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COMBINED EFFECTS OF HEAT TREATMENT AND PLASTICIZERS ON POLYVINYL ALCOHOL FILMS

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ABSTRACT

The effects of heat treatment on PVA films containing water soluble plasticizers were investigated. Propylene glycol, glycerol and polyethylene glycol were used as plasticizers. There was synergism between heat treatment and the presence of plasticizers in enhancing the water resistance of PVA films. In the absence of heat treatment, however, the plasticizers increased the aqueous solubility of PVA films. The plasticized films further showed a lower permeability to propranolol HCl compared to the unplasticized films following heat treatment.

INTRODUCTION

Polyvinyl alcohol (PVA) can be easily formulated into films[1] with potential for use in drug delivery systems. To act as a rate-controlling membrane in these systems, the aqueous solubility of PVA films has to be minimized. Although heat treatment can increase the water resistance of PVA films, it causes the films to become brittle and difficult to handle[2]. Propylene glycol (PG), glycerol and polyethylene glycol 600 (PEG) have been shown in a previous study to be effective plasticizers of PVA films[3]. Addition of the water-soluble plasticizers, however, enhanced the aqueous solubility of PVA films. It would therefore be interesting to determine the combined effects of plasticizer and heat treatment on the water resistance of PVA films, and the consequential influence of water resistance on film permeability.

MATERIALS AND METHODS

Polyvinyl alcohol (>98% hydrolysed, mw 14000 - 22000, BDH Chemicals Ltd., UK), propylene glycol (USP), glycerol (BP) (Sino Chemical Co. Pte. Ltd., Singapore), polyethylene glycol 600 (BDH Chemicals Ltd., UK) and propranolol HCl (USP) (Beacons Chemicals Pte. Ltd., Singapore) were used as supplied.

Polyvinyl alcohol (PVA) films were cast from 7.5% w/w aqueous solutions of a mixture of PVA and plasticizer (10:0, 9.5:0.5, 9:1 and 8:2 w/w) according to a method previously reported[3]. The formed films were heated in an oven at temperatures of 80°C, 120°C or 160°C for 4 hours. Film thickness was recorded as the mean of five measurements made using a thickness

gauge (Mitutoyo #7305). The difference in dry film weight before and after 3 days of immersion in 100 ml distilled water at 37°C was calculated to give the percent dissolution of a film. Swelling index was determined from the amount of water imbibed per unit weight of undissolved film retrieved from the distilled water after the period of immersion. Film crystallinity was measured in a differential scanning calorimeter (DSC) (Perkin Elmer DSC 4).

The permeability of PVA films to propranolol HCl was determined using diffusion cells. The medium in each cell was maintained at 37°C and stirred continuously at 200 rpm (Stuart stirrers). Five-ml samples were withdrawn at regular intervals and assayed spectrophotometrically (Perkin Elmer Lamda 4A) at 288 nm for propranolol HCl content.

RESULTS AND DISCUSSION

PVA films containing 5%, 10% and 20% of propylene glycol (PVA-PG-5, PVA-PG-10, PVA-PG-20), of glycerol (PVA-G-5, PVA-G-10, PVA-G-20) and of polyethylene glycol (PVA-PEG-5, PVA-PEG-10, PVA-PEG-20) were formed. Except for PVA-PEG-20, all the films were transparent and non-tacky. PVA-PEG-20 showed sweating, a result of relative incompatibility between PEG and PVA molecules. Film thickness did not vary with plasticizer content and was in the range of 201 to 240 μm.

Heat treatment reduced the compatibility between the plasticizer and PVA molecules. After heat treatment at 120°C or at 160°C, the following films : PVA-G-10, PVA-G-20, PVA-PEG-10 and PVA-PEG-20 exhibited sweating and became translucent and tacky. The degree of sweating increased with plasticizer content and was greater for films containing PEG. None of the films containing PG exhibited sweating upon treatment, indicating the high compatibility between PG and PVA molecules. The smaller size of PG molecules (mw 76) as compared to glycerol (mw 92) or PEG (average mw 646) molecules may allow for greater interaction between PG and PVA molecules. Nonetheless, the PVA matrix was able to accommodate small amounts of the larger sized plasticizer molecules because films containing 5% of either glycerol or PEG did not sweat even when treated at 160°C. Heat treatment at 160°C caused discoloration of both the plasticized and unplasticized PVA films due to unsaturation of PVA molecules[4]. Film discoloration did not occur at 80°C or at 120°C.

Prior to heat treatment, the percent dissolution of PVA films decreased in the order of PVA-PEG > PVA-G > PVA-PG > PVA (Table 1). The high aqueous solubility of the plasticized films may be attributed to enhanced water uptake by the films due to the presence of plasticizers, as well as to the leaching of plasticizers from the films. Heat treatment improved the water resistance of PVA films (Table 1), the resistance increasing with the temperature of heat treatment. The duration of heat treatment was less important in that treatment periods ranging from 1 to 4 hours at 120°C contributed only slight differences to the aqueous dissolution of both unplasticized films and of films containing 10% of plasticizers (Table 2). Similar results have been obtained for films containing 5% and 20% of the plasticizers. Heat treatment for 4 hours at 80°C reduced the aqueous dissolution of films plasticized with PG and those with PEG, but not of the unplasticized films and films plasticized with glycerol. The presence of PG or PEG molecules may have lowered the glass transition temperature of PVA ($T_g \simeq 120°C$)[2], causing PVA molecules in the amorphous regions of the films to realign to form crystals at 80°C. The heat-induced crystallites, indicated by the presence of a second endotherm in the DSC thermograms of heat treated films, in turn raised the water resistance of the films. PVA molecular alignment occurred minimally in the unplasticized film until the treatment temperature was 120°C i.e. near to its T_g.

TABLE 1

Effect of heat treatment and plasticizer on the dissolution and swelling index of PVA films

Film	Dissolution				Swelling			
	Un-treated[1]	Temperature of heat treatment 80°C[2]	120°C[2]	160°C[2]	Un-treated[1]	Temperature of heat treatment 80°C[2]	120°C[2]	160°C[2]
PVA	24.47	22.33	8.16	0.00	2.09	1.95	1.30	0.53
PVA-PG-5	27.91	17.90	6.38	0.00	2.07	1.67	0.92	0.28
PVA-PG-10	28.66	20.75	7.69	0.00	1.99	1.61	0.78	0.28
PVA-PG-20	30.34	22.99	10.53	0.00	2.01	1.47	0.61	0.27
PVA-G-5	27.77	25.54	7.20	1.58	2.07	2.13	0.76	0.29
PVA-G-10	31.55	26.55	13.92	7.93	2.09	1.93	0.76	0.26
PVA-G-20	36.93	34.91	22.10	19.80	2.08	1.89	0.68	0.32
PVA-PEG-5	30.93	19.50	7.78	2.20	2.22	1.74	0.86	0.37
PVA-PEG-10	33.70	23.51	10.68	7.30	2.37	1.80	0.92	0.45
PVA-PEG-20	43.19	34.47	29.72	18.68	2.90	2.13	1.63	0.60

TABLE 2

Percent dissolution and swelling index of PVA films heat treated for different periods at 120°C

Film	Duration of treatment (h)	Swelling Index	Percent Dissolution
PVA	1	1.28 ± 0.03	9.54 ± 0.63
	2	1.25 ± 0.11	8.64 ± 2.37
	3	1.25 ± 0.02	8.67 ± 0.29
	4	1.23 ± 0.10	8.16 ± 1.83
PVA-PG-10	1	0.79 ± 0.04	10.69 ± 0.91
	2	0.79 ± 0.04	9.63 ± 1.05
	3	0.89 ± 0.09	9.73 ± 1.37
	4	0.78 ± 0.06	7.69 ± 0.43
PVA-G-10	1	1.18 ± 0.03	17.03 ± 1.37
	2	1.11 ± 0.02	16.82 ± 0.77
	3	1.03 ± 0.01	15.40 ± 0.83
	4	0.76 ± 0.18	13.92 ± 0.76
PVA-PEG-10	1	0.78 ± 0.01	11.85 ± 0.24
	2	0.84 ± 0.01	11.74 ± 0.44
	3	0.86 ± 0.02	11.55 ± 0.33
	4	0.83 ± 0.08	10.68 ± 1.27

Glycerol was a less effective plasticizer compared to PG probably because its larger size hindered interaction with PVA molecules. The same explanation may be extended to PVA films containing PEG which are much larger molecules than glycerol. However, films plasticized with PEG showed improved water resistance after being heated at 80°C. It could be that the small amounts of PEG accommodated by the PVA matrix were sufficient to lower the T_g of PVA films to below 80°C. Both the unplasticized films and films containing PG were resistant to aqueous dissolution following heat treatment at 160°C. The percent dissolution of similarly treated PVA-G-10, PVA-G-20, PVA-PEG-10 and PVA-PEG-20 films were however, still measurable. Dissolution of these films could be attributed to the leaching of plasticizers because of heat-enhanced incompatibility between glycerol-PVA and between PEG-PVA in the films.

The swelling index (SI) of PVA films decreased with increasing temperatures of heat treatment (Table 1). When untreated, the SI values of unplasticized PVA films were similar to those of films plasticized with PG or with glycerol. Films containing PEG had greater SI values because of the porosity generated in the remnants of these films after film dissolution[3]. Like percent dissolution, the SI values of unplasticized films, and of films containing glycerol were affected significantly by heat treatment only when the temperature of treatment was 120°C or greater. Heat treatment at 80°C, however, lowered the SI values of films plasticized with PG or with PEG. The effect of plasticizer was synergistic with that of heat treatment on the SI values of PVA films. Heat treatment at 120°C or at 160°C resulted in lower SI values for plasticized films than for the unplasticized films. The mechanism by which these water soluble plasticizers reduced the capacity for water uptake in heat treated PVA films is as yet unclear. Remnants of heat treated PVA-G-10, PVA-G-20, PVA-PEG-10 and PVA-PEG-20 retrieved after immersion in distilled water were still translucent, indicating the presence of plasticizers. However, the degrees of crystallinity as measured by DSC analyses of film remnants were similar, and were thus independent of both the initial plasticizer content and the heat treatment received. Swelling indices of PVA films were also not as strongly affected by plasticizer content as they were by heat treatment (Table 1).

The permeation of propranolol HCl through unplasticized PVA films and through films containing 10% plasticizer were found to follow the Fick's Law of diffusion[5]. The permeability coefficients for the untreated films of PVA, PVA-PG-10 and PVA-G-10 were 5.62 $\pm$ 0.29, 5.46 $\pm$ 0.12 and 5.87 $\pm$ 0.42 $(x10^3)cm^2/h$ respectively. While those for the same films but treated at 120°C were 2.62 $\pm$ 0.14, 1.32 $\pm$ 0.06, 1.32 $\pm$ 0.06, 1.18 $\pm$ 0.04 $(x10^3)cm^3/h$ respectively. The permeability coefficient of treated film PVA-PEG-10 was 2.30 $\pm$ 0.12 $(X10^3)cm^3/h$. Despite enhancing the aqueous dissolution of PVA films, the presence of PG and glycerol did not affect the permeability of PVA films to propranolol HCl. SI values may therefore be more useful than percent dissolution in predicting the permeability of PVA films. PVA-PEG-20, when untreated, could not be used successfully over 6 hours for the permeation studies because of its good aqueous solubility. The high SI value of this film suggests that it would be more permeable to the model drug than the other films. The amount of propranolol HCl penetrating through the film in the initial 2 hours was indeed greater than those obtained for the other three types of films. Heat treatment at 120°C lowered the permeability coefficient of PVA films, indicating that the diffusion of propranolol HCl through heat treated PVA films was slower than through the untreated films. Film permeability was lowered further by the presence of PG or glycerol in the film, with glycerol exerting a greater influence than PG. PEG was less effective than either of these two plasticizers in reducing the permeability of heat treated PVA films to propranolol HCl. These results again correlated well with the SI values of the respective films.

CONCLUSION

The incorporation of water soluble plasticizers into PVA films was advantageous in two respects. Firstly, the plasticizers made the films pliable and therefore easy to mould and handle.

Secondly, they lowered the permeability of heat treated films to solute molecules. Of the three plasticizers used, propylene glycol was most promising in giving PVA films suitable qualities to serve as a membrane in drug delivery systems.

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REFERENCES

1. Toyoshima, K., in "Polyvinyl Alcohol - Properties and Applications", Finch, C. A. ed., John Wiley and Sons Ltd., p 339 (1973).

2. Wan, L. S. C. and Lim, L. Y., Drug Dev. Ind. Pharm., 18 (17), 1895, (1992).

3. Lim, L. Y. and Wan, L. S. C., Drug Dev. Ind. Pharm. (in press).

4. Kojima, Y., Furuhata, K. and Miyasaka, K., J. Appl. Polym. Sci., 29, 533, (1984).

5. Rosilio, V., Roblot-Treupel, L., de Lourdes Costa, M. and Baszkin, A., J. Controlled Release, 7, 171, (1988).