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Research Article

Transdermal delivery of Risedronate using the pressure sensitive adhesive patch with various permeation enhancers

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Abstract

Risedronate monosodium (RIS) is widely used for treating bone disorders. Although RIS is commonly available in the oral drug market, it has side effects such as gastrointestinal troubles, abdominal pain, and severe esophageal irritation. To address these issues associated with oral administration, a pressure-sensitive adhesive patch of RIS was developed for the transdermal delivery, and its penetration rate was evaluated using hairless mouse skin. To increase the permeation of RIS, diethylenetriamine (DETA) was used as a solubilizer and fatty acids were used as enhancers. The cumulative amount of RIS penetrating through the mouse skin using various fatty acids, such as lauric acid (LA), capric acid (C10), caprylic acid (C8), linoleic acid (LiA), and oleic acid (OA) in the patches, were 68.21 ± 17.71 µg, 2.25 ± 2.11 µg, 2.79 ± 0.79 µg, 38.86 ± 3.14 µg, and 41.76 ± 2.17 µg, respectively, compared to 3.38 ± 1.34 µg in the case of the RIS patch without an enhancer. The patch formulation with a weight ratio of 6:1:1 (pressure-sensitive adhesive Duro-Tak® 87-202A, 10% (w/w) RIS, and LA) showed the highest permeation efficiency, demonstrating the effectiveness of enhancers for the transdermal drug delivery patch of RIS

Keywords: Risedronate, Transdermal delivery, pressure adhesive patch, enhancers, fatty acids.

INTRODUCTION

Risedronate monosodium (RIS) is a pyridinyl bisphosphonate with powerful antiresorptive activity. RIS is one of the most powerful inhibitors of fanesyl pyrophosphate synthase (FPPS) among relevant bisphosphonates [1,2]. Therefore, it is extensively used for treatment of various bone diseases including myeloma and metastases, Paget's disease and osteoporosis. Although it can treat various bone diseases, there are several marginal areas, which are low bioavailability less than 0.5% and the absorption is reduced by co-administered drugs or foods [3,4]. Moreover, it has a poor solubility in water and there are some side effects, which are gastrointestinal troubles, abdominal pain and severe irritation of the esophagus [5,6]. Therefore, to avoid these adverse effects, patients have to stand up for more than 30 min after taking the drug. To overcome these in conveniences of patients, researchers have developed new delivery system to carry the drug like transdermal drug delivery system (TDDS). Transdermal drug delivery system might improve bioavailability, convenience of patients and avoids above side effects. In addition, pre-systemic metabolism is avoided, determining the dose of administration is also one of the advantage in TDDS [7,8]. Generally, matrix patch system without a rate-controlling membrane consists of backing, drug-in-adhesive and liner it can be used in the laboratory conveniently [9].

RIS is too hydrophilic and acidic ionized drug to penetrate the skin layer. Skin is composed of the stratum corneum (SC), epidermal, dermis and adnexa [10]. In special, the SC that is composed of mostly lipids, cholesterol, fatty acids and ceramide is the outer layer of the skin and it acts as a barrier for TDDS [11,12]. Fortunately, there is a way to enhance a drug permeation efficiency, which is changed in the physicochemical properties of the drug by ion pairing formation or new structural prodrug [13,14]. However, making prodrug is challenging work because developing new synthesis procedure needs long hours and many experiment skills. The skin pH has been known to be between 4.8 and 6.0 thereby ion pairing system would be perfect way to make neutralized form of drug [15,16]. It can not only increase the lipophilicity, but also decrease the charge of drug [17]. As often as not penetration enhancers are another way used to increase the permeation rate for transdermal drug delivery system.

In addition, penetration enhancers are extensively used in transdermal drug delivery system which allow

impermeable drugs to penetrate more easily compared to none enhancer drug [18-20]. Especially, fatty acids with long side chain are able to increase fluidity, disrupt between the SC and lipid bilayer and decrease the diffusional resistance [21,22].

A pressure-sensitive adhesive polymer, Duro-Tak® 87-202A (PSA87) is one of the most common material for transdermal drug delivery system, which has usual three types: polysiloxanes, polyisobutylenes and polyacrylate copolymers [23,24]. PSA87 has widely used for making hydrophilic drug patch due to containing 40 % hydrophilic acrylate with hydroxyl functionality.

In this study, RIS was formulated into a transdermal patch containing various permeation enhancers in propylene glycol, and its ability to increase drug permeation through a hydrophilic pressure-sensitive adhesive was investigated using in vitro experiments.

MATERIALS AND METHODS

Materials

Risedronate monosodium (RIS) was purchased from Langfang Shinya Chemicals Co., Ltd. (Hongkong, China). Ethanol (EtOH), dimethylsulfoxide (DMSO), diethylene glycol monoethyl ether (DGME), isopropyl myristate (IPM), N-methyl pyrollidone (NMP), oleic acid (OA), lauric acid (LA), capric acid (C10), caprylic acid (C8), Linoleic acid (LiA), diethylenetriamine (DETA) and Propylene glycol (PG) were purchased from Sigma Chemicals Co. Ltd. (St. Louis, MO, USA). High performance liquid chromatography (HPLC) grade solvents were purchased from J.T. Baker (Mallinckrodt Baker, Inc., Phillipsburg, NJ). Distilled water (DW) was obtained from the laboratory. Duro-Tak® 87-202A (a self-curing PSA containing 40 % hydrophilic acrylate and with hydroxyl functionality, PSA87) was obtained from National Starch and Chemical Investment Holding Corporation.

HPLC analysis

All of samples was analyzed by High-performance liquid chromatography (HPLC). The HPLC consisted of a pump (1100, Agilent, USA) with a UV detector set of at 262 nm and 360 nm for excitation and emission respectively. ZORBAX Eclipse XDB C-18 (4.6 x 150 mm, 5 µm) column was used for separation chromatographic peak. A mobile phase contained 5 mM sodium pyrophosphate and 5 mM tetra-butyl ammonium hydroxide 40% at pH 7 and acetonitrile in the ratio of 93:7. The total run time was 30 min and the sample was delivered at a flow rate 1ml/min.

Solubility test

Solubility of RIS were performed using PG, DMSO, EtOH, NMP, IPM and DGME respectively. The prepared solution was heated at 60 °C for 30 min and voltexed for 20 min sufficiently. After sonication for 30 min, the solution was centrifuged at 13,000 rpm for 10 min and the saturated supernatant was collected and diluted in DW. The amount of RIS was analyzed by HPLC

Partition coefficient test

For determining partition coefficient, a xylene/PG phase system was applied with and without enhancers. Prior to experiments, the lipophilic phase (xylene) and the hydrophilic phase (PG) was were thoroughly mixed together at 25°C overnight in a hybridization incubator until each phase was saturated. The stock solution containing RIS (10 %) was prepared in PG with 3 equivalents of DETA. RIS solution was put in the saturated solution and mixed vigorously for 1 hour. Subsequently, penetration enhancers were added in the final mixed solution and shaken sufficiently in hybridization incubator overnight. After centrifugation at 8,000 rpm for 5 min, we analyzed the amount of RIS in both phases using HPLC. The calculation of partition coefficient (%) was concentration RIS in xylene divided by concentration RIS in PG phase multiplied by 100.

Preparation of Patch

The patch containing RIS was prepared using PSA87, the stock solution containing RIS (10 % of RIS), and enhancer at the ratio 6:1:1 or 6:1:0.5. Mixed solution was centrifuged at 3,000 rpm for 1 min to remove the bubbles, and left it at room temperature for 2 h. The patch was prepared by spreading the mixed solution on a backing film using casting knife (elcometer 3580 film applicator). The thickness of patch was 100 µm or 150 µm. The patch was left at room temperature for 15 min to allow the solvents to evaporate, then placed in an oven set at 80 °C for 30 min. After cooling at room temperature for 10 min, the release liner (Everaid Co. Ltd) was smoothly applied to the patch. The patch was then stored at room temperature until the experiments.

In vitro skin permeation test

Hairless male mice, aged 6 weeks, were purchased from Orient Bio, Inc. (Seongnam, Gyeonggi, Korea). The skin of the hairless mice was obtained using surgical scissors, with subcutaneous fat removed. We performed in vitro tests using Franz diffusion cells (PermeGear, Inc.). The diffusion area was 1.77 cm^2 and the cell volume was 5 mL. The receptor medium was PBS without calcium chloride and magnesium chloride. The medium temperature was maintained at 37°C and was evenly mixed using a stirrer. The patch was firmly attached to the epidermal side. Aliquots of 0.5 mL were withdrawn from the diffusion cells at predetermined time intervals of 1, 2, 4, 8, 12, and 24 hours, and the medium was replenished with fresh PBS. The samples were filtered using SmartPor Syringe Filters with PVDF Membrane (Woongki Science, Korea; pore size 0.2 µm) and analyzed by HPLC. All animal studies were performed in accordance with the Seoul National University Institutional Animal Care and Use Committee (SNU-160805-11).

Statistical analysis

All the experiments were performed more than 3 times. ($p \leq 0.05$). All data was expressed as mean and standard deviation.

RESULTS AND DISCUSSION

In this study, RIS patch incorporating enhancers exhibited an improved permeation rate compared to the RIS patch without enhancers. While numerous enhancers exist for transdermal drug delivery, identifying suitable enhancers for RIS delivery presents a significant challenge [25].

To address these challenges, ion pairing system was adjusted to enhance permeation in transdermal patch system. Previous research has shown that amine-based materials can improve both the permeation rate and solubility of bisphosphonates.[13,26,27]. Therefore, DETA was used as an enhancer and a solubilizer in the patch formulation.

The solubility studies revealed that PG and DMSO were capable of dissolving RIS at concentrations of 2,435.59 ± 45.41 μg/mL and 1,174.24 ± 39.72 μg/mL, respectively. Other solvents exhibited the lower RIS solubility compared to PG (Table 1). Consequently, PG serves a dual role in PSA87 patch, functioning not only as a vehicle but also as a potential penetration enhancer.

Table 1: The solubility of RIS in various solvents. It was performed 3 times at least.

Solvent	The solubility of RIS (μg/mL)
PG	2435.59 ± 45.41
DMSO	1174.24 ± 39.72
EtOH	44.90 ± 15.73
NMP	339.64 ± 7.58
IPM	8.01 ± 3.72
DGME	4.59 ± 7.96

Due to the low penetration ability of RIS through the skin layer, additional materials were used to enhance its transdermal delivery.

First, NMP, DMSO, and EtOH were used as enhancers for TDDS of RIS. EtOH has been frequently used as a vehicle in many transdermal drug delivery systems, especially patch systems[28]. However, the mixture of RIS solution with DMSO, EtOH and NMP for the preparation of the RIS patch did not mix sufficiently, resulting in precipitation of RIS. Next, permeation experiments were conducted using various kinds of penetration enhancers. Figure 1 showed the skin permeation amount of RIS with three types of enhancers (DGME, IPM, and OA). As shown in Figure 1, the highest permeation amount of RIS was achieved with the patch formulated with PSA87, RIS with 3 equivalent DETA and OA at a weight ratio of 6:1:1 compared with the other formations. As elucidated from previous studies, the higher the enhancer content in the test sample with the drug, the greater the increase in permeation rate [29]. OA, naturally present in the skin, has been frequently utilized in delivery systems to increase permeation rates, as the majority of skin components have hydrophobic tail groups with more than 16 carbon atoms. As expected, OA demonstrated a higher permeation amount of RIS compared to several general enhancers. Additionally, the effect of other fatty acids, such as C10, C8, LiA and LA were evaluated through the penetration test. Figure 2 shows that the highest permeation amount of RIS was patch including LA that saturated fatty acid with 12 carbon chain and carboxyl group, which was 68.21 ± 17.71 μg/cm^2.

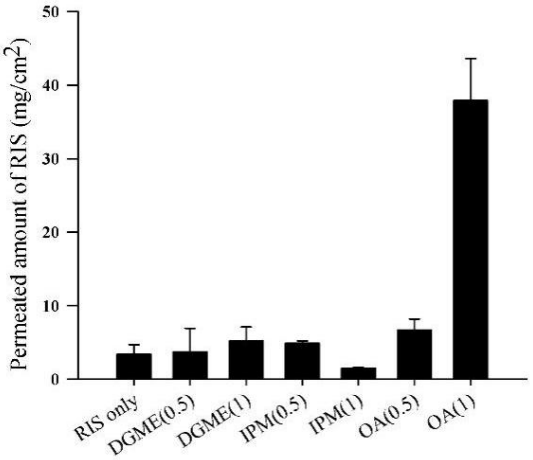

Figure 1: In vitro skin penetration test of Patch with with DGME, IPM and OA at different weight ratio (0.5 or 1) on the basis of 10% RIS with 3eq DETA in PG. The y-axia indicated the cumulated penetration amount of RIS for 24 hours. Results are presented as the mean and the standard deviation (n=3).

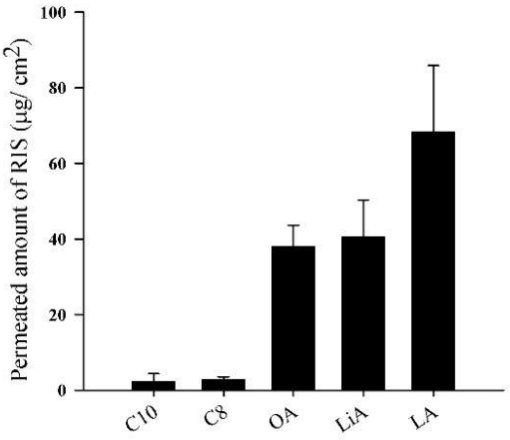

Figure 2: In vitro skin penetration test of Patch with various kind of fatty acid as the penetration enhancers. All the samples were prepared with 10% RIS in PG with 3eq DETA and the thickness of patch is 100 μm. The components ratio of RIS:PSA87:Fatty acid is 1:1:6. The y-axia indicated the cumulated penetration amount of RIS for 24 hours. Results are presented as the mean and the standard deviation (n=3).

OA and LiA were expected to show the higher permeation amount of RIS than other fatty acids because these are unsaturated fatty acid and mixed well with PG. In addition, oleic acid which has the cis double bond disorganizes intercellular lipids due to kinked structure[13]. However the saturated fatty acid with 12C, the LA exhibited the highest enhancing effect. All data were summarized in Table 1 with the cumulated amount of RIS via patch containing enhancers and enhancement ratios

Table 2: In vitro penetration test using patch containing various kinds of enhancers. The data were the cumulative amount of RIS (μg/cm²) after 24 hours. All data were expressed in mean and standard deviation (n=3).

Enhancer (Ratio vs RIS)	Cumulative amount of RIS (μg/cm²)	Enhancement ratio
RIS only	3.38 ± 1.34	1
OA (1)	41.76 ± 2.17	12.36
LiA (1)	38.86 ± 3.14	11.5
LA (1)	68.21 ± 17.71	20.18
C10 (1)	2.25 ± 2.11	0.67
C8 (1)	2.79 ± 0.79	0.83
DGME (1)	5.15 ± 1.93	1.52
IPM (1)	1.45 ± 0.17	0.43
OA (0.5)	6.96 ± 0.84	2.06
LiA (0.5)	23.44 ± 14.12	6.93
LA (0.5)	14.18 ± 0.84	4.19
C10 (0.5)	9.23 ± 2.00	2.73
C8 (0.5)	10.67 ± 0.79	3.16
DGME (0.5)	3.72 ± 3.18	1.1
IPM (0.5)	4.91 ± 0.33	1.45

Partition coefficient plays a crucial role in determining the amount of drug penetrating the skin. The octanol/water system has been extensively used for estimating partition coefficients. However, as PG vehicle dissolved in octanol, xylene was selected as an alternative hydrophobic phase due to its nonpolar organic solvent properties. The results revealed the percentage of RIS in the lipophilic phase as follows: 2.42 ± 0.49 % (PG only), 2.63 ± 0.34 % (PG with IPM), 2.68 ± 1.82 % (PG with DGME), 8.09 ± 0.62 % (PG with LA), and 1.44 ± 0.06 % (PG with OA) respectively. LA exhibited superior enhancement of hydrophobicity compared to the other enhancers, which explains its more powerful enhancing effect for the penetration of RIS.

The patch itself can potentially alter the enhancement of the drug. The patch serves as an additional impediment membrane, even though we used a simple prototype patch, and the results showed that the increasing penetration amount of RIS is not dependent on the chain length [30].

The release profiles were investigated to observe the difference of permeation amount of RIS according to patch thickness variations (100 μm and 150 μm). Figures 3 and 4 depict the release profiles at determined time intervals over 24 hours. Generally, drug content is proportional to patch thickness. The thicker patches were expected to show higher permeation amounts of RIS. However, the 100 μm patches were showed the higher penetration rate. As the patch thickness increased, the interaction between hydrophilic PSA87 and RIS created a stronger network, making it difficult for the drug inside the patch to penetrate the patch membrane. Consequently, the permeation amount of 100 μm thickness patches including OA was 41.76 ± 2.17 μg/cm², while LA showed 68.21 ± 17.71 μg/cm². For 150 μm thickness patches, the permeation amounts were 33.74 ± 12.30 μg/cm² and 4.45 ± 11.66 μg/cm², respectively.

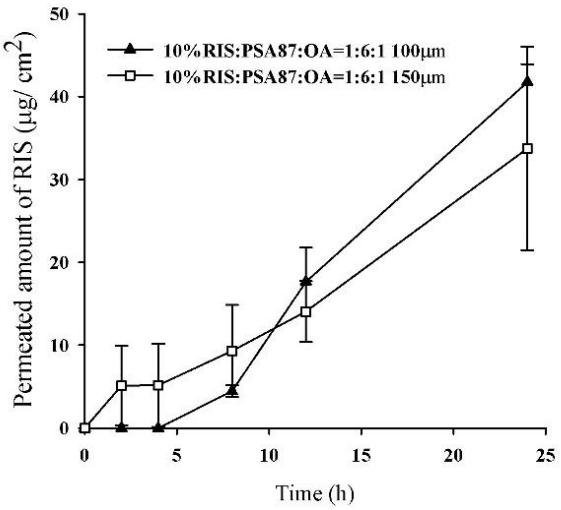

Figure 3: In vitro skin penetration test of Patch (RIS:PSA87:OA) with different thickness through the hairless mice skin. All the samples were prepared with 10% RIS in PG with 3eq DETA. Results are presented as the mean and the standard deviation (n=3).

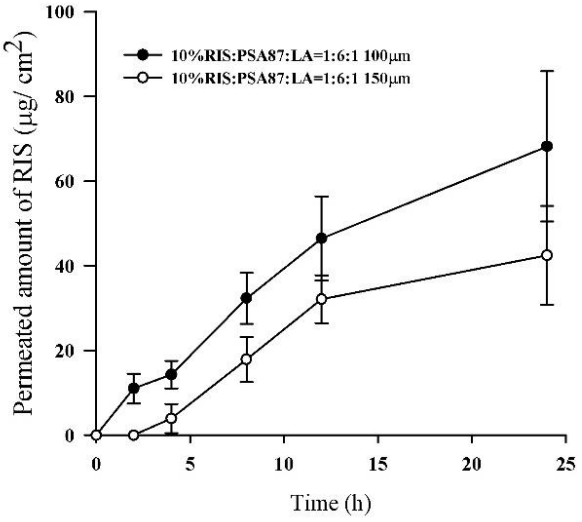

Figure 4: In vitro skin penetration test of Patch (RIS:PSA87:LA) with different thickness through the hairless mice skin. All the samples were prepared with 10% RIS in PG with 3eq DETA. Results are presented as the mean and the standard deviation (n=3).

This study, the effective transdermal patch for RIS was developed using using commercially available formulations and materials. Various enhancers demonstrated a powerful effect on the penetration amount of RIS, increasing it up to 20-fold compared to patches without enhancers when tested on hairless mouse skin. Notably, fatty acids exhibited outstanding ability to enhance permeation rates when combined with PG as a vehicle.

CONCLUSION

The development of this transdermal drug delivery system (TDDS) for RIS offers several potential advantages. Firstly, it may reduce the side effects associated with oral administration. Secondly, TDDS patches could improve patient compliance due to their ease of use and non-invasive nature.

Our findings suggest that the TDDS RIS patch with enhancers could serve as an adjuvant alternative method for administering RIS to treat bone-related diseases. However, further research is necessary to confirm the pharmacokinetic profile of the RIS patch through in vivo studies. These additional experiments will provide crucial data on the patch's effectiveness and safety in a living system, helping to bridge the gap between in vitro results and potential clinical applications.

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Conflict of Interest: The authors declare no conflict of interest.

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