Evaluation of Permeability and Mechanical Properties of Composite Polyvinyl Alcohol Films

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Among six grades of polyvinyl alcohol (PVA), PVA V (degree of hydrolysation 99.45%, molecular weight 140000—150000) and PVA VI (degree of hydrolysation 98—99%, molecular weight 85000—146000) were selected for combination with PVA I (degree of hydrolysation 99%, molecular weight 17300) to prepare composite films with different amounts of PVA I and film thickness. The permeability coefficients of diclofenac sodium through these films were determined and the elastic moduli measured. The permeability coefficients increased with the amount of PVA I in the PVA V–I films. Conversely, the presence of PVA I in the PVA VI–I films decreased the permeability of the composite films to diclofenac sodium. PVA VI–I films showed significantly higher permeability than PVA V–I films. These results indicated that PVA I content in the composite films was a critical factor, affecting the apparent solubility and/or swelling properties, and thereby permeability of the composite films. For PVA V–I films, the effect of PVA I on increasing solubility played a dominant role, but for PVA VI–I films, the effect of PVA I on decreasing swelling properties was a more important factor. Film thickness also influenced the permeability coefficients of diclofenac sodium through the composite films; film permeability decreasing with increasing film thickness. The addition of PVA I raised the elastic moduli of PVA VI–I film but showed minimal effect on PVA V–I films. Proper selection of PVA grades and weight ratio was the key element to successful preparation of PVA composite films with the desired characteristics.

Key words polyvinyl alcohol; permeability; tensile test; diclofenac sodium

In a membrane permeation-controlled system such as a transdermal delivery system, the selection of the rate-controlling layer is very important. This layer can act as both a support and a rate-control layer, depending on the relative properties of drug and polymer. For ideal support and rate-controlled layers, the film must remain intact during the course of drug delivery. A number of polymers have been investigated for transdermal delivery. Among them, polyvinyl alcohol (PVA) has unique features such as excellent film-forming property, good biocompatibility and non-toxicity. Since PVA is water soluble, PVA films are easily prepared by a casting evaporation technique from aqueous polymer solutions, thus avoiding the use of organic solvents. The resultant films are clear, homogeneous and resistant to tear. However, the water solubility of the film reduces its usefulness in transdermal delivery systems. Heat-treating the film reduces water solubility, but also renders the film brittle and difficult to handle,[1—3] hence, an alternative method to reduce the water-solubility of PVA films is necessary.

PVA is produced by the polymerization of vinyl acetate to poly(vinyl acetate) which is subsequently hydrolyzed to PVA.[4] The degree of hydrolysation represents the extent to which poly(vinyl acetate) has been hydrolyzed to produce PVA. Commercial PVAs are basically available as fully hydrolyzed grades (degree of hydrolysation≥98%) and partially hydrolyzed grades (degree of hydrolysation in range of 86—89%). The solubility of PVA in water depends on the degree of hydrolysation and the degree of polymerization, with the effect of the former being especially significant.[4] Some PVA grades with higher degrees of hydrolysation (>98%) are only soluble in hot water (50—100 °C) and form films that are insoluble in water at lower temperatures. In contrast, PVA grades with degrees of hydrolysation in the range of 75—98% are easily soluble in water. Molecular weight is another factor affecting the solubility of PVA and the extent of influence is related to the degree of hydrolysation.[4] The solubility of highly hydrolyzed PVA increases as the molecular weight decreases while the solubility of less hydrolyzed PVA is relatively independent of molecular weight. Hence, a combination of different grades of PVA may have the potential for preparation of polymer film with the desired properties.

Apart from the requirements on solubility, an ideal film should also be strong, which can be represented by mechanical properties.[5] Tensile strength test data are readily obtained and provide useful information about resistance to loading and deformation characteristics.

In this study, six grades of PVAs with different degrees of hydrolysation and molecular weight were utilized to prepare composite films. The permeability and mechanical properties of these films were determined. The permeability coefficients of diclofenac sodium (DS) and the elastic moduli of PVA films were used as indicators to characterize the composite films.

Experimental

Materials Six grades of PVAs with varying degrees of hydrolysation and molecular weights were used (Table 1). The model drug, DS (JP12 grade), was used as supplied.

Preparation of Films PVA films were produced by a casting evaporation technique from aqueous polymer solutions. Accurate weights of PVA powders with different weight ratios were added into distilled water and left to hydrate overnight. The next day, the dispersions were heated in a water bath at 80—90 °C for 30—60 min and then made up to 8% PVA solutions. The solutions were left to stand until trapped air bubbles were removed, and then cooled to ambient temperature. Different amounts of the polymer solutions (10, 15, 20 g) were poured into glass petri dishes (diameter 10 cm) and oven-dried at about 50 °C for 24 h. The dried films were peeled from the petri dishes and stored in a desiccator at room temperature. Before permeation studies and tensile tests, dried films were cut into circular test sections with area of 19.625 cm^2 and rectangular test sections with size of 1×7 cm^2, respectively. The thickness of the films was measured by using a micrometer (Mitutoyo, No. 293-721-30 CE, Japan). At least five thickness readings at

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Table 1. Characteristics and Source of PVA Used in This Study

Grade	Degree of hydrolysation (%)	Molecular weight	Source
I	99	17300	Shinetsu Chemical Company, Japan
II	99	31000—50000	Aldrich Chemical Company, U.S.A.
III	86—89	15000	Fluka Chemical Company, Switzerland
IV	86—89	100000	Fluka Chemical Company, Switzerland
V	99.45	140000—150000	Shinetsu Chemical Company, Japan
VI	98—99	85000—146000	Aldrich Chemical Company, U.S.A.

different regions were taken for each test section and the results averaged.

Determination of Apparent Solubility of Films Rectangular pieces, each of area of $1\times7\,cm^2$, were cut from the PVA films and oven-dried until constant weights were obtained. Each piece was immersed in 40 ml of distilled water contained in a boiling tube. The boiling tube was then placed in a shaker water bath at 37 °C. After 24 h, the piece was removed and spread on a clean petri dish and oven dried at about 50 °C to constant weight. The percentage weight loss, W%, expressed as the percentage of decrease in the weight of film after dissolution, represented the apparent solubility of film. For each film, at least five determinations were made and the average W% obtained.

Evaluation of Swelling Property of Films Square pieces, area $1\,cm^2$, were cut from the PVA films. The dimensions of each piece were accurately measured by using a caliper (Mitutoyo, No. 500-216, Japan) before introducing into a test tube containing 5 ml distilled water. The tube was placed in a shaker water bath at 37 °C. After 5 h, the piece was removed and spread on a clean petri dish. Accurate measurements of the dimensions were made immediately. The swelling index was defined as the percentage increase in the dimensions of the film after swelling. For each film, at least five determinations were made and the results averaged.

Film Permeation Study A specially designed horizontal diffusion cell was used. The diffusion cell comprised two compartments, the donor and receptor half-cells. The test film section was carefully mounted between the two half-cells of the permeation system, which was fastened tightly with screws. The donor compartment contained 250 ml of aqueous DS solution (50 μg/ml) while the receptor compartment was filled with an equal volume of freshly distilled water. The area of the film available for permeation was $8.042\,cm^2$. The diffusion cells were placed in a shaker water bath at 37 °C. At predetermined time intervals over a period of 5 h, 5 ml samples were withdrawn from the receptor compartment with replacement of an equal volume of distilled water to maintain constant volume. The samples obtained were analyzed spectrophotometrically (Shimadzu, UV-1201, Japan) at 277 nm. All experiments were repeated at least five times and the results averaged.

The steady-state flux, J ($\mu g/cm^2\cdot s$), of DS was calculated from the slope of the initial linear portion of the plot of the cumulative amount of drug permeated per unit film area against time. The permeability coefficient, P (cm/s), was determined by dividing the steady-state flux by the concentration of drug in the donor cell. Student's t-test for two-tailed distribution was conducted to evaluate the significance of permeability coefficient between different groups with various PVA grades, film thickness and composition. Differences were considered to be significant at a level of $p<0.05$.

Tensile Test of Films The tensile properties of films were investigated according to the procedure described by ASTM Standard D882-95a. The film was cut into strips of $1\times7\,cm^2$ size. Each strip was measured for thickness at five different points along the length. The strips employed had standard deviation of thickness less than 10%. The strip was then mounted onto the tensile tester (Shimadzu, EZ tester, Japan) with an initial grip separation of 5.0 cm and test speed of 10 mm/min. Five strips were evaluated for each film with different thickness and weight ratio and the results of mechanical properties averaged.

Results and Discussion

Apparent Solubility of Films Six grades of PVAs with different degrees of hydrolysation and molecular weights were used to prepare films (Table 1). All the films were clear, non-tacky and tough. However, when in contact with water, these films showed various solubilities. The films prepared from PVA I, II, III, or IV dissolved in water quickly and completely. Film solubilities in descending order were: PVA III>IV>I>II. In contrast, the films of PVA V or VI were slightly soluble in water and swelled to form hydrated films with good mechanical strength. Very soluble PVA III and IV resulted in composite films of high solubilities and were not selected for more extensive studies. It was also found that PVA I of lower molecular weight produced the best composite films for determination of the effects of the solubility of PVA on the properties of the resultant films.

Table 2. Apparent Solubilities (W%) of the Composite PVA Films at 37 °C

Content of PVA I (%)	PVA V–I films	PVA VI–I films
	W%±S.D. (%)	
0	15.5±3.4	47.3±8.4
40	28.2±3.4	51.4±6.4
60	35.2±2.0	49.0±7.2
80	44.0±3.9	47.8±6.6

Composite films prepared from combinations of PVA V with PVA I (PVA V–I) or PVA VI with PVA I (PVA VI–I) in different weight ratios were further studied. As shown in Table 2, the percentage of weight loss for PVA VI film was three times that for PVA V film. PVA VI–I films showed higher solubility than PVA V–I films. For PVA V–I films, apparent solubility increased significantly with increasing weight ratio of PVA I in the composite films ($p<0.05$). Whilst for PVA VI–I films, the presence and amount of PVA I in the composite films had little effect on the solubility of the films ($p>0.05$). PVA V–I films retained their integrity in water but PVA VI–I films appeared to lose their integrity to different extents after immersing the films in water for 24 h.

The observations from films prepared using individual PVAs showed that the solubility of PVA was affected by the degree of hydrolysation as well as the molecular weight of the polymer. Other workers have reported similar findings.[4] The solubility of PVA in water was attributed to the interaction of the hydroxyl groups in the polymer with water molecules through hydrogen bonds. Strong inter- and intramolecular hydrogen bonds were formed *via* hydroxyl groups between molecules of PVA with a higher degree of hydrolysation. This reduced the extent of interaction between PVA and water molecules, resulting in lower solubility in water. For PVA with a lower degree of hydrolysation, hydrogen bonding between the hydroxyl groups in the PVA molecules was reduced by steric hindrance from the significant quantities of residual hydrophobic acetate groups. This enabled greater interaction between the polymer and water molecules, resulting in greater aqueous solubility. Similarly, PVAs with higher molecular weights were less soluble since they exhibited greater intramolecular interaction. This was shown by the

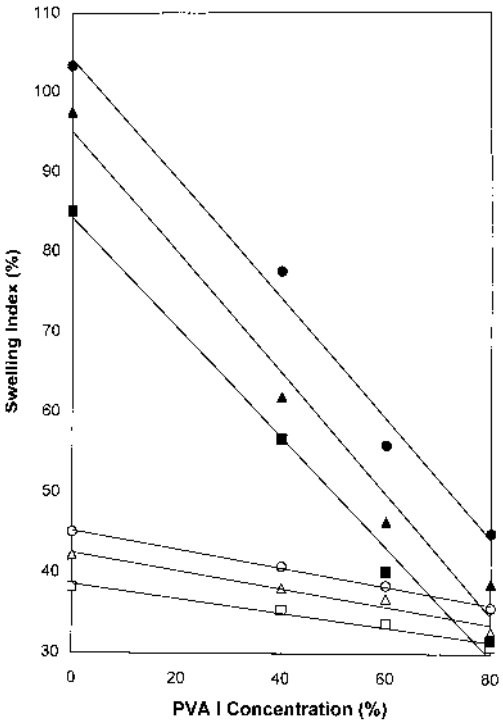

Fig. 1. Effects of PVA I Content on the Swelling Index of PVA V (Open Symbols) and PVA VI (Close Symbols) Composite Films with Thickness of 0.08 mm (○, ●), 0.12 mm (△, ▲) and 0.16 mm (□, ■)

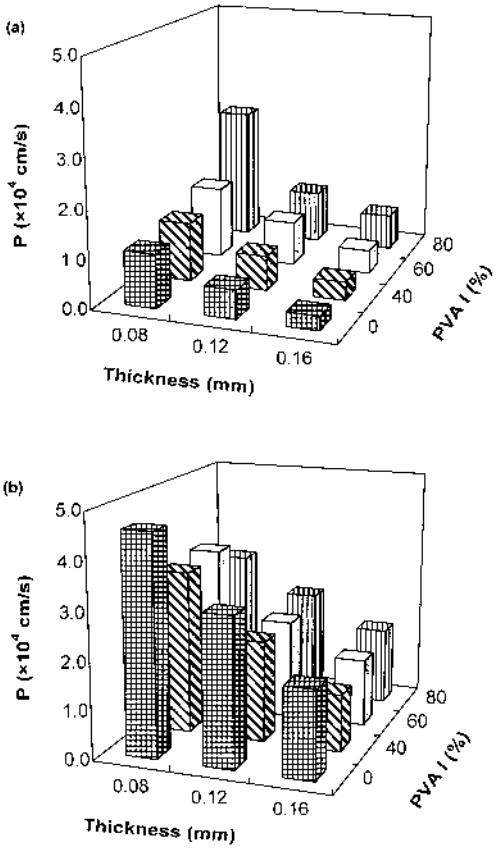

Fig. 2. Effects of Film Thickness and Composition on Permeability Coefficients of DS through Composite Films of PVA V–I (a) and PVA VI–I (b)

higher solubilities of PVA I and II compared to PVA V and VI. The addition of highly soluble PVA I enhanced the apparent solubility of the composite films to different extents. Interestingly, the effect was significant for PVA V–I films but marginal for PVA VI–I films. The marginal effect of PVA I, despite its greater solubility over PVA VI, suggested that the blend could be more than a simple mixture of PVAs. There was likely to be strong intermolecular interactions between PVA VI and PVA I.

Swelling Property of Films Figure 1 illustrates the effects of PVA grade, weight ratio and film thickness on the swelling properties of the composite films. PVA VI film had a higher swelling index than PVA V film ($p<0.05$). Increasing amounts of PVA I decreased the swelling index to a greater extent for PVA VI–I films compared to PVA V–I films. Increases in the film thickness also decreased the swelling index of PVA VI–I films to a greater extent.

The PVA molecule has both crystalline and amorphous regions. Other workers had observed that a lower degree of crystallinity and longer chain length in the amorphous region produced greater swelling of PVA.[4,5] As the degree of crystallinity increased with a decrease in the extent of polymerisation, polymer film swelling was found to decrease. Hence, the swelling property of PVA films was governed by the degree of crystallinity and the average chain length in the amorphous region of the film. It was possible that the degree of crystallinity of the composite film could be modified by using blends of PVAs. The addition of PVA I to PVA V or PVA VI film reduced the swelling index of the composite film to varying extents. The effect was more pronounced for PVA VI–I films compared to PVA V–I films. As shown earlier, PVA VI was more soluble than PVA V (Table 2). This seemed to imply that the swelling index was also affected by the solubility of the polymer. The reduction in the swelling indices of PVA VI–I films could be partially explained by the gradual dissolution of PVA VI and PVA I. Conversely, PVA V would form a swollen matrix that would dissolve less readily, resulting in less loss of film constituents and contribute to a lower reduction of the swelling indices of PVA V and PVA V–I films.

Permeation Study The permeation of DS through composite films prepared from PVA V or VI in combination with PVA I in different weight ratios and film thickness was studied. The effects of film thickness and weight ratio on the permeability coefficients of DS through the films are shown in Fig. 2.

At steady-state, the flux J of drug through the film is constant and is expressed by $J=D\cdot k\cdot(C_d-C_n)/h$, where D is the diffusion coefficient in the film, k is the partition coefficient between the film and the donor medium, h is the thickness of the film, C_n is the corrected concentration of drug in the receptor cell at time t, C_d is the concentration of drug in the donor cell and $(C_d-C_n)/h$ is the concentration gradient across the film. Under sink conditions, the concentration gradient can be considered equal to C_d/h. Combining P, which is the ratio between J and C_d, the following relationship is obtained as $P=D\cdot k/h$. If D and k are constants, then P is proportional to $1/h$. Sink conditions were maintained throughout the permeation study as the total percentage of the penetrated amount was less than 15%.[6] Therefore, the permeability coefficient of DS was found to decrease with increase in film thickness. The plots of permeability coefficient against reciprocal of thickness are nearly linear as shown in Fig. 3. The

deviation from linearity implied changes occurring in the film during the study.

The PVA VI–I films were more permeable to DS than PVA V–I films. The *P* values of the PVA V–I films increased in the following order of PVA V<PVA V–I 3 : 2<PVA V–I 2 : 3<PVA V–I 1 : 4. This indicated that the presence of PVA I in the composite films increased the permeability of films to DS. The enhancement effect was raised with increasing content of PVA I in the composite films. Among all the films in the permeation study, the PVA VI film was the most permeable. Addition of PVA I was observed to decrease the permeability of the PVA VI–I films. Interestingly, the permeability of PVA VI–I films with different weight ratios of 1 : 4, 2 : 3 and 3 : 2 were comparable, indicating that the amount of PVA I in the composite films had minimal effect on the permeation of DS across the films.

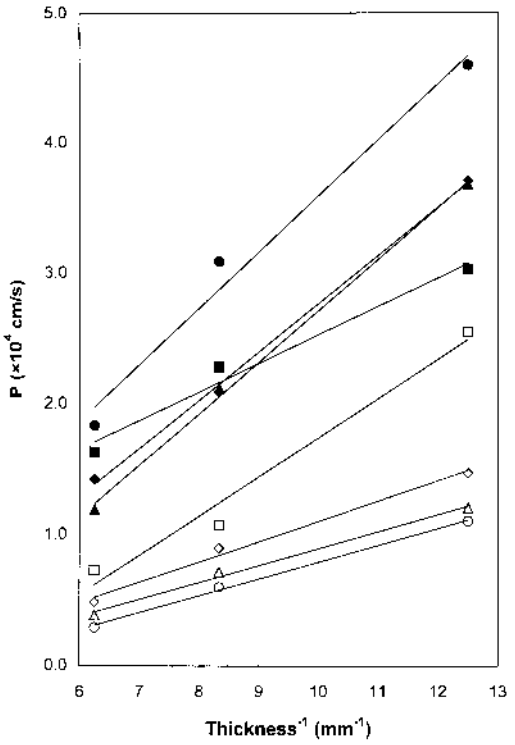

Fig. 3. Plots of Permeability Coefficient against Reciprocal of Thickness of PVA V–I (Open Symbols) and PVA VI–I (Close Symbols) Films Containing 0% (○, ●), 40% (△, ▲), 60% (◇, ◆) and 80% (□, ■) PVA I

The permeability of hydrophilic film to water-soluble drug is influenced by many factors including polymeric structure, apparent solubility and swelling property of the film.[7] When the film contacts water, water molecules will penetrate into the free spaces between the polymer chains and cause the film to swell. It has been shown that the hydrophilicity of film facilitates the penetration of water into the film. Films with a greater swelling property allow a greater extent of water penetration, thereby enhancing the permeability coefficient of drug. The increased chain mobility of the hydrophilic polymers following hydration also promoted their diffusion property.[8] The existence and amount of PVA I in the composite films made a critical contribution to the change in permeability of the films. When PVA I was added to PVA V or VI films, it had various effects on the permeability of film. Increasing the amount of PVA I either increased the solubility of the composite film or decreased the swelling property of the film. The permeability of the composite films depended on the net effect of these two properties.

In PVA V–I films, the effect of PVA I on the solubility of the films played a dominant role, with PVA I increasing the solubility of the films (Table 2). When the films were immersed in water, the portion of highly soluble PVA I dissolved quickly and hydrophilic pores were expected to form in the matrix, leading to increased permeability to DS. The permeability of these films to DS increased with increasing amount of PVA I in the composite films. While in the case of PVA VI–I films, the presence of PVA I had only a marginal effect on film solubility (Table 2), it did produce a significant reduction in the swelling properties (Fig. 1). The latter effect was expected to reduce the extent of water penetration and hence decreased film permeability. However, the results obtained showed that PVA VI–I films were generally more permeable than PVA V–I films. The higher solubility of PVA VI itself had contributed to the higher permeability of PVA VI–I films (Table 2).

Tensile Test of Films It was reported that the stress-strain or load-deformation curve of film was affected by molecular weight, crystallinity, type and proportion of additives in the composite film.[9] As the films studied exhibited plastic behaviour, the mechanical properties were characterized by elastic modulus and tensile strength. The elastic modulus

Table 3. Mechanical Properties of the Composite PVA Films

Film type	Film thickness (mm)					
	0.08	0.12	0.16	0.08	0.12	0.16
	Elasticity±S.D. (N/mm²)			Tensile strength±S.D. (N/mm²)		
PVA V	1977.1±42.5	1621.7±77.2	1381.8±144.3	50.0±3.7	40.9±1.9	30.1±1.8
PVA V–I 3 : 2	1856.3±142.8	1495.8±65.0	1294.1±61.6	50.6±8.2	40.4±2.2	28.2±2.6
PVA V–I 2 : 3	1775.0±131.8	1551.5±61.1	1247.0±93.0	51.4±2.4	39.3±4.8	27.5±1.9
PVA V–I 1 : 4	1885.2±48.9	1558.3±150.0	1249.5±75.0	54.0±2.0	40.8±4.4	26.2±2.6
PVA VI	612.1±74.8	503.0±57.1	383.7±19.9	30.8±3.3	27.2±1.3	22.1±1.2
PVA VI–I 3 : 2	805.7±88.4	659.4±46.8	586.8±23.8	34.5±1.9	28.6±1.1	26.0±1.2
PVA VI–I 2 : 3	813.6±82.5	671.6±50.5	555.9±13.6	34.8±2.9	30.3±2.6	24.9±1.0
PVA VI–I 1 : 4	904.7±73.5	775.6±60.0	618.4±22.6	33.3±2.2	27.5±2.9	23.5±1.2

was calculated from the initial straight-line portion of the load-deformation curve, which represented the resistance to deformation of materials under an applied load. Tensile strength was the maximum tensile stress sustained by the test specimen during a tensile test. Beyond the maximum tensile stress, necking of test specimen occurred and was accompanied by a fall in the tensile stress value. In general, the higher the modulus of elasticity and tensile strength, the stronger will be the film in that it is more elastic in response to stress.

As listed in Table 3, the elasticity values of PVA V–I films were found to be higher than those of PVA VI–I films. For PVA V–I films, the presence of PVA I slightly decreased elasticity, whereas for PVA VI–I films, the elasticity was significantly increased by addition of PVA I ($p<0.05$). The relationships between permeability coefficient and elasticity of the composite films are shown in Fig. 4. Lower elasticity of composite films corresponded to higher permeability. Elasticity is a measure of the stiffness and rigidity of a film, hence films with lower elasticity values were more flexible and likely to show increased drug permeability. The poorer linear correlation coefficient for 0.08 mm films could be attributed to the relative difficulty in handling the thinner 0.08 mm films. Some stretching of film or leaching out of soluble PVA I could contribute to imperfection in the film, thereby causing increased film permeability and variability.

PVA V–I films also had much higher tensile strengths than PVA VI–I films. PVA I showed minimal effects on the tensile strengths of the composite films. Tensile strength was not particularly discriminating in characterizing the mechanical property of the composite films in this study. On closer examination, it was evident that the tensile strengths of PVA V and PVA V–I films decreased as the thickness of films was increased. In contrast, PVA VI and PVA VI–I films were much less affected by thickness, showing only a small decrease in tensile strength with increased film thickness. The effect of film thickness on tensile strength was related to the homogeneity in the film forming process. As shown previously, PVA V was much less soluble than PVA VI. When thin films were cast, there was rapid deposition of less soluble PVA V, thus forming films that have higher elastic properties. When thicker films were prepared, the longer drying time enabled more orderliness in the deposition of the less soluble PVA V and films formed had much higher plastic properties. Consequently, lower tensile strengths were obtained as the yield loads and maximum loads supported by the films became lower. For the relative highly soluble PVA VI–I films, the films had a much higher degree of plasticity due to more consistent deposition of polymer molecules in the film forming process and as a result, tensile strength values were largely similar, irrespective of the thickness of the films.

The PVA films evaluated showed strong plastic behaviour and did not show any break point. This strongly plastic behaviour would certainly allow the films to maintain structural integrity and continuity under abnormal external stresses. However, the films may be distorted plastically with relative ease. Thus, a film with adequate tensile strength may be desirable to reduce the possibility of film deformation under moderate stress as changes in the film surface can alter drug permeability rate.

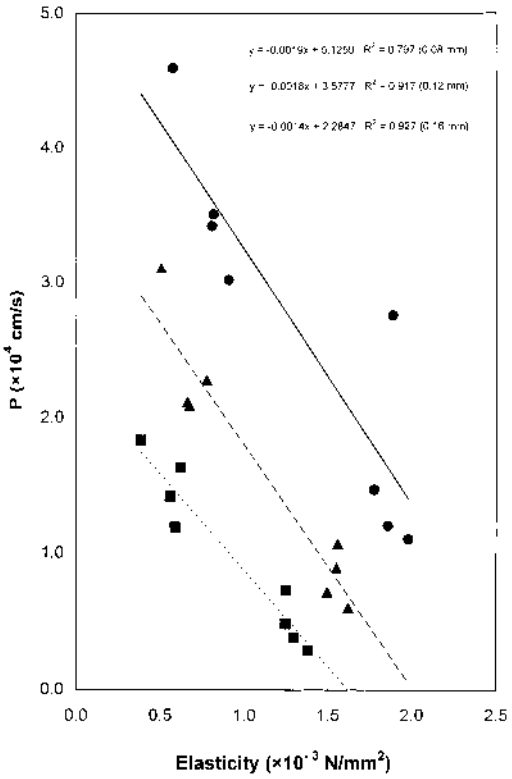

Fig. 4. Relationship between Permeability Coefficient and Elasticity of Films with Thickness of 0.08 mm (●), 0.12 mm (▲) and 0.16 mm (■)

Conclusions

The presence and amount of PVA I in PVA composite films was a key factor affecting the apparent solubility and swelling property, and consequently the permeability of the films. An increasing amount of PVA I either increased the solubility or decreased the swelling property of the composite film. For PVA V–I films, the effect of PVA I on solubility played a dominant role, whilst for PVA VI–I films, the effect of PVA I on swelling property was more important. Film thickness also affected the permeability coefficient of diclofenac sodium through composite films. The addition of PVA I raised the elastic moduli of PVA VI–I composite films but it showed only a slight effect on PVA V–I films. Proper selection of PVA grades and weight ratio was essential for successful preparation of PVA composite films with the desired characteristics.

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