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Starch-Based Membranes for Controlled Release of 5-Fluorouracil In Vitro

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Starch is a natural polymer that is among the sustainable materials and has the characteristics of being a green material in harmony with nature. In this study, a potential transdermal release system was evaluated by investigating 5-fluorouracil (5-FU) transfer through starch/poly(vinyl alcohol) (PVA) membranes in vitro. The effects of membrane thickness, starch/PVA blending ratio, pH, and temperature on the release of 5-FU from the membranes were studied. At the end of the study, it was deduced that decrease in pH reduces the released amount of 5-FU from starch/PVA membranes and 5-FU transfer from membranes could be controlled within a fairly constant range. The diffusion coefficient was determined as 4.84×10^{-3}, 4.49×10^{-3} and 2.54×10^{-3} $cm^2 s^{-1}$ for the pH of 7.4, 5.5, and 3.5, respectively. The activation energy for the permeation 5-FU from starch/PVA membrane (60/40, v/v) was found to be 9.72 $kJ\,mol^{-1}$.

Introduction

Fluctuations in blood level that occur with conventional dosage forms can be eliminated using controlled release systems. With the use of controlled release drugs, the severity and frequency of adverse effects caused by possible high concentrations with conventional preparations are reduced, and the accumulation of drugs that may occur with long-term drug use is minimized.[1] In transdermal delivery systems, the active substance is selectively transferred through permeable membranes, and is therefore among the preferred drug preparations. The polymer to be used in drug release must be inert, biocompatible, good mechanical strength, suitable for drug loading, comfortable and safe for the patient, easy to fabricate, and sterilize. Also, the polymeric material used must have the property to give the desired release rate for the bioactive or specific active substance.[1]

With regard to its completely biodegradable, low cost, and renewable structure, the starch in the polysaccharide group is highly stored in plants and is considered a promising candidate polymer in the development of sustainable materials.[2] Polysaccharides, which are defined as polymeric carbohydrate structures formed by the combination of repeating monosaccharide units with glycoside bonds, play an important role in drug release systems with their superior properties.

5-FU is used especially in the treatment of colorectal, breast, ovary, bladder, uterine cervix, endometrium, prostate, head, neck, pancreas, stomach, skin, and liver cancer.[3] But it has adverse effects on the stomach, intestines, nervous system, skin, and heart in the human body.[3a] The fact that 5-FU has various adverse effects, is sensitive to light and has low solubility in water limits the usage area of 5-FU. For this reason, it is possible to reduce the adverse effects of 5-FU by selecting an appropriate controlled release system.

In order to deliver different types of therapeutic agents to the target site, either orally or parenterally, in a rate-controlled manner, polymeric or nanospheres have been used.[4] The results of the in vivo study show that when administered transdermally, some drugs have the potential to increase absorption and hence bioavailability compared to the oral route.[5] Transdermal drug applications can be used alternatively instead of traditional drug administration methods (oral, intavenous, intramuscular etc) due to their easy application, non-invasiveness, local targeting, patient comfort, avoidance of hepatic metabolism in the first pass, uniform plasma levels, long term effect, decrease in dosing frequency, utility for potent drugs, reduction of adverse effects, and flexibility of terminating drug.[5a,6] Transdermal formulation is applied directly to the skin, providing a systemic effect at a controlled rate without entering the portal circulation.[5b,7] Controlled release transdermal drug administration is used in neoadjuvant chemotherapy as a topical or local reservoir system, in the adjuvant treatment of post-surgery tumors, and as dose adjustment in various drug categories of skin diseases (i.e antiviral, antibiotics, anticancer, and anesthetic).[8]

Sharma et al.[9] used 5-FU microemulsion topically to treat various skin cancer types. Fitzpatrick et al.[10] showed the efficacy and safety of 5-FU on hypertrophic scars and keloids in

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a clinical study conducted on 1000 patients. The dose of injectable 5-FU in adults is 50 mg mL^{-1} and should not exceed 800 mg per day. In pediatrics, the dose is not determined. While 5-FU at a concentration of 5 mg mL^{-1} is effective in prolonging the patency of microtomies in rat tympanic membranes, a concentration of 10 mg mL^{-1} does not show more effect with saline administration than a simple myringotomy procedure.[11] The effective dose of subconjunctival 5-FU injection has not been determined yet.[12] Gamelin at al.[13] investigated that 5-FU drug levels greater than 3,000 μg L^{-1} were significantly associated with increased acute toxicity.

Helaly et al.[1] studied the slow release of 5-FU from the natural polymeric composite. Lin et al.[14] performed the controlled release of 5-FU loaded chitosan/polyethylene glycol microparticles. Huang et al.[15] studied the preparation of chondroitin sulfate/chitosan complex microcapsules and their application to the controlled release of 5-FU. Mohan et al.[16] studied the calcium carbonate-nano cellulose composite for the rates of uptake and release of 5-FU. Ciftci et al.[17] have developed mesoporous montmorillonite/magnetite nanocomposites for loaded 5-FU to the controlled release. Lurciuc-Tincu et al.[18] loaded 5-FU on a biocompatible poly(2-vinyl pyridine)-β-poly(ethylene oxide) nano micelles. Cegłowski et al.[19] synthesized 5-FU molecularly imprinted polymers (MIPs) based on poly(2-isopropenyl-2-oxazoline). Farboudi et al.[20] synthesized magnetic gold-coated poly(ε-caprolactonediol) based polyurethane/poly(*N*-isopropyl acrylamide)-grafted-chitosan core-shell nano fibers for the controlled release of 5-FU. Although there are limited studies on starch based membrane systems for 5-FU release to provide an alternative material for transdermal use,[21] studies are generally directed towards the controlled release of 5-FU from starch based microspheres.[22]

Starch/PVA blend membranes have not been reported as controlled release systems for 5-FU, yet. In this study, starch was preferred as a membrane base material and PVA was used as a support polymer material due to the weak physical strength of starch. Starch/PVA membranes were prepared for the potential transdermal release of 5-FU, and the effects of stach/PVA ratio, membrane thickness, pH, and temperature on release were tested in vitro.

Results and Discussions

Characterization of the Membranes

FTIR and DSC analyses were used for the characterization of starch/PVA membranes. FTIR spectra of starch, starch/PVA, and PVA membranes were reflected in Figure 1.

The starch spectrum shows a characteristic broad band corresponding to the stretching vibrations of O–H at 3290 cm^{-1} and O–H deformation bending at 1650 cm^{-1}.[23] The transmittance at 2856 cm^{-1} is attributed to C–H stretching vibrations. The band at 1425 cm^{-1} corresponds to the deformation bending of C–H, and 1345 cm^{-1} belongs to –CH_2 deformation.[24] Meanwhile the transmittance at 1110, 1080 and 990 cm^{-1} are characteristics of C–O stretching vibrations of

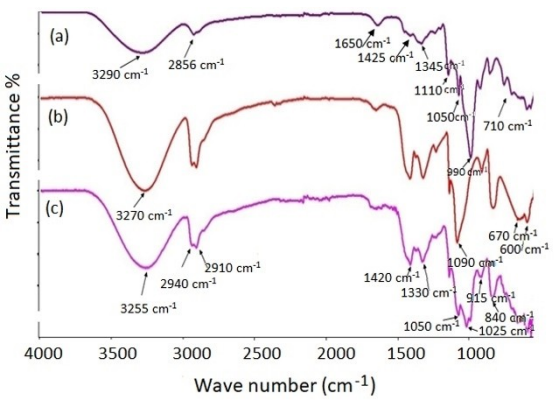


Figure 1. FTIR spectra of (a) starch; (b) starch/PVA (70/30, v/v); (c) PVA.

glucose rings.[23b] The band at 710 cm^{-1} is attributed to out-of-plane C–H bending of the glucose ring.[25]

The FTIR spectrum of PVA shows the characteristic band for –OH at 3255 cm^{-1}. The absorption bands at 2940 cm^{-1} and 2910 cm^{-1} are attributed to C–H streching vibrations, the bands in the region of 1080–1025 cm^{-1} belong to C–O vibrations of C–OH groups. The bands at 1420 cm^{-1} and 1330 cm^{-1} denote the CH–CH_2 vibrations[26] and 840 cm^{-1} belongs to –CH_2 bending.

Starch and PVA are polar substances and both have hydroxyl groups.[27] The FTIR spectrum of starch/PVA shows the characteristic stretching band of O–H at 3270 cm^{-1}. The presence of PVA shifts the O–H band of pure starch from 3290 cm^{-1} to 3270 cm^{-1}. Such a shift confirms the possible intermolecular H bonding interaction between the starch and PVA chains.[27] Meanwhile, the increase in the intensity of the –OH band of starch/PVA indicates that PVA increases the amorphous region of the starch. The peak at 670–600 cm^{-1} seen in the spectrum of starch/PVA film, is thought to be the –SO_4^{2-} ion from the cross-linker.[28] The peak at 600 cm^{-1} is due to the out-of-plane bending vibration of the SO_4^{2-}.[29] The characteristic S–O stretching of inorganic sulfates is found in the region of 1179–1083 cm^{-1}.[29] The corresponding peak in this study is observed at 1090 cm^{-1} indicating the S–O stretching vibrations due to the expected cross-linking by SO_4^{2-}. Figure 2 shows the proposed cross-linking reaction.

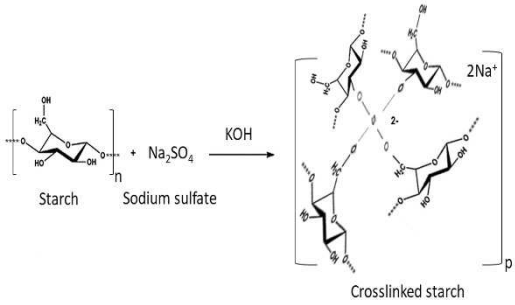


Figure 2. Proposed cross-linking reaction of starch with Na_2SO_4.

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Starch has two types of hydroxyl groups: primary (6–OH), and secondary (2–OH and 3–OH).[30] The reaction of these hydroxyl groups with sulfate ion in highly alkaline solution results in cross-linking via sulfate bridge.[28]

In Figure 3, DSC thermograms of starch, starch/PVA (70/30, v/v), and PVA films were reflected. In Figure 3, T_g of starch, starch/PVA (70/30, v/v), and PVA are shown as 63.0 °C, 41.75 °C, and 79.14 °C, respectively. Both PVA and starch polymers are polymers with –OH groups and interact via hydrogen bonding. The single T_g value observed in Figure 3 supports that these two polymers form a homogeneous mixture with each other.[31]

DSC analysis of the starch and PVA were done by using crystalline samples of starch and PVA. However, the analysis of starch/PVA was carried out by using 70/30 (v/v) starch/PVA membranes. Although the T_g value for a blend is expected between the T_g of blended polymers, the situation is somewhat different for the T_g of membranes, especially for the porous membranes having high chain mobility by the free-surface interfacial region that surrounds each pore, leading to low T_g.

The low T_g of starch/PVA can also be explained by the strong hydrogen bonding interactions of starch and PVA. Starch and PVA are hydrophilic polymers with abundant of –OH groups, which could form hydrogen bonding and improve the compatibility between them. The strong interactions between starch and PVA components could inhibit the PVA macromolecular arrangement and destroy the crystalline structure, resulting in the decrease of the degree of crystallinity. The strong hydrogen bonding interactions would also decrease the quantity of free –OH groups, therefore the intensity of secondary inter-chain interactions[32] decreases and leads to decrease in T_g.

On behalf of this fact, the glass transition behavior was explained with a percolation mechanism and this mechanism was also explained for polymer films.[33] According to such mechanism, a free-surface interfacial region that surrounds each pore results in high polymer chain mobility causing the glass transition to occur at a lower temperature compared with that of the bulk polymer.[34]

These are suggested to be the reason of the lower T_g for porous starch/PVA membranes than both of crystalline starch and PVA.

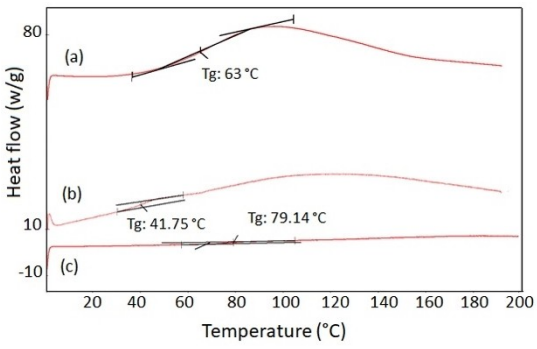


Figure 3. DSC thermograms (a) starch; (b) starch/PVA (70/30, v/v); (c) PVA.

Effect of Membrane Thickness

The effect of membrane thickness on 5-FU release was investigated and for this purpose, starch/PVA membranes were prepared at different thicknesses (40, 70, 110, and 130 μm) by keeping the starch/PVA ratio constant (70/30, v/v). The release of 5-FU (0.5 mg mL^{-1}) was performed against pH 7.4 and the temperature was set to the skin surface temperature of 32 ± 1 °C. The donor solution pH was also assigned to 7.4. The results are reflected in Figure 4, as a release percentage of 5-FU obtained after a constant 24 h release period.

As shown in Figure 4, the permeated amount of 5-FU is lower for thicker membranes, indicating that the 5-FU delivery from the stach/PVA membranes is compatible with Fick's first law of diffusion.[26] Due to the low therapeutic dose range of 5-FU,[13] the most suitable membrane thickness for the study was determined as 130 μm, with which the lowest release percentage was determined and the higher membrane thicknesses was not preferred for the lost of the homogeneity of the membrane.

Effect of Starch/PVA Ratio

The effect of starch/PVA ratio of the membranes on 5-FU release was studied. Homogeneous mixture of starch (4%, w/v) and PVA (4%, w/v) aqueous solutions were used at varying volume ratios of 60/40, 50/50, and 70/30, to prepare starch/PVA membranes. Permeation studies were conducted using 5-FU solutions (0.5 mg mL^{-1}) at pH 7.4 and the temperature was kept constant at 32 ± 1 °C during the study. The results of the permeations with respect to pH 7.4 buffer were stated in Figure 5.

From the results, it is clear that the lowest permeation was obtained at a 70/30 (v/v) starch / PVA ratio and an almost close percent release of 5-FU at 50/50 (v/v) and 60/40 (v/v) starch/PVA ratios. The increase in percent release of 5-FU with PVA could be explained by an increase in the diffusion available free volume between the polymer chains.

Cross-linking densities (ρ_x) of the membranes give an idea about the diffusion available free volume for permeation. In

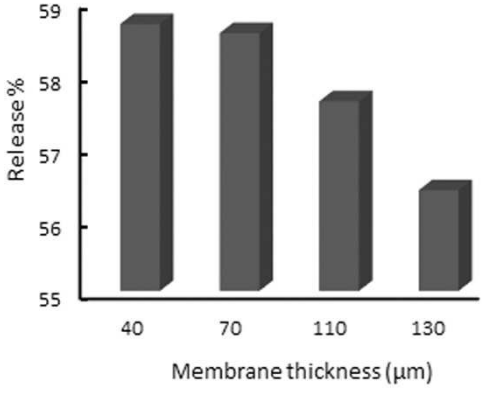


Figure 4. Effect of membrane thickness on 5-FU release (starch/PVA, 70/30, v/v; pH 7.4; $T = 32 \pm 1$ °C).

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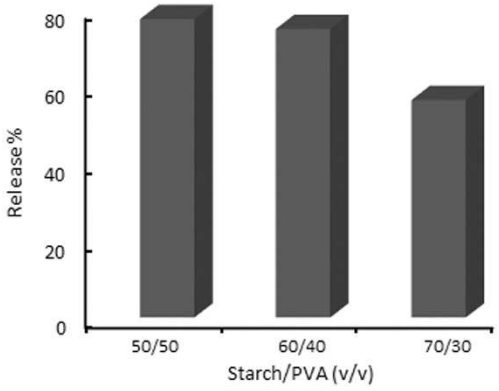


Figure 5. Effect of starch/PVA (v/v) ratio on 5-FU release (pH 7.4; $T = 32 \pm 1\,^{\circ}C$; membrane thickness = 130 μm).

order to investigate the permeation availability of the membranes, the cross-linking densities of the membranes were determined from the swelling studies and calculated by using the Flory-Rehner equation, Equations (1–3).[35]

$$M_c = \frac{V_1 \rho_2 \left[V_{2m}^{1/3} - (V_{2m}/2)\right]}{-\left[ln(1 - V_{2m}) + V_{2m} + \chi_1 V_{2m}^2\right]} \quad (1)$$

$$V_{2m} = \frac{W_0}{V_{eql}\rho_2} \quad (2)$$

$$V_{eql} = \frac{W_0}{\rho_2} + \frac{W_s - W_0}{\rho_1} \quad (3)$$

Where,

M_c: molecular weight between the crosslinks

V_1: molar volume of solvent

V_{2m}: equilibrium volume fraction of polymer

ρ_1: solvent density

ρ_2: polymer density

V_{eql}: equilibrium-swelling volume

W_0: dry polymer weight

χ_1: Flory-Rehner interaction parameter

After the determination of M_c, V_{2m} and V_{eql} by using Equations (1–3), the ρ_x values of the 70/30, 60/40 and 50/50 (v/v) starch/PVA membranes were determined by using Equation (4) and reflected in Table 1 together with the M_c values for 70/30, 60/40 and 50/50 (by volume) starch/PVA membranes, respectively.

Table 1. The cross-linking ratio and the molecular weight between the crosslinks of the starch/PVA membranes.

Starch/PVA *(v/v)*	ρ_x (mol cm^{-3})	M_c (g mol^{-1})
70/30	0.111	0.507
60/40	0.102	0.535
50/50	0.070	1.537

$$\rho_x = \frac{\rho_2}{M_c} \quad (4)$$

As it is seen from Table 1, as the cross-linking density of polymeric membranes increases, the molecular weight between the crosslinks decreases. This results in a decrease in the free volume available for permeation[36] and leads to a lower permeation through the membrane material. Therefore, greater percent release of 50/50 (v/v) membranes can be explained by their lower cross-linking densities.

Since 50/50 (v/v) starch/PVA membranes show weak physical resistance in the release medium, 60/40 (v/v) membranes were preferred as suitable membranes for the rest of the study for their greater permeation availability of 5-FU than 70/30 (v/v) membranes.

Effect of pH on 5-FU Release

The release of 5-FU from starch/PVA was performed for pH range of 3.5–7.4, using 5-FU solution (0.5 mg mL^{-1}). The temperature, starch/PVA ratio and the thickness of the membranes were all kept constant. The tests were run in triplicate and the mean cumulative drug release was calculated. The data obtained are given in Figure 6.

In Figure 6, it is seen clearly that lowering the pH decreases the released amount of 5-FU from the membranes. Swelling behaviors at different pH values were also investigated for 60/40 (v/v) starch/PVA membranes and reflected in Figure 7.

Figure 7 depicts that as the pH value increases, the swelling (water uptake tendency) of the membranes also increases. The

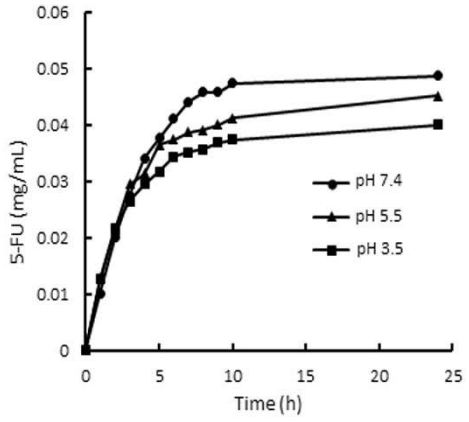


Figure 6. Effect of pH on 5-FU release from starch/PVA membranes (starch/PVA, 60/40, v/v; $T = 32 \pm 1\,^{\circ}C$; membrane thickness = 130 μm).

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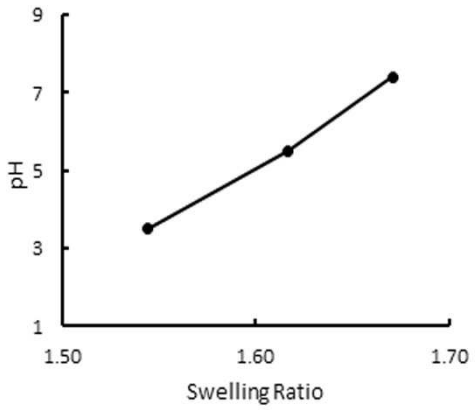


Figure 7. Swelling ratio of starch/PVA (60/40, v/v) membranes in different pH.

increase in the swelling leads to an increase in the free volume available for the release of the drug between polymer chains. Srisawanget al.[37] determined that pH affects the swelling behavior, which is defined as the capacity of starch to trap water, which increases as it approaches alkaline conditions. Olayinka et al.[38] reported that the swelling percentage of starch did not increase significantly between pH 2–6. In addition to the greater solubility of 5-FU at alkaline pH values,[39] the increase in the amount of drug released through the membranes with the increase in pH is due to the high swelling rate of the membranes at higher pH values.

The surface morphology analysis is important to get an idea about the physical structure of the films. The SEM image of starch/PVA 60/40 (v/v) membrane is given in Figure 8. Based on the SEM images, it can be stated that the surface of the membranes has pore like pits having closed backs and having a dense morphology with low pore distribution, thus the transfer through the membrane occurs mainly through the diffusion mechanism.

Diffusing ability of the drug from the membranes can be determined using Equation (5).

$$Q_t = \frac{DC_0}{l}\left(t - \frac{l^2}{6D}\right) \quad (5)$$

Q_t is the the total amount of the solute tranferred from unit area (A) at time t. C_o is the initial concentration of the drug, and D is the diffusion coefficient. The slope of the Q_t vs. t plot gives the diffusion coefficient. The slopes calculated for this study remained in the confidence limit of 94–99% and the calculated D values were listed in Table 2.

As reflected by Table 2, for a more acidic pH medium at which low swelling was observed as stated above, the diffusion coefficient for 5-FU through starch/PVA membranes shows a decrease. This result also supports the lower permeation of 5-FU at acidic pH.

Additionally, the extrapolation of the Q_t vs. t to the Q_t axis serves the (l^2/6D) term, which is called as the time-lag.[25,29] In

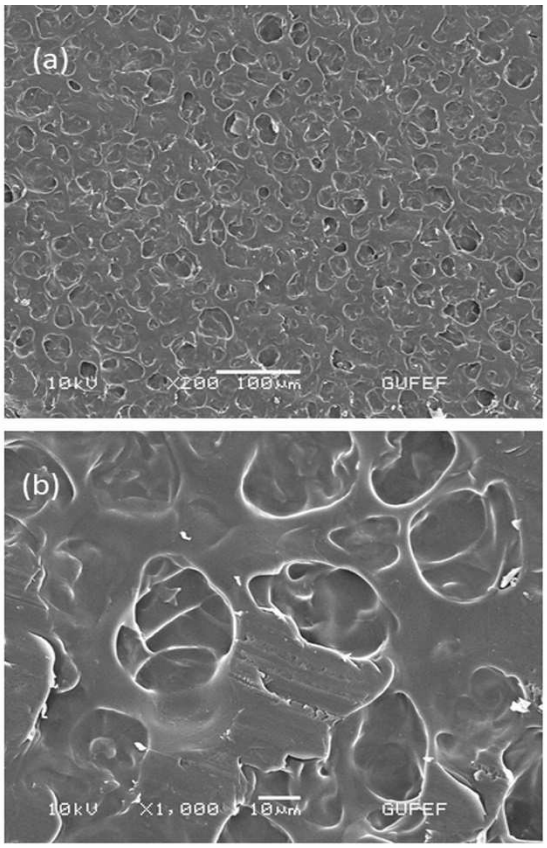


Figure 8. SEM image of starch/PVA (60/40, v/v) membrane (a) (*x*200); (b) (*x*1000).

Table 2. Diffusion coefficients of the stach/PVA (60/40, v/v) membranes at different pH values.

pH	D (cm^2 s^{-1})x10$^{3[a]}$	$R^{2[b]}$
7.4	4.84	0.9912
5.5	4.49	0.9446
3.5	2.54	0.9446

[a]Diffusion coefficient [b]Determination coefficient.

Figure 9, Q_t vs. t is stated for the transfer of 5-FU at the studied pH range.

Figure 9 shows a sligt time-lag and the burst effect. From such a slight effect, it can be said that the diffusion equilibria during the permeation of the drug are attained quickly in a short time.

Effect of Temperature

5-FU release from the membranes was carried out at a temperature of 32 ± 1 °C, 37 ± 1 °C, and 39 ± 1 °C and the results are given in Figure 10.

Figure 10 shows that with the increase in temperature, a very narrow change in the 5-FU release was observed. This can be explained by the secondary interactions within the branched structure of starch in a lattice that can eliminate the

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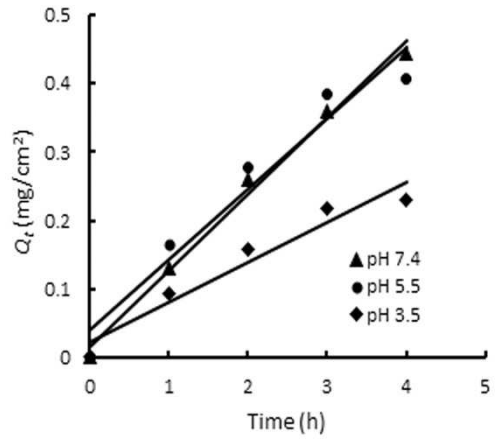


Figure 9. Effects of pH on permeability of starch/PVA (60/40, v/v) membranes ($T = 32 \pm 1$ °C; membrane thickness = 130 μm).

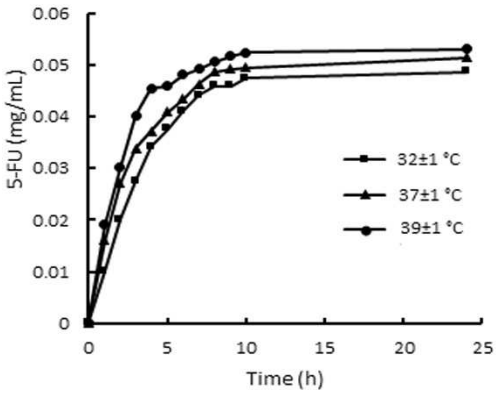


Figure 10. Effect of temperature on 5-FU transfer from starch/PVA membranes (60/40, v/v, membrane thickness = 130 μm; pH 7.4).

increase in volume under the influence of temperature. The narrow range of release despite the increase in temperature suggests that the amount of 5-FU released through the membranes prepared in our study can be controlled in a fairly constant range in cases of skin temperature, normal body temperature, and febrile body temperature. In drug release for 24 h, the drug increased steadily with a certain transfer rate until the 8th hour, and after the 8th hour, a constant release rate was obtained for 24 h for the three temperatures worked. The change in the release from membranes with temperature adapts to the Arrhenius equation, Equation (6).[40]

$$J = Ae^{-Ea/RT} \quad (6)$$

Where J is the flux (kg m^{-2} h^{-1}), A is the pre-exponential factor, T is the temperature (K), and E_a is the overall activation energy (J mol^{-1}). The slope of the linear regression line of ln$J$ vs. 1/T graph serves the E_a. For this study, it was found as 9.72 kJ mol^{-1} ($y = -1169.8x - 14.899$; $R^2 = 0.9667$).

Conclusion

In this study, membranes were prepared by using the phase conversion method with different ratios of starch/PVA solutions (60/40, 50/50, 70/30, v/v) using aqueous solutions of starch and PVA, at the same and pourable concentrations of 4% (w/v). The most suitable polymer ratio and membrane thickness were optimized as 60/40 (v/v), and 130 μm, respectively.

As a result of the study, it can be stated that the decrease in pH lowers the permeated amount of 5-FU from the starch/PVA membrane. The increase in temperature changes the drug transfer from the membranes in a narrow range meaning that 5-FU transfer from membranes can be controlled within a fairly constant range. The diffusion coefficient was determined as 4.84×10^{-3}, 4.49×10^{-3} and 2.54×10^{-3} cm^2 s^{-1} at pH 7.4, 5.5, and 3.5, respectively for the diffusion of 5-FU through the starch/PVA membrane (60/40, v/v). The activation energy for the release of 5-FU from starch/PVA membrane (60/40, v/v) was found to be 9.72 kJ mol^{-1}. In relation to this study, starch/PVA membrane can be considered as an alternative membrane for the potential transdermal controlled release drug administration of 5-FU.

Supporting Information Summary

See the supporting information for the experimental detail about chemicals, preparation of membranes, in vitro drug release studies, fourier transform infrared spectrometry (FTIR), differential scanning calorimetry (DSC) analysis, scanning electron microscopy (SEM), and swelling studies.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 5-fluorouracil · Drug delivery · Green chemistry · Polymer · Starch/PVA membrane

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