and elongation.

Hirai and collaborators [133–136] have also examined some rather interesting applications of PVA gels involving shape-memory properties. The contraction and relaxation of chemically crosslinked PVA gels in response to the exchange of the solvents, DMSO and water, was examined. The research progressed further with the application of an electric field to actuate a rapid gel response. PVA gels prepared by freezing and thawing techniques were also examined for their shape-restoring properties. In fact, chemical crosslinks were introduced into such freeze/thawed gels to enhance the shape-memory characteristics. It was proposed that the added chemical crosslinks served to "remember" the distribution of physical crosslinks within the gel to restore the shape upon elongation.

PVA gels have also been proposed for waste water cleaning applications. Okazaki et al. [137] investigated the immobilization of microorganisms on PVA gel particles as such a method for waste water treatment and compared it with the use of poly(ethylene glycol) (PEG) and polyacrylamide (PAAm) gels. PVA hydrogel particles were prepared by freezing and thawing techniques. The material was found to have a treating capacity for synthetic sewage of two to three times that of standard activated sludge processes. When compared with PEG and PAAm networks, PVA gels have the presence of voids of several microns which were formed upon freezing. Therefore, the PVA gel had many more desirable characteristics, such as a large free volume of water and good oxygen permeability. This created a favorable environment for microorganisms. An effluent treatment was created with microorganisms immobilized in the frozen PVA gel. This research has shown to be an interesting as well as a promising application of PVA gels.

7
Summary

Poly(vinyl alcohol) has been characterized on many levels and examined for numerous applications. It is a polymer of great interest because of its relatively simple chemical structure, ease of processing, and potential use in pharmaceutical and biomedical fields. The crystalline nature of PVA has been of specific interest. Crystallinity in PVA gels has been introduced by various methods including annealing, aging, low temperature crystallization, and repeated cycles of freezing and thawing. Combinations of the above techniques to enhance certain properties have also been studied. In addition, various solvents

have been introduced during preparation techniques to improve certain properties of PVA gels, specifically with freeze/thawed gels. In particular, preparing transparent gels with high mechanical integrity has been of great interest particularly for contact lens applications. Overall, PVA gels prepared by freezing and thawing methods have shown many improved properties over traditional PVA gels prepared by chemical crosslinking techniques with increased mechanical strength being the most notable.

   PVA hydrogels prepared by freezing and thawing processes have shown incredible potential for applications in medicine and pharmacy. However, the long-term stability of such gels still remains an important issue. In addition, there are numerous parameters that can impact the resulting structure and properties of the prepared gels. Initial insight has been obtained by several researchers over the past 20 to 25 years. However, there is still a need to gain a better understanding of structure-property relationships with specific emphasis on biomedical and pharmaceutical applications.

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