DEVELOPMENT OF TRANSDERMAL DOSAGE FORM USING COPROCESSED EXCIPIENTS OF XANTHAN GUM AND CROSS-LINKED AMYLOSE: IN VITRO AND IN VIVO STUDIES

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ABSTRACT

Objective: A transdermal hydrogel dosage form consists of a three-dimensional polymer network that binds water in large quantities and is used for drug delivery. The study’s aim was to prepare coprocessed excipients as a matrix for a transdermal hydrogel containing diclofenac sodium and examine in vitro and in vivo drug penetrations.

Methods: Four types of coprocessed excipients were produced using two methods that combined crosslinking and coprocessing steps. The produced excipients were formulated as transdermal gels containing sodium diclofenac. An in vitro penetration test was then performed using a Franz diffusion cell to pass the drug through a rat skin membrane. An in vivo penetration test was performed by applying the hydrogel to the abdominal skin of male Sprague-Dawley rats and then measuring the plasma drug concentration.

Results: In vitro penetration results showed that the flux from Co-CLA6-XG 1:2, Co-CLA12-XG 1:2, CL6-Co-A-XG 1:2, and CL12-Co-A-XG 1:2 transdermal hydrogels was 655.2±16.43 µg cm⁻²/h, 569.0±26.58 µg cm⁻²/h, 867.4±101.27 µg cm⁻²/h⁻¹, and 736.9±15.39 µg cm⁻²/h⁻¹. The in vivo study resulted in area under the curve for the Co-CLA6-XG 1:2, Co-CLA12-XG 1:2, CL6-Co-A-XG 1:2, and CL12-Co-A-XG 1:2 transdermal hydrogels was 655.2±16.43 µg cm⁻²/h, 34.27±8.34 µg/ml∙h, 6.20±2.90 µg/ml∙h, and 14.38±2.38 µg/ml∙h, respectively.

Conclusion: The study results showed that the excipients could be processed to form a matrix within a transdermal hydrogel formulation and deliver sodium diclofenac into systemic circulation in a controlled release manner.

Keywords: Amylose, Xanthan gum, Coprocessed excipient, Transdermal hydrogel, In vitro penetration, In vivo penetration.
In this study, the excipients of Co-CLA6-XG, Co-CLA12-XG, CL6-Co-A-XG, and CL12-Co-A-XG were used with a 1:2 ratio of amylose and xanthan gum because that ratio is expected to form a solid compact gel. Evaluations of the transdermal hydrogel included physical organoleptic observations, preparation acidity (pH), preparation consistency and thickness, and determination of drug levels in the hydrogel. We also performed in vitro and in vivo penetration tests. The in vitro penetration test was performed using Franz diffusion cells to assess drug penetration through the skin [8]. The in vivo penetration test was performed in male Sprague-Dawley rats as the most representative method to assess drug incorporation into the systemic circulation.

**METHODS**

**Materials**

Amylose (Shangqiu Kangmedia Bio-Tech, China), xanthan gum (Cargill Bioengineering, Canada), diclofenac sodium (Yung Zip Chemical, Taiwan), STMP (Shangqiu Kangmedia Bio-Tech, China), sodium hydroxide (Merck, Germany), hydrochloride acid (Merck, Germany), sulfuric acid (Merck, Germany), nitric acid (Merck Germany), ascorbic acid (Takeda, Japan), orthophosphate acid (Merck Germany), potassium dihydrogen phosphate (Merck, Germany), ammonium molybdate tetrahydrate (Merck, Germany), triethylamine high-performance liquid chromatography (HPLC) grade (Merck, Germany), methano HPLC grade (Merck, Germany), and diltiazem hydrochloride (Piramal Healthcare, India) were used. Other chemicals and solvents were of analytical grade and purchased from commercial suppliers. Sprague-Dawley rats were obtained from Institut Pertanian Bogor (Bogor Agricultural University, Bogor, Indonesia).

**Synthesis of Co-CLA6-XG and Co-CLA12-XG (1:2) (method A)**

Synthesis is a method of cross-linked amylose and coprocessed excipient to give a cross-linked amylose-xanthan gum-based on Cury et al. [9], with modification as stated in Surini et al. [7]. The first stage was synthesis of cross-linked amylose by reacting amylose with STMP as a crosslinking agent. Amylose was dispersed in distilled water while stirring with a magnetic stirrer until perfectly dispersed. Sodium hydroxide 10 N solution was dripped slowly into the mass to maintain the pH at 11–12 during the reaction. In another flask, STMP solutions were prepared to produce 6% b/v for CLA6 and 12% b/v for CLA12. Thereafter, the STMP solution was slowly added to the dispersion of amylose while stirring using a homogenizer (CKL Machinery, Malaysia) at a speed of 3000 rpm for 4 h and then allowed to stand for 12 h to ensure completion of the reaction. After that, the suspension of CLA was neutralized by hydrochloride acid 7N until a pH of six was achieved. The suspension was then washed with ethanol 96% v/v until the filtrate gave a negative result with ammonium molybdate reagent. The residues were dried at room temperature for 48 h. The dried residues were then sieved through a 35-mesh (500-μm) sieve.

The second stage was coprocessing for each 3% CLA (CLA6 and CLA12) with 3% xanthan gum in distilled water in a 1:2 ratio using a homogenizer (CKL Machinery) at 3000 rpm for 30 min. Thereafter, the mass was dried in a drum drier (R. Simon Dryers, UK) at a temperature of 109–112°C. The produced mass was mashed and sieved by a 35-mesh (500-μm) sieve.

**Synthesis of CL6-Co-A-XG and CL12-Co-A-XG (1:2) (Method B)**

The first stage was a physical modification by coprocessing amylose with xanthan gum at a concentration of 3% for each in distilled water in 1:2 ratio. The mass was mixed in a homogenizer (CKL Machinery) at 3000 rpm for 30 min to obtain a homogeneous mass. The homogeneous mass was dried in a drum drier (R. Simon Dryers) at a temperature of 109–12°C. The produced mass was mashed and sieved with a 35-mesh (500-μm) sieve. The second stage was crosslinking of the coprocessed amylose-xanthan gum using the same method as the first stage of method A.

**Substitution degree (SD) of the excipients**

The SD was determined by the colorimetry method [10] using two different solutions. The A solution was ascorbic acid 10%, and the B solution was ammonium molybdate tetrahydrate 0.42%. The sample was placed in a crucible and heated at 600°C for 3 h. The ash from the sample was dissolved in sulfuric acid 0.1 N solution and boiled for 10 min. The solution was then filtered by Whatman 40 paper and diluted with aquadest-sulfuric acid 0.1 N solutions [1:1]. Then, the A and B solutions were added to the sample solution. A solution of the sample was mixed and incubated at 45°C for 20 min in a water bath; it was then immediately analyzed using a visible spectrophotometer at a wavelength of 820 nm. The interpretation of the phosphate SD was made by comparison with a calibration curve. The phosphate SD was calculated according to the following equation:

\[
DS = \frac{162P}{3100 - 102P}
\]

where P is the percentage of phosphate from cross-linked high amylose [11]. 162 is the molecular weight of a glucose unit, 3100 is the molecular weight of phosphate, and 102 is the molecular weight of phosphorous acid - P2O7.

**Preparation of transdermal hydrogels**

The formulas of Co-CLA6-XG 1:2, Co-CLA12-XG 1:2, CL6-Co-A-XG 1:2, and CL12-Co-A-XG 1:2 transdermal hydrogels are shown in Table 1. The transdermal hydrogels containing diclofenac sodium were prepared by dissolving diclofenac sodium in propylene glycol, then adding it to polyethylene glycol (PEG) 400 and demineralized water. The hydrogel was mixed on a homogenizer at 1000 rpm until it became clear. The drug solution was homogenized in a sonicator for 10 min. Each excipient was dispersed in the drug solution and allowed to stand for 15 min. Subsequently, the mass was mixed in a homogenizer at 1000 rpm and 50°C for 15 min to give a homogenous mass. Then, up to 75 g of the homogenous mass was placed in a 10×7.5-cm mold and dried in an oven at 50°C for 5 h. After cooling, the hydrogel was cut into 1×1-cm sections.

**Evaluation of transdermal hydrogels**

Evaluation of the transdermal hydrogels included surface pH, thickness, consistency, and drug content. The surface pH of the hydrogel was measured by placing the hydrogel in demineralized water for 2 h. The electrode of the pH-meter was then placed on the surface of the hydrogel until it reached equilibrium. The thickness of a transdermal hydrogel section was measured using a caliper. The consistency of the hydrogel was determined using a penetrometer (Herzoo, Germany).

**Table 1: Formulation of transdermal hydrogel containing diclofenac sodium**

| Composition          | F1  | F2  | F3  | F4  | F5  | F6  | F7  | F8  |
|----------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Diclofenac sodium (g) | 5   | 0.5 | 5   | 0.5 | 5   | 0.5 | 5   | 0.5 |
| Co-CLA6-XG (g)       | 5   | 5   | -   | -   | -   | -   | -   | -   |
| Co-CLA12-XG (g)      | -   | -   | 5   | 5   | -   | -   | -   | -   |
| CL6-Co-A-XG (g)      | -   | -   | -   | -   | 5   | 5   | -   | -   |
| CL12-Co-A-XG (g)     | -   | -   | -   | -   | -   | -   | 5   | 5   |
| Polyethylene glycol 400 (g) | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Propylene glycol (g) | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| Demineralized water (g) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 2: Substitution degree of the excipients**

| Excipients   | Substitution degree |
|--------------|---------------------|
| CLA6         | 0.08±0.01           |
| CLA12        | 0.10±0.00           |
| CL6-Co-A-XG  | 0.10±0.00           |
| CL12-Co-A-XG | 0.17±0.04           |

Each point represents mean±standard deviation (n=3)
The diclofenac sodium content in the hydrogel was determined using an ultraviolet (UV) spectrophotometer. Each hydrogel was dissolved in phosphate buffer pH 7.4. The solution was then homogenized in a sonicator to ensure that the diclofenac sodium was completely dissolved in the phosphate buffer pH 7.4. Hydrogel F1, F3, F5, and F7 were diluted to 1/100 of their initial concentrations with phosphate buffer pH 7.4, and F2, F4, F6, and F8 were diluted to 1/10 of their initial concentrations with phosphate buffer pH 7.4. Each sample solution was measured by UV spectrophotometry at a wavelength of 276 nm. Each hydrogel was assayed 3 times.

**In vitro penetration study**

The methods used for animal sacrifice for in vitro and in vivo penetration studies were approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (approval no. 224/UN2.F1/ETIK/2015). Sprague-Dawley rats were housed under standard conditions of temperature, relative humidity, and light. Unless otherwise specified, food, and water were given ad libitum.

The in vitro penetration test method was based on that of Klimes et al. [12] with slight modifications. The penetration of diclofenac sodium through the skin was measured using Franz diffusion cells. The receptor compartment was filled with a solution of phosphate buffer pH 7.4, and the temperature was maintained at 37±0.5°C. The speed of the magnetic stirrer was set to 250 rpm. The abdominal skins were collected from the Sprague-Dawley male rats, which were approximately 8 weeks old and weighed ±200 g. The skins were placed between the donor and receptor compartment with the dermal side in contact with the receptor medium. The hydrogels (F1, F3, F5, and F7) were placed in the donor compartment. As much as 0.5 ml of the sample solutions was withdrawn at each time interval from the receptor and immediately replaced with the same amount of pH 7.4 phosphate-buffered solution. The amount of diclofenac sodium in the sample was then measured using a UV spectrophotometer (Shimadzu, Japan) at a wavelength of 276 nm.

**In vivo penetration study**

The method was based on Sintov and Botner [13] with slight modifications. The experiment used 8- to 10-week Sprague-Dawley male rats (n=6) for each hydrogel (F2, F4, F6, and F8). The rats were anesthetized by intra-peritoneal injection of urethane (1000 mg/kg). The abdominal skins of the rats were shaved, and each hydrogel (F2, F4, F6, and F8) was placed on skin with plaster to keep the hydrogel on the surface of the abdomen during the test. As much as 0.5 ml of blood sample was collected from the sinus orbital of the eye at each time interval and then inserted into a microtube that had been loaded with heparin. Blood samples were centrifuged at 10,000 rpm for 20 min to separate the blood plasma from blood cells.

**Analysis of diclofenac sodium in rat plasma**

Diclofenac sodium in rat plasma was analyzed by HPLC (Shimadzu) equipped with a photometric diode array detector at a wavelength of 283 nm. The 250 μl of plasma sample was added with 100 μl of internal standard (diltiazem hydrochloride 100 ppm) and mixed on a vortex mixer for 10 s. Thereafter, the sample was added to 250 μl methanol HPLC grade and mixed on a vortex mixer for 2 min and centrifuged at 10,000 rpm for 10 min to precipitate the proteins. Furthermore, as much as 20.0 μl of supernatant was injected into the HPLC instrument under the selected conditions. The method was partially validated by the European Medicines Agency [14].

**RESULTS AND DISCUSSION**

**SD of the excipients**

The SD was calculated as the degree of substitution of hydroxyl groups by phosphate groups from STMP in the amylose and xanthan gum. Inorganic phosphate was produced by heating the excipient to 600°C. Inorganic phosphate was reacted with ammonium molybdate tetrahydrate in acid solution to produce a phosphomolybdate complex, which was then reduced by ascorbic acid to produce a blue color [15].

Table 2 shows the differences in the SD between the excipients. The SD values were determined for CLA6, CLA12, CL6-Co-A-XG, and CL12-Co-A-XG. An SD of 0.08 indicated substitution of eight phosphate groups for hydroxy groups in every 100 anhydroglucose units of amylose and/or xanthan gum. An SD of 0.10 indicated a substitution of 10 phosphate groups for hydroxy groups in every 100 anhydroglucose units of amylose and/or xanthan gum. CL6-Co-A-XG has ten phosphate groups by phosphate groups from STMP in the amylose and xanthan gum. Inorganic phosphate was produced by heating the excipient to 600°C. Inorganic phosphate was reacted with ammonium molybdate tetrahydrate in acid solution to produce a phosphomolybdate complex, which was then reduced by ascorbic acid to produce a blue color [15].

**Evaluation of transdermal hydrogels**

Table 3 shows the evaluation results of the transdermal hydrogels’ properties, including surface pH, hydrogel thickness, consistency value, and drug content in each hydrogel. The surface pH of the transdermal hydrogel was in the range of the limits of skin pH (5.6-7.5) which indicated that the transdermal hydrogel would not cause local irritation of human skin [16]. The surface pH of the transdermal hydrogel also was affected by the other components, such as diclofenac sodium, PEG 400, and propylene glycol. As shown in Table 3, there is a slight
Table 5: Pharmacokinetic parameters of the transdermal hydrogels containing diclofenac sodium

| Hydrogel | Formula | $C_{\text{max}}$ (µg/ml) | $T_{\text{max}}$ (h) | $AUC_{\text{max}}$ (µg/ml h) | $K_e$ (h⁻¹) | $t_{\frac{1}{2}}$ (h) | MRT (h) |
|----------|---------|--------------------------|----------------------|-----------------------------|-------------|-----------------|---------|
| Co-CLA6-XG | F2 | 4.35±0.94 | 1.00±0.00 | 32.08±5.40 | 0.10±0.03 | 11.47±4.04 | 16.66±5.86 |
| Co-CLA12-XG | F4 | 4.87±1.06 | 1.00±0.00 | 34.27±8.34 | 0.12±0.03 | 7.96±1.90 | 11.89±2.67 |
| CL6-Co-A-XG | F6 | 2.87±0.48 | 0.50±0.11 | 6.20±1.19 | 0.18±0.04 | 5.29±1.50 | 4.82±0.74 |
| CL12-Co-A-XG | F8 | 4.34±0.58 | 0.50±0.00 | 14.38±2.38 | 0.10±0.02 | 8.40±1.57 | 11.23±2.00 |

AUC: Area under the curve, MRT: Mean residence time, $K_e$: Elimination constant. Data are expressed as mean±standard error, n=6

In vitro penetration study
Fig. 1 shows the penetration profiles of diclofenac sodium from the transdermal hydrogels across the rat skin membrane. The flux value and cumulative amount of drug that penetrated through the skin among the four hydrogels, comprising different polymers, are shown in Table 4. The diffusion of diclofenac sodium through the skin was passive with the concentration gradient as the driving force. The diffusion was affected by many factors, such as the solubility of diclofenac sodium and the thickness of the stratum corneum [18]. Diclofenac sodium in water solution can be hydrolyzed to diclofenac acid, which will increase the partition coefficient of the active substance so that the penetration of the drug can also be [14]. The mechanism of drug permeation through the skin begins by swelling of the hydrogel. The receptor compartment, which consists of phosphate buffer pH 7.4, caused hydration of the rat skin. The transdermal hydrogel, which consisted of a polymer matrix, could be wetted by absorbing fluid as it contacts the skin. This process causes the hydrogel to swell so that diclofenac sodium diffuses through the three-dimensional network of the polymer. During that process, the gradient concentration between the rat skin and hydrogel is high, which causes diclofenac sodium to permeate through the skin.

The highest cumulative amount of drug penetrated through the skin was achieved by the CL6-Co-A-XG 1:2 hydrogel (F5). The crosslinking in CL6-Co-A-XG 1:2 may occur between amylose and xanthan gum. The more crosslinking indicates high crosslinking density, which means the network was closely woven. In this case, the chain sections of the cross-links were short and anchored by many points. Therefore, the polymer became less flexible and more rigid [19]. This characteristic makes diffusion of the drug easier through the matrix.

The Co-CLA6-XG 1:2 (F1) and Co-CLA12-XG 1:2 (F3) hydrogels gave levels of penetration of diclofenac sodium <30% because the three-dimensional networks of hydrogels F1 and F3 consisted of some closed-hydrogen bonds and high gel strength that slowed drug release [7]. Dumoulin et al. stated that drug release could be controlled by crosslinking amylose, the degree of which was limited in CLA-3 to CLA-11, and the maximum drug release time was observed in CLA-6 (as long as 20–24 h) [20]. Furthermore, Lanaerts et al. [20] stated that the increase in the degree of crosslinking from CLA-6 to CLA-20 correlated with the decrease in crystal properties, which can lead to a decreasing ability to form a double-helix structure and acceleration of matrix hydration [20].

The percentage of cumulative drug penetrations of all hydrogels through the skin was <50%, which was caused not only by the ability of the polymer to slow drug release but also the characteristics of the diclofenac sodium as a drug model. The low partition coefficient of sodium diclofenac (log p=0.70) was an important factor related to drug permeation because the partition coefficient indicates the ability of a drug to partition into hydrophobic and hydrophilic phases [21].

In vivo penetration study
Fig. 2 shows the mean of the plasma concentration-time profiles of diclofenac after transdermal administration of diclofenac-containing hydrogel for Co-CLA6-XG (F2), Co-CLA12-XG (F4), CL6-Co-A-XG (F6), and CL12-Co-A-XG (F8), as the matrix. Green, purple, blue, and red lines represent F2, F4, F6, and F8, respectively. Each point represents the mean±standard deviation; n=6
in Table 5, the AUC, C_{max}, T_{max}, and mean residence time (MRT) values of the transdermal diclofenac hydrogel, comprising Co-CLA6-XG as a matrix (F2), showed no significant difference (p>0.005) with F4, comprising Co-CLA12-XG. In contrast, the AUC of the transdermal hydrogel F6 and F8, comprising CL6-Co-A-XG and CL12-Co-A-XG, respectively, significantly decreased. The results indicated that the crosslinking degree of amylose and the method of preparation the excipient affected their drug delivery. In addition, the MRT and K_{is} values of the transdermal hydrogels of F2, F4, and F8 indicated that the produced excipients can be used as a transdermal matrix with controlled and prolonged release behavior.

CONCLUSION

For diclofenac sodium as the model drug, the in vitro and in vivo penetration study results indicated the feasibility of developing hydrogels using Co-CLA6-XG, Co-CLA12-XG, CL6-Co-A-XG, or CL12-Co-A-XG as a matrix former that could be used as a good transdermal dosage form. The results also show the ability of these hydrogels to provide good controlled release permeation of the active model drug. Comparison of the in vitro and in vivo skin penetration data in this study was difficult, but the results of both studies suggested that the hydrogel formulations would provide good controlled drug permeation through the skin. Further studies are needed to determine if these hydrogels can be used for humans in clinical studies.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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