Effect of PassPort System on compounds with low transdermal absorption in hairless rats

Shuntarou Tsuchiya and Nobuyuki Amano

Discovery DMPK and Toxicology, Integrated&Translational Science, Axcelead Drug Discovery Partners, Inc.

Purpose

PassPort System is a novel technology for active transdermal drug delivery which combines microporation in the stratum corneum via heat ablation and transdermal patch. The system enables efficient delivery of various kinds of drugs including low molecular compounds, peptides, nucleotides, proteins, and antibodies with minimal invasiveness. Hairless rats were recently reported to be useful for predicting transdermal pharmacokinetics in humans (Yamamoto S., et al., Xenobiotica, 2019). However, there were no reports where the system was applied to pharmacokinetic studies in hairless rats. The aim of this study is to investigate the effect of PassPort System on compounds with low transdermal absorption and various molecular weights in hairless rats.

Materials

Chemicals

The following chemicals were obtained commercially.

- Furosemide (M.W.: 330.7)
- Exenatide acetate (M.W.: 4187)
- Human recombinant insulin (M.W.: 5808)
- Human IgG (hIgG) (M.W.: approx. 150000)

Animals

Hairless rats (HWY/Slc, male, 6-7-week old) were obtained from Japan SLC, Inc.

Methods

Rats were anesthetized and their backs were shaved to remove residual hair before applying the compounds. After microporation process of the rat skin by PassPort System was completed, patches with aqueous solutions of the compounds were applied on the microporated area and covered with bandage to ensure skin contact throughout the study period. The patches were also applied to intact rats. All tested compounds were also administered subcutaneously to rats. Blood samples were collected from tail vein and centrifuged to separate out the plasma. Plasma concentrations of furosemide and exenatide acetate were measured by LC-MS/MS, and those of insulin and human IgG were measured by commercially available ELISA kits. All animal protocols were approved by the Institutional Animal Care and Use Committee of Shonan Health Innovation Park. Area under the concentration-time curve (AUC) and mean residence time (MRT) were obtained by non-compartmental analysis using the trapezoidal rule. Relative bioavailability (RBA) was determined as the quotient of the dose-normalized AUC at transdermal administration divided by that at subcutaneous administration. The skin absorption rate-time profiles in rats were calculated by a deconvolution method.

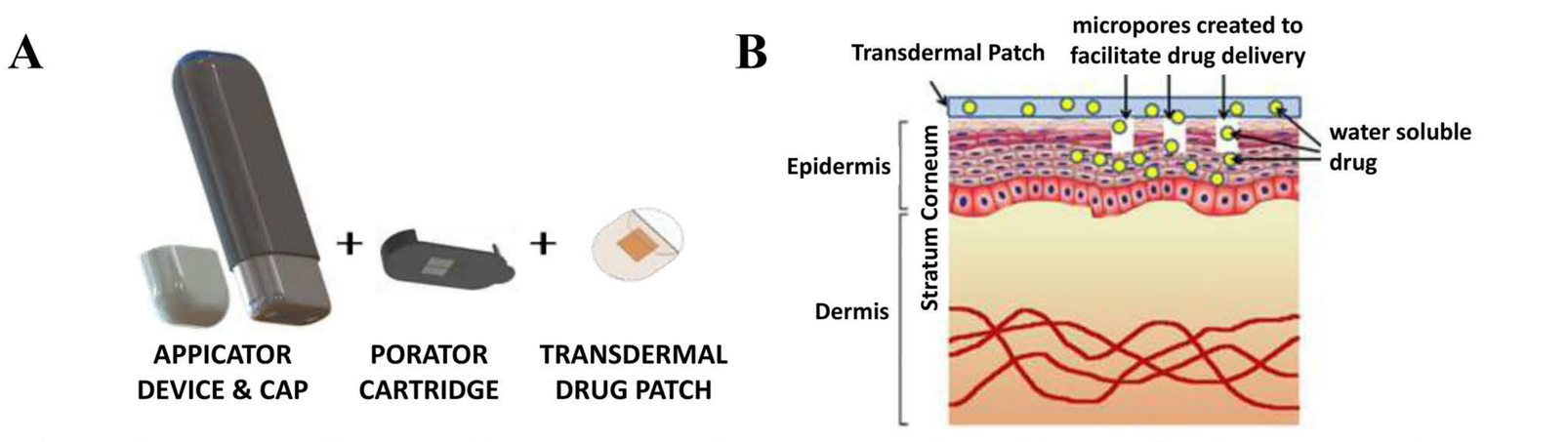
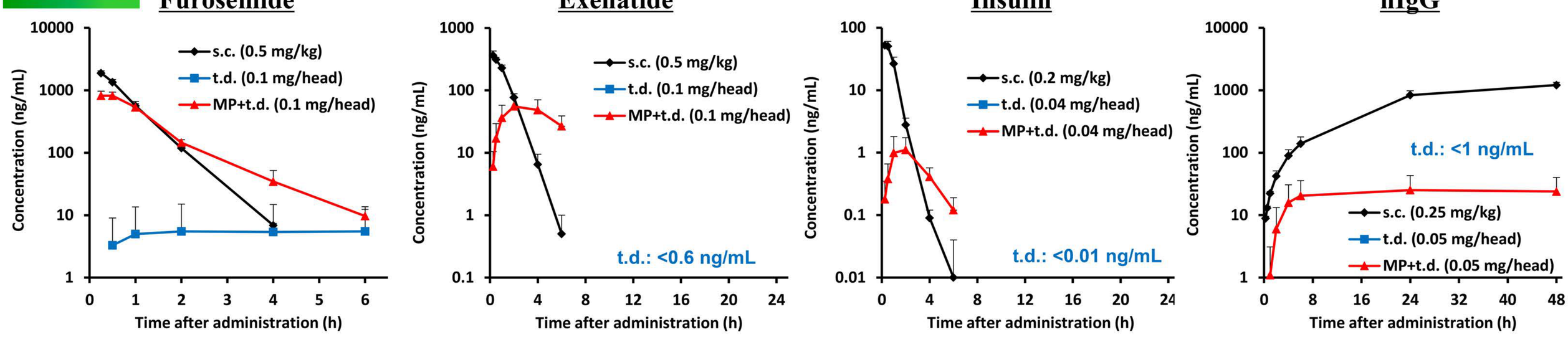


Figure 1. PassPort System (A) and schematic representation of its application to the skin to achieve transdermal drug delivery (B). An applicator device with a porator cartridge creates micropores in the stratum corneum via heat ablation. A drug patch is then placed on top of the porated skin and the drug is dissolved with the exudate from the pores. Micropores enable dissolved drugs to flow from the patch, enter the viable epidermis, and then into systemic circulation.

Results



Furosemide	RBA (%)	MRT (h)
s.c.	-	0.76
t.d.	0–6.1	n.d.
MP+t.d.	84.4	1.15

Exenatide	RBA (%)	MRT (h)
s.c.	-	1.10
t.d.	0	n.d.
MP+t.d.	97.9	4.57

Insulin	RBA (%)	MRT (h)
s.c.	-	0.75
t.d.	0	n.d.
MP+t.d.	9.3	3.27

hIgG	RBA (%)	MRT* (h)
s.c.	-	≥ 33.50
t.d.	0	n.d.
MP+t.d.	3.5	≥ 26.53

Figure 2. Plasma concentrations in hairless rats after subcutaneous (s.c.) or transdermal (t.d.) administration with or without microporation (MP). Furosemide, exenatide acetate, insulin and human IgG were subcutaneously administered or transdermally administered with or without microporation by PassPort System to hairless rats. Plasma concentations of the compounds were measured by LC-MS/MS or ELISA. Data are shown by mean + S.D. (n=3). n.d.: not determined due to the lack of data set. *Provisional data because an elimination phase in plasma concentration profile was not observed.

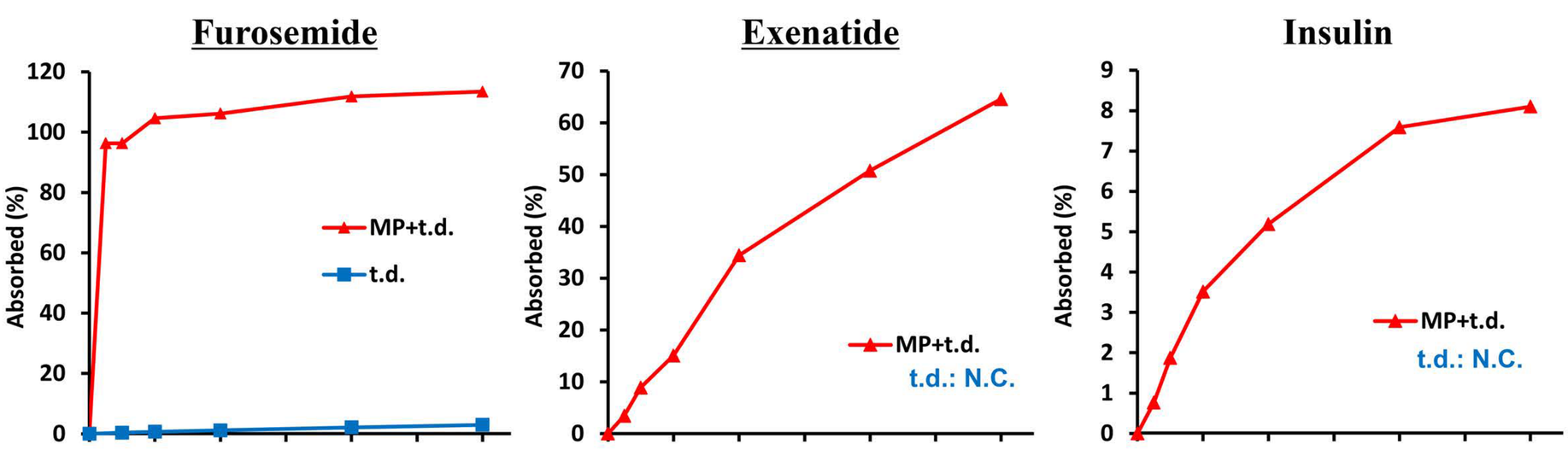


Figure 3. Time profiles of absorption after transdermal (t.d.) administration with or without microporation (MP) in hairless rats. The skin absorption rate-time profiles of furosemide, exenatide acetate and insulin in hairless rats were calculated by a deconvolution method. Appropriate solution for profiles of human IgG could not be obtained. N.C.: not calculated because plasma concentrations of all samples were less than LLOQ.

Summary and conclusion

- Microporation by PassPort system clearly increased RBA after transdermal administration of all tested 4 compounds in hairless rats.
- Transdermal administration with microporation prolonged MRT in furosemide, exenatide acetate, and insulin compared to subcutaneous administration, suggesting steadier plasma compound levels.
- Transdermal absorption of furosemide after the administration with microporation was faster than that without microporation and was mostly completed by 1 hour.
- Transdermal absorption of exenatide and insulin after the administration with microporation continued for 6 hours.
- In conclusion, PassPort System improved transdermal absorption of the tested compounds in hairless rats.

COI disclosure information

PassPort System was provided from PassPort Technologies, Inc. free of charge. We have no other financial relationship to disclose for our presentation contents.

Acknowledgement

We thank Asami Kimoto and Masako Okina in Axcelead Drug Discovery Partners, Inc. for executing animal studies and measuring plasma compound concentrations, respectively.