In Vitro Release of Salicylic Acid through Poly(vinyl alcohol-*g*-itaconic acid) Membranes

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ABSTRACT: In this study, itaconic acid (IA) was grafted on poly(vinyl alcohol) (PVA) at two different grafting percentages, 7.0% (w/w) and 14.0% (w/w), and membranes were prepared from the grafted copolymer (PVA-*g*-IA). Performances of PVA and PVA-*g*-IA membranes for the transdermal release of salicylic acid (SA) at *in vitro* conditions were investigated by using 2.0 mg/mL SA solutions. Effect of the pH on the release of SA was studied by keeping pH of donor and acceptor solutions in a range of (2.1–7.4). Permeation studies were also carried on at different SA concentrations. Effect of temperature on the release of SA was investigated in the temperature range of (32–39) (±1)°C. Results showed that presence of IA decreased the release of SA from the PVA membranes and 73% SA was released at the end of 48 h at (32 ± 1)°C from the IA-1 membranes. pH affected the release of SA through the grafted membranes and studies showed that release of SA was high with donor solution pH of 2.1. When the pH of donor and receiver solutions were kept at the same pH value, the overall SA% in permeate increased. Increase in concentration of SA decreased the release of SA for the studied membranes. Release of SA from PVA-*g*-IA membranes was temperature sensitive and increase in temperature from (32 ± 1)°C to (39 ± 1)°C increased the release percentage of SA by 24% (w/w). The overall activation energy for the permeation of SA through IA-1 membrane was found to be 22.97 kJ/mol. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 3291–3299, 2008

Key words: membranes; drug delivery systems; salicylic acid; itaconic acid; PVA

INTRODUCTION

The ways in which chemicals or drugs are administered have gained increasing attention in the past two decades. The most common form of delivery is via the oral route and this leads to a need for high and/or frequent dosing. This is not economical and sometimes results in damaging side effects. As a consequence, increasing attention has been focused on the methods of giving drugs continually for prolonged time periods and in a controlled fashion. In the pharmaceutical field, the intravenous route, the skin, the gastrointestinal tract, the nose, and the eye are of particular importance. Transdermal drug delivery system uses a small patch that is placed on the skin and holds theoretical advantage to conventional drug administration possess the potential to avoid the generally observed ''peaks'' and ''valleys'' in the plasma drug concentration profile observed in patients receiving oral drug delivery formulations and also avoids toxic or subtherapeutic drug plasma levels. So, skin penetration studies play an essential role in the optimization of drug and formulation design in dermal and transdermal delivery. Therefore, the experimental use of *in vitro* permeation techniques is highly important.[1] The two main investigative aspects of transdermal delivery studies are the determination of the release characteristics of the drug and the quantitative evaluation of the transport of the drug across the stratum corneum and its availability to the systemic system.[2] Polymers are the backbone of the transdermal drug delivery systems.[3] Poly(vinyl alcohol) (PVA) is a chemically stable hydrophilic polymer, and it has good film forming ability.[4–6] Because of its several desirable properties such as nontoxicity and noncarcinogenicity, PVA in different physical forms finds extensive applications as biomaterials[7] such as contact lenses, artificial blood vessels, intestines,[8] pancreas,[9] and kidneys.[10] Recent reports have shown that PVA is also a good candidate for controlled release of pharmaceutical components.[3,6–8,10–14] However, PVA has poor stability in water because of its highly hydrophilic character. To overcome this problem, PVA should be modified by copolymerization,[14] grafting,[3,5,15] crosslinking,[4,6,8,10,16–19] and blending.[3,7,20]

SA is an *o*-hydroxy benzoic acid and it belongs to group of nonsteroidal antiinflammatory drugs.[21] It is an active component of aspirin and the regular use of aspirin by adults appears to reduce the risk of many diseases.[3] Main risk with oral therapeutic doses of SA, is mostly gastrointestinal irritation. To

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overcome this disadvantages, some studies were carried out related to the transdermal usage of it.[1,3,21–30]

Walkow and McGinity[25] studied the effect of physicochemical properties on the *in vitro* diffusion of salicylic acid (SA) through cellulose, dimethyl polysiloxane membranes and pig skin into a receptor phase of aqueous glycol, water and buffer solutions; they concluded that the SA diffusion was decreased as the receptor phase pH was lowered. Venkatesh et al.[27] studied the *in vitro* release kinetics of SA from hydrogel patch formulations; they have determined that the release of SA followed the matrix diffusion controlled mechanism and the storage of the packaged formulations under ambient conditions for 9 months caused no change in the extent of SA release. Takanaga et al.[28] studied the pH dependent and carrier mediated transport of SA across caco-2 cells; from their results, it was concluded that the transcellular transport of [^{14}C] SA across caco-2 cells is pH dependent and carrier mediated transport mechanism is specific for monocarboxylic acids. Neuhoff et al.[29] studied the pH dependent passive and active transport of acidic drugs across caco-2 cell monolayer; their study showed that the asymmetry in bidirectional transport of acidic drugs is affected by both passive and active components in the presence of pH gradients across caco-2 cells.

In this study, we plan to use PVA as a base polymer to prepare membranes for the transdermal release of SA at *in vitro* conditions. PVA is soluble in water and to overcome its solubility it was crosslinked by heat treatment. However, by this process PVA loses its hydrophilicity and to increase the hydrophilic character of PVA membranes we tried to modify them via graft polymerization using hydrophilic vinyl monomer, itaconic acid (IA). The effect of the presence of IA on the release of SA through the PVA-*g*-IA membranes was investigated. The effects of the pH, temperature, and the concentration SA solutions on the release performance of the membranes were studied.

EXPERIMENTAL

Materials

PVA (M_w= 72,000 g/mol, degree of saponification > 98%), SA ($C_7H_6O_3$) (138.12 g/mol), acetone (C_3H_6O) (58.08 g/mol; 0.79 kg/L), and methanol (CH_3OH) (32.04 g/mol; 0.79 kg/L) were supplied by Merck Chemicals Ltd., UK. Itaconic acid ($C_5H_6O_4$) (130.10 g/mol) and ammonium cerium(IV) nitrate ($Ce(NH_4)_2(NO_3)_6$) (548.2 g/mol) were Sigma-Aldrich (Steinheim, Germany) product. Disodium hydrogen phosphate ($Na_2HPO_4{\cdot}2H_2O$) and sodium dihydrogen phosphate ($NaH_2PO_4{\cdot}2H_2O$) were purchased from Fluka (Steinheim, Germany). Sodium acetate (CH_3COONa), acetic acid (CH_3COOH), and nitric acid (HNO_3) were all Reidel (Germany) products.

Synthesis of PVA-*g*-IA copolymer

PVA-*g*-IA copolymer was synthesized as in the study of Işıklan and Şanlı.[15] PVA (6% (w/v)) and IA (0.5*M*) were introduced into a three-necked round bottom flask equipped with a magnetic stirrer, thermometer, and N_2 inlet. Then the flask was placed in a constant temperature bath. After the addition of $9.12 \times 10^{-3}M$ ammonium cerium(IV) nitrate and $0.188M$ HNO_3, polymerization reaction was carried out for 4 h. At the end of this period grafted copolymer was precipitated in an excess amount of acetone, filtered, and washed with methanol to remove the unreacted IA. Then the copolymer was dried under vacuum.

The temperature of the grafting medium was kept at two different temperatures, 40 and 60°C. The graft yields (%) of the copolymers calculated from the weight increase of the copolymers by using eq. (1) were found as 7.5% (IA-1) and 14.0% (IA-2) at 40 and 60°C, respectively.

$$\text{Graft yield } (\%) = \frac{(w_g - w_i)}{w_i} \times 100 \qquad (1)$$

where w_g and w_i denotes the weight of the grafted and original films, respectively.

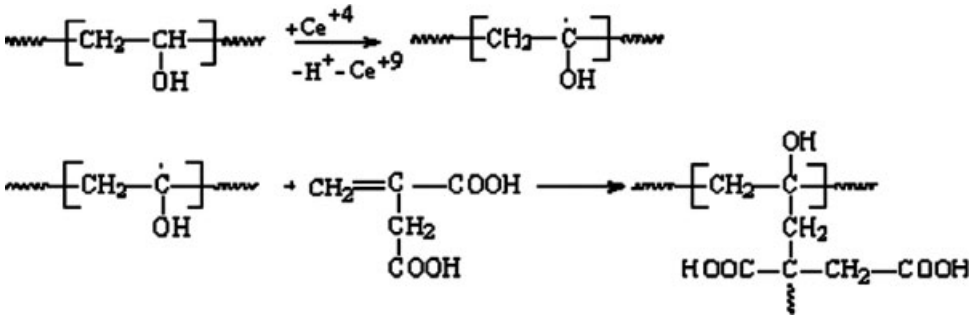
The proposed mechanism for the grafting process, in which ammonium cerium(IV) nitrate attracts hydrogen atom from the PVA chain, forms a radical and attacks itaconic acid through the methylene group to produce PVA-*g*-IA copolymer (Scheme 1).

Preparation of PVA membranes

PVA membranes were prepared by using aqueous solution of PVA at a concentration of 5.0% (w/v). Predetermined amount of polymer solution was cast onto the petri dishes. After complete dryness, membranes were removed from the petri dishes and they were crosslinked by heat treatment at 150°C for 1 h to prevent the solubility of the membranes in aqueous solutions, and the proposed crosslinking reaction was given in Scheme 2. The thickness of the PVA membranes was determined as (20 ± 5) μm by using precision micrometer (Aldrich, Milwaukee, WI). The prepared membranes were preserved in buffer solutions till to use.

Preparation of PVA-*g*-IA membranes

PVA-*g*-IA membranes were prepared from the aqueous solutions of the copolymers at a concentration of 5.0% (w/v). Similar to the PVA membranes, PVA-*g*-IA membranes were also heat treated at 150°C for crosslinking reaction. The thickness of PVA-*g*-IA membranes was determined as (20 ± 5) μm. They were preserved in buffer solutions.



Scheme 1 Proposed reaction mechanism for grafting IA on PVA.

Infrared analysis

Infrared spectra of PVA and PVA-*g*-IA membranes were measured as films with Fourier Transform Infrared (FTIR) Spectrometer of Unicam Co. (UK), Mattson 1000 and were presented in Figure 1. The spectrum of PVA shows the absorption peak around 1715 cm^{-1} that belongs to the stretching vibrations of C=O groups of unhydrolized vinyl acetate groups present in PVA at 2% w/w. The stretching vibrations at around 1150–1107 cm^{-1} belongs to C—O bonds in vinyl acetate, at 3400 cm^{-1} O—H bonds in PVA, and at 2980–2850 cm^{-1} C—H bonds in aliphatic groups.[3,15,31] The increased peak intensity of C=O group in the spectrum of IA-1 and IA-2 associates to the presence the additional C=O groups by IA.

Scanning electron microscope studies

For scanning electron microscope analysis, the dried membranes were sputtered with gold in vacuum before viewing under the microscope (Model JEOL, JEM-100CXII, Tokyo, Japan) and it was determined that both PVA and PVA-*g*-IA membranes are homogenous-nonporous membranes.

Swelling studies

Swelling degrees percentages, SD%, of the membranes were computed by using eq. (2)

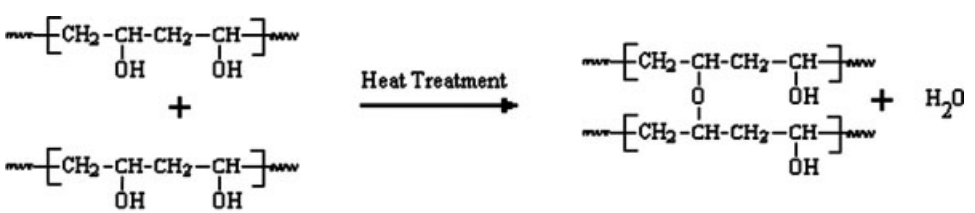
$$\mathrm{SD}\% = \frac{W - W_0}{W_0} \times 100 \qquad (2)$$

where W and W_0 are the wet and dry masses of the membranes, respectively.

Permeation experiments

Permeation experiments were carried out at skin surface temperature of (32 ± 1)°C by using Franz Diffusion Cell, which consists of two parts (donor and acceptor part) that are separated by a membrane. The donor compartment holds the drug preparation and the acceptor compartment the receiver medium. Three milliliter of 2 mg/mL SA solution at different pH values (pH 2.10–7.40) was used as donor solution in the upper compartment and a phosphate (pH 7.4) or an acetate (pH 2.1–5.0) buffer solution was used as an acceptor solution depending on the desired pH value in the lower compartment of the cell. Silicone grease was used to produce leak-proof seals between the membrane and two compartments of the cell. The sampling arm and the donor compartment of the cell were occluded to prevent the evaporation of the solvent. The lower compartment of the cell (acceptor solution) was stirred by using a magnetic stirrer operating at constant rotation rate to obtain uniform composition during the permeation. The receiver solution was sampled periodically and samples were replaced with equal volume of fresh receiver solution. The analysis of the samples was carried out spectrophotometrically at 298 nm by using Unicam UV2-100 UV–vis Spectrophotometer (UK). All of the data points are the average of at least three experimental results. The experiments are fairly reproducible.

Permeability coefficient (P) of a membrane, which is a measure of the permeation ability of the membrane, was determined from the slope of the linear portion of Q_t versus t according to the eq. (3).[6]



Scheme 2 Proposed reaction mechanism for crosslinking PVA membranes.

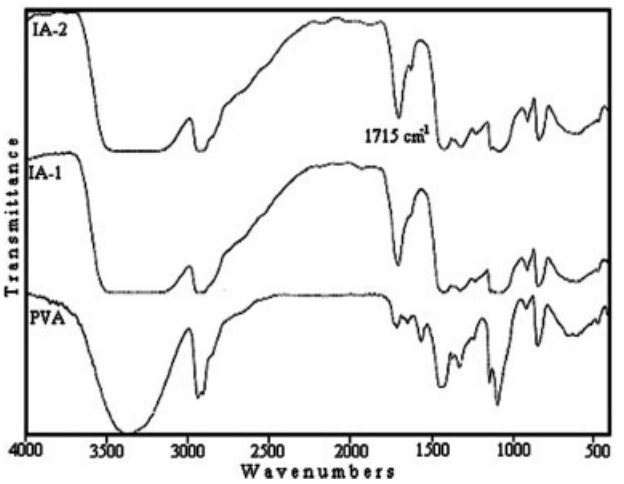


Figure 1 FTIR spectrums of PVA, IA-1 and IA-2 membranes.

$$Q_t = \frac{PC_o^D}{L}\left(t - \frac{L^2}{6D}\right) \quad (3)$$

where C_o^D is the concentration of the donor side of the cell, D is the diffusion coefficient, L is the thickness of the membrane, t is the time and Q_t is the amount of drug diffused through the membrane unit area at time t.

RESULTS AND DISCUSSION

Effect of pH of donor solution on the release of SA

The effect of the pH of the donor solution on the release characteristics of SA through PVA and IA-1 membrane was studied at (32 ± 1)°C by using 2.0 mg/mL SA solution at pH of 2.1–7.4. The pH of the acceptor solution was kept constant at 7.4 by using a phosphate buffer solution. The results of the permeation studies of the PVA and IA-1 membranes were given in Figures 2 and 3, respectively.

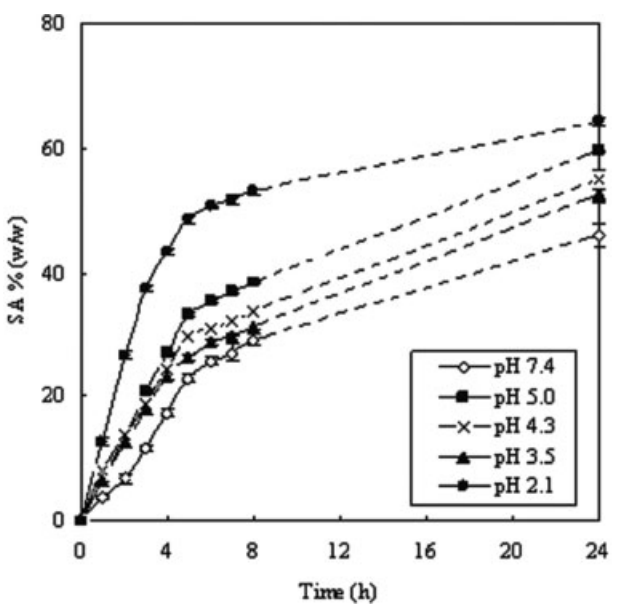


Figure 2 Effect of donor solution pH on the release of SA through PVA membranes. (SA = 2.0 mg/mL; T = (32 ± 1)°C; pH (acceptor) = 7.4).

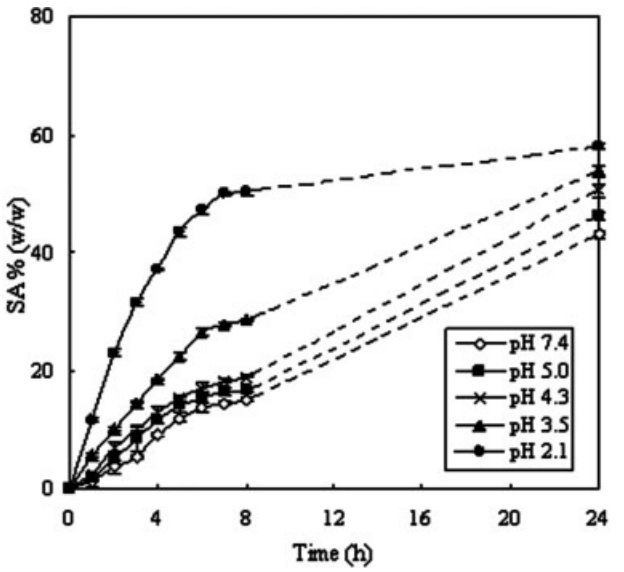


Figure 3 Effect of donor solution pH on the release of SA through IA-1 membranes. (SA = 2.0 mg/mL; T = (32 ± 1)°C; pH (acceptor) = 7.4).

As it is reflected from the figures, the released amount of SA is high at pH 2.1 for both PVA and IA-1 membranes and at pH 7.4; the permeated SA takes the lowest value among the studied pH values. Although the permeated amount of SA through IA-1 membranes decreased as the pH of donor compartment increased, the situation is somewhat different for PVA.

It is known that SA is a weak acid (pK_a(SA) = 2.9) and the percent ionization values of SA can be calculated by using Henderson-Hasselbalch equation.[22] In Table I, percent ionization values of SA at different pH values were given. As it is seen clearly from the table, ionization of SA increases with the increase in the pH of the SA solution. Decrease in the permeated amount of SA for IA-1 membranes with an increase in the pH may be connected with the fact that itaconic acid dissociation constants are in that

TABLE I
Ionization % of SA Solutions at Different pH Values

pH	Ionization % of SA
2.10	9.00
3.50	72.00
4.30	94.00
5.00	99.00
7.40	99.99

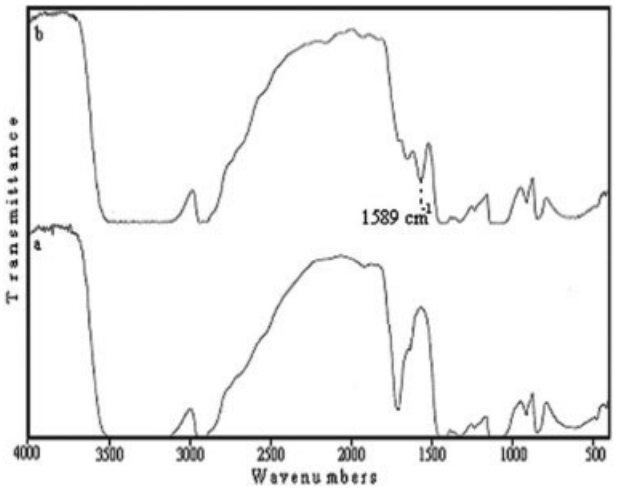


Figure 4 FTIR spectrum of PVA-*g*-IA membranes (a) before (b) after the permeation studies.

pH range (pKa_1 = 3.85, pKa_2 = 5.44)[32] and the transition occurs in the pH range 3–7, very close to the pKa_1 and pKa_2 values of itaconic acid, so ionization of the carboxylic groups possibly lead to electrostatic repulsions between the COO^- groups of itaconic acid and SA. As a result, only the unionized species of SA determines the released percentage of SA from IA-1 membranes. This should be the reason of getting high percentage SA release for IA-1 membranes at pH 2.1 at which ionization of SA is very low. In Figure 4, FTIR spectrum of IA-1 membrane before and after the use for permeation was given. As it is reflected from the spectrum, appearance of C=C ring stretch at 1589 cm^{-1} confirms interaction between the unionized SA molecules and COO^- groups of itaconic acid through hydrogen bonding leading to low permeation.

Leveque et al.[1] studied the permeability of SA through human skin. They stated that the permeation profiles determined by Franz cells and microdialysis were similar and the flux of SA decreased with the amount of ionized form of SA at high pH values, which means that the transdermal permeation is due to the unionized species.

Neuhoff et al.[29] studied the transport of SA across caco-2 cells. They observed that the permeability of the cells to SA increased with decreased buffer pH. They stated that increase in the fraction of uncharged drug provides a greater force for transcellular diffusion.

Kamal et al.[33] studied the permeation of ionized salicylate derivatives through Guinea pig dorsal skin. They concluded that at acidic pH values, the permeability of SA decreased with an increase in the ratio of the ionized form to nonionized form of weakly acidic or basic drugs.

Permeation profile for PVA membranes could be explained by examining the swelling behavior of the PVA membranes since the transfer of the molecules through a membrane is mainly affected from the swelling behavior of the membrane. The increase in the SD% value of a membrane increases the amount of the free volumes that were suitable for the permeation of diffusing molecules. SD% of the PVA membranes in 2.0 mg/mL SA solutions at different pH values were calculated by using eq. (2) and were given in Table II. From the table, it is seen that decrease in the pH increases the SD% for PVA membranes. This explains the reason of the corresponding permeated SA% values of PVA membranes at pH 2.1 and 7.4. However, the permeation just follows the reverse direction for pH 3.5, 4.3, and 5.0 in Figure 2, in spite of the decrease in the SD% of the PVA membranes. The permeation of salicylate as anions occurred during weakly acidic skin conditions (pH 4.5–6.5).[33] Therefore, the total amount of permeated SA is the sum of the ionized and nonionized forms of SA at pH 3.5, 4.3, and 5.0 for PVA membranes, so the released amount of SA increases.

Effect of the graft yield percentage of IA on the release of SA

To determine the effect of the grafted amount of itaconic acid on the release of SA, permeation of SA through IA-2 membranes were also studied at (32 ± 1)°C by using 2.0 mg/mL SA solution at pH of 2.1 which is the pH at which highest permeation was achieved. The pH of the acceptor solution was kept constant at 7.4 by using phosphate buffer solution. The results of the permeation were given in Figure 5 together with the release profiles of PVA and IA-1 membranes at the same pH. As it is seen from the figure, IA-2 membranes have distinctly lower SA% values than PVA and IA-1 membranes.

Because IA-2 membrane have higher graft yield percentage (14.0% (w/w)) than IA-1 membrane (7.5% (w/w)), they have greater number of —COOH groups than IA-1 membranes so more electrostatic repulsion of ionized SA with the COO^- of itaconic acid and more interaction of unionized SA species with membrane material will occur leading to low SA permeation.

In Table III, permeability coefficients of the PVA and IA grafted membranes for SA solutions at pH

TABLE II
Change in SD% Values of PVA Membranes in 2.0 mg/mL SA Solutions with pH

pH	SD% (w/w)
2.10	60.60
3.50	56.60
4.30	54.60
5.00	52.80
7.40	47.50

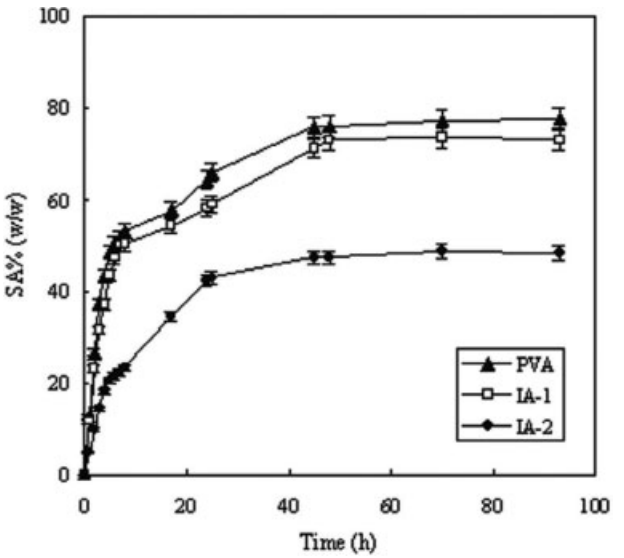


Figure 5 Comparison of the performances of PVA, IA-1 and IA-2 membranes. (SA = 2.0 mg/mL; T = (32 ± 1)°C; pH (donor) = 2.1; pH (acceptor) = 7.4).

2.1 were given together with the SD% values at this pH. As it is seen from the table, SD% value for IA-2 membrane was found to be lower than that of both PVA and IA-1 membrane. This was also the reason of getting low released percentages of SA for IA-2 membrane.

It can also be stated from Table III that PVA membranes have greater permeability for SA than IA grafted membranes and introduction of IA into PVA slows down the permeation ability of PVA membranes toward SA (Fig. 5).

Effect of SA concentration on the release of SA

To investigate the effect of the concentration of SA on the release performances of the membranes, saturated solutions of SA was prepared at pH 2.1 and the pH of acceptor solution was adjusted to 7.4. The permeation studies were carried on at (32 ± 1)°C. The results of the permeation for PVA and IA-1 were given in Figure 6.

As it is seen from the figure, the released amount of SA decreased with saturation for both PVA and IA-1 membranes. The permeability coefficients of the PVA and IA-1 membranes for the permeation of saturated SA solutions at pH 2.1 were calculated by using eq. (3) and were found as 1.03×10^{-4} cm^2/h and 0.56×10^{-4} cm^2/h, respectively. As it is reflected from the comparison of these results with that were calculated in case of 2.0 mg/mL SA solutions (Table III), P values of both types of membranes were found to be lower for the saturated than the unsaturated SA. The decrease in the permeation of SA with saturation possibly caused from the concentration polarization. Similar result was stated in the literature.[3,29]

Neuhoff et al.[29] reported that as the concentration of SA increased from 25 μM to 33 mM, the permeability was reduced by 80% by using caco-2 cells.

TABLE III
SD% and the Permeability Coefficients of the Membranes[a]

Membrane	SD% (w/w) (pH = 2.1)	P (cm^2/h) ($\times 10^4$)
PVA	60.60	2.01
IA-1	58.50	1.79
IA-2	49.70	0.87

[a] SA = 2.0 mg/mL; T = (32 ± 1)°C; pH (donor) = 2.10; pH (acceptor) = 7.4.

Effect of pH of the acceptor solution on the release of SA

In this part of the study, the pH of the acceptor solution was adjusted to the pH of the donor solution (pH 2.1–7.4). The concentrations of the SA solutions and the temperature were kept constant as 2.0 mg/mL and (32 ± 1)°C, respectively. The results of the permeation studies of the PVA and IA-1 membranes were given in Figures 7 and 8, respectively.

As it is seen from the figures, the released amount of SA increased when the pH of the acceptor compartment is kept at the same pH with that of the donor solution and the permeation profiles followed the same trend as in the case at which the pH of the acceptor solution is 7.4.

PVA membranes have high SD% values at low pH, as given in Table II. As the pH of the both sides

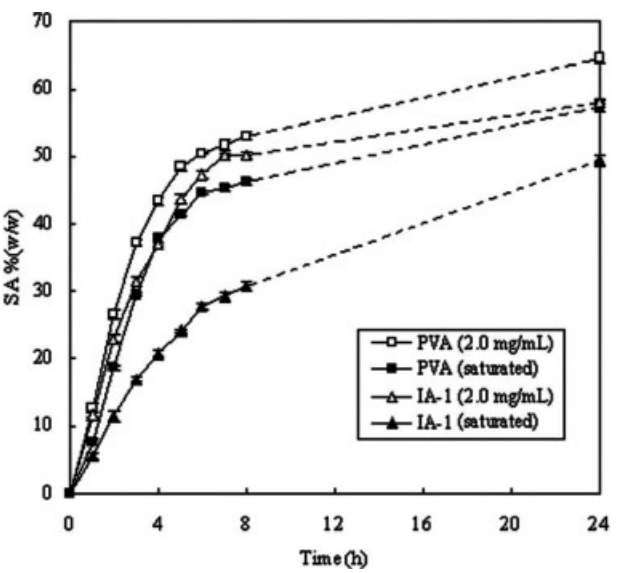


Figure 6 Effect of the concentration on the release of SA through PVA and IA-1 membranes. (T = (32 ± 1)°C; pH (donor) = 2.1; pH (acceptor) = 7.4).

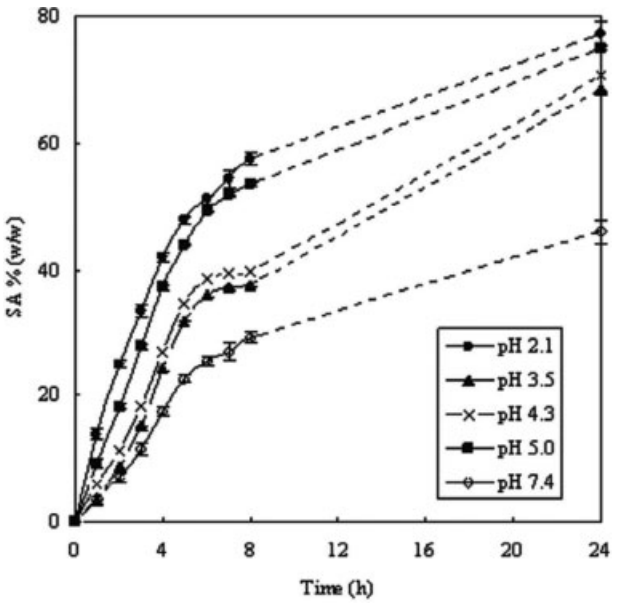


Figure 7 Effect the acceptor solution pH on the release of SA through PVA membranes. (SA = 2.0 mg/mL; $T = (32 \pm 1)^{\circ}C$).

of the membrane was kept at the same value, there occurs a symmetric swelling at both sides of the membrane surface which leads to more suitable free volume for permeation. This may be the reason getting the greater release percentages than that was obtained as the pH of the both sides of the diffusion cell was kept at different pH values.

Effect of temperature on the release of SA

To investigate the dependence of the permeation of SA on temperature for the IA-I membranes, permeation studies were performed at skin surface, normal body and fevered body temperatures (32 ± 1), (37 ± 1), and (39 ± 1)°C, respectively, by using 2.00 mg/mL SA solution at pH 2.1. The pH of the acceptor compartment was kept constant at 7.4. The results of the permeation were given in Figure 9.

As it is seen from the figure, increase in temperature increased the released amount of SA. The increase in the percent release of SA with temperature can be expressed by free volume theory.[34] According to this theory, thermal motion of polymer chains in the amorphous regions randomly produces free volume. As the temperature increases, the frequency and the amplitude of the chain jumping (i.e., thermal agitation) increase and the resulting free volumes become larger. Additionally, increase in temperature increases the mobility of the permeants.[35] Therefore, an attractive interaction between the permeating particles and also with the membrane material decreases. This also accelerates the permeation positively and results an increase in the amount of permeants. Similar results were reported in the literature.

Huang and Yeom[17] stated that the interaction between the permeated molecules and also with the membrane material decreases with an increase in the temperature for the hydrophilic membranes that have a relatively high polarity and strong interaction with hydrophilic groups through especially hydrogen bonding. The same interaction was also stated by Asman and Şanlı[19]; they prepared crosslinked poly(vinyl alcohol)/poly(acrylic acid) blend membranes and used them in the pervaporation-separation of acetic acid-water mixtures. It was concluded that temperature increased the permeation rate by

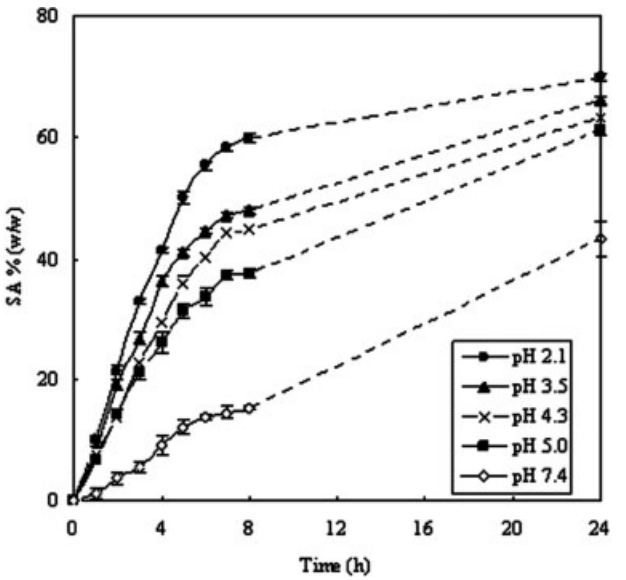


Figure 8 Effect the acceptor solution pH on the release of SA through IA-1 membranes. (SA = 2.0 mg/mL; $T = (32 \pm 1)^{\circ}C$).

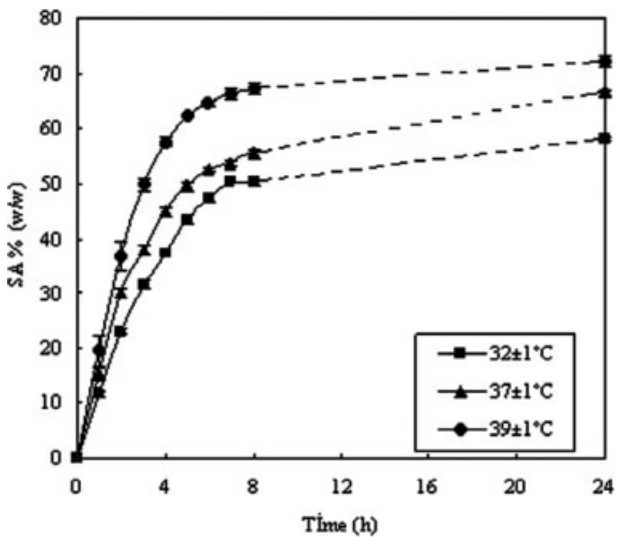


Figure 9 Effect of the temperature on the release of SA through IA-1 membrane. (SA = 2.0 mg/mL; pH (donor) = 2.1; pH (acceptor) = 7.4).

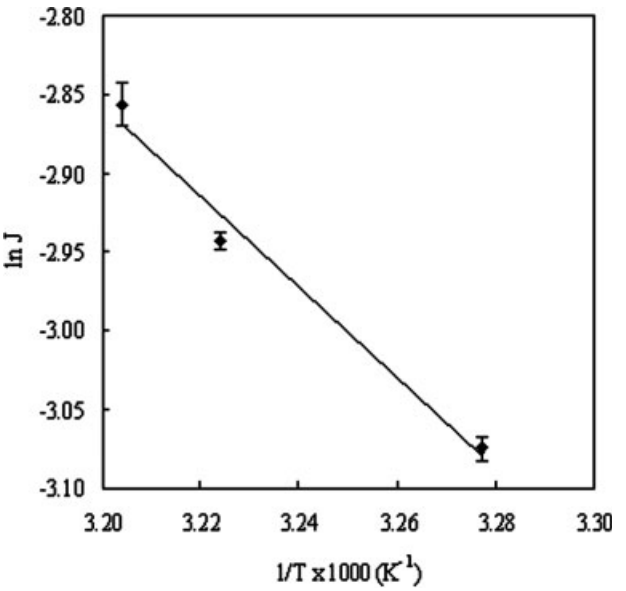


Figure 10 ln J versus $1/T$ diagram for the permeation of SA through IA-1 membrane.

increasing the free volumes that were responsible for permeation by the way as explained earlier.

The transfer of the molecules through a polymeric membrane follows an Arrhenius type of relation.[17,34,36]

$$J = A \exp\left(E_a/RT\right) \quad (4)$$

where J is the mass transferred per unit area in unit time (mg/cm^{2}h), A is the preexponential factor and E_a is the overall activation energy in kJ/mol. To determine the overall activation energy for the permeation of SA through IA-I membranes, permeation studies were carried on at (32–39) ($\pm$1)°C and E_a was determined from the slope of linear regression line of logarithmic permeation rate versus the reciprocal of the absolute temperature within one pH-gradient system for IA-I membranes (Fig. 10) and the overall activation energy was found to be as 22.97 kJ/mol.

Neuhoff et al.[29] have found that E_a for the permeation of 25 μM SA solutions through caco-2 cell monolayers changed between 50 and 70 kJ/mol depending on the pH of donor compartment (pH 5.0–7.4) when the pH of acceptor compartment was kept constant at 7.4.

CONCLUSIONS

Following results can be withdrawn from the study;

1. Grafting of IA onto PVA affected the permeation behavior of PVA membranes and the released amount of SA from PVA-*g*-IA membranes was found to be lower than that of PVA membranes. Increase in the grafted amount of IA decreased the release% of SA from the grafted membranes.
2. The pH of the donor and acceptor solutions affected the permeation of SA through PVA-*g*-IA membranes. The released amount of SA is high at pH 2.1 for both PVA and IA-1 membranes and takes the lowest value at donor pH of 7.4 among the studied pH values. It was determined that the release % of SA was high when donor and receiver pH are the same value.
3. Seventy-three percent SA was released at the end of 48 h at (32 $\pm$ 1)°C from the IA-1 membranes when the pH of donor and acceptor solutions were 2.1 and 7.4, respectively.
4. At high SA concentrations release% of SA decreased and permeation of SA through the membranes was mainly carried on by unionized SA molecules.
5. The release of SA from PVA-*g*-IA membranes was found to be temperature dependent and high temperature facilitated the permeation of SA through the membranes. Increase in the temperature from (32 $\pm$ 1) to (39 $\pm$ 1)°C increased the percent release of SA from IA-1 membranes by 24% (w/w).
6. Overall activation energy for the permeation of SA through PVA-*g*-IA membranes was found to be 22.97 kJ/mol.

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