Preparation of Chemically Crosslinked Gels with Maleate-Denatured Poly(vinyl alcohol) and Its Application to Drug Release

SATOSHI HORIIKE, SHUJI MATSUZAWA, KAZUO YAMAURA

Faculty of Textile Science & Technology, Shinshu University, Tokida 3-15-1, Ueda City, Nagano Prefecture 386-8567, Japan

Received 2 January 2001; accepted 19 May 2001

ABSTRACT: Maleate-denatured poly(vinyl alcohol) (M-PVA) was crosslinked with heating. The mechanism of crosslinking was studied with several procedures: titration, Fourier transform infrared, and solubility. The carboxyl groups of M-PVA consisted of carboxylates and a few free carboxyl groups. The crosslink was the ester linkage between hydroxyl and carboxyl groups. Several kinds of M-PVA tablets were prepared under different conditions: pressures of 200–600 kgf/cm^2 and grain sizes of 75 (pass) to 250 μm (on). The swelling behavior of these chemically crosslinked tablets was studied in a buffer solution of pH 7.4, mainly at 37°C. Moreover, the effect of temperature from 5 to 50°C and the effect of repeated swell–dry cycles on the behavior of the tablets in a buffer solution [106 μm (on), 200 kgf/cm^2] were studied. The release of *p*-acetamidophenol from those tablets in the pH 7.4 buffer solution was studied. The different release patterns were due to the differences in the swelling behavior. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 84: 1178–1184, 2002; DOI 10.1002/app.10411

Key words: maleate-denatured poly(vinyl alcohol); gels; crosslinking; swelling; release

INTRODUCTION

Poly(vinyl alcohol) (PVA) has been used in a wide variety of fields since its discovery in 1924.[1,2] It is not unusual for PVA to be used in medical applications such as artificial blood vessels, artificial intestines, contact lenses, and drug-delivery systems.[3–5] In such applications, the adverse effects to humans are important, and the biodegradability and safety of PVA in relation to human use have been examined.[6,7] Recently, many kinds of PVA and PVA derivatives have been presented. Maleate-denatured poly(vinyl alcohol) (M-PVA) crosslinked with heating is expected to useful as a high water absorption material. Several studies on drug release with PVA hydrogels have been carried out.[8–10] In this study, the characterization of a gel prepared with chemical crosslinking with M-PVA and drug release with the gel were studied.

EXPERIMENTAL

Materials

The properties of M-PVA are shown in Table I. It was supplied by Unitika Chemical Co., Ltd. A phosphate buffer solution was prepared from a phosphate buffer powder (Na_2HPO_4/KH_2PO_4).

Correspondence to: K. Yamaura (yamaura@ke.shinshu-u.ac.jp).

Contract grant sponsor: Ministry of Education, Science, Sports and Culture of Japan; contract grant number: 10CE2003.

Journal of Applied Polymer Science, Vol. 84, 1178–1184 (2002)

Table I Properties of Sample Used

Sample	DP	DS
M-PVA	1580	88.85

DP = degree of polymerization; DS = degree of saponification (mol %).

The phosphate buffer powder and *p*-acetamidophenol were purchased from Wako Pure Industries (Osaka, Japan).

Potentiometric Titration of M-PVA

The titration curves of M-PVA were taken for the estimation of the content of COONa and COOH groups with an oxidation-reduction potential meter (TOKO pH/ORP meter TP-93, Tokyo, Japan).[11,12] M-PVA (1 g) was dissolved with 20 mL of water. Then, 10 mL of 0.1 mol/L hydrochloric acid was added. The solution was titrated with 0.1 mol/L sodium hydroxide.

Titration of M-PVA

The direct titration of M-PVA was performed for the estimation of the content of free carboxyl groups. M-PVA (1 g) was dissolved in 20 mL of water. The solution was titrated with a 0.1 mol/L sodium hydroxide solution with phenolphthalein as an indicator.

Preparation of the Tablets as Chemically Crosslinked M-PVA Gels

The PVA gels were prepared with M-PVA as follows. First, the M-PVA masses were broken up with a mill, and uniform grain sizes were isolated with standard sieves. About 200 mg of M-PVA powder of uniform grain size was placed into a mold and pressed at a constant pressure. After forming, M-PVA tablets were heated in an oven at 150°C for 70 min. In this way, the chemically crosslinked M-PVA gel tablets were prepared.

Infrared Analysis of M-PVA

The infrared spectra of M-PVA films were taken, so that we could observe the differences between chemically crosslinked M-PVA and noncrosslinked M-PVA, with a Fourier transform infrared (FTIR) spectrophotometer (Jasco FTIR 7000, Tokyo, Japan).

Swelling Behavior of the Chemically Crosslinked M-PVA Gel Tablets

The swelling behavior was studied of the chemically crosslinked M-PVA gel tablets (106 μm, 200 kgf/cm^2) at different temperatures. After the tablets were weighed, they were placed in tubes containing a predetermined quantity of a pH 7.4 phosphate buffer solution. The tubes were immersed in a constant-temperature bath (5–50°C) for 24 h, and the swollen tablets were weighed. The swelling ratios of these tablets at a certain temperature were then determined. The recovered ratios (R_{ratio}) were determined with the formula $R_{ratio} = W_{dry}/W_{initial} \times 100$ (where W_{dry} is the weight after drying and $W_{initial}$ is the weight before swelling). For the study of the effect of repeated swell–dry cycles, the tablets were weighed and placed into tubes with a predetermined quantity of a pH 7.4 phosphate buffer solution, and the tubes were kept at 37°C for 6 h. After the tablets were taken out and weighed, the tablets were dried at 70°C for 12 h. The tablets were then placed into the tubes again. In this way, the effect of repeated swell–dry cycles on swelling was studied by repetition of this operation. For the study of the effect of M-PVA grain size, first M-PVA powder [75 (pass) to 250 μm (on)] made uniform in grain size with a standard sieve was weighed and pressed. The M-PVA tablets were kept at 150°C for 70 min and crosslinked. They were placed into tubes with a predetermined quantity of a pH7.4 phosphate buffer solution. The tubes were kept at 37°C for 6 h. After the tablets were taken out and weighed, the tablets were kept at 70°C for 12 h. For the study of the effect of the forming pressure, M-PVA powder [106 μm (on)] was weighed and pressed at different pressures (200, 400, and 600 kgf/cm^2). The M-PVA tablets were kept at 150°C for 70 min for crosslinking. The tablets were placed into tubes with a predetermined quantity of a pH 7.4 phosphate buffer solution. The tubes were kept at 37°C for 6 h. After this, the tablets were taken out and weighed. They were dried at 70°C for 12 h.

Preparation of the Tablets Containing *p*-Acetamidophenol for Release

About 200 mg of a uniform powder (3/1 M-PVA/*p*-acetamidophenol) was pressed at a definite pressure for the preparation of tablets. The tablets were kept at 150°C for 70 min the preparation of chemically crosslinked M-PVA tablets. Such tablets without heating were also prepared for comparison. Preparation conditions for the tablets that are not mentioned include the M-PVA grain size (106 μm) and the pressure (200 kgf/cm^2).

Verification Study on the Stability of *p*-Acetamidophenol after Heat Treatment

Purity and identification tests were performed for confirmation of the stability of *p*-acetamidophenol with and without heat treatment at 150°C for 70 min with high-performance liquid chromatography (HPLC; Hitachi HPLC L-7000, Tokyo, Japan) and an FTIR spectrophotometer (Jasco FTIR 7000). HPLC conditions conformed to Japanese pharmacopoeia.

Working Curve of *p*-Acetamidophenol in a Buffer Solution

The working curve for *p*-acetamidophenol in a phosphate buffer solution was made by the measurement of the absorbance at 240 nm with an ultraviolet–visible spectrophotometer (Shimadzu UV-160, Kyoto, Japan).

Release of *p*-Acetamidophenol from the M-PVA Tablets

An M-PVA tablet containing *p*-acetamidophenol was placed in a cubic wire net. The cube was hung in a predetermined position in a bottle with a phosphate buffer solution (400 mL). The bottle was placed in a water bath with a thermostat. The solution was stirred at 50 rpm so that the concentration of the buffer solution remained homogeneous. Three milliliters of the buffer solution was removed at a predetermined time after the dipping of the gel ($t = 0$). The concentration of *p*-acetamidophenol was determined with the working curves by measurement of the absorption of the removed solution.

RESULTS AND DISCUSSION

M-PVA

Figure 1 shows the potentiometric titration curves of M-PVA. In this case, 10 mL of 0.1 mol/L sodium hydroxide was required for neutralization. About 4 mL was estimated to be required for neutralization of free carboxyl groups produced from carboxylates by the addition of hydrochloric acid because the content of maleic acid monomethylester was 2 mol %; therefore, 6 mL was due to excess hydrochloric acid. Most of the carboxyl groups existed as salts (maybe sodium salt). This became clear from the neutralization titration described later; 0.1 mL of a 0.1 mol/L sodium hydroxide solution was required for neutralization.

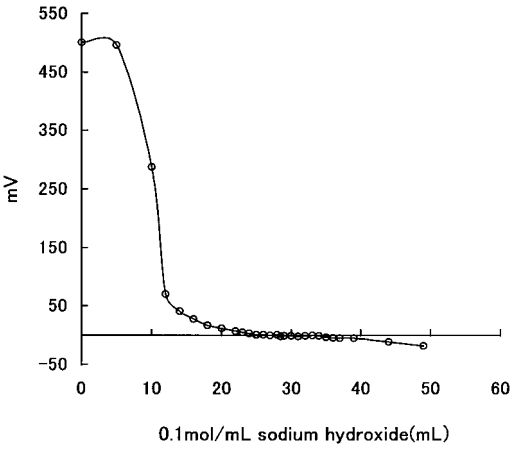

Figure 1 Potentiometric titration curves of M-PVA.

This shows that 1×10^{-5} mol of free carboxyl groups existed in 1 g of M-PVA. Approximately one carboxyl group was estimated to exist per 2000 units in M-PVA. This value corresponded to one free carboxyl group in a polymer molecule.

Crosslinking of M-PVA

No differences in the infrared spectra were observed between chemically crosslinked and noncrosslinked M-PVA films. A 1 mol/L sodium hydroxide solution was added to the chemically crosslinked film. The crosslinked film was dissolved into a 1 mol/L sodium hydroxide solution. This indicates that the crosslink was due to the esterification between hydroxyl and carboxyl groups and suggests that few free carboxyl groups existed as estimated previously.

Stability of *p*-Acetamidophenol after Heat Treatment

Purities of *p*-acetamidophenol with and without heat treatment at 150°C for 70 min by HPLC were over 99.9%, and no new impurities as a result of degradation were observed. Furthermore, no differences in these infrared spectra were observed. Therefore, *p*-acetamidophenol was unchanged after heat treatment.

Effect of Temperature on Swelling Behavior

Figure 2 shows the effect of temperature on the swelling behavior of the crosslinked M-PVA tablets [106 μm (on), 200 kgf/cm^2]. From 5 to 20°C, the swelling ratios were approximately constant. From 20 to 40°C, the swelling ratio became large with increasing temperature, and at about 40°C, it showed a maximum. Then, the swelling ratio

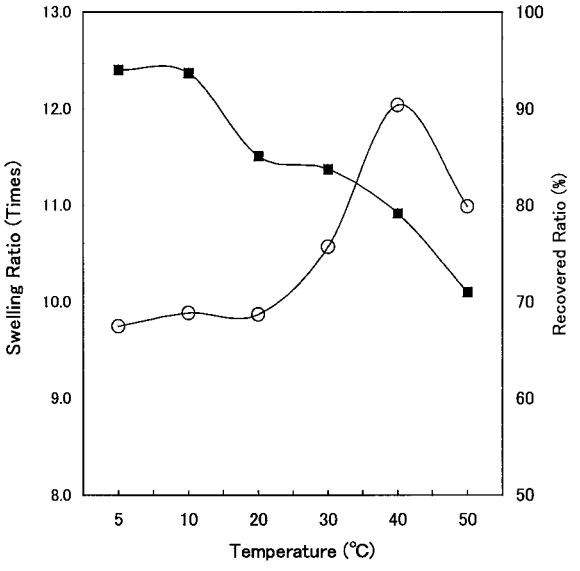

Figure 2 Effect of temperature on swelling behavior: (○) swelling ratios and (■) recovered ratios.

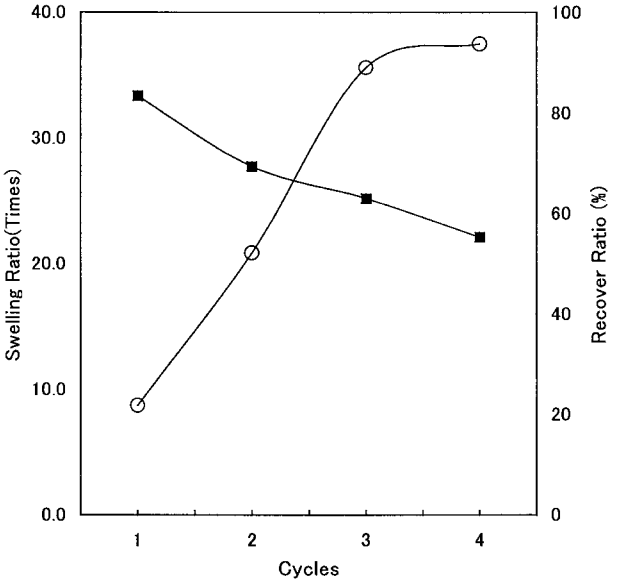

Figure 3 Effect of repeated swell–dry cycles on swelling behavior at 37°C: (○) swelling ratios and (■) recovered ratios.

became slightly smaller with increasing temperature (40–50°C). This was due to the contraction of partially saponified PVA molecules at higher temperatures. These swollen tablets were taken out of water and dried. The recovered ratio for each tablet was determined. On the whole, the recovered ratio became small with increasing temperature. It seems that the drop in the recovered ratio was due to the dissolution of low molecular weight polymers and noncrosslinked M-PVA polymers with increasing temperature.

Effect of Repeated Swell–Dry Cycles on Swelling Behavior

Figure 3 shows the effect of repeated swell–dry cycles on swelling behavior. With an increasing number of swell–dry cycles, the swelling ratio became large, but the recovered ratio became small. The dissolution of low molecular weight polymers made it possible for the buffer solution to enter deeply into crosslinked networks and made the bridge easy to lengthen. Furthermore, the looseness of the networks led to much dissolution of low molecular weight polymers. The rise in the swelling ratio and the drop in the recovered ratio are thought to occur in this manner.

Effect of Grain Size on Swelling Behavior

Figure 4 shows the effect of grain size on swelling behavior. The swelling ratio changed with the increasing grain size of M-PVA through a maximum at a grain size of 150 μm. The reason for these results is thought to be as follows. For the small-grain powder, the distances between neighboring grains are small, and many bridges are formed between grains. Therefore, the swelling ratio is low. With increasing grain size, the number of bridges per weight decreases, and the swelling ratio increases. However, larger grains have more intragrain bridges. When the grain becomes more than a definite size, more intragrain bridges are formed in comparison with the intergrain

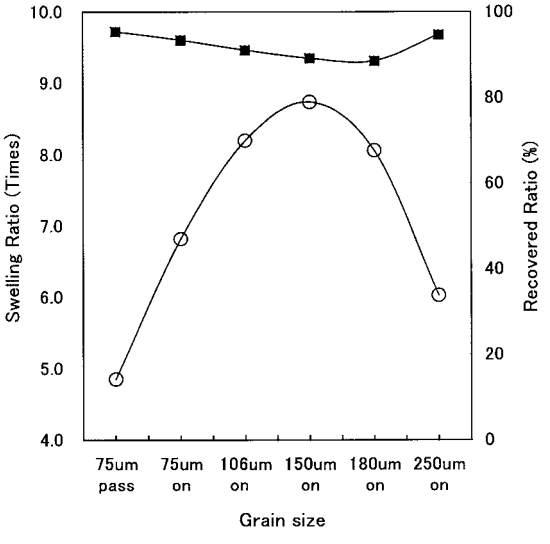

Figure 4 Effect of grain size on swelling behavior at 37°C: (○) swelling ratios and (■) recovered ratios.

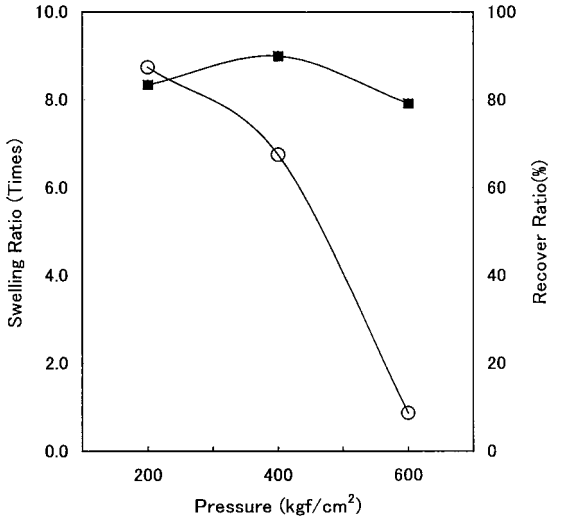

Figure 5 Effect of pressure on swelling behavior at 37°C: (○) swelling ratios and (■) recovered ratios.

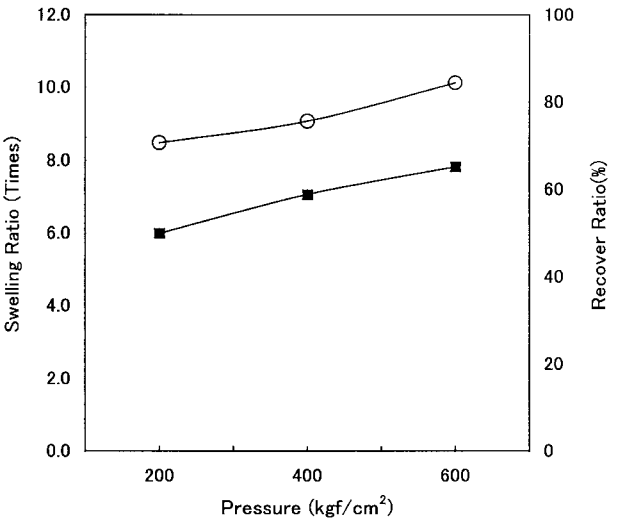

Figure 6 Effect of pressure on swelling behavior at 47°C: (○) swelling ratios and (■) recovered ratios.

bridges, and the swelling ratio becomes small. The recovered ratio depends on the dissolution from the surface and inner parts of the grains, and the dissolutions of the two parts compensate for each other to lead to a constant recovered ratio.

Effect of Pressure on Swelling Behavior

Figure 5 shows the effect of pressure on swelling behavior at 37°C. The swelling ratio decreased rapidly with increasing pressure. Compact aggregation is thought to increase with pressure, making it difficult for the buffer solution to enter deeply into networks. In contrast, the recovered ratios were almost constant. The discussion relating to the results of Figure 4 is considered to apply here also. Figure 6 shows the effect of pressure on swelling behavior at 47°C. No significant differences in the pressure dependence of the swelling ratio and recovered ratio were noticed at 47°C. The values of the swelling ratios of the tablets prepared at 400 and 600 kgf/cm^2 at 47°C were large compared with those at 37°C. The crosslinks were not strongly dependent on pressure. The compactness is thought to interfere with the crosslinking because of the difficult mobility of segments at 600 kgf/cm^2.

Differences between the Crosslinked and Noncrosslinked Tablets with Respect to Release

Figure 7 shows the release profiles of *p*-acetamidophenol from the crosslinked and noncrosslinked tablets at 37°C. On the whole, the release amount of *p*-acetamidophenol from the crosslinked tablet was larger than that from the noncrosslinked tablet. The difference in release was about 70% at 60 min. The release from the crosslinked tablet reached about 90% at 60 min and then increased slightly. The release from the noncrosslinked tablet reached about 90% at 21 h. After release, these tablets were compared. The form of the crosslinked tablet was kept after swelling, and the degree of swelling was at most 12 times, whereas the form of the noncrosslinked tablet was not kept and was transformed after

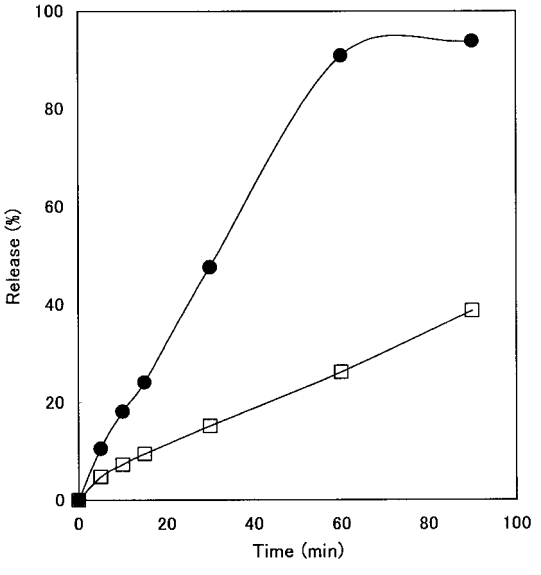

Figure 7 Differences between (●) crosslinked and (□) noncrosslinked M-PVA with respect to release.

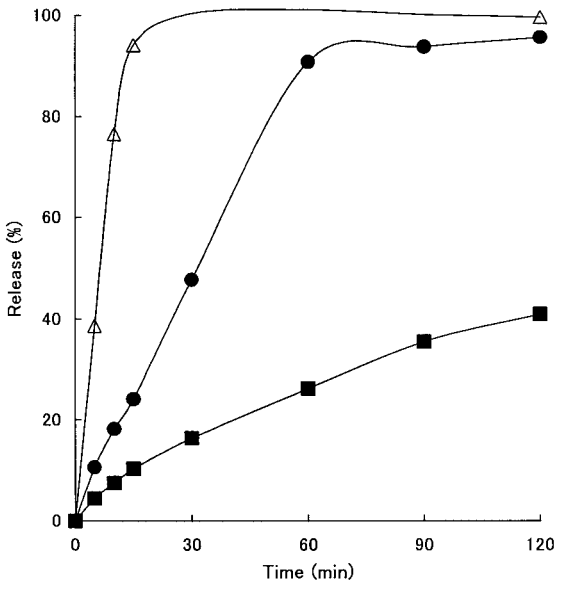

Figure 8 Effect of temperature on release: (■) 15, (●) 37, and (△) 47°C.

significant swelling. The crosslink points were formed by heat treatment; this gave a three-dimensional network structure. Therefore, the crosslinked tablet when swollen kept its form. However, for the noncrosslinked tablet, because the network structure was absent, only swelling of the polymer chain occurred, and the form was broken. The release amount from the crosslinked tablet was larger because *p*-acetamidophenol passed through the inside of the less swollen network. However, the release amount from the noncrosslinked tablet was almost lower because of the lower rate of diffusion from transformed and strongly swollen M-PVA.

Effect of Temperature on Release

Figure 8 shows the release profiles of *p*-acetamidophenol from M-PVA at 15, 37, and 47°C. The release amount of *p*-acetamidophenol from M-PVA at 37 and 47°C was larger than that at 15°C. The release at 47°C was about 100% within 30 min and then reached a plateau. The release at 37°C was 90% over 60 min and then reached a plateau, but the release at 15°C did not achieve perfection within 120 min and continued further. As shown in Figure 2, the swelling ratios at these temperatures increased with increasing temperature, especially at 20–40°C. It is thought the large differences in the release pattern at 15°C and the others are due to both the different solubilities of *p*-acetamidophenol at these temperatures and the swelling behavior of M-PVA.

Effect of Grain Size on Release

Figure 9 shows the release profiles of *p*-acetamidophenol from M-PVA tablets with two grain sizes. The release amount from M-PVA tablets with a grain size of 106 μm was larger than that from M-PVA tablets with a grain size of 75 μm. The release from M-PVA tablets with a grain size of 106 μm was 90% over 60 min and then reached a plateau. However, the release amount from M-PVA tablets with a grain size of 75 μm increased gradually and reached perfect release within 180 min. As shown in Figure 4, the swelling ratios of M-PVA increased with increasing grain sizes [75 (pass) to 150 μm (on)]. The differences in the release patterns are thought to be due to the different swelling behaviors of M-PVA tablets with different grain sizes.

Effect of Pressure on Release

Figure 10 shows the release profiles of *p*-acetamidophenol from the M-PVA tablets prepared under several pressures (200–600 kgf/cm^2) at 37°C. The release from the 200 kgf/cm^2 tablet was similar to that of the 400 kgf/cm^2 tablet, but that of the 600 kgf/cm^2 tablet was smaller than the others. The releases from 200 and 400 kgf/cm^2 tablets were 90% over 60 min and then reached a plateau. However, the release from 600 kgf/cm^2 increased gradually and reached about 90% at 150 min. The swelling ratios of M-PVA became smaller with increasing pressure as shown in Figure 5. In particular, the drop in the swelling ratio at 600 kgf/cm^2 was large, and the swelling ratio was lower

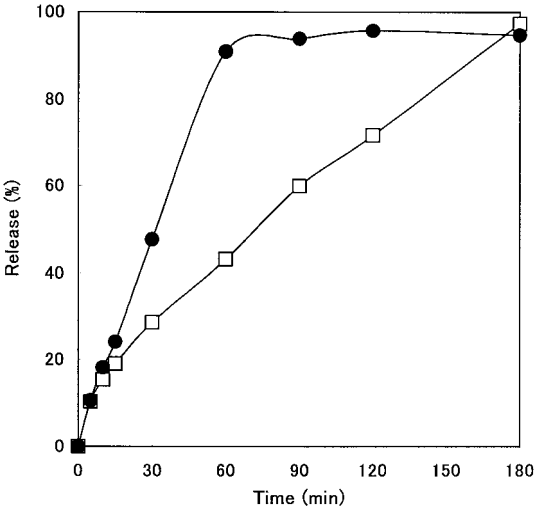

Figure 9 Effect of grain size on release at 37°C: (□) 75 (pass) and (●) 106 μm (on).

than 1. This shows that the release profile from the 600 kgf/cm^2 tablet was due to the low swelling of crosslinked M-PVA. Figure 11 shows the release profiles of *p*-acetamidophenol from M-PVA tablets prepared under several pressures (200–600 kgf/cm^2) at 47°C. On the whole, the release rate increased with increasing release temperature, and the release amounts from 200 and 400 kgf/cm^2 tablets reached 100% within 60 min They were due to the increase in the swelling ratios as described previously.

CONCLUSIONS

The state of carboxyl groups and the mechanism of crosslinking of M-PVA were studied. The carboxyl groups in M-PVA consisted of carboxylate and a few free carboxyl groups. The crosslinking by heating was by ester linkages between hydroxyl and free carboxyl groups. The swelling behavior of chemically crosslinked M-PVA tablets and the release of *p*-acetamidophenol from them were studied. The swelling ratios of tablets changed with changes in the temperature of swelling, the grain size, and the pressure for forming tablets. The different release patterns of *p*-acetamidophenol were due to the differences in the swelling behaviors.

The authors are grateful for the assistance of Mr. K. Yumoto with the experiments. Part of this work was supported by a Grant-in-Aid for COE Research from the Ministry of Education, Science, Sports and Culture of Japan.

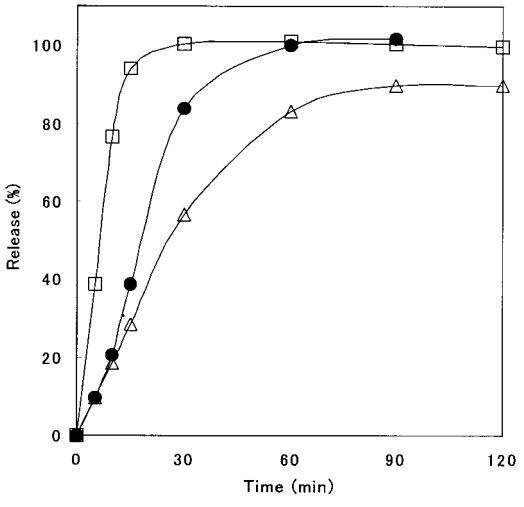

Figure 10 Effect of pressure on release at 37°C: (□) 200, (●) 400, and (△) 600 kgf/cm^2.

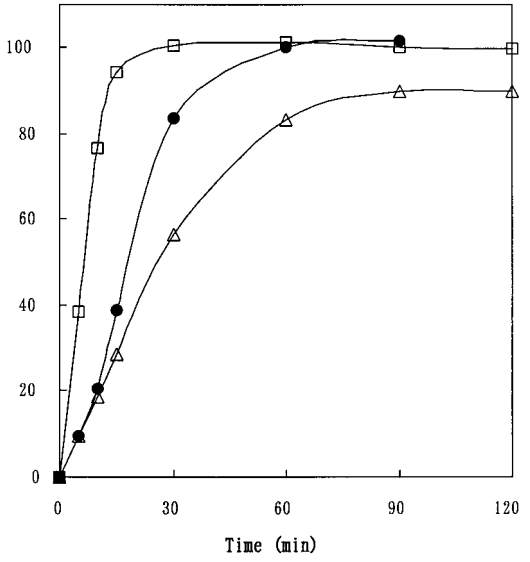

Figure 11 Effect of pressure on release at 47°C: (□) 200, (●) 400, and (△) 600 kgf/cm^2.

REFERENCES

1. Matsuzawa, S. Handbook of Thermoplastics; Marcel Dekker: New York, 1997.
2. The World of PVA; POVAL Committee, Ed.; Koubunshi Kankoukai: Kyoto, 1992.
3. Drug Delivery System; Kaetsu, I., Ed.; CMC: Tokyo, 1986.
4. Drug Delivery System; Sezaki, H.; Nankoudou: Tokyo, 1986.
5. Hashida, M. Drug Delivery System; Kagaku Doujin: Tokyo, 1995.
6. Park, K.; Shalaby, W. S. W.; Park, H. Biodegradable Hydrogels for Drug Delivery; Technomic: Lancaster, PA, 1993.
7. Yamaoka, T.; Tabata, Y.; Ikada, Y. Polym Prepr Jpn 1990, 39, 3176.
8. Horiike, S.; Matsuzawa, S. J Appl Polym Sci 1995, 58, 1335.
9. Hyon, S. H.; Ikada, Y. Pharm Factory 1986, 6, 290.
10. Horiike, S.; Yumoto, K.; Kanbara, K.; Matsuzawa, S.; Yamaura, K. J Appl Polym Sci 2000, 78, 41.
11. Britton, H. T. S.; Robinson, R. A. J Chem Soc 1931, 458.
12. Rae, N. J Chem Soc 1931, 3143.