Effect of morphology and application modes of microneedles on permeability of ibuprofen against skin

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ABSTRACT SUMMARY

Non-invasive transdermal delivery using microneedle arrays was recently introduced to deliver a variety of large and hydrophilic compounds into the skin, including proteins and DNA. In this study, a microneedle array was applied to the delivery of ibuprofen, to determine if transdermal delivery can be improved without the need for permeation enhancers. Microneedle arrays with various needle types (no tilted, flat low tilted, round middle tilted, flat middle tilted, and flat high tilted) were fabricated using a micro-mechanical process. The skin permeability of ibuprofen was examined according to the delivery systems of microneedle. The skin permeability of ibuprofen was the highest when the ibuprofen solution was applied to the skin with the flat high tilted microneedle. And the skin permeability of ibuprofen of flat-shape needle was higher than round shape needle for first 8 hours. Taken together, this study suggests that a shape of microneedle might have a different release profiles for transdermal drug delivery system of ibuprofen.

INTRODUCTION

Transdermal drug delivery systems (TDDS) have introduced as an attractive alternative to traditional oral and hypodermic delivery, as they overcome the limitation of first-pass liver metabolism encountered by oral administration and have advantages such as safe, painless, and easy to use, in contrast to intravenous injection.¹ Over the past few decades, transdermal delivery have been developed to painlessly deliver drugs into the skin. However, the barrier properties offered by the skin’s outermost 10-20 μm layer, the stratum corneum (SC), are caused poor skin permeability limiting drugs to transport across the skin.

Microneedles, which are micron-dimension needles, have been developed to increase skin permeability by creating micro-holes on the skin barrier that allow for increased transdermal transport of small and large drug molecules. Over the last years, many studies have been conducted to show that microneedles are acceptable for transdermal drug delivery. Microneedles (MN) have been used to delivery drugs such as plasmid DNA and RNA, and insulin.²³ And, many groups have been investigated of various type-MN,⁴ various MN length⁵ and various application time.⁶ But, few permeation studies of drug according to the shape of MN have been conducted.

In this study, in vitro and in vivo permeation studies of ibuprofen according to the morphology and application modes of MN.

EXPERIMENTAL METHODS

Figure 1. Schematic diagram of application methods of ibuprofen gel with MN. (A) co-application and (B) treating ibuprofen gel after applying MN.

We designed two application methods. Figure 1(A) shows simultaneously applying ibuprofen gel and MN. Figure 1(B) shows the other method that ibuprofen was treated after MN was applied to skin for 30 min.

RESULTS AND DISCUSSION

The different shape MNs used in this study are shown in Fig. 2. The MNs with different located tilted bar showed non-tilted (Figure 2A), low flat (Figure 2B), middle flat (Figure 2C), middle round (Figure 2D) and high flat (Figure 2E).

Among MNs, high-flat tilted showed highest ibuprofen concentration at all times. Low-flat tilted MN may transport much ibuprofen gel at first time. But, cumulative amount of ibuprofen was lower than that of high-flat tilted MN. We also compared flat- and round-tilted at middle location. Interestingly, there was no significant difference between flat- and round-tilted MN. (Figure 3A and 3B) Figure 1 shows the other method that ibuprofen treated after or co-treating MN was applied to
skin for 30 min. Although application method was changed, orders of permeability of MNs were not differ from results of method A (Figure 3B). High-tilted MN showed highest ibuprofen cumulative concentration in the MNs.

When applying Rhodamine B base solution only, it could not penetrate into the skin after treatment for 60 min, but rather stayed at the SC, indicating that SC was a physical barrier of skin to Rhodamine B base. However, the depth and width of skin holes increased when applying high-flat (Figure 4C) tilted MN compared to control (Figure 4A) no tilted MN (Figure 4B). According to this result, the shape of MN have effect on skin permeability.

Plasma drug concentration versus time profiles of ibuprofen gel with no MN, MN and high-tilted MN are shown in figure 5. Pharmacokinetic parameters calculated from the plasma drug concentration versus time profiles are listed in Table 1. There were significant differences in AUC and C_max between applying no MN and high-flat tilted MN. And also, there was difference T_max. The ibuprofen gel with high-flat tilted MN had a relative bioavailability of 223.7% and 12.3% compared to ibuprofen gel with no MN and no-tilted MN, respectively.

Figure 5. Plasma concentration-time profiles following transdermal application of ibuprofen gel, ibuprofen gel with non-tilted MN, and ibuprofen gel with high-flat tilted MN on dorsal skin of rats (mean±S.D., n=3).

Table 1. PK parameters of ibuprofen gel, ibuprofen gel with non-tilted MN and ibuprofen gel with high-flat tilted MN following transdermal application on the dorsal skin region of rats. (mean±S.D., n=3) * Relative bioavailability compared to reference formulation * Significantly different from the ibuprofen gel (p<0.05).

CONCLUSION

Transdermal drug delivery of ibuprofen according to different shape and application methods of MNs showed different permeation ability in vitro and in vivo. Specially, high-tilted MN showed highest permeability in rat skin regardless of order of applying ibuprofen gel and MN. These results might suggest the specification of MNs for transdermal drug delivery.

REFERENCES

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