Drug Loading onto and Release from Wheat Gluten Fibers

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ABSTRACT: Drug release and its relationship with kinetic and thermodynamic parameters of drug sorption onto wheat gluten (WG) fibers have been studied using Diclofenac, 5-Fluorouracil (5-Fu), and Metformin as model drugs. Both sorption and dissolution methods were used to examine the drug release rates in phosphate buffered saline (PBS pH 7.4) and artificial gastric juice (AGJ pH 1.2). To understand drug release of WG fibers using the sorption loading method, kinetic, and apparent thermodynamic parameters, such as diffusion coefficient, activation energy for diffusion, affinity, and sorption enthalpy and entropy, have been investigated. It has been found that the sorption method at high temperatures has a lower initial burst and more constant release than the dissolution method for Diclofenac on WG fibers. Quantitative relationship between drug release and drug loading concentration, affinity, and activation energy for diffusion was established to predict initial bursts and later release of the drugs. The study showed that the Diclofenac had high initial bursts in PBS but more constant release in AGJ because the ionic force between the drug and WG fibers was readily broken in a high pH solution. It also has been found that drugs with higher activation energy for diffusion, lower diffusion coefficients, and higher affinity (especially van der Waals force) on WG fiber, are more suitable for sorption loading at elevated temperatures to achieve higher loading capacity and more constant releasing rate. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 116: 708–717, 2010

Key words: drug delivery system; kinetics; thermodynamics; wheat gluten Fibers; sorption

INTRODUCTION

Wheat gluten (WG) is a kind of composites of proteins conjoined with starch. The proteins are mainly gliadin and glutenin, and the total protein content in WG is about 80% on dry basis.[1] There are low and high molecular weight glutenin subunits, in which the high molecular weight glutenin subunit is crosslinked by disulfide bonds.[2] WG is rich in glutamine 31.9%, Glycine 5.4%, Leucine 7.2%, Proline 14.1%, Serine 5.7%, and Valine 5.4%[3]. Because WG is abundant, biodegradable, biocompatible, annually renewable and inexpensive, it has been widely used for various applications. WG has been successfully developed into fibers and electrospun fibers with or without other materials, such as poly(vinyl alcohol) or thiolated poly(vinyl alcohol).[4–7] As one of the most important forms, fiber has been widely used for scaffolds in tissue engineering for its high surface area to mass ratio and high porosity.[8] Recently, drug controlled release from scaffolds attracts more attention.[9] For the drug loading method, generally speaking, there are two methods to load drugs onto fibers, the dissolution method and the sorption method. However, the sorption method is more suitable for WG fibers for less impurities left in the fibers after drug loading compared with the dissolution method.

To our best knowledge, there is no report on drug controlled release using WG itself as a carrier. Although little applications of gluten have been developed in the drug delivery field (for instance, as a coating material), gliadin, one of the proteins in gluten, has been investigated.[10–12] As early as in 1940s, gliadin acetate was investigated as a drug carrier to allow a restricted controlled release of the drug to the spinal fluid.[13] The drug was encapsulated by the gliadin acetate and ultimately absorbed by the body. Stella et al. studied the gliadin films as a carrier for controlled drug release in vitro.[14] In the study, soft capsules (GI.C) and chewable gums (GCG) of crude gliadin were prepared. The release profile of paracetamol from GI.C has three regions in 0.1*M* hydrochloric acid media, initial latency period followed by a

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low release and essentially constant release, while there is only one region for paracetamol release from GCG with very slow release.

Ezpeleta et al. studied the controlled release of all-tans-reionoic acid (RA) from gliadin nanoparticles.[15] Gliadin nanoparticles about 500 nm were prepared using a desolvation method with a yield closed to 90% of initial protein. Zero order diffusion (release rate 0.065 mg RA/h) was observed after about a 20% initial burst. Duclairoir et al. optimized the parameters on the size of gliadin nanoparticles and the release profile of all-trans-retinoic acid.[16] Encapsulation and in vitro release of α-Tocopherol from gliadin nanoparticles had also been studied.[17] Umamaheshwari et al. studied the preparation of mucoadhesive gliadin nanoparticles (GNP) containing moxicillin and their effectiveness in eradicating *Helicobacter pylori*.[18] The study showed that the higher gliadin concentration gave a higher mucoadhesive property of GNP. Ramteke and Jain studied oral mucoadhesive sustained release of clarithromycin and omeprazole from gliadin nanoparticles in phosphate buffered saline (PBS with pH 7.4) and simulated gastric fluid (pH 1.2) at 37 ± 1 °C.[12]

In this study, both sorption and dissolution methods were used to load drugs onto WG fibers using Diclofenac, 5 Fluorouracil (5-Fu), and Metformin as model drugs. Both kinetic and thermodynamic parameters of the drug sorption onto WG fibers, such as diffusion coefficients, activation energy for diffusion, affinities, enthalpy, and entropy of sorption at various studied temperatures have been studied. Drug release in PBS (pH 7.4) and in artificial gastric juice (AGJ pH 1.2) has been conducted.

EXPERIMENTAL

Materials

WG (Whetpro 80) was purchased from Archer Daniels Midlands Company, Decatur, IL. Diclofenac and 5-Fu used in this study was purchased from TCI America with the purity larger than 98 and 99%, respectively. Metformin was purchased from Advanced Technology & Industrial Co., with the purity larger than 99%. The structures of Diclofenac, 5-Fu, and Metformin are from SciFinder Scholar with registry number of 15,307-86-5, 51-21-8, and 657-24-9, respectively. The structures are shown in Figure 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 $NaH_2PO_4.H_2O$. 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%.

WG fiber production

WG fibers were made according the method reported by Reddy and Yang.[7] WG (30% w/w) was dissolved in a 8*M* aqueous urea solution and allowed to stay for 24 h at 21°C. The WG solution was extruded into the acetate acid solution for coagulation. The fibers were drawn from the 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. After measurement, the fibers had a diameter of 35 ± 4 μm.

Drug loading

Diclofenac was dissolved in a pH 3.0 (adjusted with 20% v/v hydrochloric acid) solution increase the interaction between Diclofenac and WG fibers, whereas 5-Fu was dissolved in a pH 10.0 (adjusted with sodium hydroxide solution) solution to increase its solubility and achieve minimum WG hydrolysis, and Metformin was dissolved in distilled water only. About 10 mg of WG fibers were loaded into a centrifuge tube, and a solution containing the drug was added to the tube at 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 or specified time 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 3 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 for 24 h before testing (21°C, 65% RH). For the dissolution method, Diclofenac was dissolved in a WG spinning dope and extruded in a pH 3.0 coagulation bath. After drying, the fibers were washed 3 times with 1 mL of 0°C water for 30 s in a centrifuge at 9000 rpm, and then dried and conditioned before testing. Diclofenac was selected to compare the sorption with the dissolution because the higher loading amount of Diclofenac on WG using the sorption method led to a more precise comparison.

Determining the amount of drug loaded on the fibers

The drug loaded WG fibers were hydrolyzed using a 2*M* aqueous NaOH solution at 50°C for 2 h with continuous shaking. Dissolved WG 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

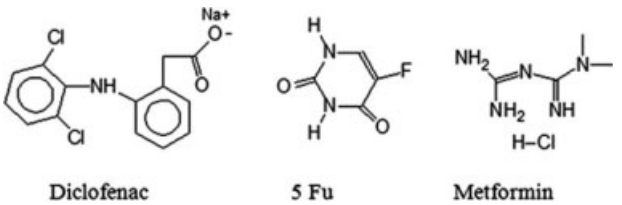

Figure 1 Structures of three drugs.

Coulter) at 275 nm, 284 nm, and 248 nm using virgin WG fibers as control. The drug loading amount on the WG fibers were calculated using calibration curves developed previously. The calibration curves for Diclofenac in the 0.952×10^{-3} mg/L WG solution had the relation of $y = 0.0386x$ ($R^2 = 0.999$); where y was the absorbance, and x was the Diclofenac concentration in the 0.952×10^{-3} mg/L WG solution with a unit of μg/ml. The calibration curve for 5-Fu in the 1.25×10^{-3} mg/L WG 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 1.25×10^{-3} mg/L WG solution with a unit of μg/ml. The calibration curve for Metformin in the 1.25×10^{-3} mg/L WG 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 1.25×10^{-3} mg/L WG solution with a unit of μg/mg.

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 WG fibers were used as control. About 10 mg of drug loaded WG 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.

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.

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)[19] and were obtained from a linear regression of C_t/C_∞ vs. $t^{0.5}$.

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

where C_t is the drug concentration in the fiber at the 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 time. The maximum diffusion coefficients and activation energies for diffusion for the drugs were calculated using eq. (2)[20] and were obtained from the intercept and slope, respectively, of a linear regression of $\ln(D_T)$ vs. $1/T$.

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

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 temperature.

Affinity, sorption enthalpy, and entropy

For Diclofenac and Metformin, the activity of the drug in solution is calculated by eq. (3)[21] because 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 solution were calculated using eq. (4).[21] The concentration of 5-Fu in solution was arbitrarily used as the activity in solution because 5-Fu is not ionized and the concentration is low.

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

where A is a constant approximately equal to 0.5 and 0.5 is used in this article, c is the concentration, and i is the component i in the drug. The activity of the drug on WG fibers were calculated by eq. (5)[22]

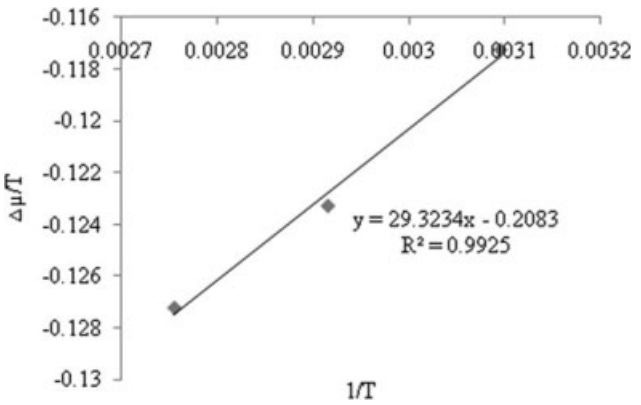

Figure 2 $\Delta\mu/T$ as a function of *1/T* for Diclofenac on WG fibers.

based on Langmuir sorption isotherm. Langmuir isotherm is selected because it has high R^2 values and a unit slope for plot of $\ln(a_f)$ vs. $\ln(a_s)$.

$$a_f = [D]_f/([S]_f - [D]_f) \tag{5}$$

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).[21]

$$-\Delta\mu = RT\ln(a_f/a_s) \tag{6}$$

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

$$\Delta H/T = -\Delta\mu/T + C \tag{7}$$

where ΔH is the apparent sorption enthalpy, and C is a constant, e.g., The $\Delta\mu/T$ as a function of *1/T* for Diclofenac on WG fibers is shown in Figure 2. The slope 29.32 is the ΔH for Diclofenac on WG fibers.

The apparent sorption entropy was calculated using eq. (8).[21]

$$-\Delta\mu = \Delta H - T\Delta S \tag{8}$$

where ΔS is the apparent sorption entropy, e.g., The ΔS of Diclofenac sorption onto WG fibers at 50°C are calculated as follows.

$$\begin{aligned}\Delta S &= (\Delta H + \Delta\mu)/T \\ &= (29.32 + 37.87)/323 \times 1000 \\ &= 208.02\ \mathrm{J(mol \cdot K)}\end{aligned}$$

Statistics

All the experiments were repeated three times. The data were reported with mean ± one standard deviation. To obtain equations to predict initial burst and drug release after burst based on affinity between drug and WG 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.

RESULTS AND DISCUSSION

Sorption rates and kinetic parameters of Diclofenac, 5-Fu, and Metformin sorption on WG fibers

Sorption rates of Diclofenac on WG fibers at different temperatures are shown in Figure 3. As seen from Figure 3, the higher temperature drives the high drug sorption rate, which can be reflected by the initial slope of the sorption rate curves. This is because the high temperature leads to fast movement of the drug both in the solution and in WG fibers. Higher temperature increases the movement of the polymer in the solution, thus increasing the movement of the drug into fibers. It also can be seen from Figure 3 that higher temperature produces higher drug exhaustion. This is probably due to the more accessible space created at higher temperatures for drugs to be sorbed into fibers. Higher temperatures can break stronger interaction among WG molecular chains and create more accessible space, which may lead to more Diclofenac sorption.

The sorption rates of 5-Fu and metformin on WG fibers at different temperatures are shown in Figures 4 and 5. As seen in the Figures, drug sorption rates

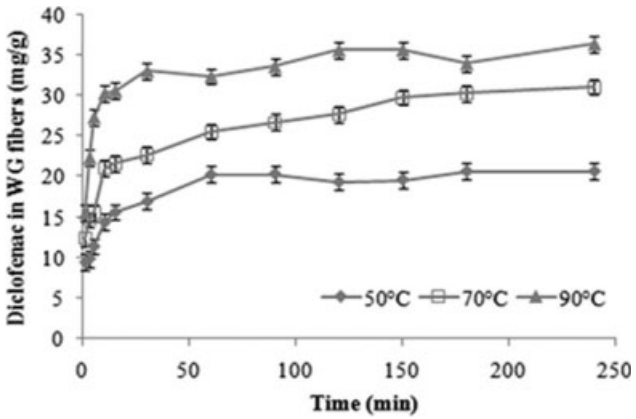

Figure 3 Sorption rates of Diclofenac on WG fibers at the temperature of 50, 70, and 90°C for different loading time with initial Diclofenac concentration of 5×10^{-3} mg/L at pH 3.0.

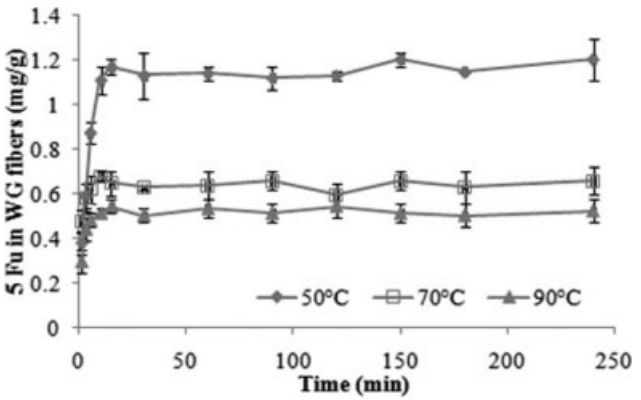

Figure 4 Sorption rates of 5-Fu on WG fibers at the temperature of 50, 70, and 90°C for different loading time with initial 5-Fu concentration of 5 $\times 10^{-3}$ mg/L at pH 10.0.

for both 5-Fu and metformin are fast as well as Diclofenac, however, the reasons are different. The reason of high sorption rates for 5-Fu and Metformin is because of the small size of the drugs, while the reason for Diclofenac is the stronger interaction. The larger the size of the drug, the slower the drug sorption rate at the same drug loading temperature. It can be seen from Figure 1 that both 5-Fu and Metformin have small structures compared with Diclofenac, and hence 5-Fu and Metformin have high drug sorption rates. Because Diclofenac carries a negative charge in the solution, it is strongly attracted by the positive protonized amine groups in WG at pH 3.0, and, thus, increases the sorption rates.[23] As seen from Figure 4, the increasing drug loading temperature decreases 5-Fu exhaustion. This is probably due to the negative sorption enthalpy of 5-Fu sorption on WG fibers. Figure 5 shows that the temperature effect on exhaustion of Metformin on WG fibers is similar to that of Diclofenac on WG fibers and the reasons are also similar.

Diffusion coefficients and activation energy for diffusion of drugs through WG fibers, which have a diameter of 35 μm, are shown in Table I. As seen in the Table, 5-Fu has the highest diffusion coefficients followed by Metformin and then Diclofenac. This is due to the drug's size and the affinity between the drug and WG fibers. 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). The larger size of the drug, the more difficult for the drug to move into the WG fibers. The drug with the large size moves slowly in the drug solution and it is more diffult to go through the openings in the WG fibers. In addition, affinity between the drug and WG fibers may also influence the diffusion coefficients. Higher affinity decreases the sorption rate because the fast sorbed drug molecule tightly interacts with WG molecular chains and blocks the next drug molecule from moving inside of the fibers. As seen in Table II, Diclofenac has the highest affinities, followed by Metformin and 5-Fu. The smaller diffusion coefficients of Metformin than those of 5-Fu through WG are probably due to the fact that Metformin has higher affinities than 5-Fu on the fibers.

Also it can be seen from Table I that diffusion coefficients at the higher temperature are larger than those at the lower temperature within a specific type of drug. This is because drugs move faster both in the drug solution and in WG fibers at higher temperatures. Diclofenac has the largest activation energy for diffusion, followed by Metformin and 5-Fu as seen in Table I. Higher activation energy for diffusion means that more energy is required to create an opening big enough for Diclofenac to move into the fibers. Because the size of Diclofenac is large compared with the other two drugs, the opening in WG fibers must be large enough to let Diclofenac move inside, and the formation of this opening requires more energy.

Isotherms and apparent thermodynamic parameters of Diclofenac, 5-Fu, and Metformin sorption on WG fibers

Isotherms of Diclofenac on WG fibers at different temperatures are shown in Figure 6. As seen from the Figure, increasing the temperature increases the drug sorption. This is probably because WG fibers create more accessible space for Diclofenac at higher temperatures. Higher temperatures can break the stronger interaction among WG molecular chains, and thus leading to more Diclofenac sorption. Also it can be seen from Figure 6 that the increase of the drug sorption from 70°C to 90°C is higher than that from 50°C to 70°C. This is probably because the

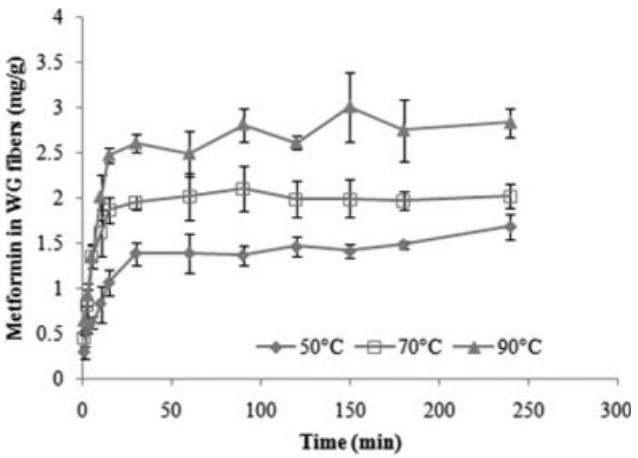

Figure 5 Sorption rates of Metformin on WG fibers at the temperature of 50, 70, and 90°C for different loading time with initial Metformin concentration of 5 $\times 10^{-3}$ mg/L.

TABLE I
Kinetic Parameters of Drug Sorption onto WG 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 $\times 10^{12}$ ($m^2 \cdot min^{-1}$)	0.786 ± 0.031	1.129 ± 0.004	1.485 ± 0.054	5.468 ± 0.054	6.851 ± 0.038	7.632 ± 0.275	2.021 ± 0.054	3.032 ± 0.019	4.000 ± 0.004
ΔE for diffusion ($kJ \cdot mol^{-1}$)		15.54 ± 0.71			8.17 ± 1.38			16.68 ± 1.25	

TABLE II
Apparent Thermodynamic Parameters of Drug Sorption onto WG 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
$-\Delta\mu$ ($kJ \cdot mol^{-1}$)	37.87 ± 1.83	42.28 ± 2.29	46.18 ± 4.45	9.85 ± 0.70	10.69 ± 0.86	11.42 ± 0.23	20.83 ± 1.51	25.41 ± 2.48	29.20 ± 1.85
ΔH ($kJ \cdot mol^{-1}$)		29.32 ± 2.54			−2.86 ± 0.50			46.86 ± 3.94	
ΔS ($J \cdot mol^{-1} \cdot K^{-1}$)	208.02 ± 5.66	209.21 ± 6.68	208.43 ± 12.26	21.64 ± 2.17	22.83 ± 2.51	23.58 ± 0.63	210.37 ± 4.67	211.46 ± 7.23	210.25 ± 1.85

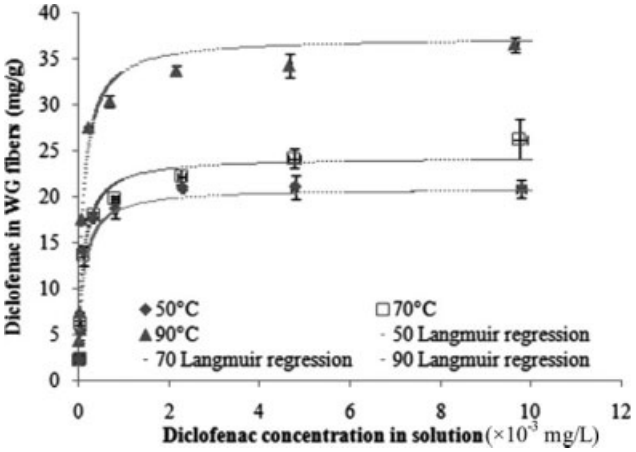

Figure 6 Isotherms of Diclofenac on WG fibers at pH 3.0 with a drug solution-to-fibers ratio 100 : 1, and 60 min equilibration time at 50, 70, and 90°C.

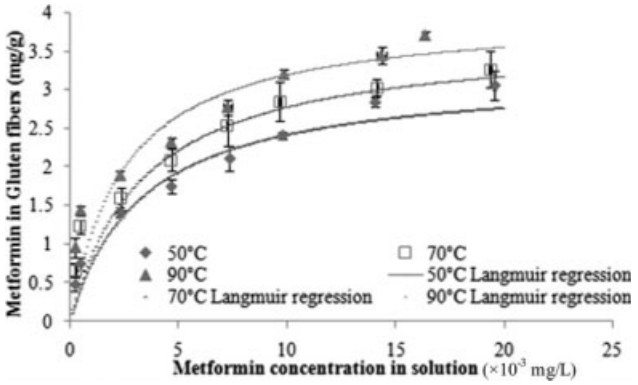

Figure 8 Isotherms of Metformin on WG fibers at pH 6.3 with a drug solution-to-fibers ratio 100 : 1 and 60 min equilibration time at 50, 70, and 90°C.

interaction among WG molecular chains is more sensitive to a temperature of higher than 70°C and less or equal to 90°C.

Isotherms of 5-Fu and Metformin on WG fibers at different temperatures are shown in Figures 7 and 8. As seen in Figure 7, lower temperatures give higher drug exhausion than higher temperatures. This is probably due to the sorption of 5-Fu on WG fibers is exothermic, which means the drug sorption decreases with the increasing temperature. Although higher temperatures may create more space in WG fibers, the space effect for 5-Fu is smaller compared to the effect of sorption enthalpy. Metformin isotherms in Figure 8 are similar to that of Diclofenac on WG fibers and the reasons are also similar. However, a drawback for both 5-Fu and Metformin using the sorption loading method is that the drug loading amount is low, less than 4 mg/g by weight of WG. This is due to the small interaction between 5-Fu and Metformin and WG fibers.

Apparent thermodynamic parameters of the drug sorption on WG fibers are listed in Table II. As seen from the Table, Diclofenac has the highest sorption affinities followed by Metformin and 5-Fu on WG fibers. This is due to the different interactions between drugs and WG fibers. As seen in Figure 1, Diclofenac has a negative charge and can form strong interactions with protonized amine in WG at pH 3.0. In addition, amine and carboxylic groups in Diclofenac can form hydrogen bonding with amine, hydroxyl, and carbonyl groups in WG. These interactions give Diclofenac high affinities with WG fibers. Metformin has higher affinities than those of 5-Fu with WG fibers because it has more positive charges, forms stronger hydrogen bonding, and has greater flexibility. Metformin carries positive charges, which can interact with the negtive charge at the end of WG molecules. Metformin can form more hydrogen bondings with WG than 5-Fu. In addition, the hydrogens on primary amine in Metformin are relatively flexible that can facilitate the amine forms hydrogen bonding with oxygen in WG.

As seen in Table II, Metformin and Diclofenac have higher apparent enthalpies than 5-Fu. This is because the sorption of Diclofenac and Metformin on WG fibers are endothermic while the sorption of 5-Fu on WG is exothermic within the temperatures studied. Metformin and Diclofenac have higher drug sorption entropies than that of 5-Fu as seen in Table II. This is because more water molecules are released from Metformin and Diclofenac during the drug sorption onto WG fibers. Both Metformin and Diclofenac carry charges which attract many water molecules around them. Once Metformin and Diclofenac were sorbed by WG fibers, the water molecules were released, which increased the entropy.

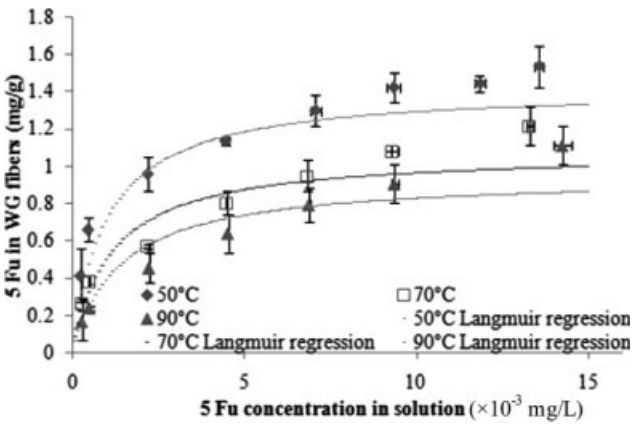

Figure 7 Isotherms of 5-Fu on WG fibers at pH 10.0 with a drug solution-to-fibers ratio 100 : 1, and 60 min equilibration time at 50, 70, and 90°C.

Diclofenac, 5-Fu, and Metformin release in PBS

Diclofenac release in PBS from drug loaded WG fibers are shown in Figure 9. As seen in the Figure,

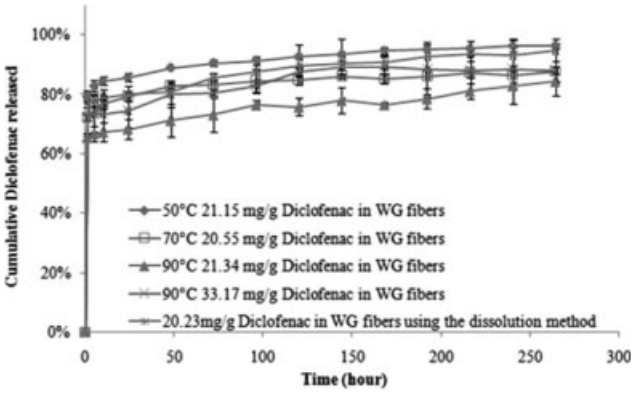

Figure 9 Diclofenac release from WG fibers in PBS (pH 7.4) at 37.2 ± 0.1°C with shaking speed at 120 rpm.

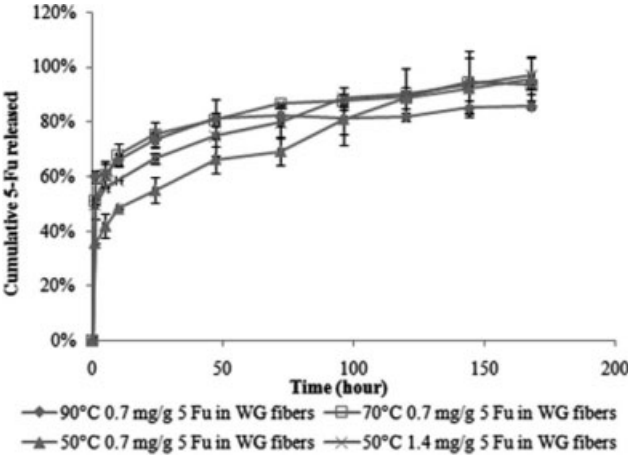

Figure 10 5-Fu release from WG fibers in PBS (pH 7.4) at 37.2 ± 0.1°C with shaking speed at 120 rpm.

all conditions have high initial bursts. This is probably because the interactions between Diclofenac and WG fibers are mainly ionic force and the drug is exchanged out of the fibers by salts in PBS. It can be seen from the figure that increasing drug loading temperature decreases the initial burst. This is because increasing the temperature increases the affinity between Diclofenac and WG, and more drugs become located in sites with stronger interactions with WG. The higher the affinity between Diclofenac and WG, the less readily drug releases from the fibers. It also can be seen from Figure 9 that WG fibers with higher amounts of loaded drug have higher initial bursts than those of WG fibers with lower drug loading concentrations. This is probably due to stronger interactions between the drug and the fibers at lower drug concentrations. In WG 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 WG fibers, and lead 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 WG fibers because most of the stronger interaction sites are occupied by other drugs. Drugs that form weaker interactions with WG fiber are released more quickly as indicated by the higher initial burst when a larger amount of drugs are loaded on WG fiber. In addition, it can be seen from the figure that Diclofenac release from WG 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 even distribution of the drug in the WG fibers.

5-Fu and Metformin release from WG fibers, after having been loaded at different temperatures, are shown in Figures 10 and 11. As seen in the figures, all drug release curves have initial bursts, and WG fibers with the drug loaded at higher temperatures have slower drug release. As seen in Figure 10, the initial bursts of 5-Fu from WG fibers are smaller compared with those of Diclofenac and Metformin. This is probably caused by the different forces between the drug and WG fibers. The force between 5-Fu and WG are mainly van der Waals force, which has smaller effect on salt exchange compared with the ionic force, and thus leading to lower 5-Fu initial bursts. Nonetheless, 5-Fu has high initial bursts, and this is because of the low activation energy for diffusion for 5-Fu on WG fibers. As seen in Table I, 5-Fu has a lower activation energy for diffusion than Diclofenac and Metformin. The lower activation energy indicates the higher diffusion coefficient, and hence leads to quick drug release out of WG fibers. Compared with Diclofenac, Metformin has lower initial bursts as seen in Figure 11. This is probably due to more charges on Metformin and thus leading to low initial bursts.

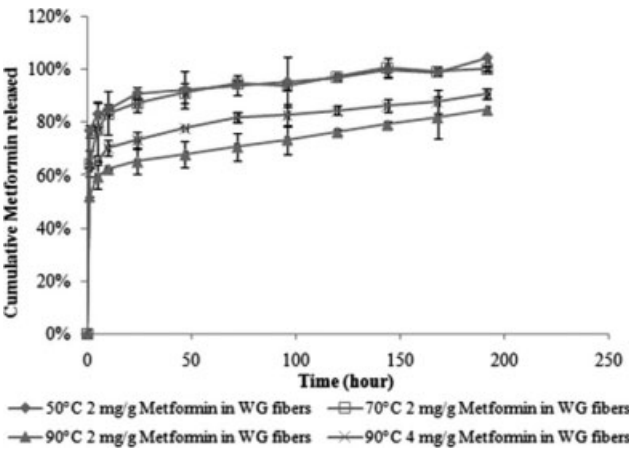

Figure 11 Metformin release from WG fibers in PBS (pH 7.4) at 37.2 ± 0.1°C with shaking speed at 120 rpm.

Diclofenac, 5-Fu, and Metformin release in AGJ

Diclofenac release from drug loaded WG fibers in AGJ are shown in Figure 12. As seen from the Figure, 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 uneven distribution of drugs in the fibers. Within the sorption method, increasing temperature decreases the initial burst. This is because the affinity between Diclofenac and WG fibers increases with the increasing loading temperature. The higher affinity leads to the less readily drug releases from the fibers. It also can be seen from the Figure that WG fibers with the higher drug loading concentration have the higher initial burst than that of WG fibers with the lower drug loading concentration. The reasons are same to the drug release in PBS. Compared with the Diclofenac release from WG fibers in PBS, Diclofenac release in AGJ is much slower and more constant as seen in Figure 12. This is because Diclofenac, carrying a negative charge, is attracted by the protonized WG fibers in AGJ. The strong interaction between Diclofenac and protonized WG fibers leads to the low initial burst and constant drug release.

5-Fu and Metformin release from WG fibers using the sorption loading method are shown in Figures 13 and 14. As seen in the Figures, 5-Fu has the highest initial bursts, followed with Metformin and Diclofenac in AGJ. This is due to the low activation energy for diffusion and the low affinity of 5-Fu on WG fibers. Within each drug studied, the drug with the higher affinity on WG fibers has lower initial bursts and more constant release after burst. This is because the stronger interaction between the drug and fibers leads to the low initial burst and constant drug release from the fibers. It also can be seen from the Figures that increasing the drug concentration in fibers leads to the higher initial burst and less constant release. This is because of the high percentage of sites with the higher affinity occupied at the lower drug concentration.

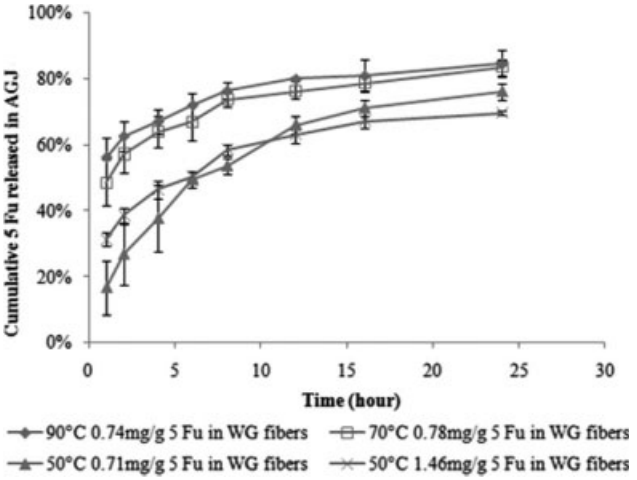

Figure 13 5-Fu release from WG fibers in AGJ (pH 1.2) at 37.2 ± 0.1°C with shaking speed at 120 rpm.

Prediction of initial burst and drug release after burst

It has been found that initial bursts in PBS have linear relationship with the drug loading concentration and the interaction between the affinity and the drug loading concentration for three drugs used in this study. Also, the initial burst in AGJ has linear relationship with the drug loading concentration, the interaction between the affinity and the drug loading concentration and $(e^{-E_a/RT})^{0.5}$. These linear regressions give eq. (9) ($R^2 = 0.632$) and eq. (10) ($R^2 = 0.617$):

$$\%IB_1 = 21.1 + 5417.4C - 106.1A \times C \quad (9)$$

$$\%IB_2 = 4.6 + 1119.2C - 22.6A \times C + 137.2(e^{-E_a/RT})^{0.5} \quad (10)$$

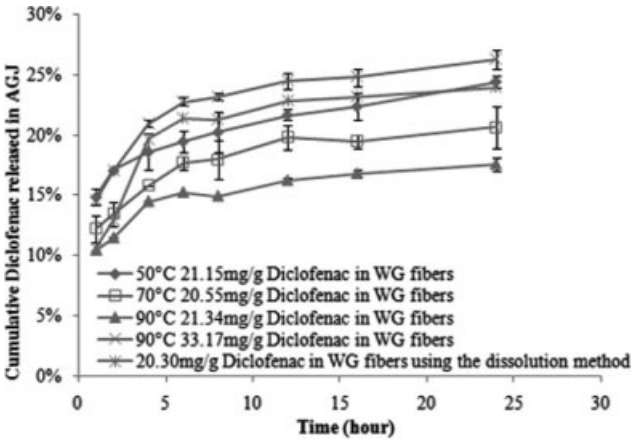

Figure 12 Diclofenac release from WG fibers in AGJ (pH 1.2) at 37.2 ± 0.1°C with shaking speed at 120 rpm.

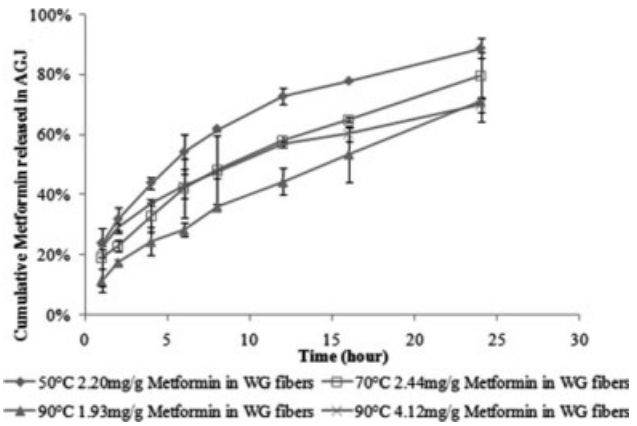

Figure 14 Metformin release from WG fibers in AGJ (pH 1.2) at 37.2 ± 0.1°C with shaking speed at 120 rpm.

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^{-1}), A is the affinity (kJ mol^{-1}) between the drug and WG fibers, E_a is the activation energy for diffusion (J mol^{-1}), R is the ideal gas constant (8.314 J $K^{-}1$ mol^{-1}), and T is the release temperature (310.2 K).

A linear regression of the drug release after burst in PBS versus the square root of time and the square root of interaction between $e^{-E_a/RT}$ and time, and a linear regression of drug release after burst in AGJ versus the affinity, the square root of time and the square root of interaction between $e^{-E_a/RT}$ and time, have been developed. These linear regressions give eq. (11) ($R^2 = 0.721$) and eq. (12) ($R^2 = 0.815$):

$$\%DR_1 = 5.7 + 0.9t^{0.5} + 12.7(e^{-E_a/RT})^{0.5} \times t^{0.5} \quad (11)$$

$$\%DR_2 = -0.3A + 10t^{0.5} + 5(e^{-E_a/RT})^{0.5} \times t^{0.5} \quad (12)$$

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^{-1}), R is the ideal gas constant (8.314 J $K^{-}1$ mol^{-1}), A is the affinity (kJ mol^{-1}) between the drug and WG 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 WG fibers with the sorption method.

CONCLUSIONS

The relationship between drug release and kinetic and thermodynamic parameters of drug sorption onto WG fibers has been discussed. Increasing loading temperature increases the diffusion coefficient of drugs. Also, increasing loading temperature increases Diclofenac and Metformin sorption on WG fibers within the temperatures studied. Nevertheless, increasing loading temperature decreases 5-Fu sorption on WG fibers within the temperatures studied. Diclofenac has less constant release rates from WG fibers in PBS than those in AGJ. Diclofenac has more constant drug release from WG fibers than those of 5-Fu and Metformin in AGJ. Loading drugs onto WG fibers by sorption at higher temperature results in a more constant drug release rate. Decreasing drug loading concentration decreases initial burst. The study also showed that the Diclofenac loaded on WG fibers using the sorption method at a high temperature has the lower initial burst and more constant drug release afterward than that using the dissolution method. General linear relationships have been established on the initial burst and drug release after burst, respectively, as dependant variables, and drug loading concentration, affinity between drug and WG fibers, square root of $e^{-E_a/RT}$ and square root of time as independent variables. Our study shows that the high affinity (specially with van der Waals force), low drug loading concentration, and high activation energy for diffusion result in lower initial burst and more constant drug release.

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