DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(17), 1895-1906 (1992)

# DRUG RELEASE FROM HEAT-TREATED POLYVINYL ALCOHOL FILMS

Lucy S. C. Wan, L. Y. Lim

Department of Pharmacy, National University of Singapore

10, Kent Ridge Crescent, Singapore 0511



## ABSTRACT

Polyvinyl alcohol (PVA) films containing 10% w/w of a model drug, sulphathiazole, were cast from aqueous solutions and subjected to heat treatment at specific temperatures for known periods of time. Heat treatment at temperatures above the $T_g$ of the PVA films slowed down the rate of drug release from the films. Increasing the temperature of heat treatment from 120°C to 160°C further decreased the rate of drug release. On the other hand, if the heat treatment were conducted at a temperature below the $T_g$ e.g. at 80°C, there were insignificant differences between the release profile of sulphathiazole from heat-treated films and that from untreated films. The duration of heat treatment affected the rate of drug release to a smaller extent compared to the temperature of heat treatment. These results correlated with the heat induced changes in the morphology of, and in the extent of water uptake by the PVA films.

## INTRODUCTION

The design of controlled release systems for the transdermal delivery of drugs has generated considerable interest in recent

years. Amongst the advantages of transdermal drug delivery is the avoidance of first pass effects and drug-induced gastrointestinal epithelial damage. Drug release from most transdermal systems is regulated by the rate of diffusion of drug molecules through a polymer. The polymer is employed either as a drug carrier or as a release rate-controlling membrane in the system.

Polyvinyl alcohol (PVA) is a hydrophilic polymer which has been investigated for use in controlled release drug delivery systems [1,2,3]. The polymer forms films which are hygroscopic and have high tear resistance[4], which make PVA a potential candidate for incorporation into transdermal drug delivery systems. The high aqueous solubility of PVA films, which can limit their applications, may be overcome by subjecting the films to heat treatment[5]. Heat treatment has been reported to improve the water resistance of PVA films by promoting the crystallization of polymer chains in the films. As drug release from a polymer is influenced by the morphology of the polymer, the aim of this study was to investigate the effects of heat induced changes in PVA films on the release of a model drug, sulphathiazole from the films.

## MATERIALS

Polyvinyl alcohol (PVA) (semicrystalline, mw 14,000, >98% hydrolysed) (Sino Chemicals Co., Singapore) and sulphathiazole powder B.P. (Luen Wah Medical Co., Singapore) were used without further purification.

## METHOD

### Preparation of polymer films

PVA was dissolved with heating in deionised water (Milli-Q Reagent water system) to form a 7.5% w/w solution. Twenty grams of the solution were weighed onto disposable plastic petri dishes having a diameter of 85 mm, and the solvent evaporated off in an oven at 60°C. The formed films were cut into circular sections of diameter 30 mm which were heated at temperatures of 80°C, 120°C or

160°C for periods of between 1 to 4 hours. The films were then stored at room temperature in desiccators for at least 24 hours prior to film characterization.

PVA films loaded with sulphathiazole were prepared and subjected to heat treatment by methods similar to those described. In this case, the polymer and drug were dissolved in a weight ratio of 9:1 in the deionised water before film casting.

Characterization of polymer films

Film morphology was studied in a Perkin Elmer DSC-4 differential scanning calorimeter using 5-mg samples of films. Triplicate samples were scanned from 50°C to 250°C at a rate of 20°C/min. The DSC was calibrated with indium. The glass transition temperature ($T_g$), and the peak temperature ($T_m$) and enthalpy ($\Delta H$) of the melting endotherm were measured.

The swelling index of PVA films was determined from the weight of water imbibed per weight of film. The films (surface area = 707 $mm^2$, thickness = 213 ± 37 $\mu m$) were immersed in 100 ml of deionised water at 37°C for 5 days. After this period, the excess water on the film surface was carefully removed using filter paper. The swollen film was weighed ($W_1$), then dried to constant weight at room temperature in a desiccator, and reweighed ($W_2$). The index of swelling was calculated as $(W_1 - W_2)/W_2$.

The release profile of sulphathiazole from PVA films was established using triplicate samples of films loaded with 10% w/w sulphathiazole (area = 707 $mm^2$, thickness = 642 ± 79 $\mu m$). Each of these films was sandwiched with the aid of screws between two plastic discs, one of which was a ring, and immersed in 300 ml of deionised water at 37°C. This arrangement ensured that only that surface of the film exposed to the atmosphere during film formation was available for drug release. The sulphathiazole content in the dissolution media was measured at regular intervals of time using UV spectroscopy at 255 nm.

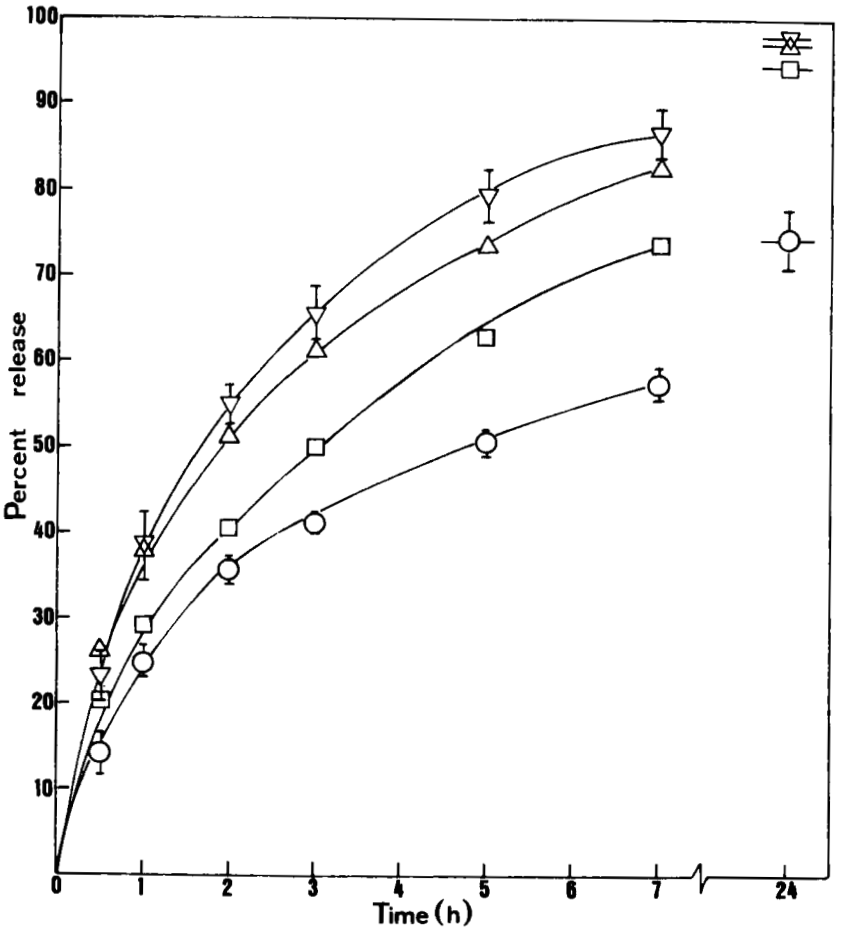


FIGURE 1
Effect of heat treatment on the release of sulphathiazole from PVA films, ▽untreated, △- 80°, □ - 120°, ○ - 160°.

## RESULTS AND DISCUSSION

Figure 1 shows the effect of heat treatment on drug release from PVA films containing 10% w/w sulphathiazole. For both the heat-treated and the untreated PVA films, the release kinetics of sulphathiazole in the initial 5 hours fitted the Higuchi's diffusion model in that the amount of drug released was proportional to time$^{1/2}$ ($r^2 \geq 0.99$). After 5 hours, the rate of release of drug decreased with time. All films except those which were heated

at 160°C for 4 hours, released more than 95% of the sulphathiazole load within 24 hours. Subjecting the PVA films to heat treatment at 80°C for up to 4 hours did not change significantly the release kinetics of sulphathiazole from PVA films. However, films which were heated for 4 hours at 120°C or 160°C showed slower rates of release of sulphathiazole in the first 5 hours compared to untreated films. Despite the initial slower rate of release, films heated at 120°C for 4 hours also released more than 95% of the drug load within 24 hours because of a slower decline in the rate of release of drug with time compared to the untreated films. On the other hand, films heat treated at 160°C released only 75% of the drug load within 24 hours, the rate of drug release being much slower than that of films heated at 120°C. These results may be accounted for by the heat induced changes in the morphology of, and consequently in the extent of water uptake by the PVA films.

DSC analyses of PVA films showed a melting endotherm and a glass transition (Figure 2). The crystalline regions of the polymer was characterized by the melting endotherm which had a peak temperature ($T_m$) of 227.12 ± 0.75°C and an enthalpy ($\triangle H$) of 76.94 ± 1.55 J/g. The amorphous regions of the polymer was characterized by the glass transition which occurred at a temperature of 122.87 ± 1.02°C ($T_g$).

Heat treatment at temperatures above the $T_g$ caused the appearance of a small endotherm in the DSC thermograms of the PVA films. This endotherm appeared at 135 - 140°C and at 160 - 170°C respectively for films subjected to heat treatment at 120°C (Figure 2) and 160°C (Figure 3). The endotherm probably represents the melting of crystallites formed in the films during heat treatment. In a semicrystalline polymer, crystallization occurs by the chain-folding of polymer chains so that stacks of lamellar layers of crystallites alternate with diffuse amorphous regions[6]. Further crystallization of polymer chains can be promoted by annealing the polymer at a sufficiently high temperature. The absence of a glass transition in the DSC thermograms of films heat treated at 120°C and 160°C suggests that the crystallites were formed from alignment of polymer chains in the amorphous regions. Since movement of

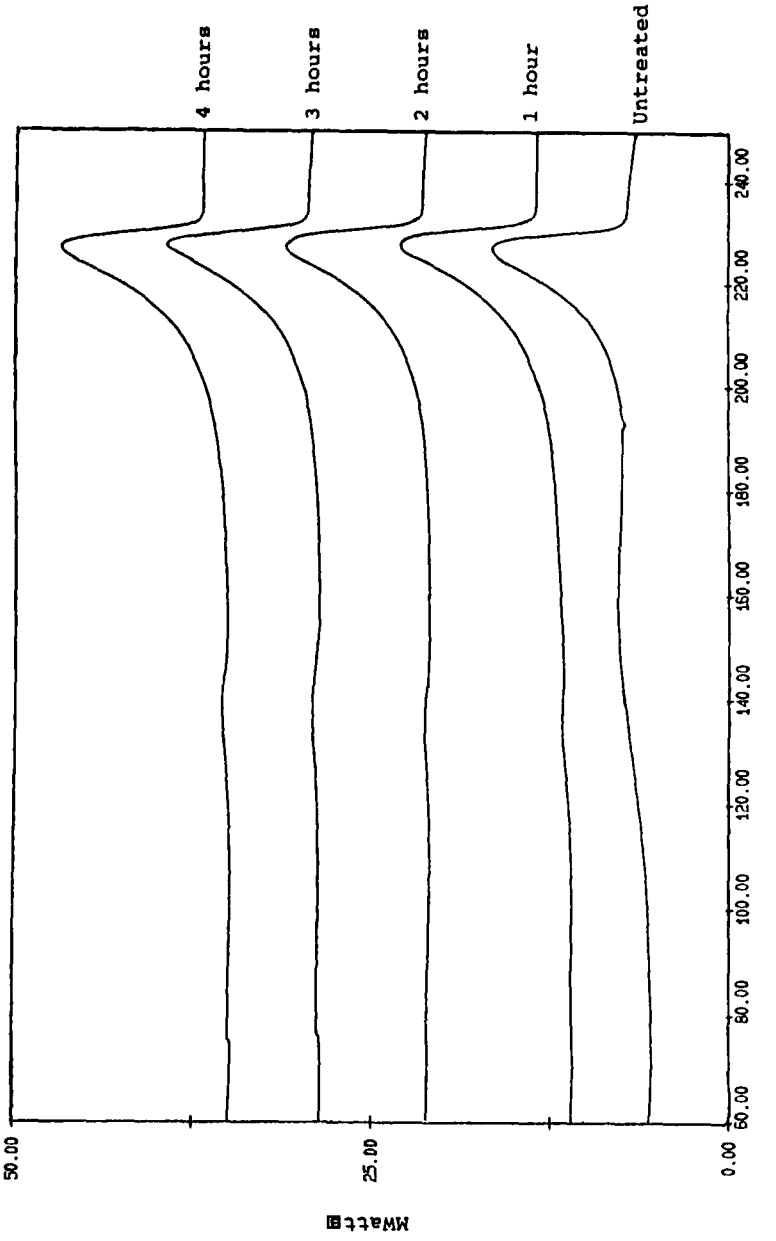


FIGURE 2
DSC thermograms of PVA films subjected to different periods of heat treatment at 120°C.

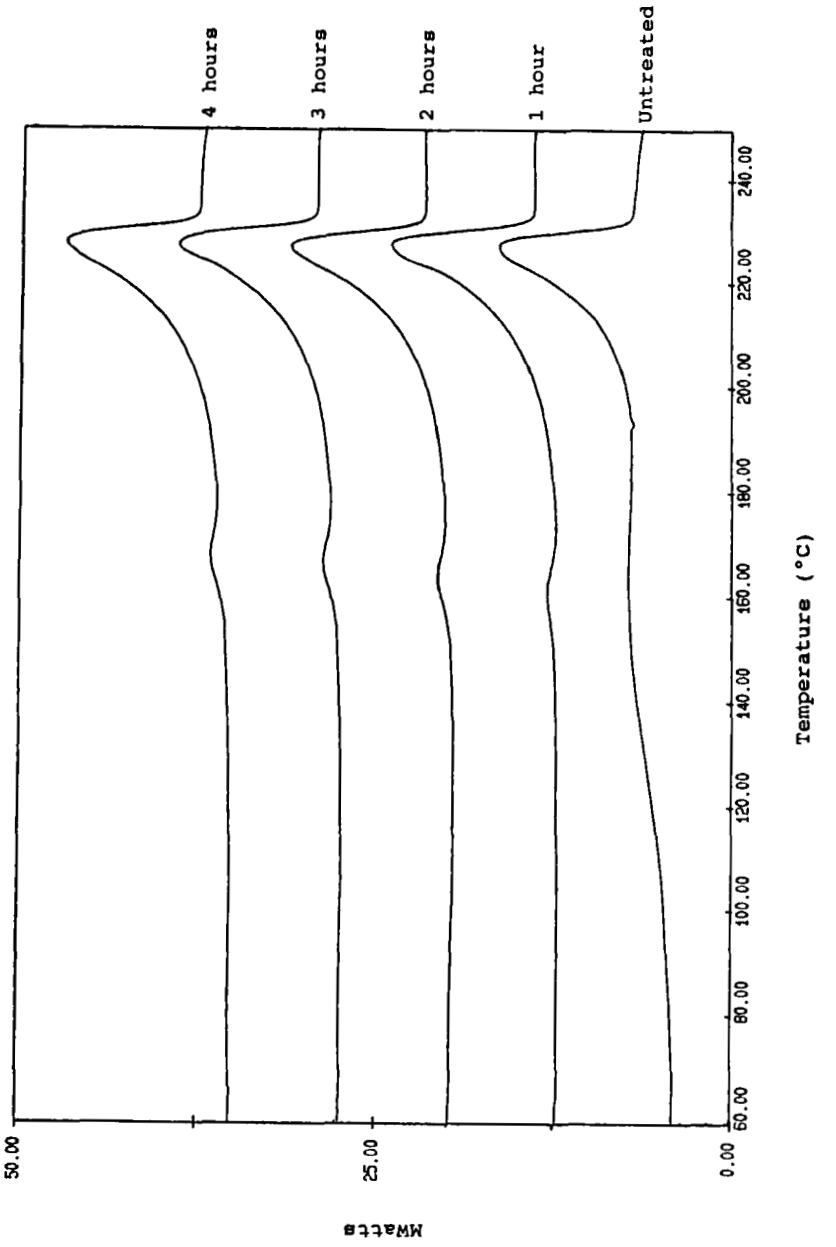


FIGURE 3
DSC thermograms of PVA films subjected to different periods of heat treatment at 160°C.

polymer chains in the amorphous regions was possible only when the polymer is in a rubbery state i.e. at a temperature at or above the $T_g$[7], the alignment of polymer chains to form crystallites may not be possible at temperatures below the $T_g$. Hence, crystallites were not formed in films heat treated at 80°C as the temperature was lower than the $T_g$ of PVA films (Figure 4). Heat treatment at 80°C did not change the DSC thermograms of PVA films except to shift the glass transition to higher temperatures. The higher $T_g$ values may be indicative of a loss of bonded water molecules which serve as plasticizers, from the untreated films following heat treatment. $T_g$ values for films heated for between 1 to 4 hours at 80°C were within the range of 127.25°C to 134.50°C (s.d. 1.96 - 3.51°C), with no particular trend with respect to the duration of heat treatment.

For films subjected to heat treatment at 160°C, the melting endotherm of the heat induced crystallites shifted to higher temperatures with increasing duration of heat treatment. Storage of a polymer at a high temperature, besides enhancing the crystallization of polymer chains, also improves crystal perfection (i.e. increases crystal thickness, corrects crystal lattice defects etc), resulting in larger crystals with higher melting temperatures[6]. This phenomenon was not so apparent in films heat treated at 120°C probably because polymer chain mobility was less intense at lower temperatures.

The loss of water molecules and the formation of crystallites in the amorphous regions of PVA films may account for the observed decrease in the values of the swelling index of the films following heat treatment (Table 1). PVA is a hydrophilic polymer capable of imbibing a large amount of water. The swelling index for untreated PVA films was 2.33 ± 0.35 (n = 6), indicating that a PVA film absorbed more than twice its weight of water. With heat treatment, the swelling index of the films decreased in value. A loss of water molecules from the PVA films reduced the flexibility of polymer chains in the films which may make the film less hygroscopic. Similarly, the extent of water uptake by a polymer is influenced by the ratio of amorphous:crystalline contents in the polymer. An amorphous polymer is better able to accommodate water molecules

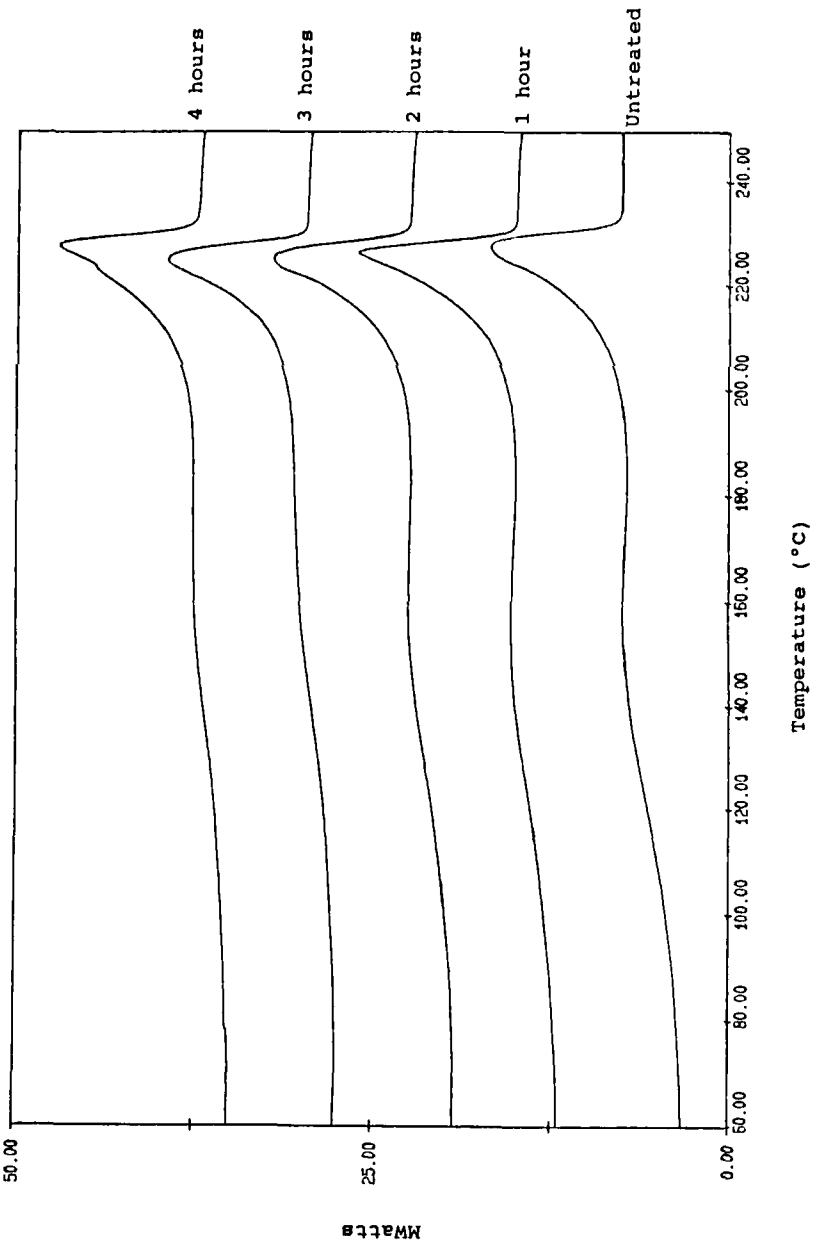


FIGURE 4
DSC thermograms of PVA films subjected to different periods of heat treatment at 80°C.

TABLE 1

The influence of heat treatment on the swelling index of PVA films (n = 3).

| Temperature of treatment (°C) | Duration of heat treatment (hours) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| 80 | 1.99 ± 0.16 | 2.03 ± 0.08 | 1.86 ± 0.05 | 1.85 ± 0.07 |
| 120 | 1.56 ± 0.06 | 1.44 ± 0.03 | 1.40 ± 0.02 | 1.37 ± 0.04 |
| 160 | 0.86 ± 0.07 | 0.75 ± 0.06 | 0.65 ± 0.04 | 0.63 ± 0.04 |

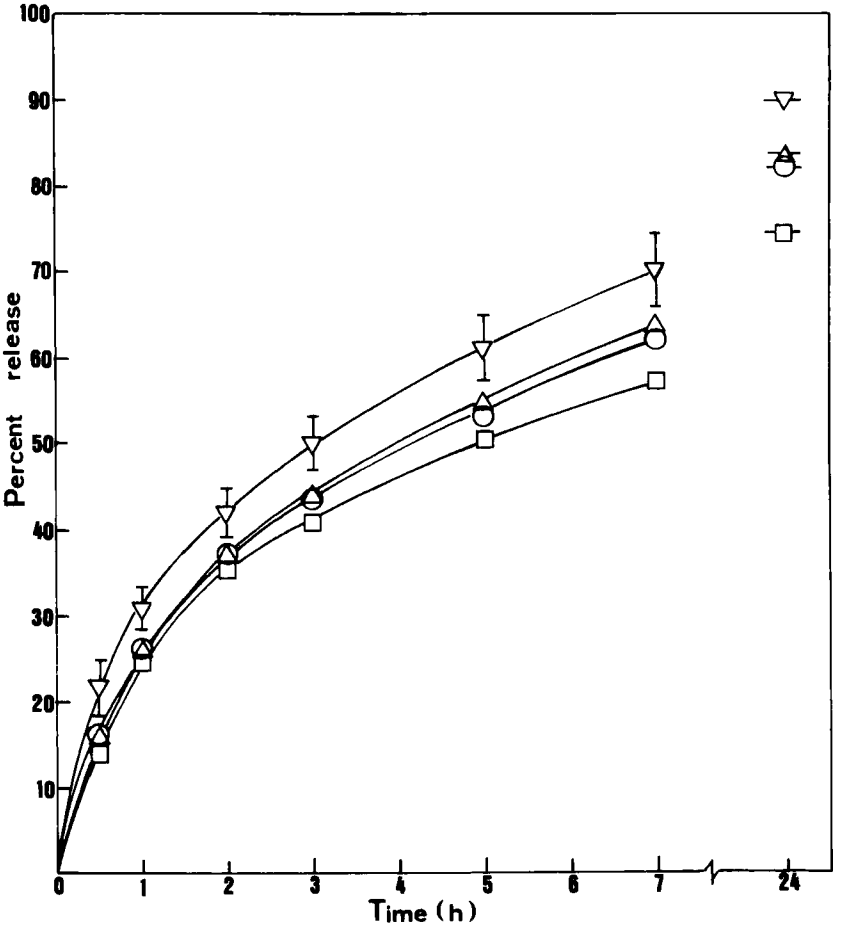


FIGURE 5

Release profiles of sulphathiazole from PVA films subjected to different periods of heat treatment at 160°C, ▽ - 1 hr, △ - 2 hr, ○ - 3 hr, □ - 4 hr.

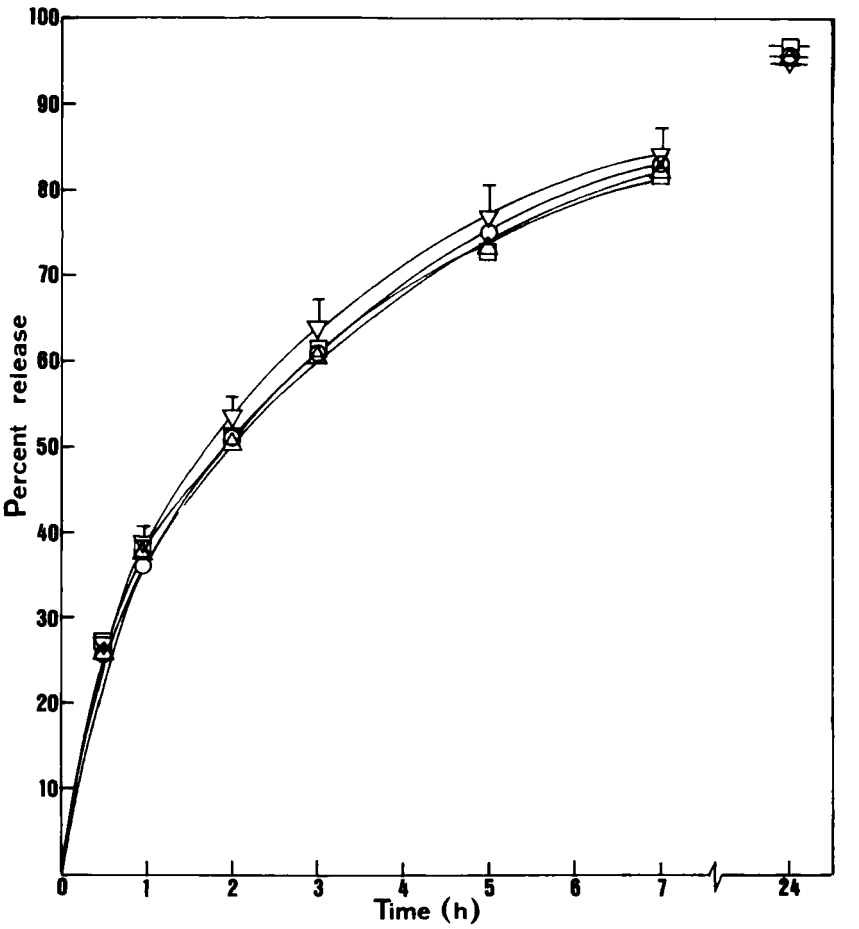


FIGURE 6
Release profiles of sulphathiazole from PVA films subjected to different periods of heat treatment at 80°C, ▽ - 1 hr, △ - 2 hr, ○ - 3 hr, □ - 4 hr.

amongst its loosely interspersed molecular chains compared to a crystalline polymer with its tightly aligned polymer chains. The formation of crystallites in the amorphous regions of heat treated PVA films would thus hinder water uptake by the films.

The swelling index of PVA films decreased with increasing temperatures of heat treatment, but for a chosen temperature, the swelling index was constant after 3 hours of heat treatment. The

implication is that the physical properties of the PVA films is strongly dependent on the temperature of heat treatment, and less so on the duration of heat treatment. This implication was supported by results from the DSC analyses of the films and further substantiated by the release profiles of sulphathiazole from films heat treated for different periods of time at a specific temperature. Except for films heat treated at 160°C (Figure 5), there was insignificant difference in the release profiles of sulphathiazole from heat-treated PVA films with respect to duration of heat treatment (Figure 6). For the former, a slightly decreasing rate of drug release was obtained with increasing duration of heat treatment.

## CONCLUSION

Heat treatment results in the loss of water from PVA films and in the formation of crystallites in the amorphous regions of films heat treated at temperatures above the $T_g$ value of the films. Consequentially, the extent of water uptake by, and hence the rate of drug release from heat-treated films are lowered. The temperature, rather than the duration of heat treatment plays an important role in influencing the physical properties of the films.

## REFERENCES

1. Morimoto, K., Nagayasu, A., Fukanoki, S., Morisaka, K., Hyon, S. and Ikada, Y., Drug Dev. Indust. Pharm., 16(1), 13 (1990).
2. Morimoto, K., Fukanoki, S., Hatakeyama, Y., Nagayasu, A., Morisaka, K., Hyon, S. and Ikada, Y., J. Pharm. Pharmacol., 42, 720 (1990).
3. Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P. and Peppas, N. A., Int. J. Pharm., 15, 25 (1983).
4. Modi, T. W., in "Handbook of Water Soluble Gums and Resins", Davidson, R. L., ed, McGraw Hill, 1980, p 20-1.
5. Toyoshima, K., in "Polyvinyl Alcohol - Properties and Applications", Finch, C. A., ed, John Wiley and Sons, 1973, p. 339.
6. Wunderlich, B., in "Thermal Characterization of Polymeric Materials", Turi, E. A., ed, Academic Press, 1981, p 91.
7. Shalaby, S. W., in "Thermal Characterization of Polymeric Materials", Turi, E. A., ed., Academic Press, 1981, p 235.