Development of Transdermal Therapeutic Formulation of CNS5161, a Novel N-Methyl-d-aspartate Receptor Antagonist, by Utilizing Pressure-Sensitive Adhesives I

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The aim of this study was to investigate the feasibility of percutaneous absorption of CNS5161, a novel N-methyl-d-aspartate (NMDA) receptor antagonist developed as a potential treatment for neuropathic pain and other neurological disorders. Six pressure-sensitive adhesives (PSA) with different physicochemical properties, namely, styrene–isoprene–styrene (1) (SIS(1)), styrene–isoprene–styrene (2) (SIS(2)), silicone, acrylate with a hydroxyl group (acrylate(OH)), acrylate without a functional group (acrylate(none)) and acrylate with a carboxyl group (acrylate(COOH)), were investigated for their release of CNS5161 and its subsequent skin permeability. Among the adhesives examined, silicone PSA provided the highest value of transdermal flux of CNS5161, which could be attributable to the highest release rate from it due to its very high thermodynamic activity. Although CNS5161 was also in the supersaturated state in SIS(1) and SIS(2) PSAs, the release and transdermal permeation from these adhesives were slower than those from silicone PSA. As for the acrylic PSAs, the highest release rate and permeability of CNS5161 were observed for acrylate(OH) PSA, followed by acrylate(none) and acrylate(COOH) PSAs, but none of them was better in terms of either the release or the permeability of CNS5161 than silicone PSA. These results clearly indicated that silicone PSA would be the most suitable for transdermal delivery of CNS5161 and silicone PSA containing 10% CNS5161 would be suitable for clinical use in humans.

Key words CNS5161; transdermal; pressure-sensitive adhesive; release; permeability; supersaturated state

CNS5161 [N-(3-methylthiophenyl)-N’-(2-chloro-5-methylthiophenyl)-N-methyl guanidine] is a novel N-methyl-d-aspartate (NMDA) receptor antagonist for the potential treatment of neuropathic pain, such as that associated with diabetic neuropathy, post-herpetic neuralgia and post-operative traumatic stress. It has been under clinical development at PAION UK Limited. The chemical structure of CNS5161 HCl is shown in Fig. 1.²

CNS5161 has a potent analgesic effect as an NMDA receptor antagonist and it can block central sensitization and reduce pain hypersensitivity. Furthermore, CNS5161 has significantly less potential to exhibit psychotropic side effects because of non-competitive inhibition of the NMDA subset of glutamate receptors in the mammalian brain; while other NMDA receptor antagonists including ketamine for the treatment of intractable neuropathic pain and dextromethorphan for the treatment of diabetic neuropathy²,⁵ have psychotropic side effects and are not ideal drug candidates for the treatment of neuropathic pain.⁶ To date, the analgesic efficacy of CNS5161 in the treatment of neuropathic pain has been evaluated after intravenous administration in clinical trials. However, as the biological half-life of CNS5161 is very short (2.95 h),⁷ other administration routes would be potentially beneficial for the prolongation of the analgesic effect and patient acceptability. It would be easy for patients to accept oral administration, but this has several possible disadvantages, such as intestinal and/or hepatic first-pass elimination, high variance in bioavailability due to variable condition of gastrointestinal tract, difficulty in long-term and rate-regulated absorption and impossibility of arbitrary drug input and its interruption.⁸ In fact, it has been found that CNS5161 is subject to a significant hepatic first-pass effect and has low bioavailability,² suggesting that oral administration would not be suitable for CNS5161.

Another alternative route of administration would be dermal application. The transdermal delivery system would provi--de the following advantages: (1) intestinal and/or hepatic first-pass elimination is avoided; (2) side effects can be reduced by regulating plasma levels of drugs; (3) drugs can be delivered at an arbitrarily controlled rate over a long period, which is, therefore, suitable for drugs with a short half-life; (4) the application is convenient and discontinuance of drug absorption is also easy.

For development of a transdermal delivery system, selection of a suitable adhesive is one of the most important factors together with choice of drug because the physicochemical properties of pressure-sensitive adhesives (PSA) can significantly affect transdermal flux of a drug from PSA.⁸—¹² Generally, rubber PSA like styrene-isoprene-styrene block co-polymers, acrylic PSA obtained by copolymerization of a variety of acrylic monomers and silicon PSA are widely used for developing the transdermal delivery system, but the release and skin permeability of a drug from these PSAs and their skin adhesion must be examined before selecting PSA for a given drug.

Therefore, in the present study, we investigated the feasibil-
ity of percutaneous absorption of CNS5161 by evaluating the release and skin permeability of CNS5161 from six PSAs with different physicochemical properties and tried to find the best adhesive for developing a transdermal delivery system for CNS5161.

MATERIALS AND METHODS

**Materials** CNS5161HCl was provided by PAION UK Limited (formerly CeNeS Limited) (Cambridge, U.K.). (±)-Methoxyverapamil hydrochloride, an internal standard, was purchased from Merck Japan (Tokyo, Japan). Styrene–isoprene–styrene block co-polymer (SIMS) was purchased from ZEON Corporation (Tokyo, Japan). Acrylic PSA solutions in ethyl acetate, DURO-TAK 87-9301, 387-2516 and 87-2194, were kindly donated by the National Starch and Chemical Company (Tokyo, Japan). Silicone PSA solution in ethyl acetate, BIO PSA 7-4602, was kindly donated by Dow Corning Toray Co., Ltd. (Tokyo, Japan). Polybutene was purchased from Nippon Oil Corporation (Tokyo, Japan). Alicyclic saturated hydrocarbon resin was purchased from Kaneda Corporation (Tokyo, Japan) and Wako Pure Chemical Industries, Ltd. (Osaka, Japan), respectively. Frozen human back skin specimens, which were from 4 male Caucasians (80—96 years) and approximately 10×10cm in size, were obtained from the non-profit Human and Animal Bridging Research Organization (Tokyo, Japan). The frozen skin specimens were stored at −80°C until the permeation study. All other chemicals used in the present study were of analytical reagent grade and used without any further purification.

**Animals** Male Wistar rats (Japan SLC, Hamamatsu, Japan), maintained at 23°C and 55% humidity, were allowed free access to standard laboratory chow and water prior to the experiment. Rats weighing 200—250g were randomly assigned to each experimental group. Our investigations were performed after approval by our local ethics committee at Teikoku Seiyaku and Okayama University.

**Preparation of CNS5161 Base** CNS5161 base was prepared in our laboratory as follows. 8N NaOH was added to aqueous solution of CNS5161 HCl (approximately 7mg/mL). The aqueous solution was saturated with sodium chloride and the free base was extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and then evaporated to dryness under reduced pressure using a rotary evaporator. By adding hexane to the residue, crystallization of CNS5161 base was performed and the obtained crystal was dried for several hours under reduced pressure. Purity of CNS5161 base was determined by HPLC with a UV detector and by sharpness of the endothermic peak in differential scanning calorimetry (DSC) to be over 99.9%.

**Evaluation of Solubility in Aqueous Vehicle** Solubility studies were conducted by adding excess amounts of CNS5161 base or its HCl salt into 10mL of distilled water or phosphate-buffered saline (PBS, pH 7.4) in screw-capped vials. The tightly sealed vials were shaken in a water bath set at 37°C for 48h. It was confirmed that 48-h incubation was sufficient for the compounds to reach saturation in the vehicle. Then, after each suspension was filtered through a 0.45-μm filter, concentrations of CNS5161 base or its HCl salt in filtrates were determined by HPLC after appropriate dilution.

**Preparation and Characterization of Pressure-Sensitive Adhesive Matrices** Acrylic PSA solution in ethyl acetate and silicone PSA solution in ethyl acetate were used as received. SIS(1) PSA solution was prepared by dissolving appropriate amounts of SIS and polybutene in toluene for several hours at 70°C. SIS(2) PSA solution was obtained by dissolving appropriate amounts of SIS, polybutene, mineral oil, alicyclic saturated hydrocarbon resin and dibutylhydroxytoluene in toluene for several hours at 70°C. A fixed amount of CNS5161 base was added to each adhesive solution and was completely dissolved or dispersed uniformly in each solution. Then, the adhesive solution was cast at a thickness of 100μm on a surface of polyester liner. The films were oven-dried at 60—100°C for 10—15min to remove any residual solvent and the resultant dried films were then laminated with polyester films.

**Evaluation of Solubility in Pressure-Sensitive Adhesive Matrices** Saturation solubility of CNS5161 base in the adhesives was measured by FT-IR (ATR method). After an adhesive without the drug was put on the detecting element of FT-IR, a given amount of CNS5161 base was placed on the adhesive. Then, the change in intensity of a specific peak derived from CNS5161 was observed at predetermined time by increasing the amount of CNS5161 base placed on the adhesive. The total amount of CNS5161 added on the adhesive when the intensity reached a constant value was determined to be the saturation solubility.

For PSA matrices where the solubility of CNS5161 could not be measured by FT-IR, the crystal seeding method was applied as described below. Briefly, adhesives containing various concentrations of CNS5161 base were prepared as described in Section 2.5. Then, CNS5161 base powder was put on the adhesives. The saturation solubility was judged by the crystal growth of CNS5161 base using polarized microscopy.

**Microscopic Observation of Crystal** Crystal conditions of CNS5161 base on the surface of adhesives were observed using polarized microscopy (Digital Polarized Microscope VHX600, KEYENCE CORPORATION, Osaka, Japan).

**Differential Scanning Calorimetric Analysis** Differential scanning calorimetric (DSC) experiments were performed on each adhesive using a Pyris 1 DSC (Perkin Elmer Japan Co., Ltd., Kanagawa, Japan). Samples were heated at the rate of 20°C/min from 40 to 220°C under a nitrogen atmosphere at a flow rate of 10mL/min. The presence of CNS5161 crystal in adhesives was confirmed by the presence of an endothermic peak.

**Adhesive Test** The 180° peel test was performed using a RHEO METER CR-500DX (SUN SCIENTIFIC Co., Ltd., Tokyo, Japan) on adhesive-coated tapes with 10-mm width. After putting adhesive-coated tapes on a board made of phenol resin, they were stored at 37°C for 30min. Peel force in the 180° direction was measured at a peel rate of 300mm/min at room temperature. The test was conducted three times for each sample.

**In Vitro Drug Release Studies** The release of CNS5161 from adhesives was characterized using Franz-type diffusion cells. The adhesive of a given area attached to a glass slide was placed on a Franz-type diffusion cell with 10mL of PBS (pH 7.4) at 37°C. At designated time intervals, 200μL of the
receptor fluid buffer was sampled and an equal volume of fresh PBS was immediately added to the diffusion cell. The concentrations of CNS5161 were determined by HPLC as described below. The release profiles were found to follow the matrix-diffusion kinetics model, where cumulative amounts of drug released per unit of area (Q) were proportional to the square root of time \((t^{1/2})\). Therefore, the obtained profiles were analyzed by Higuchi’s square-root kinetics equation described below:

\[
Q = k_h \cdot t^{1/2} \quad (\mu g/cm^2)
\]

where \(k_h\) stands for Higuchi’s rate constant.

**In Vitro Skin Permeation Studies** Rat dorsal skin or human back skin was used as a model membrane for skin permeation studies of CNS5161 from adhesives. In the case of rat skin, after the hair of rat was removed with an electric clipper (Okayama Daito Electrical Appliance Co., Ltd., Okayama, Japan) and a shaver (BRAUN, Tokyo, Japan), a piece of skin was excised from the dorsal region and subcutaneous fat and connective tissue were carefully removed from the isolated skin. In the case of human skin, frozen human skin specimens were thawed at room temperature for 5 h and the subcutaneous fat and connective tissues were carefully removed from the skin. Then, the skin was placed on a flow-through Franz-type diffusion cell, of which the effective diffusion area was 1.77 cm\(^2\), with a minor modification where the receiver fluid (PBS, pH 7.4) was circulated between the receiver compartment of the cell (10 mL) and a temperature-controlled reservoir. During the circulation, an aliquot of the receiver fluid was sampled at predetermined intervals using an automatic fraction collector (CHF100AA, ADVANTEC, Tokyo, Japan). The temperature of the diffusion cells was maintained at 37±0.5°C with a circulating water pump.

The samples were assayed for CNS5161 using the HPLC system as described below. Cumulative amount permeated to the receiver compartment was calculated at each time point and the steady-state flux \((J_{SS})\) of CNS5161 was then determined from the linear portion of the cumulative amount permeated versus time profile for each experiment by following Fick’s first law of diffusion:

\[
J_{SS} = (dQ / dt) / S = K_p \cdot C_0 \quad (\mu g/cm^2/h)
\]

where \(dQ/dt\), \(S\), \(K_p\), and \(C_0\) are the permeation rate at a steady state (\(\mu g/h\)), effective diffusion area (cm\(^2\)), apparent permeability (cm/h) and initial concentration of CNS5161 (\(\mu g/cm^2\)), respectively. \(J_{SS}\) was obtained as the slope of the apparently linear portion in the cumulative amount permeated–time profile. The lag time was determined as an intercept on the axis of time by extrapolating the linear portion of each permeation curve.

**Assay Procedure** Concentrations of CNS5161 were assayed using the HPLC system (LC-2010C, Shimadzu, Kyoto, Japan) equipped with an ODS column (ODS-AM, YMC, Kyoto, Japan). The mobile phase consisting of water–acetonitrile–tetrahydrofuran–sodium 1-dodecylsulfate–triethylamine–phosphoric acid (1375:1000:125:5.5:5:1, v/v/v/w/v/v) was delivered at a flow rate of 0.55 mL/min. UV detection was performed at 254 nm. Standard curves for CNS5161 (0.1—500 \(\mu g/mL\)) gave a coefficient of variance (CV) ranging from 0.07 to 0.14%. The squared correlation coefficient was over 0.999.

**Statistical Analysis** Results are expressed as the mean±S.D. of more than three experiments. Analysis of variance (ANOVA) was used to test the statistical significance of differences among groups. Statistical significance of the differences of the means was determined by Dunnett’s method or Student’s \(t\)-test.

**RESULTS AND DISCUSSION**

**Physicochemical Properties of CNS5161 Base and Its HCl Salt** The physicochemical properties of CNS5161 base and its HCl salt are summarized in Table 1. Molecular weights of CNS5161 base and its HCl salt are 352 and 388, respectively. Since a low molecular weight, less than 600Da, was suggested to be one of the ideal properties of drugs for transdermal absorption, both of the two compounds would be adequate in terms of molecular weight. Melting points of CNS5161 base and its HCl salt were determined to be 66 and 210°C, respectively, indicating that the melting point of CNS5161 base was extremely low compared with that of its HCl salt. The octanol–water partition coefficient \((K_{O/W})\) and octanol–PBS partition coefficient \((K_{O/PBS})\) of CNS5161 base

| Table 1. Physicochemical Properties of CNS5161 Base and Its HCl Salt |
|-----------------|------------|------------|
| Property        | Base       | HCl        |
| M (g/mol)       | 352        | 388        |
| Melting point (°C) | 66        | 210        |
| K\(_{O/W}\)     | 471.3      | 1.0        |
| K\(_{O/PBS}(pH 7.4)\) | 752.9     | 48.4       |
| Solubility at 37°C (mg/mL) |           |            |
| in water        | 0.035      | 27.4       |
| in PBS (pH 7.4) | 0.099      | 9.0        |

\(M\) is relative molar mass. \(K_{O/W}\) and \(K_{O/PBS}(pH 7.4)\) stand for the partition coefficients between octanol and water or phosphate-buffered saline (pH 7.4), respectively.
were about 471 times higher and 16 times higher than the corresponding values of its HCl salt, respectively. In contrast, the aqueous solubility of CNS5161 base was considerably lower than that of its HCl salt. These values indicate that the free base of CNS5161 is much more lipophilic than its HCl salt. The logarithm of \( K_{O/W} \) or \( K_{O/PBS} \) of CNS5161 base is 2.7 or 2.9, respectively. Since drugs with moderate lipophilicity such as \( \log K_{O/W} 2-3 \) were shown to be advantageous for skin permeation,14–17 CNS5161 base should be more favorable for skin permeation than its HCl salt. In a preliminary study, the permeability of CNS5161 base and its HCl salt across isolated rat dorsal skin was examined with side-by-side diffusion cells by applying the aqueous saturated solution. As a result, the permeability coefficient, \( K_p \), of CNS5161 base, 3.3±0.8 \((\times10^{-3})\) cm/h, was found to be significantly higher, specifically, 104 times higher \((p<0.01, n=4)\), than that of its HCl salt, 3.2±1.6 \((\times10^{-3})\) cm/h. The \( K_p \) value of CNS5161 base is comparable to \( 1.02\times10^{-3}\) cm/h calculated from the following equation: 
\[
\log K_p \text{ (cm/s)} = -6.3 + 0.71 \times \log K_{O/W} - 0.0061 \times M_w, \]
reported by Potts and Guy,18) which indicates that CNS5161 base is a reasonable and suitable compound for transdermal absorption as expected from its good physicochemical properties such as low molecular weight, low melting point and adequate \( \log K_{O/W} \). Therefore, further studies were conducted using CNS5161 base to prepare a suitable patch for CNS5161 to achieve a desired systemic effect.

**Physicochemical Properties of Pressure-Sensitive Adhesive Matrices** Six PSAs were prepared using SIS, silicone and acrylic PSA matrices with different physicochemical properties. The amount of CNS5161 base in each prepared PSA was 10% of the weight of the adhesive polymer, which was determined by considering the practical size of a patch for achieving 3-d-long therapeutics. The thickness of each PSA was determined by considering the practical size of a patch by Potts and Guy,18) which indicates, \( 0.01, n=4 \), that the absorption would be supersaturated as an amorphous form in these PSAs. It has been reported that drugs were supersaturated as an amorphous form in PSAs when PSAs were prepared by evaporating organic solvent where drugs and ingredients for PSAs were dissolved,21–23 indicating that it would be also the case with CNS5161. Furthermore, it was confirmed that the supersaturation of CNS5161 at 10% in silicone PSA was maintained at least for 6 months at room temperature, while crystallization was observed for SIS(1) and SIS(2) PSAs after around 2 and 4 months, respectively. The long term supersaturation of CNS5161 in silicone PSA would be advantageous for

<table>
<thead>
<tr>
<th>PSA</th>
<th>Detail</th>
<th>State of drug in adhesive</th>
<th>Appearance of adhesive</th>
<th>Solubility in adhesive (%a)</th>
<th>CNS5161 contained (mg)c</th>
<th>Adhesive strength (g/cm2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIS(1)</td>
<td>Styrene-isoprene-styrene block co-polymer containing polybutene</td>
<td>Supersaturated (dissolved)</td>
<td>Pale</td>
<td>3% (a)</td>
<td>10.2±0.1</td>
<td>15.6±8.2</td>
</tr>
<tr>
<td>SIS(2)</td>
<td>Styrene-isoprene-styrene block co-polymer containing polybutene, allycyclic saturated hydrocarbon resin, mineral oil, dibutylhydroxytoluene</td>
<td>Supersaturated (dissolved)</td>
<td>Pale</td>
<td>1% (a)</td>
<td>10.2±0.1</td>
<td>720.7±103.2</td>
</tr>
<tr>
<td>Silicone</td>
<td>BIO PSA 7-4602</td>
<td>Supersaturated (dissolved)</td>
<td>Pale</td>
<td>1% (a)</td>
<td>10.1±0.1</td>
<td>338.5±13.3</td>
</tr>
<tr>
<td>Acrylate(none)</td>
<td>DURO-TAK 87-9301</td>
<td>Dissolved</td>
<td>Transparent</td>
<td>12% (b)</td>
<td>10.3±0.1</td>
<td>505.2±67.5</td>
</tr>
<tr>
<td>Acrylate(OH)</td>
<td>DURO-TAK 387-2516</td>
<td>Dissolved</td>
<td>Transparent</td>
<td>13% (b)</td>
<td>10.2±0.1</td>
<td>1205.1±57.7</td>
</tr>
<tr>
<td>Acrylate(COOH)</td>
<td>DURO-TAK 87-2194</td>
<td>Dissolved</td>
<td>Transparent</td>
<td>22% (b)</td>
<td>10.1±0.1</td>
<td>494.2±18.9</td>
</tr>
</tbody>
</table>

The amount of CNS5161 used to prepare PSAs of 10cm² was 10.10±0.02 mg. Adhesive strength was measured by 180° peel test and the results are shown as the mean±S.D. \((n=3)\). The solubility of CNS5161 base in each adhesive was determined by either a) crystal seeding method or b) measured by FT-IR (ATR method). c) CNS5161 amount contained in 10cm² PSA.
transdermal therapeutic formulation of CNS5161.

Although the adhesive strength of SIS(1) PSA was very weak due to the styrene-isoprene-styrene contained in it, other PSAs were strong enough in terms of adhesive strength for practical use, since they showed an adhesive strength over 150 g/cm, which is a criterion of adhesive strength for adhesive plasters in 14th Japanese Pharmacopoeia (Part II, p. 858). In particular, a high peel value, 1205 g/cm, was observed for acrylate(OH) PSA, but if the adhesive strength is too strong, it could cause skin irritation by stripping the skin when an adhesive is removed from the skin.24)

**Release of CNS5161 Base from Pressure-Sensitive Adhesive Matrices** The release kinetics of CNS5161 from PSAs containing 10% CNS5161 base was investigated by utilizing Franz-type diffusion cells. As shown in Fig. 3, the cumulative amounts released–square root of time plots, Higuchi’s plots, provided straight lines with very good linearity for all the preparations examined, indicating that the release of CNS5161 base from these PSAs should be regulated by the diffusion within PSAs. The release kinetics of CNS5161 base from PSAs was evaluated by calculating Higuchi’s release rate constant, $k_H$ (Table 3). The value of $k_H$ obtained from silicone PSA was significantly higher than the others, and that from SIS(1) PSA followed it among the PSAs examined in the present study. The two PSAs containing CNS5161 base in an amorphous state, with the exception of SIS(2), showed very fast release, indicating that high thermodynamic activity in the PSA was advantageous for the fast release for silicone and SIS(1) PSAs. Since the thermodynamic activity of drug in the vehicle is approximately proportional to the ratio of the drug concentration to the solubility in the vehicle,25) the supersaturated condition enables the thermodynamic activity to be greater than unity.7) Even though neither the solubility nor the thermodynamic activity in SIS(2) PSA was so different from that in other PSAs, the release rate of CNS5161 base from SIS(2) PSA was around two-fifths of that of SIS(1) PSA, which was explained by the interaction of CNS5161 base with additional ingredients such as alicyclic saturated hydrocarbon resin, mineral oil and dibutylhydroxytoluene added to SIS(2) PSA. Hydrophobic interaction of C–H bonds of CNS5161 with those of alicyclic saturated hydrocarbon resin and/or mineral oil, and π–π interaction between benzene ring of CNS5161 and that of dibutylhydroxytoluene would be possible interactions to delay the release of CNS5161 from SIS(2) PSA.

On the other hand, the thermodynamic activity of CNS5161 base in acrylic PSAs was less than unity, since the values of solubility were more than 10%. However, the $k_H$ value of CNS5161 base from acrylate(OH) PSA was almost the same as, and that from acrylate(none) PSA was comparable to that from SIS(1) PSA, suggesting the relatively low affinity of CNS5161 base to acrylic PSAs, with the exception of acrylate(COOH) PSA. In the case of acrylate(COOH) PSA, the release of CNS5161 base was significantly lower ($p<0.01$) than those from other acrylic PSAs, which could be attributable to the low thermodynamic activity in it, around half of those in other acrylic PSAs, and to the interaction between the carboxyl group of acrylate(COOH) and the secondary amine group of CNS5161 base, as is the case with tacrine, a centrally acting acetylcholine esterase inhibitor, reported by Kim et al.26) Therefore, the functional group that the adhesive includes is an important factor for selecting an appropriate adhesive matrix.26)
**Effect of Pressure-Sensitive Adhesive Matrices on Skin Permeation of CNS5161 Base**  
The effects of PSAs on the permeation of CNS5161 were investigated for SIS(1), SIS(2), silicone, acrylate(none), acrylate(OH) and acrylate(COOH) PSAs containing 10% CNS5161 base (Fig. 4 and Table 4). Cumulative amount permeated–time courses clearly indicate that silicone PSA provided the fastest transdermal permeation of CNS5161 base and was followed by SIS(1) PSA (Fig. 4). Steady-state fluxes and $K_p$ values calculated from Fig. 4 also indicate that silicone PSA is the most favorable for the transdermal absorption of CNS5161 base, although there was no significant difference in lag time among all the preparations examined. This result coincides with that of release study shown in Fig. 3 and Table 2, indicating that the highest release rate due to very high thermodynamic activity in silicone PSA was reflected in the transdermal permeation from silicone PSA.\(^\text{25,27,28}\) This would also be the case with SIS(1) PSA, as the relationship between skin permeation and release from PSA. \(^\text{25} \)

The permeation rate of CNS5161 base from SIS(2) PSA was almost the same as that from acrylate(OH) PSA, which was then followed by acrylate(none) and acrylate(COOH) PSAs. These adhesives including silicone and SIS(1) PSAs, with the exception of SIS(2) PSA, provided almost the same value, around $3 \times 10^{-2} \text{h}^{1/2}$, of the permeation/release index, meaning that skin permeation flux was proportional to $k_f$. This result indicates that the skin permeation of CNS5161 base would be regulated by its release rate from these adhesives, which would be the reason why the skin permeation rates from PSAs were much lower than that from solution. In the case of SIS(2) PSA, the permeation/release index, $6.6 \times 10^{-2} \text{h}^{1/2}$, was greater than those of other PSAs. Although the reason for this remains to be clarified, it might be attributable to the discrepancy between the actual release of CNS5161 base in the permeation study and that observed in the release study. Since SIS(2) PSA contains several hydrophobic ingredients that are not in the other PSAs, the affinity between CNS5161 base and SIS(2) PSA is quite high. Therefore, its release was the second lowest following acrylate(COOH) PSA, which has a strong electrostatic interaction with CNS5161 base, in the release study where the PSAs were in contact with highly hydrophilic PBS (Fig. 3, Table 3). On the other hand, since the PSAs were directly placed on the isolated skin and facing the hydrophobic stratum corneum in the permeation study, the partition and release of CNS5161 base from SIS(2) PSA into the skin would be promoted more than expected from the results of the release study.

The effects of the loading concentration (10, 15, 20, 25, 30, 35, 40%) of CNS5161 base on the permeation flux were preliminarily examined for acrylate(OH) PSA because acrylate(OH) PSA provided high solubility of CNS5161 base in it and relatively high release and skin permeation rates. The state of CNS5161 in the PSA was supersaturated above 15% loading. The highest skin permeation flux, $11.5 \pm 2.2 \text{µg/cm}^2/\text{h}$ ($n=4$), was obtained for 40% CNS5161 base, but it was almost the same as that of silicone PSA containing 10% CNS5161 base, also indicating the usefulness of silicone PSA for CNS5161 base.

The results obtained in the present study clearly indicated that silicone PSA would be the most adequate for CNS5161 base among all the PSAs examined, while the lag time was still quite long. Then, to obtain some information about the long lag time, the amount of CNS5161 in the skin as well as its permeated amount was sequentially monitored (Fig. 5). The result shows that the drug already penetrated into the skin at $55.2 \text{µg/cm}^2$ at 6h after the skin permeation study started. The amount in the skin is not much lower than that at steady state, $111.2 \text{µg/cm}^2$, but the cumulative transport of the drug until 6h was only $3.7 \text{µg/cm}^2$. This result suggests that this compound would need the higher skin concentration that would be able to facilitate the partition from the skin to phosphate buffer and/or the diffusion through the skin because of its high lipophilicity, and that it would take a relatively long time for

![Fig. 4. Skin Permeation of CNS5161 Base from Pressure-Sensitive Adhesives Containing 10% CNS5161 Base](image)

Cumulative permeated amounts of CNS5161 base are expressed as the mean with the bar showing S.D. values of four experiments. Key: ● SIS(1); ○ SIS(2); ■ silicone; □ acrylate(none); ▲ acrylate(OH); Δ acrylate(COOH).

### Table 4. Steady-State Flux of CNS5161 Base through Rat Skin from Pressure-Sensitive Adhesives Containing 10% CNS5161 Base

<table>
<thead>
<tr>
<th>PSA</th>
<th>Steady-state flux ($\mu$g/cm$^2$/h)</th>
<th>Permeability coefficient, $K_p \times 10^{-3}$ (cm/h)</th>
<th>Lag time (h)</th>
<th>Permeation/release index ($h^{1/2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIS(1)</td>
<td>$7.5 \pm 1.1^{**}$</td>
<td>$7.5 \pm 1.1^{**}$</td>
<td>$13.0 \pm 1.7$</td>
<td>$3.3 \times 10^{-2}$</td>
</tr>
<tr>
<td>SIS(2)</td>
<td>$5.7 \pm 0.4^{**}$</td>
<td>$5.7 \pm 0.4^{**}$</td>
<td>$13.9 \pm 2.3$</td>
<td>$6.6 \times 10^{-2}$</td>
</tr>
<tr>
<td>Silicone</td>
<td>$11.4 \pm 1.9$</td>
<td>$11.4 \pm 1.9$</td>
<td>$13.0 \pm 1.8$</td>
<td>$3.4 \times 10^{-2}$</td>
</tr>
<tr>
<td>Acrylate(none)</td>
<td>$4.6 \pm 0.3^{**}$</td>
<td>$4.6 \pm 0.3^{**}$</td>
<td>$11.2 \pm 2.6$</td>
<td>$3.7 \times 10^{-2}$</td>
</tr>
<tr>
<td>Acrylate(OH)</td>
<td>$5.4 \pm 0.6^{**}$</td>
<td>$5.4 \pm 0.6^{**}$</td>
<td>$12.8 \pm 1.7$</td>
<td>$3.1 \times 10^{-2}$</td>
</tr>
<tr>
<td>Acrylate(COOH)</td>
<td>$0.8 \pm 0.1^{**}$</td>
<td>$0.8 \pm 0.1^{**}$</td>
<td>$13.5 \pm 2.1$</td>
<td>$2.7 \times 10^{-2}$</td>
</tr>
</tbody>
</table>

Steady-state flux and lag time were determined on the basis of cumulative amount permeated–time profile shown in Fig. 4. Results are shown as the mean±S.D. ($n=4$). Permeation/release index was obtained by dividing the steady-state flux by Higuchi’s release rate constant, $k_f$, shown in Table 3. **p<0.01, compared with silicone.
and Human Pressure-Sensitive Adhesive Containing 10% CNS5161 Base between Rat and Human skins. The skin permeation rate for human skin was 3.3 ± 0.2 μg/cm²/h, which was about 30% of the rate obtained for rat skin (11.1 ± 3.6 μg/cm²/h). On the other hand, the lag time, 7.2 ± 3.0 h, was shorter than that for rat skin (13.3 ± 2.5 h), which would be acceptable, considering its 3-d-long therapeutic use. The difference in skin permeability between human and rat would be ascribed to the difference in skin thickness and lipid content of skin surface including stratum corneum. Among the six preparations examined, silicone PSA provided the highest skin permeation rate dependent on the highest release rate due to very high thermodynamic activity because CNS5161 should be absorbed stably supersaturated in silicone PSA. Silicone PSA would be the most favorable for the development of a transdermal therapeutic system of CNS5161 and silicone PSA containing 10% CNS5161 would be suitable for 3-d-long clinical use in humans.

### CONCLUSION

Six PSAs with different physicochemical characteristics were evaluated to develop a transdermal therapeutic formulation of CNS5161, a novel NMDA receptor antagonist and potential compound for the treatment of neuropathic pain. Among the six preparations examined, silicone PSA provided the highest skin permeation rate dependent on the highest release rate due to very high thermodynamic activity because CNS5161 base was stably supersaturated in silicone PSA. Silicone PSA would be the most favorable for the development of a transdermal therapeutic system of CNS5161 and silicone PSA containing 10% CNS5161 would be suitable for 3-d-long clinical use in humans.

#### Acknowledgements

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#### REFERENCES


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