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Ultrapure poly(vinyl alcohol) hydrogels with mucoadhesive drug delivery characteristics

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Abstract

Poly(vinyl alcohol) (PVA) hydrogels were prepared by treating 15 or 20% aqueous PVA solutions to repeated cycles of freezing for 6 or 12 h at −20°C and thawing for 2 h at 25°C. The resulting gels did not contain any leachable toxic crosslinking agents or other residues. Their adhesive characteristics were examined using tensile experiments in contact with bovine submaxillary mucin. As the number of freezing/thawing cycles increased, the work of fracture (detachment) decreased due to the increase in the PVA degree of crystallinity. The PVA gels prepared from the 20 wt.% solution and exposed to two freezing/thawing cycles exhibited the largest work of adhesion. Surface contact angle measurements of the PVA gel in contact with water were used to evaluate their wettability. As the number of freezing/thawing cycles was increased and the degree of crystallinity increased, there was a decrease in the contact angle. The degree of crystallinity of PVA gels was determined by comparing the heat required to melt a PVA sample to the heat required to melt a 100% crystalline sample. The average degree of crystallinity of PVA samples prepared from 20 wt.% solutions was 19.3% on a dry basis. Oxprenolol and theophylline delivery studies were conducted using PVA samples prepared from a 20 wt.% solution and exposed to two, three or four cycles of freezing for 12 h followed by thawing for 2 h. Drug release was affected by the number of freezing/thawing cycles. Thus, the mucoadhesive characteristics and drug release could be optimized by controlling the freezing/thawing conditions.

Keywords: Controlled release; Freezing/thawing processes; Hydrogels; Mucoadhesion; Poly(vinyl alcohol)

1. Introduction

Bioadhesive polymers play an important role in biomedical and drug delivery applications. Good adhesion and intimate contact between a polymer carrier and a tissue are desirable for use in these applications. It is therefore necessary to understand the mechanisms of adhesion and study the surface characteristics of the polymers in order to develop bioadhesive systems that can be used for drug delivery devices.

Bioadhesive polymers are used for many hard and soft tissue applications [1,2]. Bioadhesive and mucoadhesive systems can be used also as carriers for drug delivery. Mucoadhesion is defined as the attachment of synthetic or natural polymers to the mucosa [2]. Mucoadhesive systems are advantageous over conventional drug delivery systems due to their ability to increase the contact time of the drug with the biological substrate, thus increasing drug absorption. Mucoadhesive systems can also adhere to specific sites of the body leading to greater bioavailability [3–5]. Currently, buccal, nasal, ocular, and vaginal mucoadhesive systems are available as release systems [2,6,7].

Bioadhesive systems require that the polymer exhibit strong interactions with the biological substrate. The polymer should also be biocompatible and should not alter the tissue structure [2]. Thus, an ideal bioadhesive polymer should be non-toxic and non-carcinogenic, and have good biocompatibility. In general, the drug may be contained within the polymer network structure of the gel and may be released out of the gel over time. As

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the gel network swells, the linear distance between junctions (crosslinks) increases, allowing the drug to diffuse out of the gel. Adhesion is caused by a combination of several mechanisms [2]. Adhesion between the polymer and the biological substrate may be due to interdiffusion of polymer chains across the interface. Diffusion occurs due to chain concentration gradients across the interface of the two substances. This requires that the polymer chain ends and substrate molecules be significantly mobile, and that the two substances be mutually compatible [2,7]. This interdiffusion may ultimately lead to entanglements and physical bonds between the polymer and the substrate. The level of penetration of the polymer chain ends into the substrate is a function of the polymer degree of crosslinking and the contact time between the two substances [2].

2. Poly(vinyl alcohol) as a bioadhesive biomaterial

Poly(vinyl alcohol), henceforth designated as PVA, has a number of desirable characteristics that make it a good bioadhesive polymer. It has mechanical strength and high elasticity and swells upon immersion in water. PVA gels crosslinked with glutaraldhyde [8], glyoxal or borate have been proposed as drug delivery carriers. In these gels, the drug is able to be released fast or slowly due to the gel's high or low swelling ratio upon immersion in water. Previous studies by Morimoto et al. [9] have shown that several drugs such as indomethacin, glucose, insulin, heparin, and albumin can be released from crosslinked PVA gels.

PVA properties depend upon the degrees of polymerization and hydrolysis. The solubility of PVA in water increases greatly as its degree of hydrolysis increases [10]. Properties such as water solubility, high tensile strength, and tack make PVA useful as an adhesive with fully hydrolyzed grades of PVA being water-resistant adhesives [11].

To avoid chemical crosslinking of PVA with the ensuing toxicity and leaching problems, a method of PVA solidification has been developed by freezing and thawing of aqueous PVA solutions, thus resulting in an ultrapure three dimensional network held together by crystallites acting as physical crosslinks. The freezing/thawing method involves casting aqueous PVA solutions in molds, freezing them for 6–48 h at −20°C and then allowing them to thaw at 25°C for 2–6 h. This process may be repeated for up to five cycles. These PVA gels are stable at room temperature and retain their original shape. They are highly elastic and can be extended five or six times their initial size [12]. Gels formed by the freezing/thawing method are thermoreversible, dissolving in water at temperatures >50°C [12,13]. The freezing/thawing method produces gels that are held together by crystallites. As the frozen PVA solution is allowed to thaw to 25°C and refreeze, additional crystallites are formed [12–16].

The preparation of ultrapure PVA hydrogels using the freezing/thawing method was first reported by Peppas [17] in 1975. His studies characterized the crystallites in the PVA gel using measurements of the change in turbidity of PVA solutions as they were subjected to cycles of freezing/thawing. It was shown that crystallite formation was a function of freezing time, thawing time, and PVA solution concentration. As the time of freezing increased, the crystallinity increased. During thawing, the size of the crystalline structures initially increased and then decreased probably due to the breakdown of the crystallite structures. It was also shown that increasing PVA solution concentration increased the crystallite concentration. Urushizaki et al. [15] studied the dependence of the properties of the PVA gels upon the number of freezing/thawing cycles. They found that the gels became harder and more rigid as the number of cycles increased. Work has also been completed by Stauffer and Peppas [12,16] and Peppas and Scott [13] to characterize the gel properties as a function of number of freezing/thawing cycles, freezing time, PVA solution concentration, and molecular weight of PVA used. The freezing temperature also affects the properties of the gels. Gels produced by freezing at 0°C could not hold their own weights after four cycles, whereas those produced at −20°C were stable after two cycles.

Limited studies on the use of these PVA gels as controlled release systems have been reported. Peppas and Scott [13] conducted release studies on PVA gels with bovine serum albumin (BSA) incorporated before freezing and thawing. Release studies with gels produced from five cycles of a 15 wt.% solution frozen for 18 h and thawed for 6 h indicated that BSA release was controlled by a pure diffusional mechanism. Ficek and Peppas [14] studied the release of BSA from PVA microparticles prepared by dispersing an aqueous solution consisting of a 15 wt.% PVA solution to which 1.25 wt.% sodium lauryl sulfate was added in a corn oil phase. The resulting droplets of PVA underwent two cycles of freezing and thawing. The BSA was incorporated into the particles and then the freezing/thawing process was repeated.

There have also been two studies indicating that such PVA gels can exhibit bioadhesive and mucoadhesive behavior [18,19]. Of these studies, the one by Tsutsumi et al. [19] reported novel buccal delivery systems for ergotamine tartrate.

Based on analysis of previous research, it is obvious that although PVA gels produced by the freezing/thawing method have been used in conventional drug delivery, there has been relatively little reported on their use as bioadhesive/mucoadhesive carriers for drug delivery.

Therefore, the overall objective of this research was to develop mucoadhesive, drug releasing PVA hydrogels by the freezing/thawing method. More specific goals of the project were: (i) to develop a reproducible method of producing PVA hydrogels using the freezing/thawing method; (ii) to evaluate the crystallinity and surface characteristics of the PVA hydrogels produced; (iii) to develop a method to characterize the adhesive characteristics of the PVA hydrogels; and (iv) to study time dependent release of two drugs, theophylline and oxprenolol.

3. Experimental part

3.1. Hydrogel preparation

Aqueous solutions of 15 and 20 wt.% PVA were prepared by dissolving PVA (Elvanol 85–82, E.I. duPont de Nemours, Wilmington, DE, $\overline{M}_n = 48\,000$, $\overline{M}_w = 103\,000$, polydispersity index = 2.1, degree of hydrolysis 99.0%) in deionized water for 6 h at 90°C. To produce ultrapure PVA hydrogel samples, these solutions were cast into flat molds and exposed to 2–5 cycles consisting of freezing for 6 or 12 h at −20°C followed by thawing at 25°C for 2 h.

3.2. Adhesive behavior

Adhesive studies of the ensuing PVA samples in the form of films to various substrates were performed in a saturated air environment (relative humidity 98%) using a tensile apparatus (Instron model 4301, Instron, Canton, MA) with a 10 N load cell. Metal discs were attached to the clamps of the apparatus and used as sites for adhesive testing. PVA films wee cut as discs with diameters of 19 mm and an average thickness of 2.1 mm were used for the adhesive testing. Each PVA disc tested was glued to the top metal disc using cyanoacrylate medical grade adhesive (Pacer Technology, Cucamonga, CA) whereas a substrate was attached to the bottom metal disk. Four materials were used as substrates for the adhesive testing: metal, polyethylene, a chemically crosslinked PVA sample with a well-characterized surface, and a mucin gel prepared from a 5 wt.% aqueous solution of bovine submaxillary mucin (Sigma, St. Louis, MO).

The two surfaces of the PVA sample and the substrate were brought together and kept in contact for 5 min. They were then pulled apart at a crosshead speed of 1 cm/min until the point of detachment, and the force was measured as a function of length. The area under the curve of force vs. length (see Fig. 1) was integrated to determine the work of fracture of the adhesive bond.

3.3. Surface contact angle measurements

Surface contact angles of the PVA disc in contact with deionized water were measured using a contact angle goniometer (model 100–00, Rame-Hart, Mountain Lakes, NJ). A 0.1 ml drop of water was placed on the PVA sample with an autopipette. Contact angle measurements were taken every min until the angle remained constant.

3.4. Differential scanning calorimetry

A differential scanning calorimeter (model DSC 2910, duPont de Nemours, Wilmington, DE) was used to determine the degree of crystallinity of the PVA gels. Approximately 65 mg of the ultrapure PVA gels prepared from a 15 wt.% solution were dried in ethanol for 2 h and then vacuum dried for 24 h to remove all the water. We have shown that this method did not produce additional crystallinity in the samples. The dried sample (16.5 mg) was heated in the DSC equipment from 35 to 220°C at a scanning rate of 2°C/min. The heat required to melt the sample was calculated by integrating the peak due to melting. The degree of crystallinity on a dry basis was calculated by comparing the heat required to melt the sample to the heat required to melt [20] a 100% crystalline PVA sample (138.6 J/g).

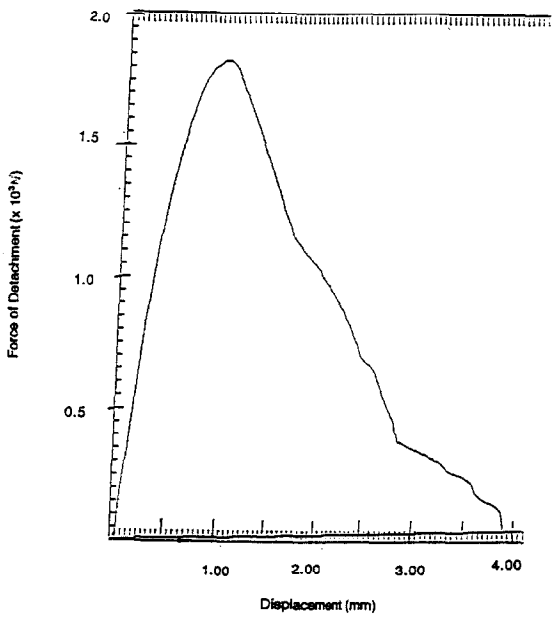

Fig. 1. Force of detachment as a function of displacement for an adhesive study of a PVA gel in contact with mucin using the tensile method.

3.5. Drug delivery studies

Theophylline and oxprenolol hydrochloride solutions (Aldrich Chemical, Milwaukee, WI) were prepared by dissolving 10 mg of the drugs in 20 ml of deionized water. PVA discs prepared from a 20 wt.% solution with a diameter of 19 mm and thickness of 2.2 mm were placed in the 0.5 mg/ml solutions for 24 h to incorporate the drugs into the PVA discs. The samples were then allowed to dry for 48 h. Alternatively, the same drug solutions were added to the PVA solutions described in Section 3.1 and the freezing/thawing process was repeated for direct incorporation of the drug in the gels.

A dissolution apparatus with constant mixing was used as the testing environment for drug release. Each PVA disc was placed in 200 ml of deionized water at 37°C with constant stirring at 102 rpm. Samples of 3 ml were taken every 5 or 10 min and analyzed using a UV/VIS spectrophotometer (model 559, Perkin Elmer, Oak Brook, IL) to determine the drug concentration. The mass of drug released at time t, M_t, was calculated and the mass of drug released at long times, M_∞, was measured after 24 h of drug release. This value was found to be equal to the amount of drug incorporated at the beginning, M_0. Then, the term, M_t/M_∞ was plotted vs. time to study the drug release kinetics from PVA discs.

4. Results and discussion

4.1. Analysis of adhesive behavior

Samples prepared from 15 and 20 wt.% aqueous PVA solutions that were exposed to two, three, or four cycles of freezing for 6 or 12 h and thawing for 2 h were used to evaluate the adhesive characteristics of PVA gels produced by the freezing/thawing technique. The force vs. elongation or displacement behavior was measured for all of the samples prepared. A typical profile of a force vs. displacement curve is shown in Fig. 1. Adhesion throughout the contact surface was achieved only for a short period of time, as indicated by the shape of the curve. Integration of the force vs. displacement curves was used to determine the work of fracture of the adhesive bond [21]. For purely elastic gels, this work of fracture is approximately equal to the work of adhesion [2].

Four substrates were studied for the adhesive testing: metal, polyethylene, a chemically crosslinked PVA film and a mucin gel. When the metal was used as the substrate, the average value of work of fracture of the PVA/metal adhesive bond was relatively low and had a very large statistical error. This was due to the low wetting of the metal by the PVA gel. Polyethylene was also studied as a possible substrate for the adhesive testing, but low values of the work of fracture were determined. This was due to the hydrophilic/hydrophobic nature of the interface and the lack of chain interdiffusion between PVA and polyethylene.

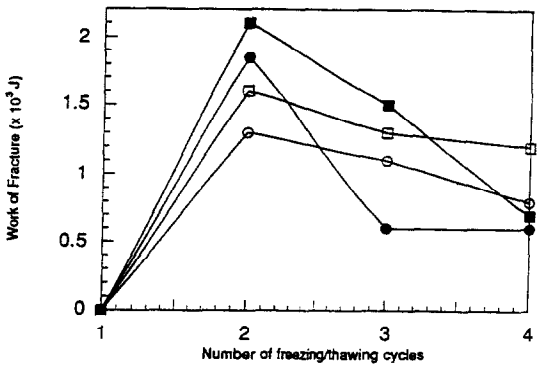

Fig. 2. Work of fracture as a function of number of freezing/thawing cycles for PVA samples exposed to freezing followed by thawing for 2 h. Sample with 15 wt.% PVA, 6 h freezing (○); 15 wt.% PVA, 12 h freezing (□); 20 wt.% PVA, 6 h freezing (●); 20 wt.% PVA, 12 h freezing (■).

Fig. 2 shows results of the work of fracture (adhesion) as a function of the number of freezing/thawing cycles for studies in contact with mucin gel. Gels studied included those produced from 15 and 20 wt.% PVA solutions. In general, the denser solutions led to more mucoadhesive gels. The work of fracture decreased with increasing number of freezing/thawing cycles. This observation agrees with that of Tsutsumi et al. [19] and is attributed to loss of adhesive linear PVA chains as crystallization occurs due to the slow incorporation of all the linear PVA chains in the crystalline structure formed upon repeated cycles. Thus, a gel produced after two cycles contains relatively mobile, non-crystalline chains which exhibit strong adhesive behavior either because of hydrogen bonding due to their hydroxyl groups [19] or because of significant chain interpenetration or because of both. Contrary to this, after four cycles very few linear PVA chains are available for this interaction with mucin. It must be noted that the figure indicates that samples produced after one freezing/thawing cycle were not solid enough to be able to be tested with this system, rendering them useless.

The relationship between freezing time and the adhesive characteristics of the prepared PVA gels was also studied. An increase in the freezing time slightly increased the value of fracture of the adhesive bond due to the higher cohesive energy of the systems and the higher strength of the gels due to the increased degree of crystallinity in the samples frozen for longer times. Desirable gels for bioadhesive systems would be those that exhibited high values of the work of adhesion and high mechanical strength. Based on our studies, the PVA gels prepared from a 20 wt.% solution that were

exposed to two cycles of freezing/thawing could be considered the best samples for mucoadhesive applications.

4.2. Surface contact angle measurements

Samples of PVA gels prepared from 15 or 20 wt.% aqueous PVA solution that were exposed to two, three, or four cycles of freezing for 6 h followed by thawing for 2 h were used for surface contact angle measurements to evaluate their wettability of the PVA samples. Good wetting of the substrate by the gel is an important factor influencing the adhesive characteristics [7]. A 0.1 ml drop of water was placed on the PVA sample and contact angles were measured every min using a goniometer until the value of the contact angle remained constant.

The results of the surface contact angle experiments are shown in Fig. 3. For all samples tested, the contact angle decreased as time increased, becoming constant after 10–11 min. The results also show that there was a decrease in the contact angle with increasing number of cycles of freezing/thawing. As shown in previous studies, as the number of freezing/thawing cycles increases, there is an increase in strength and a decrease in swelling of the PVA gels due to an increase in crystallinity [13,16]. Therefore, increasing the crystallinity of the PVA gel decreased the contact angle and increased the wettability.

This trend can be explained by considering the unique properties of PVA. Aqueous PVA solutions are known to form a stable monomolecular film at the air-water interface (Biegajski J, pers. commun., 1995). At this interface, the hydroxyl groups are directed towards the aqueous phase, whereas the non-polar backbone chains are directed towards the air phase. This configuration lowers the surface energy at the

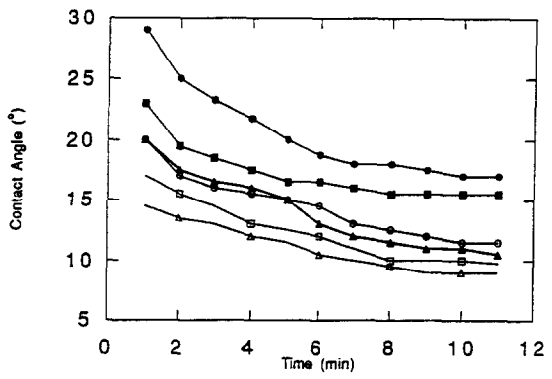

Fig. 3. Contact angles of PVA samples in contact with water as a function of time. PVA samples were exposed to cycles of 6 h of freezing followed by 2 h of thawing. Sample with 15 wt.% PVA, 4 cycles (△); 20 wt.% PVA, 4 cycles (□); 15 wt.% PVA, 3 cycles (○); 20 wt.% PVA, 3 cycles (▲); 15 wt.% PVA, 2 cycles (■); 20 wt.%, 2 cycles.

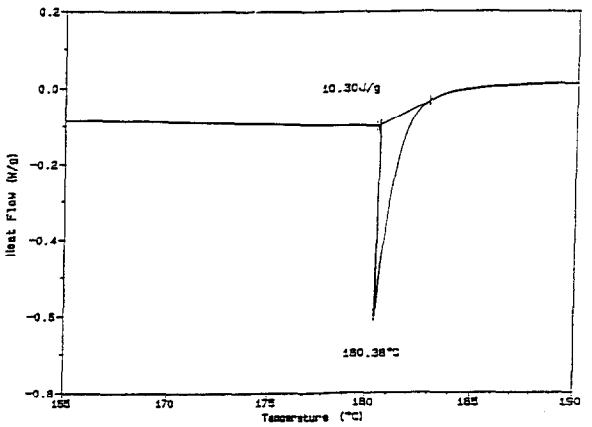

Fig. 4. Differential scanning thermogram of a PVA sample produced by the freezing/thawing process.

interface, decreasing the hydrophilicity and increasing the contact angle. When PVA undergoes cyclic freezing and thawing and the degree of crystallinity increases, the monolayer may become less ordered. This would then create a more hydrophilic interface, therefore decreasing the contact angle. Based on this explanation, the contact angles would be the highest for the samples that were prepared by exposing the PVA solutions to the smallest number of cycles.

4.3. Differential scanning calorimetry

Differential scanning calorimetry was used to monitor the net energy flow to or from a sample as it is being heated. An endothermic peak resulted at the melting temperature of the sample. The heat required to melt the sample was calculated by integration of this peak. The degree of crystallinity of the PVA gel was computed by comparison of the heat required to melt the PVA sample to the heat required to melt a 100% crystalline PVA sample. A typical DSC profile is shown in Fig. 4 for a sample that was exposed to three cycles of freezing for 6 h followed by thawing for 2 h. The temperature of the onset of melting of this PVA sample occurred at 180.4°C. The average degree of crystallinity of PVA samples prepared was $19.3 \pm 4.2\%$. This crystallinity was large enough to provide mechanical stability to the samples. A detailed analysis of the change of degree of crystallinity with processing conditions has been reported by Hickey and Peppas [22].

4.4. Drug delivery studies

Samples of PVA prepared from a 20 wt.% solution that were exposed to two, three or four cycles of freezing for 12 h followed by thawing for 2 h were used to study the release kinetics of theophylline and oxprenolol hydrochloride from PVA discs placed in deionized water at 37°C. The mass of the drug released

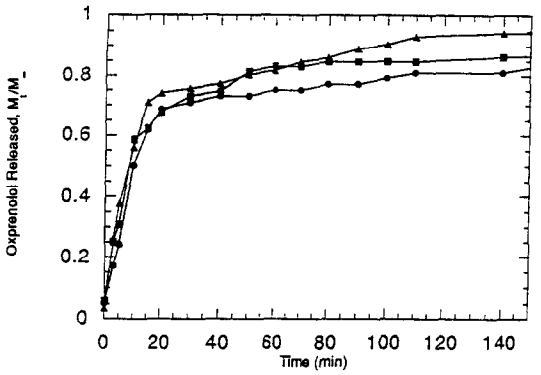

Fig. 5. Oxprenolol fractional release from PVA gels prepared from a 20 wt.% solution exposed to two (▲), three (■) and four (●) cycles of freezing for 12 h followed by thawing for 2 h. The drug was incorporated before the freezing/thawing cycle.

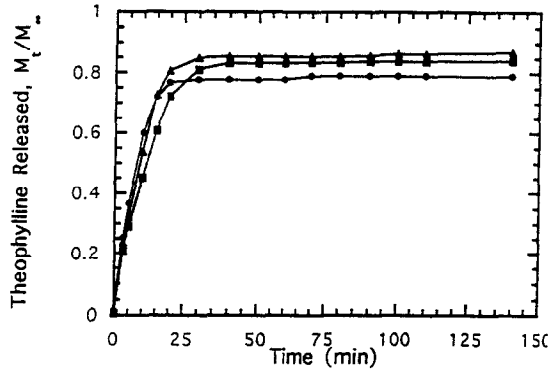

Fig. 7. Theophylline fractional release from PVA gels prepared from a 20 wt.% solution exposed to two (▲), three (■) and four (●) cycles of freezing for 12 h followed by thawing for 2 h. The drug was incorporated before the freezing/thawing cycle.

over time was monitored by measuring the drug solution concentration using UV spectrophotometry.

Fig. 5 presents the data of oxprenolol release from PVA gels exposed to two, three or four cycles of freezing and thawing. The drug was loaded in the solution before the cyclical process at a level of five wt.% with respect to the drug PVA content. Very good reproducibility was attained in the drug release profile. About 80% of oxprenolol was release during the first 80 min. It must be recalled that 100% release was achieved at 24 h. Repeated freezing/thawing cycles led to a denser crystalline structure as discussed by Hickey and Peppas [22], thus leading to a reduction in the amount of drug release. Indeed, as Fig. 5 indicates the slopes of the release curves decreased significantly as the number of freezing/thawing cycles increased. Fig. 6 shows that the release rate was influenced by the freezing/thawing cycles (or by the associated degree of crystallinity). However, the effect was not significant and the overall normalized release rate varied from 0.015 to 0.04 min^{-1}.

The theophylline release behavior is shown in Figs. 7 and 8. Again, as the number of freezing/thawing cycles increased, the fractional release and release rate decreased. Previous analysis of theophylline release through PVA membranes prepared by the same procedure [22] showed that as the cycles increased, the degree of crystallinity increased. As shown by Hickey and Peppas [22] an increase of crystallinity by 2–4% led to a reduction of the theophylline diffusion coefficient.

The mode of drug incorporation made a significant difference in the release behavior. In general, theophylline released much faster if it had been loaded to these gels by equilibrium partitioning after their preparation as shown in Fig. 9, rather than during the PVA solution preparation. Clearly, almost all the drug can permeate through the amorphous portion of the PVA gel. Finally, Fig. 10 shows results of theophylline release from equilibrium partitioning loaded samples. Clearly, drug release is much faster during this release process than in samples that were loaded during the preparation of the solution.

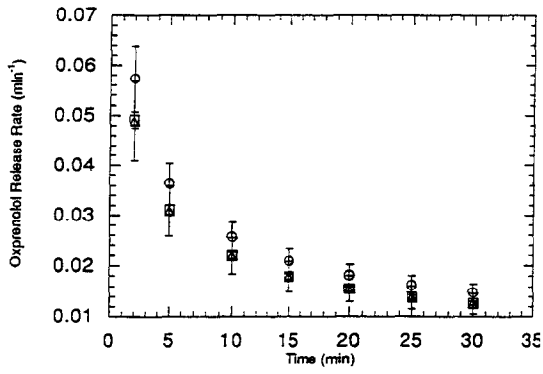

Fig. 6. Oxprenolol release rate as a function of time for PVA samples loaded with drug, prepared from a 20 wt.% solution and exposed to two (○), three (△) and four (□) cycles of freezing for 12 h followed by thawing for 2 h.

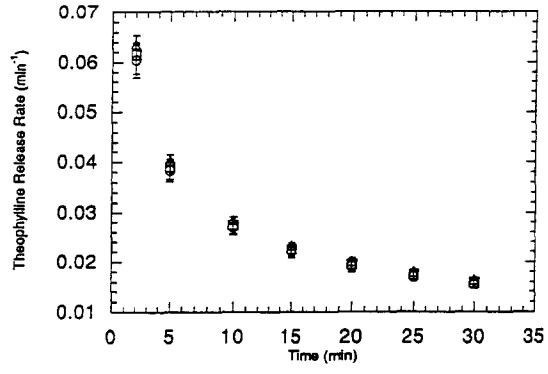

Fig. 8. Theophylline release rate as a function of time for PVA samples loaded with drug, prepared from a 20 wt.% solution and exposed to two (○), three (□) and four (△) cycles of freezing for 12 h followed by thawing for 2 h.

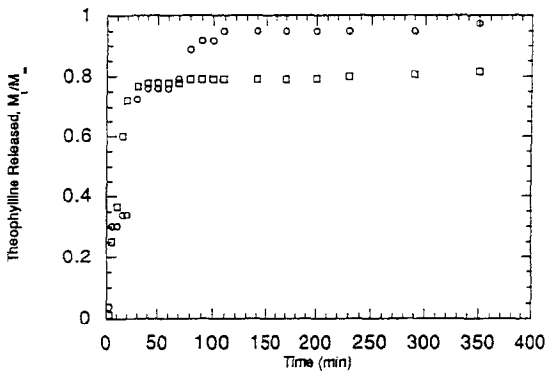

Fig. 9. Theophylline fractional release from PVA gels prepared from a 20 wt.% solution and exposed to two cycles of freezing for 12 h followed by 2 h of thawing. The drug was incorporated before the freezing/thawing cycle (□) or by imbibition (equilibrium partitioning) from a concentrated drug solution (○).

These studies indicate that the crystalline structure formed during the freezing/thawing process acted as a barrier for drug release, although the rate decrease observed was not as drastic as one would expect. Clearly, the drugs studied were much smaller than the mesh size of the semicrystalline networks formed [22]. However, from a controlled release applications point of view, the overall mucoadhesive behavior was retained during release. Thus, these systems can be excellent candidates for buccal applications.

5. Conclusions

In conclusion, mucoadhesive PVA controlled release systems can be produced by a freezing/thawing process of aqueous PVA solutions containing theophylline or oxprenolol hydrochloride. Although maximum adhesion was achieved after two cycles, samples prepared after three or four cycles still exhibited adhesive characteristics. The mucoadhesive and drug release behavior could be adjusted by degree of crystallinity which was affected by the number of cycles and the time of freezing of the solutions.

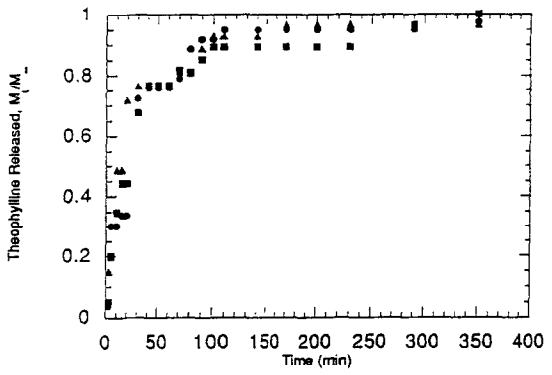

Fig. 10. Theophylline fractional release from PVA gels prepared from a 20 wt.% solution exposed to two (▲), three (■) and four (●) cycles of freezing for 12 h followed by thawing for 2 h. The drug was incorporated by equilibrium partitioning.

Acknowledgements

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