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Drug sorption onto and release from soy protein fibers

Weijie Xu · Yiqi Yang

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Abstract Drug release in phosphate buffered saline (PBS pH 7.4) and artificial gastric juice (AGJ pH 1.2) and its relationship with kinetic and thermodynamic parameters of drug sorption onto soy protein (SP) fibers have been studied using Diclofenac, 5 Fluorouracil and Metformin as model drugs. Since SP is biodegradable, biocompatible, abundant and annually renewable, it has been widely used in medical applications. To understand drug release from SP fibers using sorption, kinetic and thermodynamic parameters have been investigated. Quantitative relationship between drug release and drug loading concentration, affinity, and activation energy for diffusion was established to predict initial bursts and later drug release. The study showed that Diclofenac had high initial bursts in PBS but more constant release in AGJ. It also has been found that drugs with lower diffusion coefficient and higher affinity (especially van der Waals force) on SP fiber are more suitable for sorption loading to achieve higher loading capacity and more constant releasing rate.

W. Xu · Y. Yang (✉)
Department of Textiles, Clothing and Design, University of Nebraska-Lincoln, 234, HECO Building, Lincoln, NE 68583-0802, USA
e-mail: yyang2@unl.edu

Y. Yang
Department of Biological Systems Engineering, University of Nebraska-Lincoln, Lincoln, NE 68583-0802, USA

Y. Yang
Nebraska Center for Materials and Nanoscience, University of Nebraska-Lincoln, Lincoln, NE 68583-0802, USA

1 Introduction

Soy protein (SP) is extracted from soy beans, which has a high content of proteins (40–50%) and is one of the most cultivated plants in the world [1]. The purified SP has a protein content of at least 90% on a dry weight basis. Since SP is biodegradable, biocompatible, abundant and annually renewable, it attracts attention as a biomaterial in tissue engineering and drug delivery fields [2–5]. SP have been fabricated into films and fibers using several methods [6, 7]. Within the various forms, fibers have been widely used in scaffolds for its high surface area to mass ratio and high porosity [8]. In addition, drugs have been loaded in the scaffold in order to achieve controlled release to promote the tissue regeneration and functional recovery [9]. Generally speaking, there are two methods to load drugs onto the scaffold. One is the dissolution method that is to dissolve the drug in the polymer solution or molten polymer. The other method is sorption that is to sorb drugs after fabricating the scaffold [10]. The sorption method is more suitable for SP fibers for either higher drug using efficiency or fewer impurities left in the fibers compared with the dissolution method. Since the SP has to be dissolved with chemicals and go through the coagulation bath in order to obtain high mechanical properties, washing is required to remove these impurities. Drugs will be removed during the washing leading to lower drug using efficiency, while inefficient washing will result in impurities left in the fibers if the dissolution method is used.

SP has been mixed with other polymers, such as dextran, chitosan, gelatin, carrageenan and starch in order to improve properties [11–15]. The degradation behavior of SP uncrosslinked and crosslinked with glyoxal has been studied in an isotonic saline solution either with or without bacterial collagenase [16]. The study demonstrated that the

weight loss of SP was directly proportional to the crosslinking degree and the degradation of the SP could be controlled by the crosslinking. Vaz et al. used double-layer co-injection moulded SP-based materials as the drug delivery carrier [17]. The study showed that the drug release was affected by swelling, drug diffusion, and polymer dissolution. Vaz et al. also investigated the mechanical properties, degradation and drug release profile of SP films non-crosslinked and crosslinked with glyoxal [18]. The study showed that the drug release rate was dependent on the pHs of buffered saline. In another study, Chen et al. investigated the mechanical properties and drug release of SP films crosslinked with formaldehyde [19]. The study showed that the crosslink density was dependent on the formaldehyde concentration, and the initial burst was dependent on the drug solubility and zero order subsequence release was observed. SP used in hydrogels by itself or combined with other materials has been investigated [20, 21]. The hybrid microspheres based on alginate and SP has been investigated as a drug delivery carrier [22].

However, the SP solution prepared with aqueous NaOH cannot be used to fabricate SP fibers for poor mechanical properties, while the SP fibers can be obtained from the SP solution prepared with the urea and the reducing agent [23]. In order to remove the toxic impurities, it is necessary to the sorption method to load drugs onto SP fibers.

In this study, both the sorption and the dissolution methods were used to load drugs onto SP fibers using Diclofenac, 5 Fluorouracil (5-Fu) and Metformin as model drugs. Both kinetic and thermodynamic parameters of the drug sorption onto SP fibers, such as the diffusion coefficient, activation energy for diffusion, affinity, enthalpy and entropy of sorption have been investigated. The quantitative relationship between drug release and kinetic and thermodynamic parameters has been established. Furthermore, the effects of the loading temperature and the drug loading concentration on drug release in phosphate buffered saline (PBS pH 7.4) and in artificial gastric juice (AGJ pH 1.2) have been studied.

2 Experimental

2.1 Materials

SP (Pro-FAM® 646) was purchased from Archer Daniels Midlands Company, Decatur, IL, USA. Diclofenac and 5-Fu used in this study were purchased from TCI America with the purity larger than 98 and 99%, respectively. Metformin was purchased from Advanced Technology & Industrial Co., Ltd., with the purity larger than 99%. The structures of Diclofenac, 5-Fu and Metformin are from SciFinder Scholar with registry number of 15307-86-5, 51-21-8 and 657-24-9, respectively. The structures are shown in Fig. 1. These three drugs were selected based on charge difference. Sodium phosphate monobasic was purchased from Fisher Scientific Company with the purity 100.2% based on $NaH_2PO_4 \cdot H_2O$. Anhydrous sodium phosphate dibasic was purchased from J. T. Baker with the purity larger than 99.7%. Sodium chloride was purchased from EMD with purity larger than 99.5%.

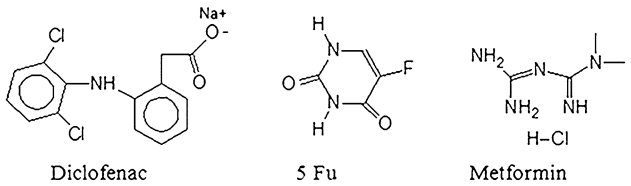

Fig. 1 Drug structure of three model drugs

2.2 SP fiber preparation

SP fibers were made according the method reported by Zhang et al. [23]. SP (25 wt%) was dissolved in 8 M aqueous urea solution with 3% (wt% based on the weight of SP) sodium sulfite and allowed to stay for 48 h at 21°C. The SP solution was extruded into the 10% (wt%) sodium sulfate solution with slight acetate acid for coagulation. The fibers were drawn from coagulation bath, dried and collected on a roller. The dry fibers were dipped in distilled water at 50°C for 2 h and later rinsed to remove any remaining impurities. The fibers were dried at room temperature and conditioned for at least 24 h before using them for drug loading. The diameters of the fibers were observed by a scanning electron microscope and measured with the Photoshop software.

2.3 Drug loading

Diclofenac was dissolved in a pH 3.0 (adjusted with 20% v/v hydrochloric acid) solution in order to increase the interaction between Diclofenac and SP fibers. The pH 3.0 was selected in order to reduce hydrolysis of SP and achieve a higher drug loading amount. The 5-Fu was dissolved in a pH 10.0 (adjusted with sodium hydroxide solution) solution in order to increase its solubility, and Metformin was dissolved in distilled water (pH 6.3) only. About 10 mg of SP fibers were loaded into a centrifuge tube and a solution containing the drug was added to the tube at a liquor-to-fiber ratio of 100:1. The tube was held at a particular temperature with oscillation of 120 rpm in a shaking water bath (Model: 1217 VWR). After the required time (1, 3, 5, 10, 15, 30, 60, 90, 120, 150 and 180 min) of loading, the centrifuge tube was immediately dipped in an ice bath for 2 min. The drug solution was removed from the tubes and the fibers were washed three times with 1 ml of 0°C water for 30 s in a

centrifuge at 9000 rpm to remove drugs that were not well attached on the surface of the fibers. The washed fibers were dried at 50°C and then kept in a conditioning room (21°C, 65% RH) for 24 h before testing. For the dissolution method, Diclofenac was dissolved in a SP spinning dope and extruded in a pH 3.0 coagulation bath. After drying, the fibers were washed three times with 1 ml of 0°C water for 30 s in a centrifuge at 9000 rpm, and then dried and conditioned before testing.

2.4 Determining the amount of drug loaded on the fibers

The drug loaded SP fibers were hydrolyzed using a 2 M aqueous NaOH solution at 50°C for 2 h with continuous shaking. Dissolved SP solution was diluted with distilled water and the drug concentration in the solution was calculated by measuring the absorbance with a UV spectrometer (Model DU® 720 Beckman Coulter) at 275, 284 and 248 nm using virgin SP fibers as control. The drug loading amount on the SP fibers were calculated using calibration curves developed previously. The calibration curves for Diclofenac in the 0.952 mg/ml SP 2 M NaOH solution had the relation of $y = 0.0085x$ ($R^2 = 0.999$); where y was the absorbance and x was the Diclofenac concentration in the 0.952 mg/ml SP 2 M NaOH solution with a unit of μg/ml. The calibration curve for 5-Fu in the 1.25 mg/ml SP 2 M NaOH solution had the relation of $y = 0.0442x$ ($R^2 = 0.999$); where y was the absorbance and x was the Diclofenac concentration in the 1.25 mg/ml SP 2 M NaOH solution with a unit of μg/ml. The calibration curve for Metformin in the 1.25 mg/ml SP 2 M NaOH solution had the relation of $y = 0.0346x$ ($R^2 = 0.999$); where y was the absorbance and x was the Metformin concentration in the 1.25 mg/ml SP 2 M NaOH solution with a unit of μg/mg.

2.5 Drug release

The drug release experiments were carried out in PBS solution with pH 7.4 and AGJ with pH 1.2 in a shaking water bath maintained at 37.2 ± 0.1°C and shaking at 120 rpm. Virgin SP fibers were used as control. About 10 mg of drug loaded SP fibers were immersed in the PBS solution or in the AGJ with a solution to fiber ratio of 1000:1. Precisely 0.5 ml of PBS solution and 1 ml of AGJ was removed at various time intervals and an equal amount of fresh PBS/AGJ was added. The collected solution containing the drug was diluted with 5 ml distilled water and the light absorbance was measured. The amount of Diclofenac, 5-Fu and Metformin in the solution from PBS were calculated with the calibration curves $y = 0.0308x$ ($R^2 = 0.999$), $y = 0.0532x$ ($R^2 = 1$) and $y = 0.0779x$ ($R^2 = 0.999$), respectively. The amount of Diclofenac, 5-Fu and Metformin in the solution from AGJ were calculated with the calibration curves $y = 0.0274x$ ($R^2 = 0.999$), $y = 0.0556x$ ($R^2 = 0.999$) and $y = 0.0243x$ ($R^2 = 0.999$), respectively.

2.6 Measurement of the size of Diclofenac, 5-Fu and Metformin by molecular modeling

The gradient-corrected Perdew–Burke–Ernzerh (PBE) exchange-correlation functional and the double-numerical polarized basis set (DNP), implemented in DMOL3 software, were chosen for geometric optimization.

2.7 Diffusion coefficient and activation energy for diffusion

The diffusion coefficients of the drugs through the fibers at 50, 70 and 90°C were calculated using Eq. 1 [24] and were obtained from a linear regression of C_t/C_∞ versus $t^{0.5}$.

$$C_t/C_\infty = 4(Dt/\pi r^2)^{0.5} \quad (1)$$

where C_t is the drug concentration in the fibers at the loading time t, C_∞ is the drug concentration in the fibers at the infinite time, D is the diffusion coefficient of the drug through fibers, r is the radius of the fibers, and t is the loading time. The maximum diffusion coefficient and the activation energy for diffusion for the three drugs were calculated using Eq. 2 [25] and were obtained from the intercept and slope, respectively, of a linear regression of $\ln(D_T)$ versus $1/T$.

$$D_T = D_0 e^{(-E_a/RT)} \quad (2)$$

where D_T is the diffusion coefficient at temperature T of the drug through fibers, D_0 is a constant (maximum diffusion coefficient of a drug through a specific fiber), E_a is the activation energy for diffusion, R is the ideal gas constant, and T is the loading temperature.

2.8 Affinity, sorption enthalpy and entropy

For Diclofenac and Metformin, the activity of the drug in solution is calculated by Eq. 3 [26] since they are completely ionized drugs.

$$a_s = \gamma^{z+1}[Na^+]_s^z[D]_s \quad (3)$$

where γ is the activity coefficient, a_s is the drug activity in the solution, z is the number of charges on the ion, $[D]_s$ is the drug concentration in the solution, and $[Na^+]_s$ is the sodium ion concentration in the solution. The activity coefficients of Diclofenac and Metformin in the solution were calculated using Eq. 4. The concentration of 5-Fu in the solution was arbitrarily used as the activity in the solution because 5-Fu is not ionized.

$$-\ln\gamma = Az^2\left(0.5\sum_i c_i z_i^2\right)^{0.5} \quad (4)$$

where A is a constant approximately equal to 0.5 and 0.5 is used in this manuscript, c is the concentration, and i is the component i in the drug. The activity of the drug on SP fibers was calculated by Eq. 5 [27] based on Langmuir sorption isotherm. Langmuir is selected because it has high R^2 values and a unit slope for plot of $\ln(a_f)$ versus $\ln(a_s)$.

$$a_f = [D]_f/([S]_f - [D]_f) \quad (5)$$

where a_f is the drug activity in the fibers, $[D]_f$ is the drug concentration in the fibers, and $[S]_f$ is the saturated drug concentration on the fibers. The apparent sorption affinities were calculated using Eq. 6 [26].

$$-\Delta\mu = RT\ln(a_f/a_s) \quad (6)$$

where $-\Delta\mu$ is the apparent sorption affinity, R is the ideal gas constant, and T is the loading temperature. The apparent sorption enthalpy was calculated according to Eq. 7 and was obtained by the slope of the linear regression of $\Delta\mu/T$ versus $1/T$.

$$\Delta H/T = \Delta\mu/T + C \quad (7)$$

where ΔH is the apparent sorption enthalpy, and C is a constant. The apparent sorption entropy was calculated using Eq. 8 [26].

$$\Delta\mu = \Delta H - T\Delta S \quad (8)$$

where ΔS is the apparent sorption entropy.

2.9 Statistics

All the experiments were repeated at least three times. The data were reported with mean ± one standard deviation. To obtain equations to predict initial burst and sequence drug release based on affinity between drug and SP fibers, drug loading concentration, activation energy for diffusion and time, linear regressions were preformed. The linear regressions were performed on initial burst or drug release after burst versus the affinity, drug loading concentration, $e^{-E_a/RT}$, $(e^{-E_a/RT})^{0.5}$, t, $t^{0.5}$ and their two-way interactions.

3 Results and discussion

3.1 Sorption rates and kinetic parameters of Diclofenac, 5-Fu and Metformin onto SP fibers

After measurement, the fibers had a diameter of 45 ± 4 μm. Sorption rates and kinetic parameters of Diclofenac, 5-Fu and Metformin on SP fibers at different loading temperatures are shown in Figs. 2, 3 and 4 and Table 1, respectively. As seen from the figures, higher temperature

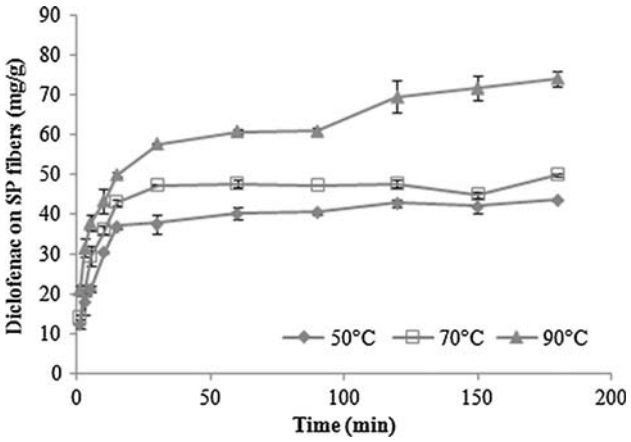

Fig. 2 Sorption rates of Diclofenac on SP fibers at 50, 70, and 90°C with initial Diclofenac concentration of 5 mg/ml at pH 3.0

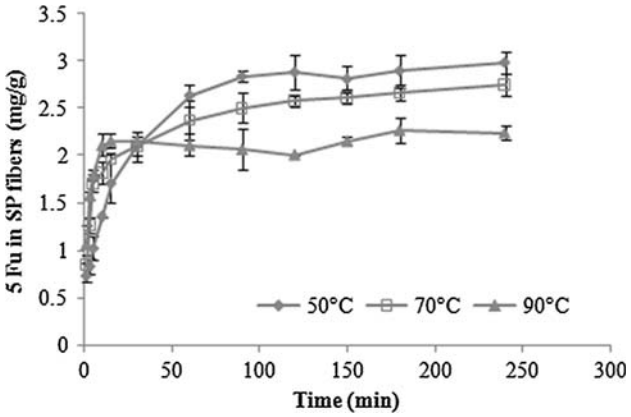

Fig. 3 Sorption rates of 5-Fu on SP fibers at 50, 70, and 90°C with initial 5-Fu concentration of 5 mg/ml at pH 10.0

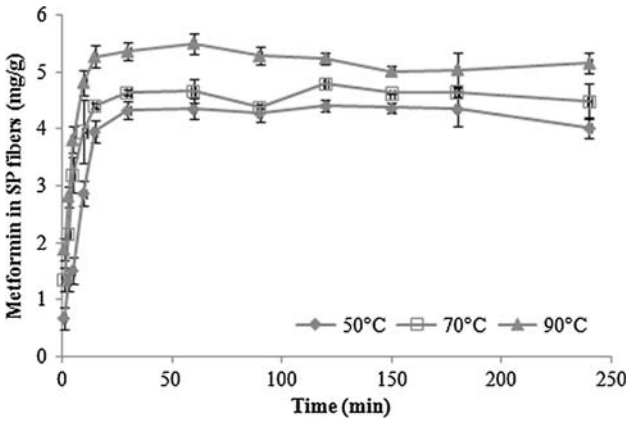

Fig. 4 Sorption rates of Metformin on SP fibers at 50, 70, and 90°C with initial Metformin concentration of 5 mg/ml at pH 6.3

Table 1 Kinetic parameters of drug sorption onto SP fibers at different temperatures

	Diclofenac			5-Fu			Metformin		
	50°C	70°C	90°C	50°C	70°C	90°C	50°C	70°C	90°C
Diffusion coefficient $\times 10^{12}$ (m^2/min)	1.688 ± 0.008	2.596 ± 0.004	4.044 ± 0.009	2.534 ± 0.000	3.207 ± 0.005	4.460 ± 0.006	2.713 ± 0.009	4.022 ± 0.003	5.186 ± 0.012
E_a (kJ/mol)	21.26 ± 0.89			13.93 ± 1.79			15.84 ± 1.43		

leads to higher drug sorption rate reflected by the slope of the sorption rate curves. The sorption rate can be quantified as the diffusion coefficient in Table 1. Diffusion coefficients increase with increasing temperatures for all three different drugs because of three reasons. First, at a higher temperature, drugs moved faster in both bulk solution and the boundary layer leading to a faster sorption rate. Second, with increasing the temperature, the boundary layer on the surface of SP fibers became thinner resulting in an increasing rate for drugs to move onto the surface of fibers. Third, there were smaller aggregates of drugs at higher temperatures than those at lower temperatures, which facilitated the drugs through the fiber surface, thus leading to the fast movement of drugs into fibers.

It can be seen from Figs. 2–4 and Table 1, drug sorption rates for both 5-Fu and Metformin are higher than that of Diclofenac on SP fibers probably because of the size of the drugs. Metformin (with a diameter of 7.54 A) and 5-Fu (with a diameter of 5.42 A) are smaller than Diclofenac (with a diameter of 10.01 A). Increasing the size of drugs increases the difficulty to go through the openings in the SP fibers, leading to the slower drug sorption rate at the same drug loading temperature. Compared with Diclofenac sorption onto polylactic acid (PLA) and starch acetate (SA) fibers, rates of Diclofenac sorption onto SP and wheat gluten (WG) fibers are faster because of the larger opening on the fiber surface and stronger forces between the drug and fibers. SP and WG are more hydrophilic than PLA and SA. Increasing hydrophilicity increases the swell of SP and WG leading to the larger opening and wider channels in the fibers, resulting in faster drug sorption rates. Furthermore, the strong forces between Diclofenac and SP/WG increase the movement of the drug onto fibers, although the drugs tightly interacted with protein fibers take some spaces of the channels, the remaining spaces are wide enough for Diclofenac to go through.

Figures 2 and 4 show that higher temperatures give higher drug equilibrium exhaustion for Diclofenac and Metformin. This is probably due to more accessible space created at higher temperatures for drugs to be sorbed in SP fibers. Higher temperature can break stronger interactions among SP molecular chains and hence leads to more sorption of Diclofenac and Metformin. As shown from Fig. 3, higher drug loading temperature leads to lower drug exhaustion for 5-Fu. This is probably because the sorption of 5-Fu on SP fibers is exothermic within the temperatures studied. The space effect on 5-Fu sorption onto SP fibers is smaller than the effect of sorption enthalpy.

Diclofenac has the largest activation energy for diffusion, followed by 5-Fu and Metformin as seen in Table 1. Higher activation energy for diffusion means that more energy is required to let drugs to move into the fibers. Since the size of Diclofenac is large compared to the other two

drugs, the opening in SP fibers must be large enough in order to let Diclofenac move inside, and the formation of this opening requires more energy.

3.2 Isotherms and thermodynamic parameters of Diclofenac, 5-Fu and Metformin sorption onto SP fibers

Isotherms of Diclofenac, 5-Fu and Metformin on SP fibers at different temperatures are shown in Figs. 5, 6 and 7, respectively. As seen from Figs. 5 and 7, higher temperature leads to higher drug sorption for Diclofenac and Metformin on SP fibers. This is probably because SP fibers create more accessible space at higher temperatures. Higher temperature can break stronger interactions among SP molecular chains leading to more sorption of Diclofenac and Metformin.

As seen in Fig. 6, lower temperature gives higher 5-Fu exhaustion on SP fibers. This is probably because the sorption of 5-Fu on SP fibers is exothermic, meaning that drug exhaustion decreases with increasing temperature.

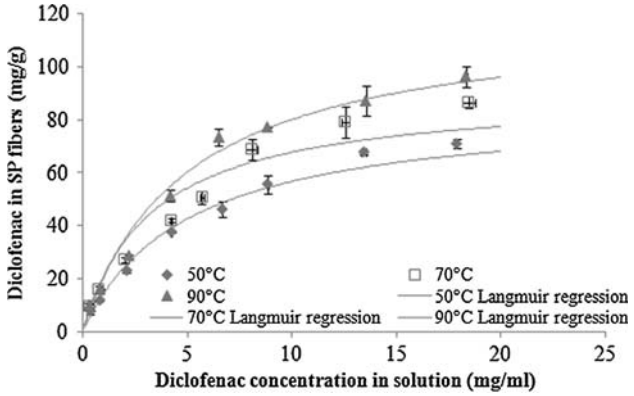

Fig. 5 Isotherms of Diclofenac on SP fibers at various temperatures with a drug solution-to-fibers ratio 100:1, and 60 min equilibration time

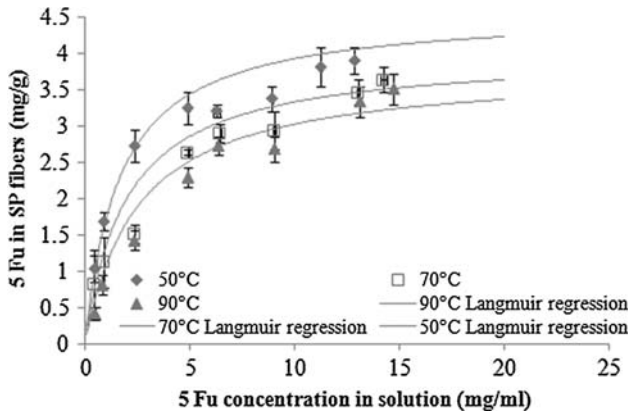

Fig. 6 Isotherms of 5-Fu on SP fibers at various temperatures with a drug solution-to-fibers ratio 100:1, and 60 min equilibration time

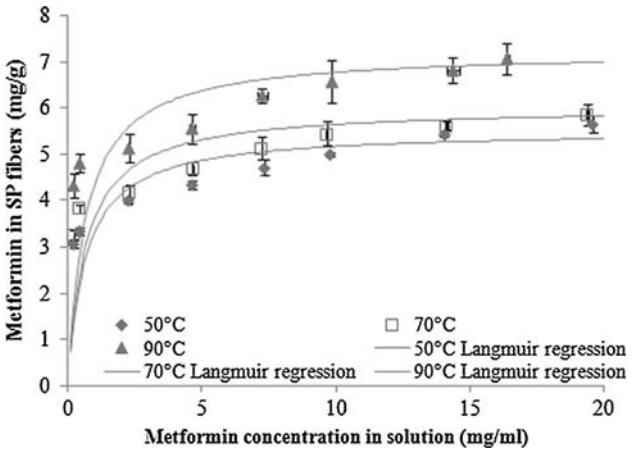

Fig. 7 Isotherms of Metformin on SP fibers at various temperatures with a drug solution-to-fibers ratio 100:1 and 60 min equilibration time

Although higher temperature may create more space in SP fibers for 5-Fu, the space effect for 5-Fu is smaller compared to sorption enthalpy. A drawback for both 5-Fu and Metformin loading using sorption method is that the drug loading amount is low, less than 8 mg/g by weight of soy protein. This is due to the small interactions between the drugs and SP fibers.

Thermodynamic parameters of drug sorption on SP fibers are listed in Table 2. As seen from the table, Diclofenac and Metformin have similar sorption affinities followed by 5-Fu on SP fibers. This is due to the different forces between drugs and SP fibers. As seen in Fig. 1, Diclofenac and Metformin has a negative charge and a positive charge, which can form strong interactions with amine and carboxylic groups in SP via the ionic force at sorption conditions, respectively. In addition, amine and carboxylic groups in Diclofenac can form hydrogen bonding with amine, hydroxyl and carbonyl groups in SP. These interactions give Diclofenac high affinities with SP fibers. Metformin has more atoms which can form hydrogen bonding with SP than 5-Fu. In addition, the hydrogens on primary amine in Metformin are less rigid than that in 5-Fu, leading to easy formation of hydrogen bonding with oxygen elements in SP, resulting in higher affinities with SP fibers than 5-Fu.

As depicted in Table 2, Metformin and Diclofenac have positive sorption enthalpies, while 5-Fu has a negative sorption enthalpy on SP fibers. This is because the sorption of Metformin and Diclofenac on SP fibers are endothermic while the sorption of 5-Fu on SP is exothermic within the temperatures studied. Metformin and Diclofenac have higher drug sorption entropies than that of 5-Fu as seen in Table 2. This is because more water molecules are released from Metformin, Diclofenac and SP during the drug sorption onto the SP fibers. Since Metformin and Diclofenac

Table 2 Thermodynamic parameters of drug sorption onto SP fibers at different temperatures

	Diclofenac			5-Fu			Metformin		
	50°C	70°C	90°C	50°C	70°C	90°C	50°C	70°C	90°C
$-\Delta\mu$ (kJ/mol)	25.17 ± 0.92	27.53 ± 0.90	29.60 ± 2.12	12.02 ± 0.66	12.34 ± 0.86	12.66 ± 0.41	24.48 ± 0.79	27.21 ± 0.84	30.73 ± 1.05
ΔH (kJ/mol)	10.62 ± 1.46			−8.23 ± 0.82			25.88 ± 3.95		
ΔS (J/mol/K)	110.80 ± 2.85	111.22 ± 2.62	111.80 ± 5.84	11.74 ± 1.61	11.99 ± 2.80	12.21 ± 3.50	155.91 ± 2.44	154.78 ± 2.45	155.95 ± 2.89

carried charges which attracted many water molecules around them, once Metformin and Diclofenac were sorbed by SP fibers, the water molecules were released, which increased the sorption entropy. Metformin can form more hydrogen bonding with SP than Diclofenac, leading to more water molecules released from the SP fibers, resulting in a higher entropy than Diclofenac.

3.3 Diclofenac, 5-Fu and Metformin release in PBS

Diclofenac, 5-Fu and Metformin release in PBS from drug loaded SP fibers are shown in Figs. 8, 9 and 10, respectively. As seen in the figures, Diclofenac and Metformin have high initial bursts for all the conditions. This is probably because the interactions between drugs and SP fibers are mainly ionic force and SP are readily swell in PBS. Ionic force can be readily broken by the salt exchange in PBS, while the swell of SP increases the drug release rates. The initial bursts of 5-Fu are lower than those of Diclofenac and Metformin due to the van der Waals forces between the 5-Fu and SP fibers. The van der Waals forces

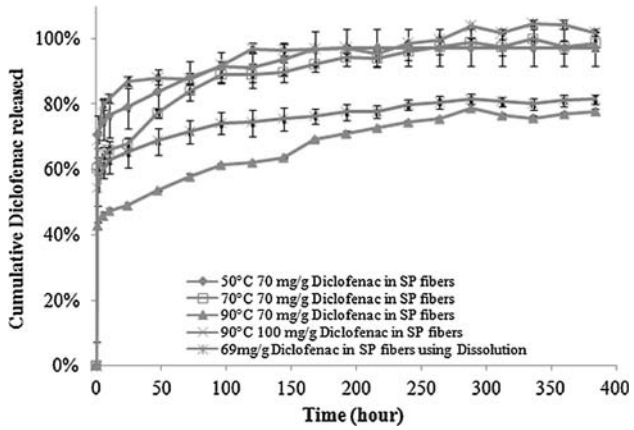

Fig. 8 Diclofenac release from SP fibers in PBS (pH 7.4) at 37.2 ± 0.1°C with shaking speed at 120 rpm

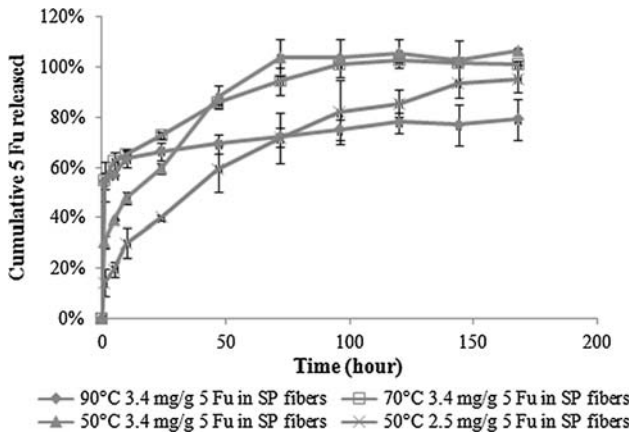

Fig. 9 5-Fu release from SP fibers in PBS (pH 7.4) at 37.2 ± 0.1°C with shaking speed at 120 rpm

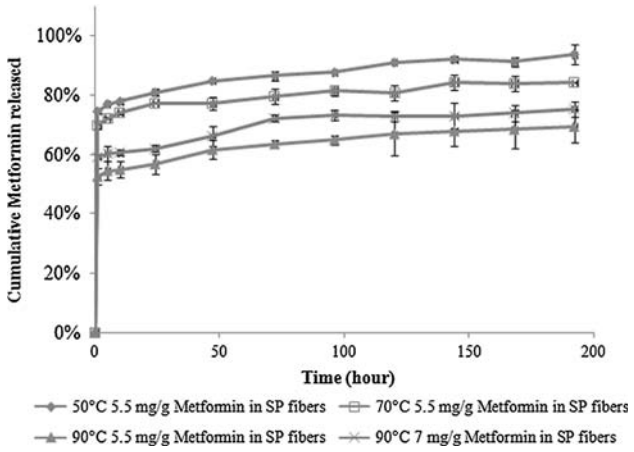

Fig. 10 Metformin release from SP fibers in PBS (pH 7.4) at 37.2 ± 0.1°C with shaking speed at 120 rpm

have a few effects on the salt exchange compared with the ionic force, leading to lower initial bursts. It also can be seen from the figures that increasing the drug loading temperature for Diclofenac and Metformin and decreasing the drug loading temperature for 5-Fu decreases the initial bursts. This is most likely because increasing the temperature for Diclofenac and Metformin and decreasing the temperature for 5-Fu increases the affinities between drugs and SP as seen in Table 2, leading to more drugs located in sites with stronger interactions with SP.

The figures also show that SP fibers with higher amounts of loaded drug have higher initial bursts than those of SP fibers with lower drug loading amounts. This is probably due to stronger interactions between the drug and the fibers at lower drug concentrations. In SP fibers, there are various sites the drug can occupy, and these sites have different affinities with the drug. At the lower drug loading concentration, drugs mainly occupy the sites with the strongest interaction with SP fibers, leading to lower initial bursts than the high drug loading concentration. When the amount of drug loaded on the fibers is higher, more drugs occupy sites in the fibers where they form weaker interactions with SP fibers because most of the stronger interaction sites are occupied by other drugs. Drugs that form weaker interactions with SP fibers are released more quickly as indicated by the higher initial burst when a larger amount of drugs are loaded on SP fibers. In addition, it has been found from Fig. 8 that Diclofenac release from SP fibers using the sorption method at 90°C has a lower initial burst and more constant release than that using the dissolution method because of the higher affinity between the drug and SP fibers.

Compared with drug release rates in PBS from the drug loaded polylactic acid (PLA), starch acetate (SA) and wheat gluten (WG) fibers using the sorption and the dissolution drug loading methods, SP has higher initial bursts and less constant subsequence release than PLA and SA, and similar release profiles with WG. This is most likely because of the swell of the fibers, and the swell can be reflected by the moisture regains. The moisture regain of PLA is 0.48% which is lower than 4.5% of SA, 10.8% of WG and 12.0% of SP at 21°C and 65%RH. PLA has the lowest initial burst and most constant drug release, followed by SA, WG and SP. Increasing the swell of the fibers increases the openings and channels in the fibers, resulting in a quick drug release rate.

3.4 Diclofenac, 5-Fu and Metformin release in AGJ

Diclofenac, 5-Fu and Metformin release from drug loaded SP fibers in AGJ are shown in Figs. 11, 12 and 13, respectively. As seen from Fig. 11, the dissolution method has a similar initial burst with 50°C but higher than 90°C of the sorption method. This is probably due to the lower affinity between drugs and SP fibers for the dissolution method. Since the drugs could not completely dissolve in the spinning solution, the drugs were physically entrapped in the solidified SP fibers after the fiber fabrication, resulting in lower affinity between the drugs and fibers. Within the sorption method, increasing temperature decreases the initial burst of Diclofenac and Metformin as seen in Figs. 11 and 13, while increasing temperature decreases the initial burst of 5-Fu as observed in Fig. 12. This is because the affinity between drugs and SP fibers increases with the increasing loading temperature for Diclofenac and Metformin, and decreases with the increasing loading temperature for 5-Fu as shown in Table 2. The higher affinity leads to the less readily drug releases from the fibers.

It also can be seen from Figs. 11, 12 and 13 that SP fibers with higher drug loading concentration have higher initial bursts than that with lower drug loading concentration. This is because of the high percentage of sites with the

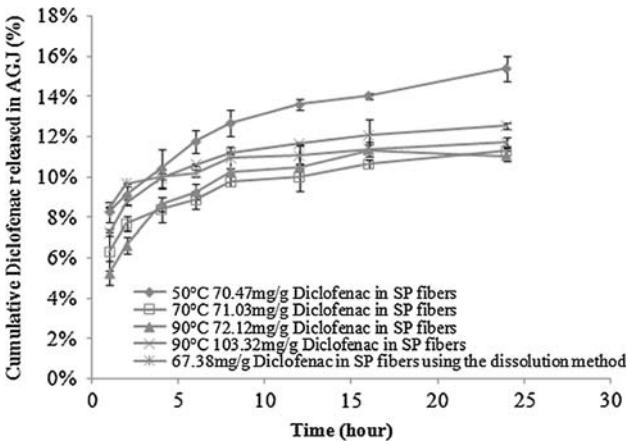

Fig. 11 Diclofenac release from SP fibers in AGJ (pH 1.2) at 37.2 ± 0.1°C with shaking speed at 120 rpm

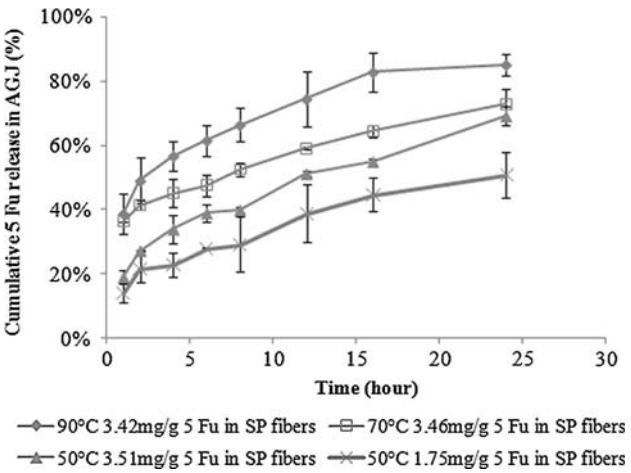

Fig. 12 5-Fu release from SP fibers in AGJ (pH 1.2) at 37.2 ± 0.1°C with shaking speed at 120 rpm

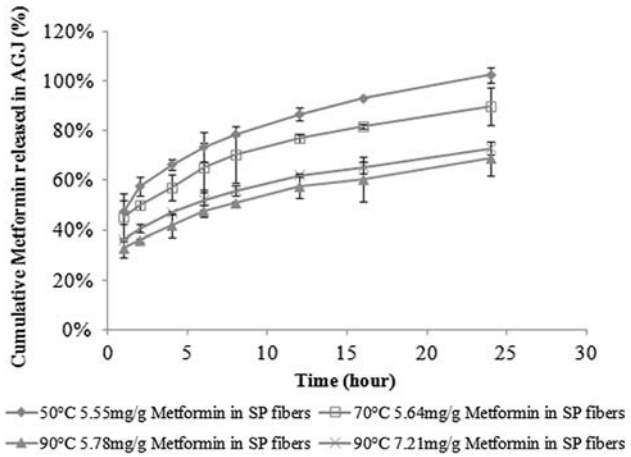

Fig. 13 Metformin release from SP fibers in AGJ (pH 1.2) at 37.2 ± 0.1°C with shaking speed at 120 rpm

higher affinity occupied at the lower drug concentration, which is same to the drug release in PBS. Compared with the Diclofenac release from SP fibers in PBS, Diclofenac release in AGJ were much slower and more constant. This is because Diclofenac, which carries a negative charge, is attracted by the protonized SP fibers in AGJ. The strong interaction between Diclofenac and protonized SP fibers leads to the low initial burst and constant drug release. As seen in Figs. 11, 12 and 13, 5-Fu has the highest initial bursts in AGJ, followed by Metformin and Diclofenac. This is due to the low affinity of 5-Fu on SP fibers as seen in Table 2. The weak interactions between 5-Fu and fibers leads to the high initial burst.

3.5 Prediction of initial burst and drug release after burst

It has been found that initial bursts in PBS and in AGJ have linear relationship with the drug loading concentration, the interaction between the affinity and the drug loading concentration and $(e^{-E_a/RT})^{0.5}$ for three drugs used in this study. These linear regressions give Eq. 9 ($R^2 = 0.920$) and Eq. 10 ($R^2 = 0.941$):

$$\%IB_1 = 978C - 30.1A \times C + 1080.5(e^{-E_a/RT})^{0.5} \quad (9)$$

$$\%IB_2 = 93.5C - 4.3A \times C + 881(e^{-E_a/RT})^{0.5} \quad (10)$$

where $\%IB_1$ is the initial burst in PBS, $\%IB_2$ is the initial burst in AGJ, C is the drug loading concentration (mol/kg), A is the affinity (kJ/mol) between the drug and SP fibers, E_a is the activation energy for diffusion (J/mol), R is the ideal gas constant (8.314 J/K/mol) and T is the release temperature (310.2 K).

A linear regression of the drug release after burst in PBS against the affinity, square root of time and square root of $e^{-E_a/RT}$, and a linear regression of drug release after burst in AGJ against the affinity, square root of time and square root of interaction between $e^{-E_a/RT}$ and time, have been developed. These linear regressions give Eq. 11 ($R^2 = 0.701$) and Eq. 12 ($R^2 = 0.948$):

$$\%DR_1 = -0.9A + 3t^{0.5} + 437.8(e^{-E_a/RT})^{0.5} \quad (11)$$

$$\%DR_2 = -0.5A + 1.7t^{0.5} + 233.6(e^{-E_a/RT})^{0.5} \times t^{0.5} \quad (12)$$

where $\%DR_1$ is the drug release percentage minus the initial burst in PBS, $\%DR_2$ is the drug release percentage minus the initial burst in AGJ, t is the release time (hour), E_a is the activation energy for diffusion (J/mol), R is the ideal gas constant (8.314 J/K/mol), A is the affinity (kJ/mol) between the drug and SP fibers and T is the release temperature (310.2 K).

The high R^2 values of four equations indicate that there are strong relationship between drug release and kinetic and thermodynamic parameters. These equations can be used to predict initial burst and drug release after bursts for drugs loaded on SP fibers with the sorption method.

4 Conclusions

The quantitative relationship between drug release and kinetic and thermodynamic parameters of drug sorption onto SP fibers has been discussed. Increasing loading temperature increases the diffusion coefficient of drug sorption onto SP fibers and increases Diclofenac and Metformin sorption on SP fibers within the temperatures studied. Nevertheless, increasing loading temperature decreases 5-Fu sorption on SP fibers within the temperatures studied. It has been found that Diclofenac has less constant release rates from SP fibers in PBS than those in AGJ and Diclofenac has more constant drug release from SP fibers than those of 5-Fu and Metformin in AGJ. Decreasing drug

loading concentration decreases initial bursts of the drug release.

The study also showed that Diclofenac loaded on SP fibers using the sorption method at a high temperature has the lower initial burst and more constant subsequence drug release than that using the dissolution method. General linear relationships have been established on the initial burst and subsequence drug release as dependant variables, and the drug loading concentration, affinity between drug and SP fibers, square root of $e^{-E_a/RT}$ and square root of time as independent variables, respectively. Our study shows that high affinity (specially with van der Waals forces), low moisture regain and low drug loading concentration result in lower initial burst and more constant drug release.

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