Insulin Transdermal Drug Delivery System - Study Conclusion

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Introduction and Protein Properties

Transporting molecules, especially large proteins, through the skin is a challenging task due to the skin's efficient barrier function. Nevertheless, with the right approach, it can be achieved! The protein particles exhibit a range of sizes and can even combine with other proteins or cofactors to form larger complexes, which are essential for their biological function.

For instance, insulin particles have a size of 5.5 kDa, insulin dimers have a size of approximately 11.6 kDa, and hexamers have a size of approximately 35 kDa. Most of these particles are hydrophilic in nature, with insulin having a logP value of -1.61. These particles can be modified by adding lipid or sugar moieties, which can affect their water/oil partition ratio. It is worth noting that these modifications can have a significant impact on their biological activity, which is an exciting area of research. It is worth noting that these properties are in contrast to the five Lipinski rules proposed for efficient transdermal delivery.

Benefits of using Protein

Proteins possess unique properties that make them valuable for certain applications, despite their challenges in handling. However, it is important to acknowledge that these rules are not absolute and may not apply in all cases. While it is true that proteins are susceptible to various physical and chemical factors, and have a tendency to stick to surfaces and air bubbles, with proper handling and formulation, these issues can be mitigated.
Moreover, the benefits of using proteins, such as their high specificity and potency, make them a promising avenue for drug delivery.

Challenges in Insulin Delivery and Research Focus

Insulin faces significant challenges, including chemical and physical denaturation, as well as autoproteolysis and proteolysis by skin-embedded proteases. Despite these obstacles, insulin remains a crucial component in the treatment of diabetes. Ongoing research focuses on developing more stable physiological conditions due to partial unfolding, highlighting the need for continued investigation and innovation in this field.

Biotts' solution: Noninvasive Transdermal Insulin Deliver - In Vitro Results

In response to the identified challenges, we have optimized our Biotts' carrier for insulin delivery. We are pleased to present the initial findings from our in vitro and in vivo studies on noninvasive transdermal insulin delivery.

To evaluate the efficacy of Biotts' carrier with insulin, we conducted release tests using porcine skin following OECD guidelines. Two formulations were selected for testing: MTC-Y+Insulin modification 1 (MOD1) and modification 2 (MOD2). The formulation was carefully weighed into the donor chamber and the skins were mounted on top of the chambers, which acted as a separation membrane. This method allowed for a thorough evaluation of the formulation's performance. Subsequently, the chambers were placed in dissolution vessels, and the acceptor medium was added.

The results of the release tests were promising. A study [Fig.1] on porcine skin, similar to human skin, confirmed that the MTC carrier effectively transports insulin through the skin barrier. **After 72 hours**, the concentration of insulin reached nearly **60ng/mL.** Moreover, in vivo studies have also been conducted, which further supports the potential of this method.

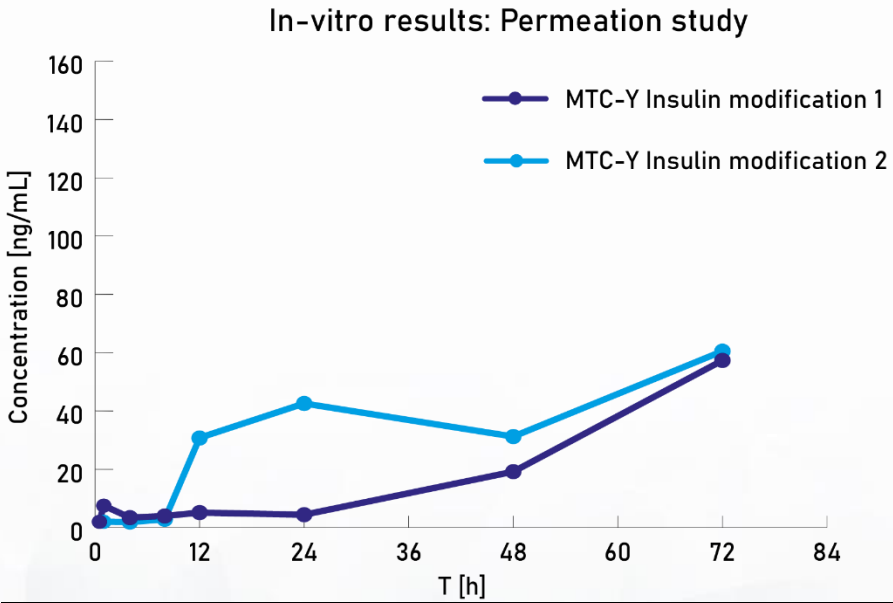

Fig.1 Release analysis, form.: MTC-Y+Insulin modification 1, MTC-Y+Insulin modification2; Acceptor medium : Phosph. Buffer 7,4+propylene glycol+EDTA+BSA; Membrane : porcine skin

A porcine skin permeation study (the structure most similar to human skin) confirmed the ability of the MTC carrier to transport insulin through the natural skin barrier.

LC-MS/MS Method Development

Biotts' team has developed an innovative LC-MS/MS method that enables the determination of insulin concentrations in acceptor medium and rat plasma in vivo. The expected insulin concentration in rat plasma samples is approximately 0.1-2 ng/ml. To validate the results, ELISA data was also generated.

In Vivo Results

Male Wistar rats were employed as the animal model for this study.
The objective was to compare the insulin plasma concentration after subcutaneous administration to transdermal administration of both formulations of MTC-Y+Insulin Modifications.

Subcutaneous administration of insulin

Following subcutaneous administration of insulin, the maximum concentration (C_{max}) peaked at approximately 3.8 ng/ml before gradually declining to zero over a period of roughly 32 hours.

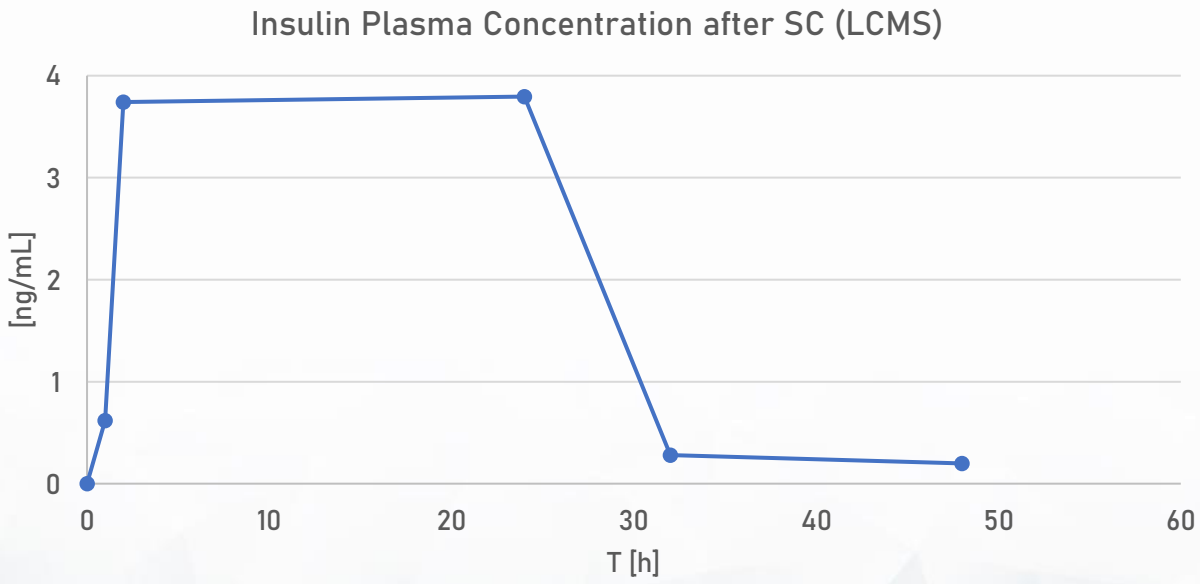

Fig.2 Insulin SC (Gensulin N) - (0.035 mg/animal)

Transdermal administration of MTC-Y+Insulin MOD1 formulation

MOD1 shows sustained stability and prolonged presence of insulin in plasma following transdermal administration using the MTC carrier. Notably, insulin concentrations reach 1.4 ng/mL after 48 hours and maintain consistency until the 78th hours, with levels sustained around 0.5ng/mL.

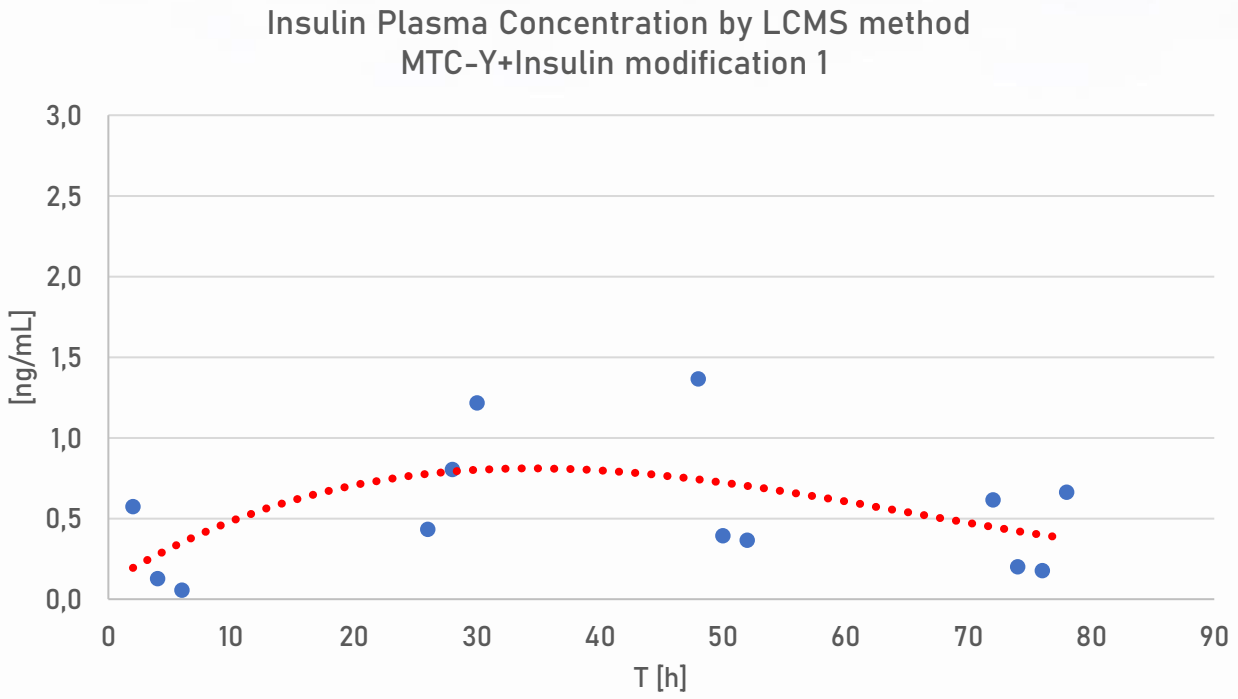

Fig.3 Plasma profile of insulin - after transdermal administration of Formulation MTC-Y+Insulin_MOD1 (0.72 mg/ animal) (LCMS method)

In contrast, MOD2 presents a notable escalation in C_{max} level to 8.5 ng/ml when insulin is administered transdermally using a modified MTC carrier. Subsequently, the C_{max} level reaches approximately 2.5 ng/ml, with the measured concentration remaining at around 2 ng/ml after 54 hours, and consistently so after 48 hours.

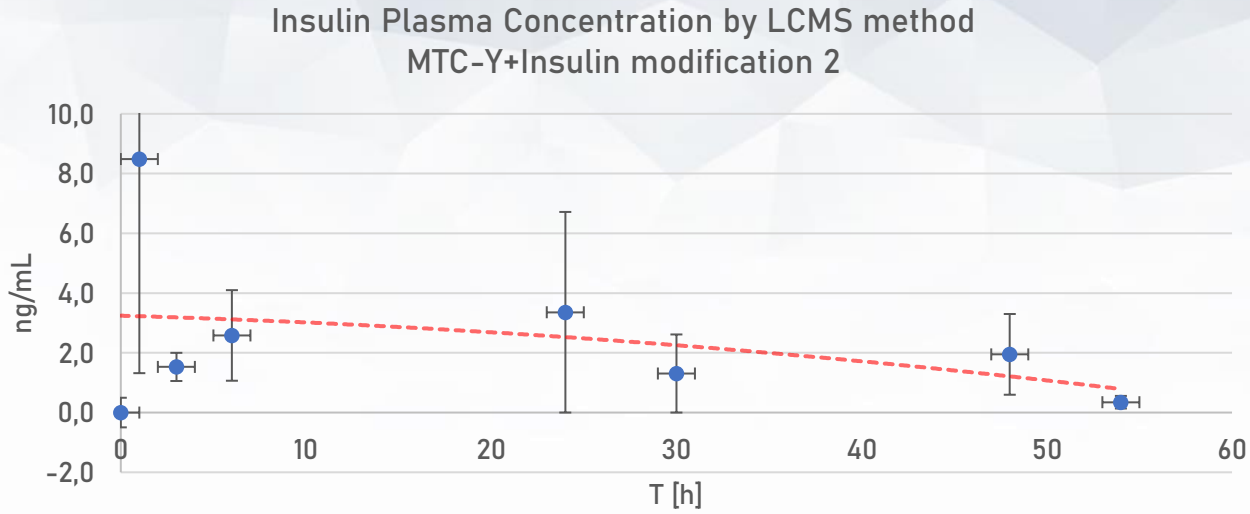

Fig.4 Plasma profile of insulin - after transdermal administration of Formulation MTC-Y+Insulin_MOD2 (0.37 mg/animal) (LCMS method)

Insulin Plasma Concentration Comparison – MTC-Y + Insulin to Subcutaneous administration (SC) [LC-MS]

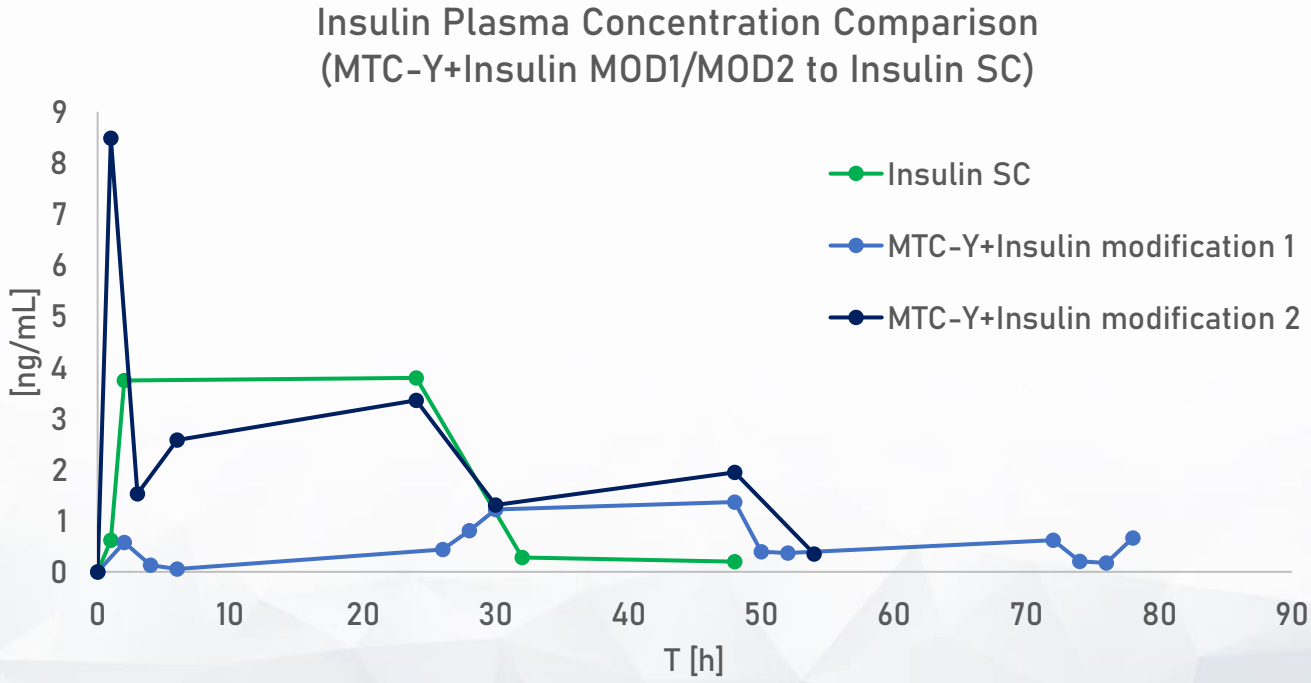

Fig.5 Comparison of insulin concentrations profiles after SC and transdermal MTC-Y+Insulin formulations (Modification 1 and Modification 2) administration.

These findings suggest that **insulin can be effectively administered transdermally without breaking the skin layers**, which could have significant implications for patients who require insulin therapy. The MTC carrier has been found to be an effective method of transporting insulin into the bloodstream via the transdermal route.

Studies have shown that API concentrations achieved through this method are comparable to those achieved through subcutaneous administration. Moreover, **a single transdermal administration of insulin with the MTC carrier can maintain therapeutic concentrations for up to 72 hours**, providing an extended and convenient treatment option.

Conclusions

These promising results pave the way for further research in this area. Future studies should focus on confirming and expanding upon these findings to establish transdermal insulin delivery as a viable alternative to traditional injection methods.

In conclusion, the development of transdermal insulin delivery using the MTC carrier represents a significant advancement in diabetes management. These initial study demonstrate the effectiveness of our innovative approach in offering a non-invasive, convenient, and long-lasting treatment option for patients requiring insulin therapy. With continued research and innovation, we are confident that this approach will not only enhance patient outcomes but also significantly elevate the quality of life for individuals living with diabetes.