Development of cornstarch-based hydrogel drug delivery patch controlled by the electric field for hypertension

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Abstract. To study electrical controlling drug delivery from poly(vinyl alcohol) (PVA), PVA was prepared at various crosslink ratio. Hydrochlorothiazide (HCTZ), which is used to treat high blood pressure, was selected as a model drug. The release characteristic of hydrochlorothiazide from PVA matrix was studied by using modified Franz diffusion cells at pH 7.4 and temperature of 37 ºC for 48 h. The amounts of drug permeation was characterized by UV-vis spectrophotometry. The degree of swelling and mesh size of crosslinked PVA was investigated. The degree of swelling increase with decreasing crosslinking ratio. The amount of drug permeation is decreased with increasing crosslinking ratio which corresponded to degree of swelling. When external electric field was applied, the amount of HCTZ increases with increasing electrical voltage due to electro-repulsion force and generation of micropore in pigskin. To increase solubility and biodegradability of hydrogel matrix, corn starch (CS) was blend with PVA hydrogel. For passive permeation, the amount of HCTZ permeation from PVA/CS and PVA at similar crosslinking ratio is 7.56 and 7.93%, respectively. Thus presenting of CS do not affect the permeation characteristic.

1. Introduction
Drug delivery systems are the methods that distribute the drug via a variety of drug carriers to target tissues, muscles, cells, and subcellular muscles. Transdermal drug delivery system is a drug delivery system in which the drug penetrates the skin into the bloodstream. This system uses the patch as a drug container to apply on the skin to deliver the drug. The drug delivery system through the skin has many advantages, namely the drug delivery system that can avoid drug destruction in the digestive system. [1] But the drug delivery system through the skin may not be suitable for delivering drugs with large molecules and polarity drugs. [2]

Therefore, there is a method called electrical stimulation of drug delivery through the skin (Iontophoresis delivers transdermal drugs). The working principle of this system is electro-repulsion force between electrode and drug. [3] Hypertension or High blood pressure is one of the more common diseases in adults. It is found more in men than in women and is also more common in the elderly. [4] Hydrochlorothiazide is a diuretic that classifies as a group of Thiazide (HCTZ); the World Health Organization prescribed hydrochloride. Thiazide is a drug for basic public health in each country. The main function of hydrochloride is to lower blood pressure. [5]
The hydrogel is a hydrophobic polymer with a three-dimensional lattice structure. The hydrogel is used in medicine because it is a bioplastic with human biological compatibility, such as chitosan, gelatin, polyacrylamide. The hydrogel is highly moisturizing, it can absorb the liquid that flows out of the wound, and the porosity of the hydrogel also helps with oxygen diffusion, preventing the wound from becoming damp. Currently, researchers are interested in using hydrogel for drug delivery systems. [6]

Poly(vinyl alcohol) (PVA) is an important hydrophilic water-soluble synthetic polymer with a broad range of applications such as TDDs matrix. PVA structure consists of –OH bonds that is absolutely biodegradable. To increase solubility and biodegradability of hydrogel matrix, cornstarch (CS) was selected to blend with PVA. [7]

This research work aims to fabricate the soft and flexible PVA/cornstarch hydrogel for using as TDDs patch. The effect of crosslink ratio, electrical voltage and presence of cornstarch on permeation characteristic was studied.

2. Materials and methods

2.1. Materials
Polyvinyl alcohol, PVA (AR grade, Chem-Supply Pty Ltd, Australia), glutaraldehyde (AR grade, Sigma Aldrich, Co., Germany), cornstarch (AR grade, Sigma Aldrich, Co., Germany) were used as hydrogel matrix and the crosslinking agent, respectively. Hydrochlorothiazide, HCTZ (AR grade, Sigma Aldrich, Co., Germany) was selected as the model drug.

2.2. Preparation of HTZ-loaded PVA hydrogels
The effect of crosslink density on drug permeation characteristics was investigated. PVA hydrogel at the various amount of glutaraldehyde (MolGA/MolPVA:25, 50, 150, and 250). The PVA solution concentration of 9.65 % w/v was prepared in distilled water at 80±5 ºC for 1 h. The solution was then cooled down to room temperature and cast into mold (5-6 h.). For HCTZ-loaded PVA hydrogels, the HCTZ was loaded into the PVA solution for 30 min and cast into mold (9 cm). The actual amount of drug in the drug-loaded PVA film was determined by dissolving the HCTZ loaded PVA hydrogel (diameter of 2 cm, the thickness of 0.2 mm) in 20 ml of dimethyl sulfoxide (DMSO). The amount of drug was measured by the UV-visible spectrophotometer at the wavelength of 272 nm.

To study the effect of presenting of cornstarch on permeation characteristic, the PVA solution at given amount of glutaraldehyde (concentration of 9.65 %w/v) was mixed with cornstarch solution concentration of 10 %w/v at 80±5 ºC for 1 h. The solution was cooled down and cast into the mold.

2.3. Characterizations
The degrees of swelling and the weight losses of crosslinked PVA hydrogels were measured from the following equation [8]

\[
\text{degree of swelling (\%) } = \frac{M-M_d}{M_d} \times 100
\]

where \(M\) is the sample weight after submersion in the solution for 24 h, \(M_d\) is the sample weight after submersion in the solution for 24 h and after removal of the solution (through vacuum oven) or in its dry state.

The hydrogel mesh size, \(\xi\), defines the linear distance between consecutive crosslinks. It indicates the diffusional space available for solute transport and can be calculated as follows equation (2) [9]

\[
\xi = v^{1/3} \left[ C_n \left( \frac{M}{M_c} \right) \right]^{1/2} l
\]

where \(C_n\) is the Flory characteristic ratio (8.3), \(l\) is the carbon–carbon bond length (1.54 Å), \(M_f\) is the molecular weight of the repeating unit of polymer, and \(M_c\) is the molecular weight between crosslinks.

To study the chemical bonding between drug and matrix, the functional group of PVA, HCTZ and HCTZ-loaded PVA hydrogel was characterized by FT-IR spectrophotometer.
2.4. Preparation of pigskin
A pigskin (abdominal part) was washed with normal saline. The hair and subcutaneous fat on the pigskin surface were removed. The prepared pigskin was cut into a circular shape (diameter of 4 cm) and thickness of 1-1.5 mm.

2.5. Permeation characterization
To study the permeation characteristic, HCTZ loaded PVA and HCTZ loaded PVA/CS was prepared. The custom-built modified Franz-Diffusion cells were used for the permeation studies. The buffer solution pH 7.4 and maintained at 37 ºC by a circulating water bath. An HCTZ loaded PVA and HCTZ loaded PVA/CS was placed between the copper cathode and the pigskin, which was mounted onto the receptor compartment. For the study of the effect of external electrical voltage on permeation characteristic, the copper electrode was connected to a power supply (GW Instek PSH-3620A), which provided different electrical voltage (V = 0, 0.01, 0.05, 0.1 and 0.3 V) across the hydrogel, the pigskin, and the buffer solution. The drug diffused through the polymer matrix and the pigskin into the solution. A sample of 1 ml was withdrawn at various time intervals and simultaneously replaced with an equal volume of fresh buffer solution. The UV-visible spectrophotometer determined the drug concentrations in these samples at the wavelength of 272 nm.

3. Results and discussion

3.1. PVA hydrogel and HCTZ-loaded PVA hydrogel characterization
To study the effect of crosslinking ratio on drug permeation characteristic, the PVA hydrogels were prepared at various crosslinking ratios. Glutaraldehyde was used as a crosslinker. The effect of the crosslinking ratio on the swelling behavior was studied. Figure 1 shows the degree of swelling of PVA hydrogels at various crosslinking ratios (MolPVA/MolGA 25, 50, 150, and 250 for PVA_GA1, PVA_GA2, PVA_GA3 and PVA_GA4, respectively) after immersions in the DI at 37 ºC for 72 h. The pore size of crosslinked hydrogel was calculated from equation (2). The pore size of PVA_GA1, PVA_GA2, PVA_GA3 and PVA_GA4 are 1.69±0.73, 0.45±0.39, 0.11±0.10, 0.05±0.04 µm. The results show that the degree of swelling and the weight loss decrease with increasing crosslinking ratio which corresponds to calculated pore size of PVA.

![Figure 1. Degree of swelling of PVA hydrogels at various crosslinking ratios.](image)

The functional group of HCTZ, PVA and HCTZ-loaded PVA hydrogel was characterized by FT-IR spectrophotometer as shown in figure 2. For HCTZ-loaded PVA hydrogel, the FT-IR spectrum peak at 3300, 1732 and 1086 cm\(^{-1}\) is corresponding to OH group of PVA, C=O stretching and C-O-C of HCTZ, respectively. The new emerging peak can not be observed, thus no interaction between HCTZ and PVA occurred.
3.2. Permeation characteristic

3.2.1. Effect of electrical voltage. Under cathode electrode, the amount of permeation from PVA under electric field strengths was shown in figure 3 and figure 4. The amounts of HCTZ increase with increasing electric field strengths due to the electrorepulsion force and micropore generation in pigskin.[10] When increasing a crosslinking ratio, the amounts of drug permeation decreases due to decreasing of pore size of PVA hydrogel.
3.2.2. Presenting of cornstarch. To increase solubility and biodegradability of hydrogel matrix, corn starch (CS) was blend with PVA hydrogel. For passive permeation, the amount of HCTZ permeation from PVA/CS and PVA at given crosslinking ratio is similar as shown in figure 5. Thus presenting of CS do not affect the permeation characteristic.

4. Conclusion
The HCTZ-loaded PVA and PVA/CS hydrogels were successfully prepared. To study of effect of crosslinking ratio, the degree of swelling and mesh size of PVA hydrogel was studied. The degree of swelling of PVA hydrogels decreases with increasing crosslinking ratio. The permeation characterization under various amounts of electrical voltage was studied. The amount of HCTZ increases with increasing electrical voltage due to the electro repulsion force and the generation of micropore in pigskin. To increase the solubility and biodegradable of TDDs patch, CS was blend with PVA. Presenting of CS do not affect the permeation profile and amount of HCTZ permeation.

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