Permeation Enhancement of Ascorbic Acid by Self-Dissolving Micropile Array Tip through Rat Skin

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Ascorbic acid (AA) loaded self-dissolving micropiles (SDMP) were prepared using chondroitin sulfate as the base for the percutaneous administration of AA. AA solution was added to dense solution of chondroitin solution, glue, and array tip, 1.0 cm^2, containing 100 SDMPs of which length was 500 μm and basal diameter was 300 μm, were prepared. Two kinds of AA array tips containing 1344.2±1.7 μg (high content ones) and 638.7±4.3 μg (low content ones) were used. *In vitro* dissolution study showed that more than 90% of AA were released from both SDMP array tips within 5 min. Stability experiment showed that 99.2—99.4% of AA was detected in SDMP array tips when stored at 23 °C for 1 week. When *in vitro* permeation experiments were performed after AA SDMP array was inserted to the isolated rat abdominal skin, extremely high amounts of AA, 1285.3±369.0 μg (95.3%) for high content SDMP tip and 405.6±84.3 μg (65.8%) for low content SDMP tip, were permeated for 6 h into the receptor compartment due to the break down of the skin barrier function. When AA SDMP array tip was administered to the rat skin under anesthetized condition with the different contact times, 10, 20 and 30 min, the permeated amount of AA was dependent on both the AA content in SDMP array tips and the contact time. When AA SDMP was contact to the skin for 30 min, permeated amounts of AA were 146.8±22.9 μg (10.9%) for high content-SDMP tip and 61.2±18.2 μg (9.6%) for low content SDMP tip. These results suggest the usefulness of SDMP array tip for the percutaneous absorption of AA.

Key words micropile; self-dissolving; ascorbic acid; skin permeability; enhancement; rat

Ascorbic acid (AA, vitamin C) is a hydrophilic vitamin that cannot be produced endogenously in rats and primates including human and is widely used for the protection of the aging of the skin due to the exposure to the UV light and for the acceleration of the synthesis of collagen in the skin.[1—4] AA was shown to be absorbed from the gastrointestinal tract by an active transport system, though limited amount of AA was transported by this system.[5] In addition, after AA was absorbed, AA was rapidly eliminated from the body by the oxidative metabolism through both enzymatic and non-enzymatic processes.[2] Therefore, even if we intake excess amount of AA, sufficient amount of AA is not absorbed into the systemic circulation and is not delivered to its target tissue, skin.[2] To conquer this problem, percutaneous delivery of AA has been challenged. The advantage of percutaneous delivery of AA is (1) to obtain high concentration of AA in the skin and (2) to escape the hepatic first-pass effect before reaching to the systemic circulation. However, when AA is percutaneously administered, the penetration of AA to the dermal tissue is difficult because of the high barrier function of the skin. To increase the permeability of AA, derivatives such as 6-*o*-acyl-2-*o*-alpha-D-glucopyranosyl-L-ascorbic acid[6], 2-*o*-α-D-glucopyranosyl L-ascorbic acid (AA-2G),[7] ascorbic acid 2-sulfate[8] and disodium isostearyl 2-*o*-L-ascorbyl phosphate,[9,10] has been developed. Also Gopinath *et al.* designed ascorbyl palmitate vesicles (Aspasomes) for the transdermal delivery of ascorbic acid.[11] Furthermore, recent advances in pharmaceutical technology have promoted the research on the permeability enhancement of AA using physical absorption enhancing method like iontophoresis[12] and microemulsion technologies.[11,13] Iontophoresis uses an electric field to drive ionized molecules across the skin by electrophoresis and non-ionized molecules by electro osmosis.[14] Despite concerns about skin irritation, iontophoresis may be useful to deliver some peptides and small proteins.[15] On the other hand, microneedles are also one of the physical methods for the percutaneous absorption of drugs. With microneedles, small microconduits are formed on the skin. Recent advance in microfabrication technology has made it possible to prepare microneedles that have a possibility of novel transdermal drug delivery system (TDDS). Since the first publication by Henry *et al.*,[16] microfabrication techniques for the production of silicon, metal, glass and polymer microneedle arrays with micrometer dimensions have been developed.[17—20] The microneedles are either solid or hollow and posses a geometrical shape. Microneedle TDDS is roughly defined by a micron size needle preparation for percutaneous administration. Microneedle TDDSs are classified as follows; (1) extremely small needle through which drug solution can be injected into the skin, (2) metallic and/or silastic microneedles on which surface drug is coated, and (3) metallic and/or silastic microneedles by which microconduits are made on the skin and drug solution is applied after removing the microneedles. However, these systems are not pharmaceutical preparation and have some problems. Especially, the allergic problem of metallic and silastic microneedles have not been solved yet.

To overcome these pitfalls, we designed self-dissolving micropile (SDMP) for the percutaneous delivery of hydrophilic macromolecular drugs. SDMPs are composed of water-soluble thread-forming polymer such as sodium chondroitin sulfate, dextran and albumin for the base and active pharmaceutical ingredient that exists as solid dispersion. Those polymers have high safety, because dextran and albumin are clinically used as drugs. Chondroitin sulfate is one of the glycosaminoglycan existing widely in the body including skin, brain and cartilage tissues. When SDMPs are inserted into the skin, microconduits are created for the penetration of drug across the stratum corneum (SC). Once a drug penetrates the SC, it can diffuse rapidly through the deeper tissue

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and permeate into the underlying capillaries for systemic absorption.[21] Kolli and Banga reported that micropiles with a length of 500 μm are applied to the skin and pressed using a finger with a pressure of approximately 0.35—0.5 N, the whole micropile is not inserted into the skin.[22] The usefulness of SDMP was studied with macromolecular compounds such as insulin,[23] low molecular weight heparin (LMWH)[24] and erythropoietin (EPO)[25] from both pharmacokinetic and pharmacodynamic aspects. From these studies, SDMPs were shown to be an effective TDDS for the percutaneous absorption of hydrophilic macromolecular drugs. However, an applicator was needed to be inserted into rat skin. To accelerate the development of SDMP as pharmaceutical preparation, we designed SDMP array tip, 1.0×1.0 cm, on which 100 SDMP arrays with 10 lines and 10 columns were formed.[26] The length and the basic diameter of each SDMP were 500 and 300 μm, respectively. After the SDMP was inserted to rat skin, the dissolution was occurred immediately in the epidermis, and SDMPs were not harmful to the dermis. In this study, the applicability of SDMP array tip to low molecular weight organic compound, AA, and the skin permeability of AA were evaluated in rat.

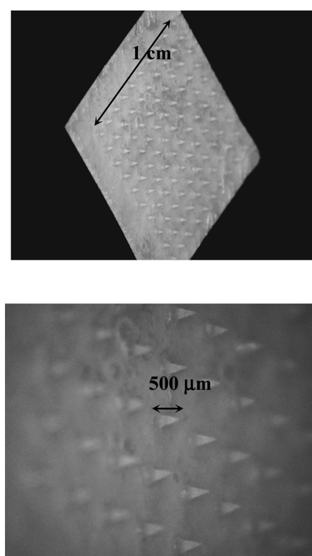

Fig. 1. Photographs of SDMP Array Tip Containing Ascorbic Acid (AA)

One hundred SDMP arrays comprising 10 lines and 10 columns were formed on a 1.0 cm^2 tip. The length of SDMP arrays were 500 μm and one SDMP array tip contained 638.7±27.2 μg of AA.

Experimental

Materials L(+)-Ascorbic acid (AA, vitamin C), dehydroascorbic acid (DHAA) and Hiviswako 103 were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Sodium chondroitin sulfate and acetonitrile were obtained from Nacalai Tesque Inc. (Kyoto, Japan). Male Wistar Hannover rats were obtained from Japan SLC Inc. (Hamamatsu, Japan). All other materials used were of reagent grade and were used as received.

Preparation of SDMP Array Tip Containing AA Two kinds of AA SDMP array tips, high and low AA content, were prepared. For low AA content SDMP array tips, 200 mg of AA and 600 mg of sodium chondroitin sulfate were dissolved with 0.6 ml of distilled water. For high AA content SDMP array tips, 400 mg of AA and 400 mg of sodium chondroitin sulfate were dissolved with 0.6 ml of distilled water. After the mixture was degassed under reduced pressure, it was dispensed into a mold containing 100 inverted cone-shaped wells with an area of 1.0 cm^2. Each well had a depth of 500 μm and a diameter of 300 μm at its top. The mold was covered with a 300 g steel plate. The mixture of AA and polymer was filled into the wells and was dried under the pressure of the stainless steel plate for 3 h. Thereafter, the plate was removed and SDMP array tips were obtained by detaching with a supporting material. The obtained high AA SDMP tip is shown in Fig. 1.

Measurement of AA in SDMP Array Tips One SDMP array tip containing 100 SDMPs was dissolved with 1.0 ml of isotonic phosphate buffer, pH 7.4, and AA content was measured by HPLC method as described below.

***In Vitro* Dissolution Experiment** *In vitro* dissolution experiment was performed using SDMP array tip with 20 ml of 10 mM phosphate buffer, pH 7.4, as the dissolution medium at 23 °C under dark condition. To determine the amount of AA released from SDMP array tip, 0.2 ml of the dissolution medium was collected for the assay at 0, 10, 20, 30, 40, 50 s and 1.0, 1.5, 2.0, 3.0, 5.0, 10.0, 15.0 and 30.0 min and replaced with fresh dissolution medium that was degassed before. To exclude the degradation of AA during the assay process, the obtained sample was immediately injected into the HPLC system. The cumulative released amount of AA from SDMP array tip was defined by the following equation:

$$\text{cumulative amount released} = \left(\sum_{t=0}^{t} M_t / M_{30\,\text{min}} \right) \times 100\%$$

Where M_t is the amount of AA dissolved at time t, and $M_{30\,\text{min}}$ is the dissolved amount of AA at 30 min after the start of the dissolution experiment.

Stability Experiment SDMP array tips were kept under three different conditions, *i.e.* 23, 40 and 60 °C for 1 week. Thereafter, SDMP array tips were dissolved with 20 ml of phosphate buffer, pH 7.4, and AA contents were measured by HPLC method.

***In Vitro* Skin Permeation Experiment with AA Solution** Male Wistar Hannover rats, 308—353 g, were anesthetized with an intraperitoneal injection of sodium pentobarbital, 50 mg/kg. After the hair of the abdominal skin was carefully removed, the stratum corneum was removed by 10 times tape stripping.[27] Thereafter, skin specimens (full-thickness, 3.0×3.0 cm^2 each) were freshly excised from the abdominal region of the rats. The subcutaneous tissue was trimmed and was mounted on the Franz-type diffusion cell at 23 °C.[28] As a control group, rat skin was removed without tape stripping treatment and was used for the permeation experiment. For the skin permeation experiments from AA solution, 100 μl of AA solution was applied to the epidermal surface of the skin. The receptor compartment was filled with 20 ml of isotonic phosphate buffer, pH 7.4.[29] Permeation experiment was performed at 23 °C under dark condition and stirred at 600 rpm throughout the experiment. After the start of the experiment, 0.35 ml of assay sample was collected from the receptor compartment over 6 h and was immediately replaced with an equal volume of fresh buffer equilibrated at 23 °C. The obtained samples were centrifuged for 2 min at 14000 rpm and the supernate was immediately used for AA assay to exclude the degradation of AA.

Skin Permeation Experiment of AA from SDMP Array Tip SDMP arrays were inserted to the abdominal skin of anesthetized rats by pressing the tip on the skin by the fingers for 10, 20 and 30 min with a pressure of approximately 0.35—0.5 N,[22] and thereafter the abdominal skin was removed. The excised skin was mounted on the diffusion cell and the permeation experiment was performed as described above. All animal experiments were carried out in accordance with the Guidelines for Animal Experimentation, Kyoto Pharmaceutical University.

HPLC-UV Assay Method of AA One hundred microliters of the AA sample was injected into HPLC system (Shimadzu LC-10A, Kyoto, Japan) equipped with a UV detector (Shimadzu SPD-10A) and a reversed phase column, Chemcosorb 5C18-H (4.6×125 mm, Chemco Scientific Co., Ltd., Osaka, Japan). The mobile phase was the mixture of 0.15 M–KH_2PO_4 and acetonitrile (99.5 : 0.5). The flow rate was 1.0 ml/min and the column temperature was 60 °C. AA eluted from the column was detected at 254 nm. The run time of each assay was 6.0 min and the retention time of AA was 3.5 min.

LC/MS/MS Assay Method of AA To chemically clarify AA on the HPLC chromatogram, the fraction eluted from HPLC-UV system from 3.0 to 4.0 min was collected and was injected to LC/MS/MS system according to the method reported by Frenich *et al.*[30] The LC/MS/MS system consisted of an API 3200 triple quadrupole mass spectrometer equipped with turbo ion spray sample inlet as an interface for electrospray ionization (ESI) and Analyst Workstation (Applied Biosystems, CA, U.S.A.), LC-10AD micropump (Shimadzu, Kyoto, Japan) and AS8020 automatic sample injector (Toso, Tokyo, Japan). The mobile phase of acetonitrile/0.1% formic acid (70 : 30, v/v) was degassed and pumped through a Quicksorb ODS column (2.1 mm i.d.×100 mm, 3 μm, Chemco Scientific Co., Ltd.) at a flow-rate of 0.2 ml/min and column temperature was maintained at 25 °C. The ionization

was *via* the turbo ion spray inlet in the negative ion mode. The flow rates of nebulizer gas, curtain gas and collision gas were set at 8.0, 8.0 and 3.0 l/min, respectively. The ion spray voltage and temperature were set at −4500 V and 500 °C, respectively. The declustering potential, the entrance potential, the collision energy and the collision cell exit potential were set at −25, −6.5, −28 and −1.5 V, respectively. Multiple reaction monitoring analysis was performed with the transition *m/z* 174.9→114.8 for AA.

Statistics All values are expressed as their mean±S.D. Statistical differences were assumed to be reproducible when $p<0.05$ (Student's unpaired *t*-test).

Results and Discussion

SDMP arrays containing AA were formed on a 1.0 cm^2 tip with 10 lines and 10 columns. The AA contents in the prepared SDMP array tips were measured and the results are shown in Table 1. AA contents in the two kinds of SDMP array tips were 1344.2±22.4 μg for high content SDMP and 638.7±27.2 μg for low content SDMP, respectively. Relative standard deviations (RSD) were 1.7% and 4.3%, respectively. As those values were less than 5.0%, the SDMP array tips satisfied the requirement of percutaneous pharmaceutical preparation.

Figure 2 shows the results of *in vitro* dissolution experiment of AA from SDMP array tips. Ho and Chien[31] used pH 5.0 phosphate buffer for the dissolution experiment of nicotine to simulate the skin surface, because they studied the permeation of nicotine through the skin including stratum corneum. As SDMP array tips physically made microconduits on the skin, the barrier function of the stratum corneum against the permeation of AA was lost. Henning *et al.* described that the permeation of drugs through the skin was not dependent on the pH of the medium used for permeation experiment.[32] Therefore, pH 7.4 isotonic phosphate buffer was used as the receptor medium.[29] The dissolution rate of AA from SDMP array tip was very fast and more than 90% of AA was released from SDMP array tips within 5 min after the start of the dissolution experiment. As the dissolution experiment was performed under dark condition and low temperature, 23 °C, we may exclude the degradation of AA during the dissolution experiment.

Figure 3 shows the results of the *in vitro* permeation experiment of AA solution. In the case of intact skin, AA was not detected in the receptor compartment up to 6 h. In other words, the intact skin was revealed to have a strong barrier function against AA. When the stratum corneum was removed by tape stripping, permeated AA was detected in the receptor compartment and the mean cumulative permeated amount of AA for 6 h was 66.5±10.2 μg which corresponded to 6.5% of the applied amount of AA. Thus, tape stripping treatment enhanced the permeation of AA through rat skin.

Figure 4 shows the permeation profiles of AA through the rat skin from two SDMP array tips, where SDMP array were inserted into the excised rat skin and permeation experiment was performed after mounted to diffusion cell. The cumulative permeated amounts of AA for 6 h from the two SDMP

Table 1. AA Content in SDMP Array Tips

No. of tips	AA content [μg]/tip	
	High content SDMP	Low content SDMP
1	1344.6	657.3
2	1366.6	647.2
3	1313.5	651.8
4	1351.9	598.4
Mean±S.D.	1344.2±22.4	638.7±27.2
RSD (%)	1.7	4.3

RSD (%): Relative standard deviation (%).

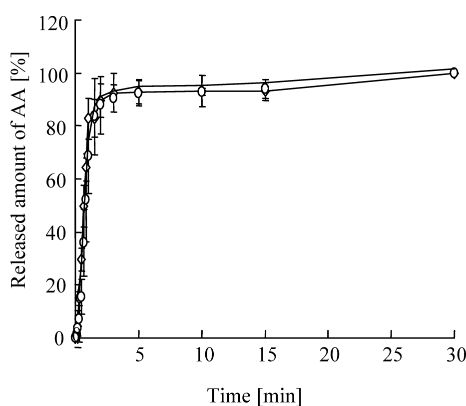

Fig. 2. *In Vitro* Dissolution Profiles of AA from SDMP Array Tip

◇: high AA content (1344.0±22.4 μg) SDMP, ○: low AA content (638.7±27.2 μg) SDMP. Each point shows the mean±S.D. of 3—4 experiments.

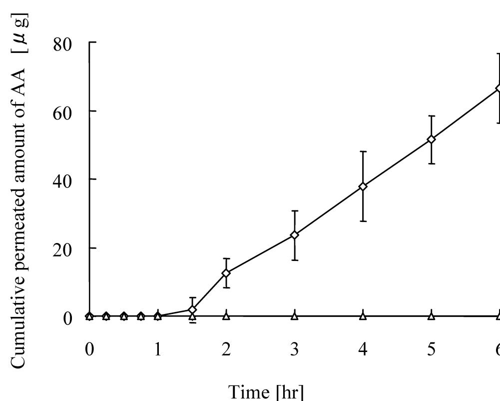

Fig. 3. *In Vitro* Permeation Profiles of AA Solution across Excised Rat Skin

Rat skin specimens (full-thickness, 3.0×3.0 cm^2 each) were freshly excised from the abdominal region of the rats and were used for permeation experiment. ◇: whole skin without stratum corneum, △: whole skin. Each point shows the mean±S.D. of 3—4 experiments.

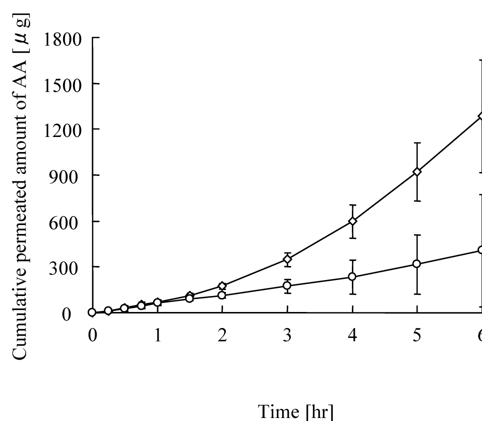

Fig. 4. Permeation Profiles of AA across Excised Rat Skin Following *in Vitro* Insertion of SDMP Array Tip

◇: high AA content (1344.0±22.4 μg) SDMP, ○: low AA content (638.7±27.2 μg) SDMP. Each point represents the mean±S.D. of 3—4 experiments.

array tips were 1285.3±369.0 μg for high content SDMP array tip and 405.6±84.3 μg for low content SDMP array tip, respectively. The permeated %s of AA from SDMP arrays were 95.3% and 65.8%, respectively. As those values were extremely high for the permeation of drugs through the rat skin, the barrier function of the skin was completely broken due to the death of the skin tissue. Therefore, in the next experiment, SDMP array was administered to the anesthetized rat abdominal skin by pressing the tip for 30 min and thereafter the skin was isolated and used for the *in vitro* permeation experiment. The results are shown in Fig. 5. The permeated amount of AA for 6 h were 146.8±22.9 μg for high content SDMP array tip and 61.2±18.2 μg for low content SDMP array tip, which corresponded to 10.9% and 9.6% of the applied amount of AA, respectively. As the permeated % of AA obtained with the tape stripped rat skin was 6.5%, SDMP array showed the stronger enhancing effect on permeability than that with the removal of stratum corneum by tape stripping treatment. To study the effect of contact time of SDMP array tips to the rat skin on the permeation enhancement of AA, the contact time was reduced from 30 min to 20 and 10 min and the results on the permeability experiments using high content SDMP array tip are shown in Fig. 6. The mean permeated amounts of AA decreased to 102.9±13.0 μg (20 min) and 21.6±1.2 μg (10 min), respectively. Thus, the permeability of AA was found out to be dependent on the contact time of SDMP array tip to the rat skin.

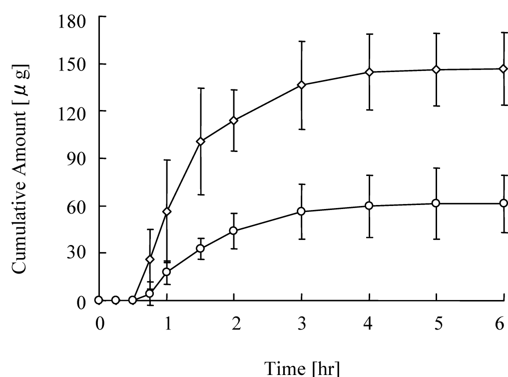

Fig. 5. Permeation Profiles of AA across Excised Rat Skin Following *in Vivo* Insertion of SDMP Array Tip to Rat Skin for 30 min

◇: high AA content (1344.0±22.4 μg) SDMP, ○: low AA content (638.7±27.2 μg) SDMP. Each point represents the mean±S.D. of 3—4 experiments.

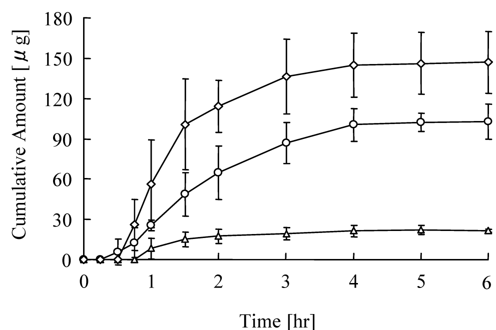

Fig. 6. Effect of Contact Time of SDMP Array Tip to Rat Skin on the Permeation Profiles of AA across Excised Rat Skin Following *in Vivo* Insertion of High AA Content SDMP Array Tip to Rat Skin for (◇) 30 min, (○) 20 min and (△) 10 min

Each point shows the mean±S.D. of 3—4 experiments.

Finally, the stability of AA in SDMP array tips was studied by an *in vitro* experiment. After the storage of AA SDMP array tips under dark condition at 23 °C for 1 week, more than 99% of AA was detected in the tip after the start of the experiment as shown in Table 2. Assay samples were treated immediately just after obtained and were quickly injected into HPLC system in order to prevent the oxidative degradation of AA as less as possible. As Karlsen *et al.* reported that dehydroascorbic acid (DHAA) was the main degradation product of AA under mild condition,[33] DHAA was analyzed in the same HPLC system. However, DHAA was not detected on the HPLC chromatogram, *i.e.* DHAA was not eluted till 10 min on the chromatogram. In addition, the eluted fraction from 3.0 to 4.0 min was collected and was further analyzed by LC/MS/MS system. The chromatographic peak having a retention time of 3.5 min was confirmed to be AA.

The percutaneous absorption of AA has been thought to be impossible because of the strong barrier function of the skin and the extremely hydrophilic property of AA molecules as Lee and Tojo suggested.[34] Teichamann *et al.*[27] showed that the stratum corneum was removed by the 10 times tape stripping operation. Consequently, the permeability of drugs through the skin was enhanced by tape stripping treatment, though the rate of enhancement was dependent on the physicochemical property of drug molecules. In this study, the permeability of AA through rat skin was also enhanced by the tape stripping operation. Therefore, stratum corneum was revealed to be the primary diffusion barrier against AA. On the other hand, when AA SDMP array tip was inserted to the excised rat skin, the barrier function of the skin was completely broken and extremely high permeation efficiencies, 95.3% for high content SDMP array tips and 65.8% for low content SDMP array tips, were obtained. The used SDMP arrays had the length of 500 μm that was longer than the thickness of the epidermis. The epidermal thickness was reported to be 11.58±1.02 μm for rats and 22.47±2.40 μm for dogs.[35] With respect to human skin, the epidermal thickness was reported to be 60.3±15.0 μm.[36] The dermal region of the skin contains components of both the microcapillary and pain receptors found in deeper tissue. Clinical phase I study by Wermeling *et al.* showed the safety of microneedles having 620 μm length and 160 μm in width at the base.[37] As SDMP array tip was inserted into the epidermis of rat skin, bleeding was not detected. After insertion of SDMP array tip, dissolution and diffusion of AA were immediately occurred, since SDMP arrays were made of water-soluble thread-forming biopolymers, chondroitin sulfate and AA. In another experiment, the time course of the diffusion of the drug in rat skin was evaluated using fluorescein isothiocyanate (FITC)-insulin, and those support the results in this study.[38] The microconduits disappeared within 2 h

Table 2. Stability of AA in SDMP Array Tip after 1 Week Storage

SDMP	% Remaining of AA		
	23 °C	40 °C	60 °C
High content	99.2±15.1	100.7±15.2	98.8±13.4
Low content	99.4±8.9	96.6±6.1	95.0±9.2

Each value represents the mean±S.D. of three experiments.

macroscopically as well as our previous report.[39] In addition, the shape of SDMP was conical and the tops of the SDMP array were very narrow, approximately 10 μm. Therefore, after the insertion of SDMP array into the skin where SDMP encountered the environmental water, hydration and dissolution occurred. Caspers *et al.* reported that the water content in the skin was as high as 70%.[40]

Generally, percutaneously absorbed drugs are cleared by the microvasculature that exists in the dermis.[41,42] The microvasculature begins close to the dermal/epidermal junction. However, the microvasculature system was not alive when permeation experiment was performed using Franz-type diffusion cells. As Henning *et al.*[32] pointed out, results obtained from different skin permeation studies were often inconsistent and sometimes even controversial. Skin permeation experiments do not escape from those pitfalls. Therefore, extremely high permeability of AA through the rat skin, over 65.8—95.3%, was obtained in our preliminary permeability experiment. In this experiment, the skin was removed from rats and was mounted onto the diffusion cell. Thereafter, SDMPs was inserted to the isolated skin and permeability experiment was performed. In this case, 100 microconduits were formed on the isolated rat skin and the microconduits were not fixed till the end of the permeation experiment. As a result, extremely high permeability of AA was observed. Therefore, we improved the experimental protocol where SDMP arrays were inserted to the rat skin before the skin was removed from the rat abdomen for permeation experiment. The permeated amount of AA was increased in accordance with the contact time of SDMP array tip to the skin. In the case of 30 min contact time, the permeated % of AA from two kinds of SDMP array tips were 10.9% and 9.6%, respectively. Pinnell *et al.* studied the percutaneous absorption of AA using intact pig skin where AA concentrations in the pig skin were measured.[43] The maximum skin AA concentration was 176.1 ng/mg. In addition, the cumulative permeated amount of AA reached to the steady state at 4 h after the start of the permeation experiment. Thus, skin has a strong barrier function against the permeation of AA. By taking those points into the consideration, the absorption of AA from SDMP array tip through the rat skin was thought to occur as follows; just after the insertion of AA SDMP array to the rat skin, the barrier function of the stratum corneum was broken and SDMP arrays encountered the environmental water and were dissolved immediately and permeated with high efficiency. As SDMP arrays are solid pharmaceutical preparation, AA was formulated into SDMP arrays as solid dispersion. Solid dispersion technology has been used to increase the solubility of hydrophobic compounds and as a result bioavailability of those drugs were significantly increased after oral administration.[44—48] In the case of SDMP array tip, we did not intend to use solid dispersion technology to increase the solubility of AA, because both AA and base polymer, sodium chondroitin sulfate, were highly water-soluble compounds. AA dissolved in accordance with the dissolution of SDMP base polymer. When the contact time of SDMP array tip to the skin increased, the amount of AA dissolved in the epidermis was thought to be increased. Subsequently, the permeated amount of AA was increased in correspondence with the contact time of SDMP array tip to the skin.

Recently, Oh *et al.*[49] reported in the *in vitro* permeation experiment that calcein, a hydrophilic molecule, well permeated the skin after treated with microneedle array made of polycarbonate of which depths were 200 and 500 μm and densities were 45, 99 and 154 ea/cm^2. Therefore, microneedle technology is a hopeful transdermal delivery system for the percutaneous absorption of hydrophilic compounds like AA. On the other hand, to increase the percutaneous absorption of AA, physical methods like iontophoresis have been challenged.[12] In addition, many AA derivatives have been synthesized.[6—10,50] However, no percutaneous AA preparation has been clinically available up to now. SDMP array tip is expected to be the first success to deliver AA through percutaneous route.

Conclusion

Skin permeability of AA from SDMP array tip has been studied by an *in vitro* permeation experiment. When permeation experiment with a diffusion cell was performed after AA SDMP array tips were inserted into the isolated skin, erroneous results were obtained. Permeated percentages for 6 h were 95—65%. When rat skin was removed at 30 min after SDMP array tip was applied to the rat skin and thereafter *in vitro* permeability experiment was performed, 10.9—9.6% of AA permeated for 6 h. The permeated amount of AA through the skin was dependent on the contact time of SDMP array tip on the skin. By decreasing the contact time, the permeated amount of AA from SDMP tip was decreased.

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