FABRICATION AND PROPERTIES OF PECTIN HYDROGEL FOR ELECTRICALLY CONTROLLED DRUG DELIVERY

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ABSTRACT
Transdermal drug delivery system (TDDS) is the alternative route to transport drug molecule to a systematic circulation through the human skin. The major advantage of TDDS is the ability to avoid the first-pass metabolism. However, TDDS has certain limitations: the level of drug permeated across the skin is low and the drug size has an adverse effect on the permeation. To improve these limitations, the electrical potential was utilized. Hydrogels from biomaterials have been used in drug delivery application due to their non-toxic, biocompatibility, and similarity to biological tissues. This work attempted to design a transdermal patch consisting of ibuprofen as a model drug and pectin hydrogel as a matrix. The effects of the crosslinking agent type, crosslinking ratio, mesh size, and electric potential were investigated. The diffusion coefficients and the release mechanism of the ibuprofen on the pectin hydrogels were determined by using a modified Franz-Diffusion cell in an MES buffer solution of pH 5.5, at a temperature of 37 ºC, for 48 h. The amount of ibuprofen release was analyzed by UV-Visible spectrophotometry. The result showed the amount of ibuprofen released increased with increasing mesh size and electric potential.

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INTRODUCTION
TDDS has made important contributions in medical practices. There are many advantages of TDDS when compared with the oral route and hypodermic injections. This method avoids the highest point and lowest point of unstable dosage regimens which can lead to side-effects such as sedation, nausea and vomiting, and respiratory depression. In addition, an immediate termination of drug delivery can be accomplished with ease (Margetts et al., 2007). Pectin is a naturally occurring biopolymer that is finding increasing applications in many pharmaceutical and biotechnological areas. Its unique properties are biocompatibility, biodegradability, and high transparency that enable it to be used as a matrix for the entrapment and delivery of a variety of drugs. Pectin and pectin-based hydrogels have been used in various applications, such as TDDS, agriculture, and separation processes (Mishra et al., 2012). A pectin hydrogel can be formed by the gelation through covalently (citric acid, glutaraldehyde, and divinylsulfone) and ionically crosslinkings (FeCl₂, CaCl₂, and BaCl₂). However, one limitation of hydrogel in TDDS is the slow drug release which restricts its ability to deliver various drug molecules (Lira et al., 2005). In TDDS, a drug release can be enhanced owing to the change in the polymer structure which can be sensitive to many factors such as temperature, pH, electrical or magnetic field. To remedy the slow release rate, an external stimulus such as applied electric field is one approach that can be applied to improve the amount of drug release and the release rate (Chien et al., 1990).
The objectives of this work is to fabricate the pectin hydrogels of various mesh sizes for controlled drug release and to investigate the drug release characteristics.

EXPERIMENTAL

A. Preparation of Ibuprofen-Loaded Pectin Hydrogels (Ibu-Loaded Pectin Hydrogels)

A ibuprofen powder (0.1 g) was mixed with 25 ml distilled water under stirring at 27 °C for 1 h, and then a powder of the pectin (1 g) was slowly added into the solution. The solution (0.04 g/ml) was gently stirred for 3 h to formulate a clear, viscous and homogenous solution without bubbles. The crosslinking of pectin was carried out by two crosslinkers which were ferrous chloride (FeCl₂) as an ionic crosslinker and citric acid as a chemical crosslinker. For the ionic crosslinking, the FeCl₂ solution (0.01, 0.015, 0.02, 0.025, and 0.03 g/ml) was added into the pectin solution at various crosslinking/monomer mole ratios of 0.1, 0.15, 0.2, 0.25, and 0.3, respectively. For the chemical crosslinking, citric acid (0.1, 0.2, 0.3, 0.4, and 0.5 g) was added into the pectin solution at various crosslinking/monomer mole ratios of 0.1, 0.2, 0.3, 0.4, and 0.5, respectively. The obtained solutions were stirred at 27 °C for 5 h. The uniform solutions were casted on molds (10 cm in diameter). After that, the solutions were kept at 27 °C for 48 h and 80 °C for 24 h for crosslinking to proceed for FeCl₂ and citric acid, respectively. Finally, the hydrogels were obtained with a thickness 0.11 ± 0.01 mm.

B. Preparation of MES Buffer

A MES buffer solution was used as the receiving medium. The MES solution of 0.1 M (at pH 5.5) was prepared and poured into the receptor chamber of the modified Franz-Diffusion cell.

C. In vitro Drug Release Study

The diffusion study of the drug was carried out by a modified Franz-Diffusion cell which consisted of two compartments; a donor compartment, and a receptor component which was filled with the MES buffer solution of pH equal to 5.5 (Niamlang and Sirivat, 2009). The buffer solution was magnetically stirred throughout the experiment period (48 h) and maintained at 37 ± 0.5 °C by a circulating water jacket. A sample was placed on the nylon net mounted on the receptor component. An aluminum plate (cathode) connected to a power supply (KETHLEY 1100V Source Meter) was placed on top of the sample. The drug diffused through the polymer matrix and the nylon net into the MES buffer solution. A sample of 0.1 ml was withdrawn from the receptor compartment at various times and simultaneously replaced with an equal volume of the fresh buffer solution. The drug amount in the withdrawn solution sample was determined by the calibration curve as obtained from the UV-visible spectrophotometer.

RESULTS AND DISCUSSION

A. Types of Crosslinking Agent Effect

The amounts of ibu released from the ibu-loaded pectin hydrogels versus time\(^{1/2}\) at the 0.1 crosslinking ratio of FeCl₂ and citric acid in the absence of electric potential during 48 h are shown in Figure 1. For both crosslinkers, the amounts of ibuprofen released...
gradually increase with time and then reach equilibrium values of 5.92 mg and 0.65 mg for the 1Pec_0.1Fe_0.1Ibu and 1Pec_0.1Cit_0.1Ibu, respectively. Moreover, the diffusion coefficient and equilibrium time of the 1Pec_0.1Fe_0.1Ibu are $7.16 \times 10^{-7}$ cm$^2$/s and 10 h which are higher than those of the 1Pec_0.1Cit_0.1Ibu which are $1.07 \times 10^{-7}$ cm$^2$/s and 9 h, respectively. The degrees of swelling and the mesh sizes of the pectin hydrogels as crosslinked with FeCl$_2$ are higher than those crosslinked with citric acid; the formers provide larger pathways for drug to diffuse resulting in the higher drug release amounts and diffusion coefficients (Amsden, 1998, Gratton, et al., 2008 and Li and Mooney, 2016). However, the increase in drug release amount needs a longer equilibrium time for the 1Pec_0.1Fe_0.1Ibu.

**Figure 1** Amounts of ibuprofen released from ibu-loaded pectin hydrogels vs. time$^{1/2}$ at crosslinking ratio $= 0.1$, $E = 0$ V, pH 5.5, and 37 °C.

**B. Crosslinking Ratio Effect**

**Table 1** Kinetic factors and diffusion coefficients of Ibuprofen released from pectin hydrogels at $E = 0$ V, thickness $= 0.11 \pm 0.01$ mm and film area of 3.14 cm$^2$

<table>
<thead>
<tr>
<th>Sample code</th>
<th>$D_1$ (cm$^2$/s)</th>
<th>$D_2$ (cm$^2$/s)</th>
<th>Amount of Ibu release (mg)</th>
<th>$C$ (g/cm$^3$)</th>
<th>Time to equilibrium (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Pec_0.1Fe_0.1Ibu</td>
<td>-</td>
<td>$7.16 \times 10^{-7}$</td>
<td>5.92 $\pm$ 0.39</td>
<td>0.28</td>
<td>10.24</td>
</tr>
<tr>
<td>1Pec_0.2Fe_0.1Ibu</td>
<td>$6.13 \times 10^{-8}$</td>
<td>$1.97 \times 10^{-7}$</td>
<td>1.23 $\pm$ 0.07</td>
<td>0.25</td>
<td>7.84</td>
</tr>
<tr>
<td>1Pec_0.3Fe_0.1Ibu</td>
<td>$9.72 \times 10^{-8}$</td>
<td>-</td>
<td>0.65 $\pm$ 0.08</td>
<td>0.27</td>
<td>7.61</td>
</tr>
<tr>
<td>1Pec_0.1Cit_0.1Ibu</td>
<td>$1.07 \times 10^{-7}$</td>
<td>-</td>
<td>0.65 $\pm$ 0.03</td>
<td>0.19</td>
<td>8.82</td>
</tr>
<tr>
<td>1Pec_0.3Cit_0.1Ibu</td>
<td>$8.97 \times 10^{-8}$</td>
<td>-</td>
<td>0.33 $\pm$ 0.03</td>
<td>0.18</td>
<td>4.20</td>
</tr>
<tr>
<td>1Pec_0.5Cit_0.1Ibu</td>
<td>$3.58 \times 10^{-8}$</td>
<td>-</td>
<td>0.21 $\pm$ 0.02</td>
<td>0.16</td>
<td>2.25</td>
</tr>
</tbody>
</table>

From Table 1, the amount of drug released decreases from 5.92 mg to 0.65 mg and from 0.65 to 0.21 mg with increasing crosslinking ratio from 0.1Fe to 0.3Fe and 0.1Cit to
The diffusion coefficient of drug increases from $9.72 \times 10^{-8}$ to $7.16 \times 10^{-7} \text{ cm}^2/\text{s}$ for the pectin hydrogel crosslinked with FeCl$_2$ and from $3.58 \times 10^{-8}$ to $1.07 \times 10^{-7} \text{ cm}^2/\text{s}$ for the pectin hydrogel crosslinked with citric acid. In the “crosslinking ratio-effect”, increasing crosslinking mole ratio provides a denser crosslinked network resulting in a shorter pectin strand between crosslink points or a shorter mesh size, and producing a lower free volume which limits the swelling ability and drug pathway resulting in the lower amounts of drug released and diffusion coefficients (Lee, 1985, Serra et al., 2006, Zarzycki et al., 2010, Hezaveh et al., 2011 and Paradee et al., 2012).

C. Electric potential effect

Figure 2 shows the diffusion coefficient of ibu released from the 1Pec_0.1Fe_0.1Ibu and 1Pec_0.1Cit_0.1Ibu hydrogels under various electric potentials using negatively charged electrode as the cathode in the donor part. Under electric potentials from 0 to 5 V, the diffusion coefficient increases from $7.16 \times 10^{-7}$ to $1.96 \times 10^{-6}$ and from $1.07 \times 10^{-7}$ to $3.29 \times 10^{-7} \text{ cm}^2/\text{s}$ for the pectin hydrogels cross-linked with FeCl$_2$ and citric acid, respectively. These results may stem from 2 main reasons namely the electro-repulsive force between the negatively charged drug and the negatively charged electrode (Kantarial et al., 1999 and Sittiwong et al., 2012) and the hydrogel expansion, called the “pectin-expansion” (Paradee et al., 2012).

**Figure 2** Diffusion coefficients of ibuprofen from pectin hydrogels versus electrical potential at the crosslinking ratio = 0.1, pH 5.5, and 37 °C.

**CONCLUSIONS**

The ibu-loaded pectin hydrogels and the ibu-doped P3DPA/pectin composites at various crosslinking ratios were fabricated in order to study the effects of crosslinking ratio, crosslinking agent types on the ibu release behavior and diffusion coefficients with and without electric field. For the effect of crosslinking agent types, the diffusion coefficients of the ibu from the pectin hydrogels as crosslinked with citric acid were lower than those crosslinked with FeCl$_2$ at the same crosslinking ratio because the chemical crosslink produced the lower mesh sizes. The diffusion coefficients of ibu from the pectin hydrogels under applied electric potential were shown to be greater than
those without electric potential due to the electro-repulsive force and the electric potential induced mesh size expansion.

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