Characteristics of transdermal topical delivery patch (MILTAX®) containing the anti-inflammatory and analgesic drug, ketoprofen

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Characteristics of transdermal topical delivery patch (MILTAX®) containing the anti-inflammatory and analgesic drug, ketoprofen, are here evaluated with reference to formulation, pharmacological and clinical aspects. Included is a comparison of skin permeation of ketoprofen with that of indometacin and piroxicam. The flux of ketoprofen was higher than that of other two drugs, while indometacin showed high skin permeability, but low saturated solubility, and therefore relatively poor skin permeation. L-menthol was found to be useful not only for enhancement of skin permeation, but also for giving a cool feeling to the skin.

Atomic force microscopic (AFM) observations here revealed the existence of micro-domains sized a few nanometer in diameter on the surfaces of hydrophilic gels like MILTAX®. Moreover, ketoprofen might exist as micelles surrounded by polyoxyethylene sorbitan trioleate (PST) which could play an important role in both skin permeation and maintaining drug stability. The adhesion characteristics, probe tack, sticking strength and cohesion strength, were weaker with the poultice-type patch, MILTAX®, than with KP-T.

In generally, the permeation of drugs is lower with human than with animal skin. Similarly, the flux of ketoprofen from MILTAX® for rat skin was 2~3 times higher than with human skin. The release of ketoprofen from the patch was approximately 60~70% at 24 hour, with a relative bioavailability (BA) of 80~90% in comparison with oral administration. The muscle concentration of ketoprofen after MILTAX® application was twice that after oral administration.

No severe toxicity was seen in the primary and 7-day cumulative skin irritation tests in rabbits. Clinically, MILTAX® shows comparable anti-inflammatory and analgesic efficacy to oral administration of ketoprofen, but with much reduced side effects.

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Ketoprofen is a conventional non-steroid anti-inflammatory drug (NSAID) which inhibits cyclooxygenase (COX), the enzyme responsible for the first step in synthesis of various prostaglandins (PGs) from arachidonic acid. COX exists as two isoforms, COX-1, which presents in almost all cells and constitutively producing PGs concerned with protection of the gastric mucosa.
and kidney functions, and COX-2, which is induced by cytokines or hormones in inflammatory regions\(^1\). When ketoprofen is given as a medication by the oral route, serious side effects sometimes occur, with decrease in blood flow to the gastric mucosa or the kidney because of non-selective COX inhibition\(^2,3\).

Transdermal administration of drugs has many advantages when compared with oral or injection administration, such as the avoidance of the first pass effect in the liver and side effects on the gastrointestinal tract, a prolonged steady-state blood concentration of the drug and the fast discontinuation on removal\(^4,5\). The skin has a large surface area of about 1.8 m\(^2\) and consists of the stratum corneum, epidermis, dermis and associated elements, such as the hair follicles, sebaceous glands and sweat glands\(^6\). The stratum corneum of the outermost layer plays an important role in preventing not only water loss through the skin, but also penetration of foreign substances from the outside\(^7\).

Ketoprofen has high skin permeability compared to other NSAIDs\(^8,9\) a characteristic which makes it highly suitable for topical application, in poultice or tape-type patches. The poultice-type patch, MILTAX\(^\circledR\), is basically a water-soluble polymer and contains approximately 56% water. Tape-type patches, in contrast, consist of hydrophobic polymers without water. Although it has been reported that poultice-type patches are safer\(^10\), skin absorption of ketoprofen is slightly lower than with the tape-type patch\(^11\).

In the present study, skin permeation of ketoprofen from MILTAX\(^\circledR\) was assessed with pharmaceutical, biological and clinical properties. Included were several comparative investigations of MILTAX\(^\circledR\) and a tape-type patch containing ketoprofen.

**In vitro skin permeation of ketoprofen in comparison with other NSAIDs (indometacin and piroxicam)**

Excised skin, with the stratum corneum, epidermis and dermis intact, and skin\(^12\) stripped the stratum corneum with adhesive tape (Teraoka, Japan), in both from hairless mice (Japan SLC, Japan), were cut into pieces of 23mm diameter and applied 2-chamber diffusion cells. Ketoprofen, indometacin and piroxicam were suspended in purified water, as the donor solutions and their concentrations confirmed by HPLC. The speed of permeation at steady state (flux) was calculated from the slope of the straight-line portion of the cumulative permeation-time profile, and the lag time, defined by the time intercept of the straight-line portion of the profile.

Data for permeation, flux and lag time, for the three drugs with the excised intact and stripped skin are summarized in Fig. 1a. The flux was in the order of ketoprofen > indometacin > piroxicam. However, no significant difference was observed in the lag time among three drugs.

In generally, skin permeation of drugs is expressed with the following equation\(^13\).

\[
\text{Flux} = K \cdot C \cdot \frac{D}{L} = (av/r_s) \cdot \frac{D}{L}, \quad \text{Lag time} = \frac{L^2}{6D}, \quad P = \frac{\text{Flux}}{C}
\]

where \(K\) is the partition coefficient, \(C\) is the drug concentration at the start of the experiment, \(D\) is the diffusion coefficient, \(L\) is the skin thickness, \(av\) is the drug activity in the vehicle, \(r_s\) is the coefficient of drug activity in skin and \(P\) is permeability coefficient.

As shown in Fig. 1b, although the flux of ketoprofen was higher than those of indometacin and piroxicam, indometacin showed the highest \(P\) (permeability coefficient) value. However, since indometacin showed the lowest saturated solubility among three drugs, the actual skin permeation from the patch was thought to be low. Given
the fact that the flux, a product of \( P \) and \( C \), was greatest for ketoprofen among the three drugs, it was concluded to be the most suitable ingredient for the transdermal delivery patch. The ratios (stripped/intact skin) for flux and lag time are shown in Fig. 1.c. That with piroxicam was 30 : 1. For ketoprofen and indometacin, they were 5 ~ 8 : 1. Since no significant difference in lag time was observed, \( D \) (diffusion coefficient) was the same level for the three drugs but \( K \) (partition coefficient) differed. Therefore, the stratum corneum can be considered the rate-limiting membrane for skin permeation of the three drugs.

Preparation of transdermal delivery poultice-type patches

1. Effect of pH and solubility on the skin permeation

Excised intact skin from a wistar rat (Japan SLC, Japan) was applied in 2-chamber diffusion cells. A 3mL aliquot of ketoprofen solution to the stratum corneum side as donor was added up to the concentration of 100 \( \mu g/mL \) at various pH values of 3 to 7 in solutions. 3mL of phosphate buffer (pH 7.4) was applied to the dermis side (receiver side).

Results for effects of pH on the skin permeation, flux and lag time, and saturated solubility are shown in Fig. 2. The calculated concentra-
tions of nonionic and ionic ketoprofen in the saturated solutions are given in Fig. 2 c.

The flux and the saturated solubility of the ketoprofen suspension increased with the pH. On the other hand, in the case of the 100 µg/mL concentration, the flux decreased with increasing of pH. However, the lag time was not affected in either case. The increase of flux, in the case of ketoprofen in suspension, may depend on an increasing of the saturated solubility resulted in an increase of passive diffusion that derives its driving force from the concentration gradient of a drug. The skin permeation of drugs is thought to be proportional to thermodynamic activity (i.e. drug content) in the vehicle when the concentration is below the saturation solubility. Thus, decrease of flux would be expected with decrease the drug activity in the 100 µg/mL donor solution with an increasing of pH. Therefore, the drug concentration (i.e. drug activity) in the vehicle is important to maximize skin permeation.

Permeation also varies with the state of drug dissociation and is generally believed to be higher with nonionic than ionic forms\textsuperscript{14}. However, in the diclofenac and piroxicam cases, the ionic forms may demonstrate greater permeation\textsuperscript{15,16}. The molecular state of ketoprofen varies with the pH, and dissociation is the ionic form (pKa : 3.9) occurring in the pH range of 5 to 8 with various external formulations. The saturated solubility of ketoprofen increases with the pH of the solution, and the ionic form appears to account for much of this increase. Therefore, the ionic form may predominate in the skin permeation.
tion of ketoprofen.

2. Effect of skin permeation enhancers

When permeation enhancers, such as alcohols, fatty acids, esters and 1-menthol, were added at 0.2% to excised intact wistar rat skin in 2-chamber diffusion cells, permeation of ketoprofen suspensions was greatly increased. Enhancement ratios (vs. skin permeation ratio of ketoprofen with and without enhancers) with reference to the number of carbon atoms in alcohols, acids and esters are summarized in Fig. 3a, and results for effects of concentration of 1-menthol on the skin permeation, flux and lag time, are illustrated in Fig. 3b.

Since the skin inherently acts as a barrier to external substances, permeation of almost drugs is low\textsuperscript{17,18}. For enhanced permeation, various techniques have been employed, such as prodrug delivery\textsuperscript{19,20} and application of permeation enhancers as passive methods, with iontophoresis\textsuperscript{21-23}, ultrasound\textsuperscript{24} and electroporation\textsuperscript{25,26} as active approaches. Enhancement with molсидомин has been reported to depend on the number of carbon atoms in alcohols, acids and esters\textsuperscript{27}. In our ketoprofen case, with 10–12 carbon atoms, the enhancement ratio was 4–9 times higher than with other numbers. Increase in proportion with the concentration of 1-menthol was also observed up to 1%, but remained constant at higher concentrations. Furthermore, the enhancement above 0.2% of 1-menthol was almost same as that with 10–12 carbon alcohols, acids and esters. In fact, 1-menthol proved the most effective enhancer of skin permeation of ketoprofen. With transdermal delivery patches, especially for external use with anti-inflammatory and analgesic drugs, most patients prefer the cool feeling with 1-menthol.

3. Preparation of poultice-type patch

In poultice-type patches, a cross-linking agent like aluminum produces ionic bonds with a water-soluble polymer like sodium polyacrylate, leading to retention of a large amount of water. This ionic bonding depends on the pH of the patch and the desirable range is adjusted to 4–6 with tartaric or lactic acid\textsuperscript{28}. Moreover, the cross-links should not be formed during the manufacturing process so that disodium edetate, a chelating agent for aluminum, is used to prevent cross-linking for a short period of a few
have a domain structure, depending on the thickness of the gel and the density of cross-linking. Moreover, a multiple layer structure was apparent with micro-domains a few nanometers in size.

2. State of ketoprofen in MILTAX®

N-methyl-2-pyrrolidone (NMP) and PST were added to MILTAX® to dissolve ketoprofen. However, since NMP is miscible to water, it does not act as a solvent for the drug. As shown in Fig. 5, observation of MILTAX® under a confocal laser scanning microscope, suggested ketoprofen to exist as micelles surrounded by PST, which are dispersed in the water31). These micelles presumably may play an important role in skin permeation and stability of ketoprofen in MILTAX®.

3. Adhesion characteristics of patches

In general, the parameters of adhesive strength of a patch on skin are the tack, sticking strength and cohesion strength32,33). The adhesion characteristics of the poultice-type patch, MILTAX®, comprising 0.3% of ketoprofen, 56% of water and water-soluble polymer, were compared with those of the tape-type patch, KP-T, (MOHRUS® TAPE, Hisamitsu Pharmaceutical Co., Inc., Japan), which consists of 2% of ketoprofen in a hydrophobic adhesive (styrene/isoprene/styrene block copolymer). The results are shown in Fig. 6. The probe tack, the sticking strength and the cohesion strength of KP-T were significantly higher than those of MILTAX®. They respectively reflect a short term wetting ability of the surface, resistance to adhesive removal, and shearing resistance against a constant load34). Thus, adhesion with KP-T is clearly stronger.

Fig. 4 Observation of surface of a hydrophilic gel under atomic force microscopy (AFM)

Fig. 5 Observation of MILTAX® under a confocal laser scanning microscope
The image size of the micrograph is 97.6 × 97.6 μm. The objective used here is ×40.

Pharmaceutical properties of the poultice-type patch, MILTAX®

1. Surface structure of poultice-type patches

As shown in Fig. 4, a recent study26,30) showed the surface of a hydrophilic gel under AFM to
Biological evaluation of MILTAX®

1. Effect of species (wistar rat and human skin)

Excised intact skin of wistar rats was purchased from Japan SLC and excised intact human skin was provided by HAB research organization (Japan). Using vertical diffusion cells, MILTAX® and KP-T were applied. Animal skin is often used for research purposes, and human skin is helpful to predict the clinical efficacy.

As shown in Fig. 7, the flux was approximately 3 times higher for the wistar rat than human skin with MILTAX® and 1.9 times higher with KP-T. Moreover, the KP-T flux was 1.3~1.9 times higher than with MILTAX®. It is known that the skin permeation of drugs is generally lower with human than with animal skin, due to differences in epidermal lipid concentration, thickness of the stratum corneum, and number and diameter of hair pores. In addition, since skin permeation depends on drug concentration in a patch, it was expected that KP-T containing 2% ketoprofen would exhibit higher skin permeation than MILTAX® containing only 0.3%.

2. Tissue distribution of ketoprofen in rats

Ketoprofen distribution to tissue was compared between MILTAX®, KP-T and oral administration in wistar rats, with doses of 2.9, 3.6 and 3.6 mg/12.56 cm²/body, respectively. The examination was carried out using single- and multiple-dose administration of the patch to a diameter of 4cm on the abdomen. Blood was collected from the abdominal cava at 2, 4, 8, 12, 16, and 24 hour after application when the patches were removed or 24 hour after removal of the patches, and centrifuged (10°C~3,000 rpm~10 min) to obtain plasma samples. Muscle was collected at the application site immediately after removal of the patches, and also from the untreated back, then the plasma and the tissue concentrations of ketoprofen were determined by HPLC. Multiple-dose patches were applied to the same sites every 24 hour for 3 days. Blood and muscle were collected at 12 hour after every application by the same method as for single-dose administration.

(1) Residual rate of ketoprofen in the patches

As shown in Fig. 8a, when the drug release from the patches was calculated from the remained drug content in the patch after 24 hour of application, MILTAX® and KP-T had similar values of approximately 60~70% of the administered dose.

(2) Ketoprofen concentrations in the plasma

As shown in Fig. 8b and Tab. 1, in the case of single-dose administration, the plasma concentration after oral administration was 2~5 times...
higher than either of the patch applications until 8-hour. Moreover, there was no significant difference in plasma concentration between MILTAX® and KP-T applications. The relative BA of patches was approximately 80~90% of that after oral administration.

As shown in Fig. 9a, with multiple-dose administration, no increase in plasma concentration was observed over the single-dose cases.

Table 1 Pharmacokinetic parameters of ketoprofen after application of patches to rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/rat)</th>
<th>Cmax (µg/mL)</th>
<th>Tmax (hr)</th>
<th>AUC 0-48 (µg×hr/mL)</th>
<th>Relative BA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILTAX®</td>
<td>2.9</td>
<td>8.9</td>
<td>12</td>
<td>184</td>
<td>92</td>
</tr>
<tr>
<td>KP-T</td>
<td>3.6</td>
<td>7.3</td>
<td>12</td>
<td>197</td>
<td>80</td>
</tr>
<tr>
<td>p.o.</td>
<td>3.6</td>
<td>13.2</td>
<td>4</td>
<td>246</td>
<td>100</td>
</tr>
</tbody>
</table>

*Relative BA: Value as against 100 for AUC(µg/mL×hr) after oral administration

(3) Ketoprofen concentrations in the treated and untreated muscle

As shown in Fig. 8c, in the case of single-dose administration, the muscle concentration of ketoprofen with KP-T was approximately twice that with MILTAX®. Moreover, the muscle drug concentration after either transdermal application was higher than with oral administration. The dorsal muscle drug concentrations were
approximately 25~70% of the treated muscle (abdominal) values, no differences being evident with either patch.

As shown in Fig. 9 be, in the case of multiple-dose administration, no increase in treated muscle drug concentration was observed. Moreover, there was no significant difference in ketoprofen in treated muscle between MILTAX® and KP-T cases. The drug concentration in the untreated muscle was approximately 50~60% of that in the treated muscle (abdominal) on day 1 and approximately 80~100% on days 2 and 3.

Plasma levels of flurbiprofen have been reported to differ little between topical application and oral administration in rats. It is known that 99% or more of flurbiprofen or piroxicam applied to the skin is distributed to the blood in hairless rats. Moreover, the distances of direct diffusion of NSAIDs, such as salicylic acid, diethylamine salicylate, indometacin, naproxen, diclofenac, piroxicam, from the skin surface are about 3 to 4 mm depth in rats. The tissue distribution of drugs is thought to be governed by their physicochemical properties and is influenced by additives. For example, the distribution to muscle of piroxicam was increased by the addition of diisopropyl adipate. Furthermore, it has been reported that when MILTAX® was applied to patients with osteo-arthritis of knee joints, the achieved concentrations were 26.579 ng/g, 292.32 ng/g and 13.49 ng/mL in the skin, synovial membrane and serum, respectively. Thus, ketoprofen was directly distributed from the application site to the target without systemic involve-
In the present study, the plasma concentration of ketoprofen after oral administration (3.6 mg/body) was 2~5 times higher than after transdermal application (2.9 mg/body, MILTAX®), while, muscle concentrations were approximately twice higher with transdermal application than with oral administration. This direct route is more important. The skin permeation of KP-T was higher than that of MILTAX® in the in vitro study but no significant difference regarding the tissue distribution was apparent in the in vivo study. The discrepancy may be explained by the indirect distribution via the blood circulation.

Safety evaluation of MILTAX®

1. Primary and 7-days cumulative skin irritation in rabbits

The backs of male rabbits (Kitayama Rabes, Japan) at 18 weeks of age were clipped free of hair with electric clippers the day before the start of the experiment and patches cut to 2.5×2.5 cm² were applied. In the primary irritation test, they were removed 24 hour after application, the site was lightly wiped with a wad of cotton soaked with lukewarm water, allowed to stand for 30 min, and then observed. It was further observed 48 and 72 hour after application. Skin irritation was evaluated according to the criteria of Draize et al., and a primary irritation index (P. I. I.) was calculated from scores after 24 and 72 hour of application. In the 7-day cumulative irritation test, the period of exposure was 6 hour on each day. The sites were observed every day 30 min and 24 hour after the patch removal and observation was continued until 72 hour after the last application of the patch. Skin irritation was evaluated according to the criteria mentioned above, and the sum total of daily mean skin irritation indices was calculated as a cumulative skin irritation index.

As shown Fig. 10, P. I. I. of MILTAX® and KP-T were similar or lower than that of JP plaster in rabbits. Moreover, the cumulative skin irritation indices of MILTAX® and KP-T were significantly lower. In our recent study in human, since the amount of stripped stratum corneum with KP-T was higher than with MILTAX®, the bio-adhesive strength of the latter was concluded to be lower. A clear relationship existed between the amount of stripped stratum corneum and skin moisture after KP-T removal, but this was not found with MILTAX® because of its hydration effects. Peeling intensity, one parameter to predict pain at the time of patch removal, was higher with the KP-T. Regarding mechanical conditions, when the patch is removed, it should be as slowly as possible and horizontally, to avoid rise in skin temperature. Finally, when a patch is applied to a region with little skin moisture, the amount of stripped stratum corneum may increase accordingly.

2. Clinical evaluation of MILTAX®

MILTAX® has been marketed since 1988, and is well established to be effective for the following: osteoarthritis, scapulohumeral periartthritis, tendinitis and peri-tendinitis, epicondylitis humeri, muscle pain and pain after trauma, with improvement values of approximately 58.3, 55.7,
References

17) Sugiyayashi K: Theoretical consideration for enhanced transermal delivery. Yakubutsu-doutai (Japanese) 2:

3. Conclusions

MILTAX® has been used for more than 15 years, and the formulation has been changed several times to improve the quality of the patch and reduce the side effects. For example 1-menthol is now included as a suitable skin permeation enhancer. MILTAX® features the cross-linking between aluminum and sodium polyacrylate, this being controlled by the pH of the patch and the amount of admixed disodium edetate. Ketoprofen exists in micelles with PST in the patch and these may improve drug release, skin permeation, and bio-adhesion. Direct transfer from the skin to the target tissue is the major route of action. There was no significant difference between the poultice-type type patch, MILTAX®, and the tape-type patch, KP-T, on primary and cumulative skin irritation in rabbits. However, the amount of stripped stratum corneum with MILTAX® and other adhesive parameters were found to be lower KP-T. While KP-T exhibited greater skin permeation of ketoprofen than MILTAX® in vitro, this was due to a higher drug concentration in the patch. However, in the in vivo study, there was no significant difference between the MILTAX® and KP-T cases with regard to muscle distribution.

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