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Porcine and Fish Gelatin Hydrogels for Controlled Release of Salicylic Acid and 5-sulfosalicylic Acid

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Abstract:
The controlled release of drugs from gelatin hydrogel was studied undereffects of crosslinking ratio, gelatin type, namely porcine and fish gelatins, and drug size. The drug-loaded gelatin hydrogels, using glutaraldehyde as the crosslinker, were fabricated by solution casting, with salicylic acid, and 5-sulfosalicylic acid as the model drugs. The release mechanism and the diffusion coefficients of the drug from gelatin hydrogels were determined prusing a modified Franz-Diffusion cell and the Higuchi equation to determine the effects of the hydrogel and drug sizes.The time release profiles were obtained with the time exponent *n* close to 0.5, indicating the process was the Fickian diffusion. The diffusion coefficients of the model drugs decrease with decreasing hydrogel pore size and increasing drug size. The diffusion coefficients of the two model drugs and of both gelatinsdisplay a common scaling behavior: $D = D_0/(drug\ size/pore\ size)^m$ with the scaling exponent *m* equal to 0.45 and with nearly the same D_0.Both porcine and fish gelatins are thus shown to be equally effective
drug release matrices with the same ease in preparation.

Keywords: gelatin; hydrogels; crosslinking ratio; drug size, transdermal drug delivery

Introduction

There are many routes for introducing a drug into a body: oral, injection, and transdermal administration. The benefit of the oral and injection routes is to provide the maximum sufferable dose, however the dose level reduces over a short period of time [1].The transdermal drug delivery system (TDDS) is a candidate when frequent administration and prolonged release are required. In addition, TDDS provides advantages of avoiding first-pass metabolism, maintaining blood levels for a long period of time, and reducing side effects without pain [2].

A hydrogelis a type of three-dimensional network that consists of a hydrophilic functional group within its structure,such as a carboxylic (–COOH), amidic (–CONH–), primary amidic ($–CONH_2$), hydroxyl (–OH), orsulphonic ($–SO_3H$), which can be found within the polymer backbone or as sidegroups of the chains [3-5]. Hydrogels have been widely studied in the application of controlled drug release because they are three-dimensionallycrosslinked structures utilizing water-soluble polymers. Many hydrogel forms are available for fabrication, for example, slabs, microparticles, nanoparticles, coatings, and films. The hydrogel properties strongly depend on the building blocks and the production process. Biopolymers are also used available to form hydrogels viaa physical or chemical crosslinking reaction, especially gelatin,which is a well-defined hydrogel matrix [6].

Gelatin is generally either acid or alkaline. It is extracted from mammal, poultry, or fish collagen, which is primarily composed of polydispersed polypeptides. Well-known sources are bovine hides, pig, and fish skins [7].The risk of contracting

bovine spongiform encephalopathy (BSE) has changed manufacturing steps [8] and foot-and-mouth disease (FMD) [9]is now strictly monitored. Thus, porcine and fish gelatin products are normally used for safety reasons.Because gelatin is a water soluble polymer that uses chemical modification to become insoluble,hydrophilicity is required in the application oftransdermal drug delivery. Chemical crosslinking has been applied to form interconnected chains [10]. Cross-linking of gelatin is easily completed with glutaraldehydevia the unprotonated ε-amino groups of lysine, hydroxylysine, and amino groups of the N-terminal amino acid in the gelatin structure [11].

The aim of this work includes the preparation, characterization, and comparison of properties of porcine and fish gelatin hydrogels for controlled drug release using different drug sizes.The scope of the work also covers the morphology, swelling, diffusion, and drug release rate which will be reported here for both gelatins and model drugs.

Materials and Methodes

Materials

Porcine gelatin (PorGel; Fluka, AR grade) and cold-water fish gelatin (FishGel; Sigma, AR Grade) were used as the matrices. Salicylic acid (SA; 3.28 Å) and 5-sulfosalicylic acid (SS;9.25 Å) (Fluka, AR Grade) were used as the model drugs. Glutaraldehyde (Fluka, 50% in water AR grade) was used as the crosslinking agent. Sodium acetate (Ajax Finechem, AR Grade) and glacial acetic acid (Merck, AR Grade) were used as the buffer solutions.

Preparation of Drug-loaded GelatinHydrogels

A 10%w/vgelatin solution was produced by dissolvinggelatin (PorGelor FishGel)powder in deionized water at 60°C for 1 h, and then coolingto room temperature (25°C). The model drugs (SA/SSA) were loaded into the gelatin solution at 1 wt% (based on the weight of the gelatin powder) under constant stirring for 1 h. Then glutaraldehydewas added to the solution at various crosslinking ratios of 0.25, 0.50, 0.75, 1.00, 3.00, and 7.00wt%for PorGel and 1.00, 3.00, and 7.00wt% for FishGel. The gelatin-glutaraldehyde solution was mixed slowly to prevent the formation of air bubbles.[12]The mixture was cast on a petridish(diameter of 9 cm, film thickness of 0.45-0.50mm) immediately after mixing, and then cooled to room temperature (25°C).

Characterizations

The functional groups of SA and SSAwere identified using afourier transform infrared spectrometer (FTIR;Bruker, Equinox 55/FRA 1065).Each drug-loaded gelatin hydrogel was investigated for the polymer/drug interaction by an attenuated total reflection fourier transform infrared spectrometer(ATR-FTIR; Thermo Nicolet, Nexus 670).A scanning electron microscope, or SEM (JEOL, model JSM-5200), was used to investigate the morphology of each crosslinked hydrogel. The hydrogel samples were prepared by immersing each hydrogel in anacetate buffer solution at 37°C, before they were rapidly frozen in liquid nitrogen and then dried them in a vacuum chamber at -50°C. SEMmicrographs of the crosslinked hydrogels were obtained by using an acceleration voltage of 15 kV at a magnification of 3000x.

The degree of swelling and weight loss of the gelatin hydrogels were measured in pH 5.5 buffer solutions at 37°C for 48 h [13] usingEquations 1 and 2:

Degree of swelling (%) = $\frac{M_s - M_d}{M_d} \times 100$ (1)

and

Weight loss (%) = $\frac{M_i - M_d}{M_i} \times 100$ (2)

where M_s is the weight of the sample after submersing in the buffer solution, M_d is the weight of the sample after submersing in the buffer solution in the dry state, M_i is the initial weight of the sample before submersing in the buffer solution in the dry state.

To measure the molecular weight between crosslinks, $\overline{M_c}$, and the mesh size, ξ, a sample (1 cm^2)of gelatin film was cut after crosslinking. The sample was weighed in air and heptane. Next it was immersed in distilled water at 37°C for 5 days until it swelled to equilibrium, then weighed in air and heptane again. Finally, the sample was dried at 2°C in a vacuum oven for 5 days. Once again, it was weighed in air and heptane [12].

The $\overline{M_c}$, was estimated from the swelling data by using Equation 3 [12]:

$$\frac{1}{\overline{M_c}} = \frac{2}{\overline{M_n}} - \frac{\frac{\bar{v}}{\bar{V}_1}\left[\ln(1-v_{2,s}) + v_{2,s} + \chi v_{2,s}^2\right]}{v_2\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{v_{2,s}}{v_{2,r}}\right)\right]} \quad (3)$$

where $\overline{M_n}$ is the number averaged molecular weight of the polymer before cross linking ($\overline{M_n}$ = 69480 g/mol for porcine gelatin and 36800 g/mol for fish gelatin), $\bar{v}$ is the specific volume of gelatin ($\bar{v}$ = 0.69 cm^3/g of gelatin) [14], $\bar{V}_1$ is the molar volume of water ($\bar{V}_1$ = 18.1 mol/cm^3), χ is the Flory interaction parameter of gelatin (χ = 0.49) [15], and the dissociation constant pKa is 4.7.

The ξ of a hydrogel, describes the linear distance between consecutive cross links. It indicates the diffusional space available for solute transport. The ξ was calculated by using Equation4 [16]:

$$\xi = v_{2,s}^{-1/3}\left[C_n\left(\frac{2\overline{M}_c}{\overline{M}_r}\right)\right]^{1/2} \cdot l \quad (4)$$

where C_n is the Flory characteristic ratio for gelatin (C_n = 8.8) [7], $\overline{M}_r$ is the molecular weight of the repeating unit of gelatin ($\overline{M}_r$ = 100 g/mol) [14], and *l* is the carbon–carbon bond length (*l* = 1.54 Å) [17].

Drug Release Experiments

Preparation of Acetate Buffer

Acetate buffer (pH 5.5)was chosen to simulate human skinand was prepared by dissolving 150 g of sodium acetate in 1000 mL of distilled water.Then glacial acetic acid (15 mL)was added to the aqueous sodium acetate solution. The solution was poured into the receptor chamber of a modified Franz-diffusion cell [17].

Spectrophotometric Analysis of Model Drug

A UV-Visible spectrophotometer (TECAN Infinite M200) was used to examine to determine the maximum absorption wavelength of the model drugs. Each model drug, in aqueous solution, was prepared for scanning at the maximum absorption wavelength so the characteristic peak could be observed. The absorbance value at the maximum wavelength of the model drug was plotted inrelationto the model drugconcentration, so that the calibration curves of the model drugs could be generated [17].

Actual Drug Content

The actual amount of drug in the drug-loaded gelatin hydrogels (circular disc of 2.5 cm, thickness of 0.45-0.50 mm) was quantified by dissolving the sample in 4 mL of dimethyl sulfoxide (DMSO). Then 0.5 mL of DMSO, mixed with the drug solution, was added to 8 mL of the acetate buffer solution. The amount of drugs in the solution was measured by

using the UV-Visible spectrophotometer at a wavelength of 298 nm for SA and SSA [17].

Transdermal Transport Studies

Custom built modified Franz-diffusion cells were used. The diffusion cellsconsisted of two compartments. The first was a water jacket, whichwas exposed to ambient conditions. The other was a receptor chamber that contained a 5.5 pH acetate buffer solution and was maintained at 37°C by a circulating water bath. Drug-loaded gelatin hydrogels at various crosslinking ratios–0.25, 0.50, 0.75, 1.00, 3.00, and 7.00 wt%–forthe PorGelhydrogels and–1.00, 3.00, and 7.00wt %–of the FishGel hydrogels, were placed over a nylon net (mesh size = 2.25 mm^2) onthe receptor chamber that contained the acetate buffer solution. The buffer was magnetically stirred during the experiment (48 h) at a temperature 37±2°C. The drugs diffused through the polymer matrices towards the buffer solutionand 0.1 ml of the sample was withdrawn at specific time intervals and concurrently replaced with0.1 ml of fresh buffer solution. The amount of drug in the solution was determined by the UV-Visible spectrophotometer [17].

RESULTS AND DISCUSSION

Characterization

Fourier Transforms Infrared Spectroscopy (FTIR)

The absorption infrared spectra of the pure PorGel hydrogel and SA powderare shown in Fig.1. For pure SA, the peaks at 867 and 1483 $cm^{-1}$are observed as the characteristic peaks of the C-H out of plane bending and the C-C ring stretching, respectively [18]. For the PorGel hydrogel, the peaks at 1400, 1540, and 3290 cm^{-1} are observed as the characteristic peaks of CH=N bending [19], N–H bending of amide II [20], and N-H stretching from the primary amine [19], respectively. TheSA-loaded PorGel hydrogel peak at 3290 $cm^{-1}$is slightly shifted to 3250 cm^{-1} due to the hydrogel bonding interaction between the carboxylic group of the SA model drug and the amine group of the gelatin hydrogel matrix. The interactions of SSA-loaded PorGel, SA-loaded FishGel, and SSA loaded Fishgel are similar.

Swelling Behaviour of Drug-loaded Gelatin Hydrogels

The swelling behavior, $\overline{M}_c$, ξ, and drug diffusion ability of gelatin hydrogels prepared at various cross linking ratios were examined. Figure 2 shows the degree of swelling and the weight loss of the cross linked gelatin hydrogels at various cross linking ratios after immersing in the acetate buffer solution for 5 days at 37°C. The degree of swelling and weight loss of both PorGel and Fish Gel decreased with increasing crosslinking ratio. Since glutaraldehyde reacts with the ε-amino group of lysine [20], hydroxylysine, and the amino group of the N-terminal amino acid [11], this leads to an increase in cross linking density, which results in limited swelling capacity and improved gel strength. Thus, a lower cross linked hydrogel has a longer gelatin strand between cross links and a looser network which promotes diffusion [17, 22].At the same cross linking ratio (1wt%), the degree of swelling and the weight loss of PorGel were higher than those of FishGel because the PorGel hada higher amount of hydroxyproline and proline. This created a hydrophilic structure leading to easier water penetration and a higher degree of swelling in the PorGel hydrogels [23].

The swelling data can be used to estimate the cross linked structure of the hydrogels. The $\overline{M}_c$,and ξ are used to identify the porous structure of the hydrogels in regard to the drug delivery system.

Peppas and Wright (1998) developed the equilibrium swelling theory that determined the values of each hydrogel matrix. Table 1 shows the $\overline{M}_c$ and ξ, of the cross link edge latin hydrogels at various cross linking ratios. The $\overline{M}_c$ and ξ values of both the PorGel and FishGel hydrogels are larger at lower cross linking ratios. The mesh sizes of PorGel and FishGel vary between 148 Å to 9 Å (with cross linking ratios between 0.25wt% and 7wt%) and 27 Å to 9 Å (with cross linking ratios between 1wt%and 7wt%), respectively. At the same cross linking ratio (1wt%),ξ of the PorGel hydrogel is higher than that of the Fish Gel hydrogel because the molecular weight average, M_w of PorGel is higher than that of Fish Gel. At a higher M_w,a higher degree of entanglement is present, leading to a screening effect of the cross linking agent, making it possible to penetrate and react with the polymer chain. Figure 3showsthe morphology of different PorGel and Fish Gelhydrogels through SEM micrographs. The micro graphs suggest that larger pore sizes are obtained with lower cross linking ratios. At the same cross linking ratio (Figs.3b and d), PorGel has a larger pore size than that of Fish Gelas PorGel has a lower degree of cross linkng.

Release Kinetics of Model Drugs from Drug-loaded Gelatin Hydrogels

The actual amount of drug present in each sample is reported as the percentage of the weight of the drug loaded over the weight of cross linked gelatin in the gelatin solution. The actual amounts of SA and SSA present in each sample are 91.75 ± 5.51 % and 92.83 ± 3.96 %, respectively.

To investigate the SA and SSA transport mechanism in the PorGel and Fish Gel hydrogels, experimental data were analyzed by two diffusion models. Released drug behavior is shown with the Ritger-Peppas equation [24], which describes the released drug from the polymeric system, as in Equation 5 or Model 1:

$$\frac{M_t}{M_\infty} = k_1 t^n \quad (5)$$

where M_t/M_∞ is the fractional drug release, k_1 is the kinetic constant (with the unit of T^{-n}), t is the release time, and *n* is the scaling exponent which can be correlated to the drug transport mechanism. For a thin hydrogel film, Case I occurs when *n* = 0.5, and the drug release mechanism is known as Fickian diffusion. When *n* = 1, Case II transport occurs, corresponding to zero-order release, or the constant release rate. Case III occurs when 0.5 <*n*< 1, where anomalous transport behavior is observed.

Model 2 is based on the Higuchi equation [25], which describes the Fickian diffusion of the drug or Case I, shown as Equation 6;

$$\frac{M_t}{M_\infty} = k_H t^{1/2} \quad (6)$$

where M_t and M_∞ are the masses of drug released at times equal to*t* and infinite time, respectively, and k_H is the Higuchi constant (with the unit of T^{-n}).

The diffusion coefficients of the model drugs from the PorGel and FishGel hydrogels were determined from the slopes of plots of drug accumulation versusthe square root of time according to Higuchi equation 7 [26-27]:

$$Q = \frac{M_t}{A} = 2C_0\left(Dt/\pi\right)^{1/2} \quad (7)$$

where Q is the amount of material flowing through a unit cross-section of barrier (g/cm^2)in unit time, *t* (s);$M_t$is the amount of drug released (g); *A* is the diffusion area (cm^2); C_0 is the initial drug

concentration in the hydrogel (g/cm^3); and *D* is the diffusion coefficient of the drug(cm^2/s).

Effect of Crosslinking Ratio

Figure 4 shows the amount of SA released from the drug-loaded FishGel hydrogels with time$^{1/2}$.The data indicate that the amount of drug release increases very rapidly over the first 1h, then slows down until itreachesan equilibrium value. The scaling exponent value (*n*) in Equation 5 was determined from the plots of ln(M_t/M_∞) versus ln (t) over the total experiment period. The scaling values *n* of all systems are tabulated in Table 2;they are quite close to the Fickian exponential value (*n* = 0.5).Therefore, the Fickian diffusion mechanism appears to control drug diffusion in the systems investigated. The slopes of these plots, through Higuchi's equation, provide the diffusion coefficients (*D*).In Fig.4,the amount of drug released increases with decreasing cross linking ratio due to relatively larger pore size.Figure5ashows*D* of SA of both gelatin hydrogels at 37°C.The diffusion coefficients increase with decreasing cross linking ratio for both hydrogels due to the easier drug movement and the larger pore size [27].

Effect of Gelatin Type

The diffusion coefficients of SA in PorGel are lower than that of FishGel because there is a higher percentage of hydroxyl proline and proline as the amino acid groups in the PorGel structure, as seen in Fig. 5a [21,23,28]. These two groups create a hydrogen bond between the drug and the gelatin matrix, which can retard drug diffusion, as evidenced from the FTIR spectra (Fig. 1).

Effect of Model Drug

Figure 5b shows *D* of SA (molecular size (a_d) =3.28 Å) [17, 22] and SSA (molecular size (a_d)= 9.25 Å) [29] from the drug-loaded PorGel hydrogels at various cross linking ratios and mesh sizes. The data indicate that *D* of SA is higher than that of SSA, because SA is a smaller, resulting in easier diffusion.

The log-log plots of *D*, as a function of the ratio of the drug size over mesh size, a_d/ξ, of the cross-linked gelatin hydrogels are shown in Fig.6.The scaling exponent *m* was determined from Equation 8:

$$D = D_0 \left(a_d/\xi\right)^{-m} \quad (8)$$

where D is the diffusion coefficient of the drug, D_0 is the diffusion coefficient for a small drug size, a_d is the drug size, ξ is the mesh size of the hydrogels, and *m* is the scaling exponent [29].

The scaling exponent *m* and D_0 values of the SA and SSA diffusion through the cross linked PorGel and FishGel hydrogels are 0.45 and 1.48 × 10^{-6} cm^2/s, respectively. Data show that *D* decreases with increasing a_d/ξ as smaller drug molecule can diffuse easier with a smaller drug size through a larger mesh size.

Table 3 shows the comparison of the *D* of SA and SSA from the gelatin hydrogels of previous works, consisting of the *D* values of SA released from polyacrylamide (PAAM) [17], SSA released from polyvinyl alcohol(PVA) [29], an dlysozyme and trypsine released from gelatin (HU4) hydrogels [14].The diffusion coefficients of SA and SSA from bothgelatin hydrogels decrease with increasing cross linking ratio due to smaller mesh sizes. The diffusion coefficient of SSA is higher than SA since SA is smaller than SSA(SA =3.28 Å and SSA= 9.25 Å). The *D* of FishGelis higher than PorGel because the hydrogen bonding interaction between the matrix and the drug of PorGel is stronger than that of

FishGel. This interaction originates from the lysine and hydroxylysine as the amino acid groups in the gelatin structure, and the amount of the amino acid groups in PorGel is higher. The *D* of SA from PAAM [17] is greater than *D* from the gelatins because the mesh size of PAAM hydrogels is larger than those of the gelatin hydrogels. Where as, *D* of SSA from PVA [29] is lower than those of both gelatins. The data suggest that the hydrogen bonding interaction between SSA and vinyl alcohol is greater than that of the gelatins. The amount of hydroxyl groups in the PVA structure is higher than those of the gelatins at a given mole; this creates more hydrogen bonds between the PVA hydrogel relative to the gelatin hydrogels, and thus a lower *D*. Sutter *et al*., (2007) studied the release behavior of a protein from a gelatin (HU4) hydrogel [14]. The diffusion coefficients decreased with increasing crosslinking ratio and gelatin concentration due tothe smaller mesh size. They also studied the effect of protein type; lysozyme and trypsin were chosen as the model proteins. The diffusion coefficients of trypsin were higher than lysozyme due to the electro-replusive force between the negatively charged trypsin and the negatively charged gelatin hydrogel. On the other handlysozome was positively charged and the electro-attractive force between the lysozome and the negatively charged gelatin induced a lower *D* value.

Thus, the above results confirm that the diffusion coefficients of the substances from the hydrogels depend on many factors such as the drug molecular size, drug charge, chemical composition of the drug, polymer matrix, drug-matrix interaction, and the experiment set up [27].

Table 1: Summary of the molecular weights between crosslink, $\overline{M}_c$, and mesh size, ξ, of hydrogels at various crosslinking ratios

Crosslinking ratio, *X*(%wt)	Molecular weight between crosslinks, $\overline{M}_c$ (g/mol)		Mesh size, ξ (Å)	
	PorGel	FishGel	PorGel	FishGel
0.25	16 673 ± 2070	-	148 ± 15	-
0.50	8851 ± 2371	-	101 ± 16	-
0.75	2950 ± 739	-	49 ± 8	-
1.00	1610 ± 143	1103 ± 113	35 ± 2	27 ± 1
3.00	529 ± 66	467 ± 136	17 ± 1	15 ± 2
7.00	254 ± 41	220 ± 17	11 ± 1	9 ± 0

Table 2: Release parameters of drugs from hydrogels at various cross linking ratios

Drug	Crosslinking ratio (%wt)	PorGel		FishGel	
		Diffusional exponent (*n*)	Kinetic constant k_H (h^{-n})	Diffusional exponent (*n*)	Kinetic constant k_H (h^{-n})
SA	0.25	0.4228	0.9944	-	-
	0.50	0.4304	1.0659	-	-
	0.75	0.4533	1.0852	-	-
	1.00	0.4672	1.1928	0.4615	1.1418
	3.00	0.4750	1.2608	0.4918	1.2049
	7.00	0.5025	1.3171	0.5300	1.3153
SSA	0.25	0.5555	1.0603	-	-
	0.50	0.5638	1.0770	-	-
	0.75	0.5714	1.0924	-	-
	1.00	0.5882	1.1145	0.6154	1.1733
	3.00	0.5970	1.1505	0.6250	1.2116
	7.00	0.6154	1.2069	0.6452	1.2822

Table 3: Diffusion coefficients of model drugs from gelatins, PAAM, and PVA hydrogels at 37 ºC

Solute	M_w	Drug size (Å)	Mesh size, ξ, (Å)	D (cm²/s)	pH	Remarks
SA	138	3.29	148	6.49×10^{-6}	5.5	PorGel CR = 0.25 %
			101	5.68×10^{-6}	5.5	PorGel CR = 0.50 %
			49	4.31×10^{-6}	5.5	PorGel CR = 0.75 %
			35	3.42×10^{-6}	5.5	PorGel CR = 1.00 %
			17	2.58×10^{-6}	5.5	PorGel CR = 3.00 %
			11	2.21×10^{-6}	5.5	PorGel CR = 7.00 %
			27	4.14×10^{-6}	5.5	FishGel CR = 1.00 %
			15	3.54×10^{-6}	5.5	FishGel CR = 3.00 %
			9	2.37×10^{-6}	5.5	FishGel CR = 7.00 %
SSA	254	9.25	148	4.42×10^{-6}	5.5	PorGel CR = 0.25 %
			101	4.04×10^{-6}	5.5	PorGel CR = 0.50 %
			49	3.04×10^{-6}	5.5	PorGel CR = 0.75 %
			35	2.64×10^{-6}	5.5	PorGel CR = 1.00 %
			17	2.07×10^{-6}	5.5	PorGel CR = 3.00 %
			11	1.71×10^{-6}	5.5	PorGel CR = 7.00 %
			27	2.96×10^{-6}	5.5	FishGel CR = 1.00 %
			15	2.00×10^{-6}	5.5	FishGel CR = 3.00 %
			9	1.65×10^{-6}	5.5	FishGel CR = 7.00 %
SA[17]	138	3.29	252	8.46×10^{-5}	5.5	PAAM CR = 2.0×10^{-3}
			158	5.85×10^{-5}	5.5	PAAM CR = 5.0×10^{-3}
			128	3.70×10^{-5}	5.5	PAAM CR = 1.0×10^{-2}
			85	2.00×10^{-5}	5.5	PAAM CR = 1.6×10^{-2}
			75	3.52×10^{-6}	5.5	PAAM CR = 2.4×10^{-2}
SSA[29]	254	9.25	232	2.08×10^{-9}	5.5	Uncrosslink of PVA
			143	1.08×10^{-9}	5.5	PVA CR = 0.5
			71	5.13×10^{-10}	5.5	PVA CR = 2.5
			36	2.76×10^{-10}	5.5	PVA CR = 5.0
Lysozyme	-	~40	-	2.33×10^{-7}	7.4	10% of Gelatin concentration (DS 0.24)
(+) charge[14]			-	1.94×10^{-7}	7.4	10% of Gelatin concentration (DS 0.67)
			-	1.05×10^{-7}	7.4	10% of Gelatin concentration (DS 0.82)
			-	1.03×10^{-7}	7.4	10% of Gelatin concentration (DS 0.97)
			-	2.19×10^{-7}	7.4	5% of Gelatin concentration (DS 0.97)
			-	0.69×10^{-7}	7.4	15% of Gelatin concentration (DS 0.97)
			-	0.43×10^{-7}	7.4	20% of Gelatin concentration (DS 0.97)
Lysozyme	-	~40	-	3.87×10^{-7}	7.4	10% of Gelatin concentration (DS 0.97)
(+) charge[14]						

*CR is cross linking ratio

Fig. 1: Absorption infrared spectra of pure SA, pure PorGel, and SA-loaded PorGel hydrogel.

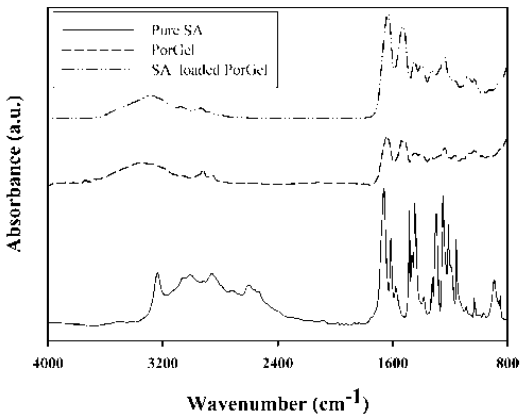


Fig. 2: Degree of swelling and weight loss of hydrogels at various crosslinking ratios.

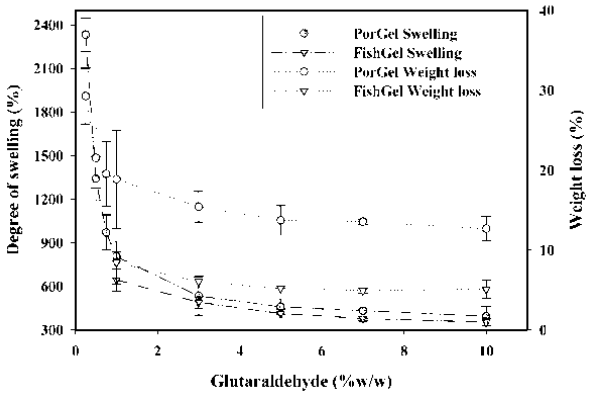


Fig. 3: Morphologies of PorGel and FishGel samples after swelling: (a) PorGel 0.25%; (b) PorGel 1.00 %; (c) PorGel 3.00 %; (d) FishGel 1.00 % at 3000X magnification.

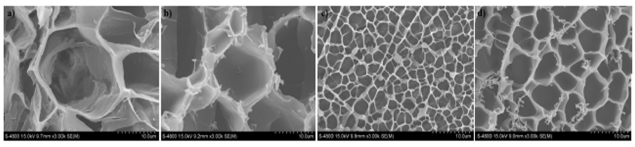


Fig. 4: Amount of SA released from SA-loaded FishGel hydrogels at various crosslinking ratios.

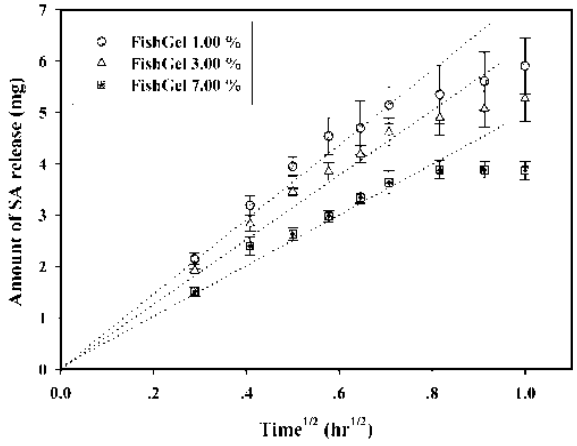


Fig. 5: Diffusion coefficient of drug-loaded gelatin hydrogels in relation to crosslinking ratios and mesh sizes; effect of gelatin type (a) and effect of drug size (b).

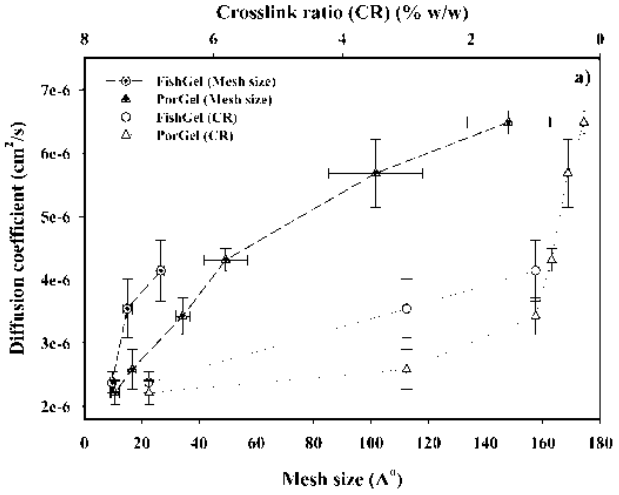
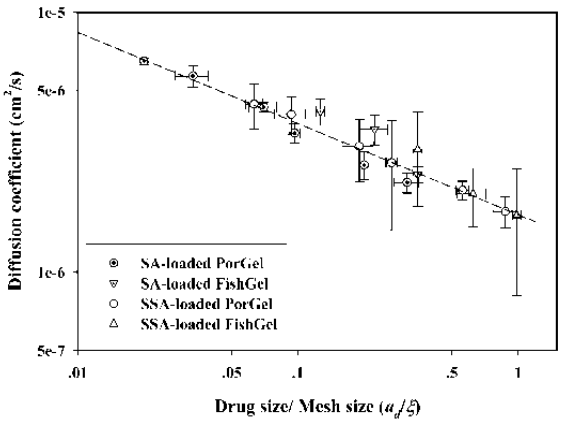


Fig. 6: Log-log plots of the diffusion coefficient as a function of drug size over mesh size of SA and SSA of drug-loaded hydrogels.



Conclusion

Drug-loaded gelatin hydrogels were prepared at various cross linking ratios to investigate and to compare the release mechanisms and the diffusion coefficients of drugs from drug-loaded porcine and fish gelatin hydrogels. Each hydrogel was characterized for swelling characteristics and mesh size. The degree of swelling, weight loss, and mesh size of both gelatin hydrogels decreased with increasing cross linking ratios. The cross linking ratio, mesh size, drug size, and type of gelatin were investigated for the diffusion coefficients. The diffusion coefficients of the drugs from the drug-loaded gelatin hydrogels decreased with increasing cross linking ratio since the mesh size of the gelatin hydrogelwas larger. The diffusion coefficients of the drugs from the drug-loaded gelatins decreased with increasing drug size, at the same crosslinking ratio and a given gelatin matrix. The diffusion coefficients of the drugs from the drug-loaded fish gelatin hydrogels were higher than those of the porcine gelatin hydrogels at the same cross linking ratio because the fish gelatinhydrogel hada weaker

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hydrogen bond interaction with the drug.

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References

1) Im JS, Bai BC, Lee YS. The effect of carbon nano tubes on drug delivery in an electro-sensitive transdermal drug delivery system. Biomaterials 2010; 31:1414-1419.
2) Kim J, Kim WJ, Kim SJ, Cho CW, Shin SC. Release characteristics of quinupramine from the ethylene-vinyl acetate matrix. Int. J. Pharm.2006; 315:134-139.
3) Hosseinkhani H, Hosseinkhani M, Kobayashi H. Design of tissue-engineered nanoscaffold through self-assembly of peptide amphiphile. J.Bioact.Compat.Pol. 2006;21:277-296.
4) Hosseinkhani H, Hosseinkhani M. Biodegradable polymer-metal complexes for gene and drug delivery. Current Drug Safety2009; 4: 79-83.
5) Ganji F, Abdekhodaie MJ. Synthesis and characterization of a new thermo reversible chitosan PEG diblock copolymer. Carbohydr. Polym. 2008; 74:435-441.
6) Schacht EH. Polymer chemistry and hydrogel systems.J. Phys. Conf. Ser.2004; 3: 22-28.
7) Deiber JA, Ottone LM, Piaggio MV, Peirotti MB. Characterization of cross-linked polyampholytic gelatin hydrogels through the rubber elasticity and thermodynamic swelling theories. Polymer 2009; 50: 6065-6075.
8) Hidaka S, Liu SY. Effects of gelatins on calcium phosphate precipitation: A possible application for distinguishing bovine bone gelatin from porcine skin gelatin. J. Food Compos. Anal. 2003;16:477-483.
9) Songchotikunpan P, Tattiyakul J, Supaphol P. Extraction and electrospinning of gelatin fromfish skin. Int. J. Biol.Macromol.2008; 42:247-255.
10) Vandelli MA, Rivasi F, Guerra P, Forni F, Arlett R. Gelatin microspheres crosslinked with D, L-glycerraldehyde as a potential drug delivery system: Preparation characterization, in vitro and vivo studies. Int. J. Pharm.2001; 215:175-184.
11) Farris S, Song J, Huang Q. Alternative reaction mechanism for the cross-linking of gelatin with glutaraldehyd. J.Agr. Food Chem.2010;58:2.
12) Peppas NA, WrightSL. Drug diffusion and binding in ionisable interpenetrating networksfrom poly(vinyl alcohol) and poly(acrylic acid).Eur. J. Pharm.Biopharm. 1998;4:15-29.
13) Taepaiboon P, Rungsardthong U, Supaphol P. Drug-loaded electrospun mats of poly (vinylalcohol) fibres and their release characteristics of four model drugs. Nanotechnology 2006;17:2317-2329.
14) Sutter M, Siepmann J, Hennink WE, Jiskoot W. Recombinant gelatin hydrogels for the sustained release of proteins. J. Controlled Release 2007;119:301-312.
15) Bohidar HB. Hydrodynamic properties of gelatin in dilute solutions. Int. J. Biol. Macromol.1998;23:1-6.
16) Peppas NA, Wright SL. Solute diffusion in poly(vinyl alcohol)/poly (acrylicacid) interpenetrating networks. Macromolecules1996; 29:8798-8804.
17) Niamlang S, Sirivat A. Electrically controlled release of salicylic acid from poly(p-phenylenevinylene)/polyacrylamide hydrogels. Int. J. Pharm.2009;371:126- 133.
18) Mohan J. Organic Spectroscopy: Principles and Application. U.K.:Harrow; 2004.
19) Stancu IC. Gelatin hydrogels with PAMAM nano structured surface and high density surface-

localized amino groups. React. Funct. Polym. 2010; 70:314-324.

20) Muyonga JH, Cole CGB, Duodu KG. Fourier transform infrared (FTIR) spectroscopic study of acid soluble collagen and gelatin from skins and bones of young and adult Nile perch (Latesniloticus). Food Chem. 2004; 86:325-332.

21) Chiou BR, Roberto JAB, Bechtel PJ, Jafri H, Narayan R, Imama HS, Glenn GM, Orts WJ. Cold water fish gelatin films: Effects of cross-linking on thermal, mechanical, barrier, and biodegradation properties. Eur.Polym. J.2008; 44:3748-3753.

22) Niamlang S. 2008. Development of poly (p-phenylenevinylene) for actuator and controlled drug delivery application. Dissertation Thesis, The Petroleum and Petrochemical College, Chulalongkorn University, Bangkok, Thailand.

23) Avena-Bustillous RJ, Olsen CW, Olson DA, Chiou B, Yee E, Bechtel PJ, Mchugh TH. Water vapor permeability of mammalian and fish gelatin films.J. Food Sci. 2006; 71:202-207.

24) Venkatesh S, Hodgin L, Hanson P, Suryanarayanan R. In vitro release kinetics of salicylic acid from hydrogel patch formulations. J. Controlled Release 1992;18:13-18.

25) Serra L, Domenech J, Peppas NA. Drug transport mechanisms and release kinetics from molecularly designed poly (acrylic acid-g-ethylene glycol) hydrogels. Biomaterials 2006; 27: 5440-5451.

26) A-sasutjarit R, Sirivat A, Vayumhasuwan P. Viscoelastic properties of carbopol 940 gels and their relationships to piroxicam diffusion coefficients in gel bases. Pham. Res. 2005;22: 2134-2140.

27) Paradee N, Sirivat A, Niamlang S, Prissanaroon-Ouajai W. Effects of crosslinking ratio, model drugs, and electric field strength on electrically controlled release for alginate-based hydrogel.*J.* Mater.*Sci*.-Mater.Med.2012; 23:999-1010.

28) Karim AA, Bhat R. Fish gelatin: Properties, challenges, and prospects as an alternative to mammalian gelatins. Food Hydrocolloid 2009; 23:563-574.

29) Juntanon K, Niamlang S, Rujiravanit R, Sirivat A. Electrically controlled release of sulfosalicylic acid from crosslinked poly(vinyl alcohol) hydrogel. Int. J.Pharm. 2008; 356:1-11.

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