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The editing of this proceeding has been carried out by B. Kuswandi with assisted by the Scientific Committee of ICPBAR 2006.
Preface

The 2nd International Conference on New Techniques in Pharmaceutical, Biomedical and Analytical Research (ICPBAR 2006), took place in Sanur Paradise Plasa Hotel, Denpasar Bali Indonesia on 21 – 23 August 2006. This conference, the second series after the first one held in Kuala Lumpur, Malaysia in 2005, is the only one conference focused on all aspects related to pharmaceutical, biomedical and analytical research.

This proceeding contains papers that have been presented at the ICPBAR 2006 as plenary lectures, keynote, oral and poster presentations. About 100 participants attended the conference, with 8 plenary lectures, 22 oral and 24 poster presentations. The proceeding of ICPBAR 2006 has been published in electronic form as *.pdf file for simple and easy publication and to avoid heavy book of proceeding. We hope that this publication can be easily read, handled and transferred to other form. Furthermore, this paperless proceeding can be fruitful for all participants of the conference.

My sincerely thanks go to all the members of Scientific Committee for their valuable help in the review of the submitted papers, and also to the authors for their collaborative attitude. A special mention must go to Tri Kuncoro, our Conference Secretary, who has put in a terrific amount of effort not only in general conference matter but also in the assembly of the papers for this proceeding. Finally, I congratulate the authors of all papers for producing the new and novel idea for research on pharmaceutical, biomedical and analytical developments, which are currently emerging fields of research in South East Asia, particularly in Indonesia.

Jember, August 2006

B. Kuswandı
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ICPBAR 2006 Proceeding
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The Development of Transdermal Piroxicam Using HPMC Matrices With PVP K-30 as a Penetration Enhancer

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Abstract

The physicochemical properties such as solubility, partition coefficient, and membrane permeability of a drug are required for formulating and estimating drugs absorption that pass through biological membranes. The research studied about solubility, partition coefficient in octanol-phosphate buffer, rabbit skin permeability and release from the transdermal delivery system of piroxicam with addition of 6% PVP K-30 in vitro into phosphate buffer solution pH 7.4 at temperature 32±1°C. The results showed that the solubility of piroxicam was 904.44 ± 20.92 μg/mL. The values of log IPC and APC were 1.99 ± 0.01 and 0.08 ± 0.01, respectively. The flux, permeability coefficient, and diffusion coefficient of the piroxicam permeation process were 2.07 x 10⁻⁴ μg/cm²/sec, 4.96 x 10⁻⁶ cm/minute, and 4.13 x 10⁻⁸ cm²/minute, respectively. The release mechanism of piroxicam from transdermal delivery system was more dominant by diffusion than erosion. The fluxes of piroxicam release were 0.169 and 0.107 mg/cm²/minute for formulation with 2% HPMC and 4% HPMC, respectively.

Keywords: Piroxicam, HPMC, PVP K-30, Transdermal delivery

1. Introduction

Piroxicam is a nonsteriod antiinflamation drug (NSAID) which is often used in rheumatoid arthritis treatment. It is like other NSAIDs, piroxicam provides side effects in gastrointestinal. Thus, transdermal delivery system is an attractive option to overcome this problem. Piroxicam was reported that had poor skin permeability. So that was suggested to enhance the skin permeability with a penetration enhancer (1-4).

Skin is largest organ of the body, is composed of several layers: the stratum corneum (uppermost layer), viable epidermis, dermis and hypodermis. One commonly hears that the skin is too good barrier to permit the delivery of all but a few compounds. Low skin permeability originates from unique hierarchical structure of the stratum corneum. Stratum corneum consists of several layers of keratinocytes within which lipid bilayer are stacked (5-7). Hence, the attempts have been made to circumvent this barrier by using "penetration enhancer", i.e., compounds which would temporarily and reversibly diminish the barrier function of the stratum corneum and make possible percutaneous absorption of drugs. Penetration enhancer should be nontoxic, pharmacological inert, nonirritant, non-allergenic, reversible, pharmaceutical stable, cosmetically acceptable (8-11).

One of the penetration enhancer is polyvinyl-pyrrolidone (PVP). PVP is the pyrrolidones, which the primary site of action is most likely the polar route, and there intrinsic humectant activity, is a significant factor in their little doubt that hydration of the skin, owing to their effectiveness (12).

The skin permeability of drugs with certain polarity depends on the skin/vehicle partition coefficient. It is not easy to measure skin/vehicle partition coefficient of permeant. Hence, it is usually used partition coefficient octanol/water instead. Partition coefficient octanol/water is lipophilicity parameter of drugs. It is an important factor to determine permeability of drug across biological membranes (13, 14). Beside the partition coefficient, the skin permeability of drugs depends on solubility of drugs also (14, 15).

Beside the physicochemical properties, the release rate of the drugs is also required for formulating and estimating drug absorption pass through biological membranes. The release rate of the drugs is influenced by the dosage form (16). The research studied about solubility, partition coefficient in octanol-phosphate buffer, rabbit skin permeability and the release from the transdermal delivery system of piroxicam with addition of 6% PVP K-30 in vitro. In this study, the transdermal delivery system developed by using hydroxilpropil-metilcellulose (HPMC).
2. Materials and Methods

2.1. Materials

Piroxicam (obtained from PT Coronet Crown, Surabaya, Indonesia), HPMC K-100M (Colorcon), PVP K-30 (The Dow Chemical Company), NaH₂PO₄, Na₂HPO₄, NaOH, octanol, ethanol, methanol (E Merck), rabbit skin, cellophane membrane, all solvent and reagent were analytical grade.

2.2. Methods

2.2.1. Solubility Study

Piroxicam solubility study was done by addition of excess of the drug into the phosphate buffer pH 7.4 solution containing 6% PVP K-30. The mixture was allowed to equilibrate using shaker at 32 ±1°C for 24 hours. After that, the suspension was filtered, suitably diluted, and analyzed spectrophotometrically at 354 nm.

2.2.2. Partition Coefficient Study

Piroxicam partition coefficient study was done by adding of piroxicam 10 mg/L with addition of 6% PVP K-30 into octanol saturated phosphate buffer pH 7.4. Using incubator shaker water bath this mixture was agitated with 200 rpm at 32±1°C for 24 hours and then centrifuged. After that, the phases were separated. The water phase was suitably diluted and analyzed spectrophotometrically at 354 nm. The partition coefficients were calculated with the following equations:

\[
\text{IPC} = \frac{[HA]_o}{[HA]_w} = \frac{C_o}{[HA]_w} \quad (1)
\]

\[
C_w = [HA]_w + [A^-]_w \quad (2)
\]

\[
\text{APC} = \frac{[HA]_w}{[HA]_o + [A^-]_w} = \frac{C_o}{C_w} \quad (3)
\]

where IPC is the intrinsic partition coefficient, [HA]₀ is the concentration of unionized drug in octanol phase, [HA]₀ is the concentration of unionized drug in phosphate buffer phase, [A⁻]₀ is the concentration of ionized drug in phosphate buffer phase, C₀ is the concentration of drug in octanol phase, Cw is the concentration of drug in water phase, APC is the apparent partition coefficient.

2.2.3. In vitro Permeation Study

An in vitro permeation study was carried out by using a diffusion cell modified from Higuchi diffusion cell (Figure 1). The diffusion cells were maintained at 32±1°C by the electrical water bath. The rabbit skin was mounted on the diffusion cell with the stratum corneum side facing the donor compartment and the dermal side facing the receptor compartment. The rabbit skin samples were placed into isotonic phosphate buffer solution pH 7.4 and kept in the refrigerator at 4°C for 24 hours prior to the experiment. Piroxicam solution 20µg/mL in phosphate buffer pH 7.4 with addition of 6% PVP K-30 was placed in the donor compartment. The phosphate buffer pH 7.4 was then introduced into the receptor compartment. The capacity of donor compartment and receptor compartment were 125 mL, respectively. The samples from the receptor were taken at predetermined time intervals and immediately replaced by an equal volume of fresh buffer solution. The samples were analyzed spectrophotometrically at 354 nm. The permeability parameters were calculated from the penetration data with the following equations:

\[
\frac{dM}{dt} = J = k_p \cdot C_d \quad (4)
\]

\[
\frac{M}{S} = k_p \cdot C_d \cdot t \quad (5)
\]

\[
k_p = \frac{D \cdot P}{h} \quad (6)
\]

where M is the amount of piroxicam penetrated, S is the area of rabbit skin membrane (4.9cm²), k_p is the permeability coefficient, C_d is the piroxicam concentration in donor compartment, t is time, D is the diffusion coefficient, P is the partition coefficient octanol/ phosphate buffer.

Figure 1. Diffusion cell assembly (side by side model)

2.2.4. Formulation

The quantities used for preparing the gel formulations are listed in Table 1.

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<tr>
<th>Ingredient</th>
<th>Formulation I</th>
<th>Formulation II</th>
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<tbody>
<tr>
<td>Piroxicam</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>HPMC</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>NaOH 10% solution</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Ethanol</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Nipagin</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Aqua ad</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
The Formulations were prepared as follows: HPMC was dissolved into hot water and stirred constantly. Piroxicam was dissolved into ethanol and NaOH solution. PVP K-30 was dissolved into water and added into Piroxicam solution. The mixture was added into the HPMC gel base and stirred until homogeneous.

2.2.3. In Vitro Drug Release Study

An *in vitro* drug release study was carried out by using dissolution testing apparatus 5 USP (paddle over disk). The disk was filled with the gel (2 g) and placed into the receptor medium containing 900 mL of phosphate buffer pH 7.4 solutions. The cellophane was mounted on the disk. The apparatus was run at 50 rpm, and temperature was maintained at 32 ±1°C. The samples from the receptor were taken at predetermined time intervals and immediately replaced by an equal volume of fresh buffer solution. The samples were analyzed spectrophotometrically at 354 nm.

3. Results and Discussion

The solubility of piroxicam with addition of 6% PVP K-30 was 904.44±20.92 µg/mL. The dissociation constant (pKa) of Piroxicam is 5.5 (1). Thus, base on Handerson-Haselbalch equation, percentage of ionization of piroxicam in phosphate buffer pH 7.4 was 98.75% or almost 100%. In the last study was reported that solubility of piroxicam in phosphate buffer pH 7.4 at temperature 32 ±1°C was 856.06 ± 46.72 µg/mL (17). Increasing solubility of piroxicam with addition of PVP K-30 might be due to forming of complex Piroxicam-PVP which was more soluble in water. Solubility of piroxicam has an important role in the permeability. The maximum flux depends on drug solubility in vehicle, it is increases with growing water solubility in the case of hydrophilic gel (14).

Partition coefficient could be determined as apparent partition coefficient (APC) or intrinsic partition coefficient (IPC). The values of log APC and IPC of piroxicam with addition of 6% PVP K-30 were 1.99 ± 0.01 and 0.08 ± 0.01, respectively. In the last study was reported that APC and IPC of piroxicam in octanol/phosphate buffer pH 7.4 at temperature 32 ±1°C were 1.97 and 0.0637, respectively (17). The partition coefficient is the lipophilicity parameter of the drugs. Thus, the lipophilicity of piroxicam was not influenced in addition of PVP.

The diffusion process of piroxicam across rabbit skin was analyzed from the diffusion profile (Figure 2). The Regression equation of the profile was $Y = 0.0124X + 5.2181$ with correlation coefficient (r) = 0.957. The regression equation was obtained using the last 5 data. The regression line was linear, so it represented that the transport process of the drug from the donor compartment into the receptor compartment followed zero order kinetics. Thus, the diffusion parameter could be determined using Ficks Equation. The diffusion parameters of piroxicam diffusion process with addition of PVP K-30 are listed in Table 2.

![Figure 2. Plot of cumulative amount of piroxicam penetrated across rabbit skin versus time.](image)

![Table 2. The diffusion parameter of diffusion process of piroxicam with addition of PVP K-30](table)

<table>
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<th>Parameter</th>
<th>Values of Parameter</th>
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<tr>
<td>Permeability coefficient (cm/minute)</td>
<td>$4.96 \times 10^{-6}$</td>
</tr>
<tr>
<td>Diffusion coefficient (cm$^2$/minute)</td>
<td>$4.13 \times 10^{-8}$</td>
</tr>
<tr>
<td>Flux (µg/cm$^2$/seconds)</td>
<td>$2.07 \times 10^{-4}$</td>
</tr>
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Permeability is a diffusion parameter which determines capability of solute across membrane. Beside nature of the membrane, the permeability of solute also depends on the solute movement rate to achieve the membrane surface.

Diffusion coefficient is diffusion parameter which relate to membrane area. The diffusion coefficient of piroxicam with addition of 6% PVP K-30 was determined with assuming that the partition coefficient membrane-water as same as the partition coefficient octanol-phosphate buffer solution pH 7.4.

Release mechanisms of drugs from dosage form could be by diffusion or erosion. The release mechanisms by diffusion follow Higuchi equation; it could be analyzed from the amount of piroxicam release from the HPMC gels as a function of square root of time. These profiles are showed in Figure 3. The release by erosion mechanism was analyzed from the amount of piroxicam release from the HPMC gels as a function of time. These profiles are showed in Figure 4. Regression equation of the release profiles in Figure 3 and 4 are showed in Table 3 and 4.
Table 3. Regression equation of release profiles of formulation I

<table>
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<th>Release Mechanism</th>
<th>Formulation I</th>
<th>Regression equation</th>
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<tr>
<td>Diffusion</td>
<td></td>
<td>Y = 0.169X - 0.198</td>
<td>0.993</td>
</tr>
<tr>
<td>Erosion</td>
<td></td>
<td>Y = 0.009X + 0.529</td>
<td>0.975</td>
</tr>
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Table 4. Regression equation of release profiles of formulation II

<table>
<thead>
<tr>
<th>Release Mechanism</th>
<th>Formulation II</th>
<th>Regression equation</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion</td>
<td></td>
<td>Y = 0.107X - 0.213</td>
<td>0.994</td>
</tr>
<tr>
<td>Erosion</td>
<td></td>
<td>Y = 0.005X + 0.252</td>
<td>0.965</td>
</tr>
</tbody>
</table>

The values of coefficient correlation (r) of the regression equation of release by diffusion for formulation I and II are greater than by erosion. Thus, the release mechanisms of the gels were more dominant by diffusion than erosion.

Figure 3. Plot of amount of piroxicam released from HPMC gels versus square root of time. Note: (●) formulation I and (■) formulation II

Figure 4. Plot of amount of piroxicam released from HPMC gels versus time. Note: (●) formulation I and (■) formulation II

The release mechanisms of piroxicam from the HPMC gels with 6% PVP K-30 were analyzed from the Figure 3 and 4. Slope of the regression equation which is listed in table 3 and 4 represented of the flux release of piroxicam from the gels. The flux release of piroxicam from the gels formulation I and II by diffusion were 0.169 and 0.107 mg/cm²/minute, respectively. The concentration of HPMC in formulation II was higher than in formulation I, thus the viscosity of formulation II was higher than formulation I. Increasing in viscosity caused decreasing in diffusity, thus the flux released of formulation II lower than formulation I.

4. Conclusion

The solubility of piroxicam increased with addition of 6% PVP K-30. The solubility of piroxicam with addition of 6% PVP K-30 was 904.44 ± 20.92 μg/mL. The flux, permeability coefficient, and diffusion coefficient of piroxicam with addition of 6% PVP K-30 across rabbit skin were 2.07x10⁻²μg/cm²/sec, 4.96x10⁻⁶ cm/minute, 4.13x10⁻⁸ cm²/minute, respectively. The flux release of formulation I, which contained 2% HPMC and 6% PVP K-30, was higher than formulation II, which contained 4% HPMC and 6% PVP K-30. The viscosity of the formulations influenced the piroxicam release from the gels.

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References


