Medical Devices: Evidence and Research

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ORIGINAL RESEARCH

Evidence of the Utility of Needle-Free Injectable Devices for Subcutaneous Administration of Biopharmaceuticals: Comparable Study of in vivo Pharmacological and Vaccination Ability to Normal Injection

Toru Taharabaru[1], Yuto Kubohira[1], Kensuke Taniguchi[2], Taiji Horita[2], Taishi Higashi[1], Keiichi Motoyama[1]

[1]Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan; [2]Taisei Kako Co., Ltd., Medical Division, Osaka, Japan

Correspondence: Keiichi Motoyama, Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan, Email motoyama@kumamoto-u.ac.jp

Background: Needle-free injectable (NFI) technology has attracted increasing attention as a promising alternative to conventional needle-based injections. NFI devices offer several advantages, including reduced pain, minimized medical waste, and the elimination of needlestick injury risks. However, quantitative evidence comparing their pharmacological performance with that of standard subcutaneous (SC) injections remains limited, particularly for different biopharmaceuticals.

Methods: We compared a novel NFI device (SAIJECT®) with conventional needle-based SC injection for the administration of model biopharmaceuticals. The pharmacological activities of insulin were evaluated based on blood glucose levels, including time-dependent hypoglycemic response. The antigen-specific antibody production levels after the injection of Ovalbumin (OVA, a model antigen for vaccination) were also evaluated. Furthermore, the physical mechanism of drug delivery by the NFI device was visualized by studying the penetration of Evans blue dye after injection.

Results: There was no significant difference in the pharmacological activities of insulin and OVA delivered via the NFI-device and those via standard SC injection, suggesting that the NFI device was comparable to normal injection. Evans blue dye injected by the NFI device was broadly distributed throughout the dermis and subcutaneous tissue without skin perforation, leakage, or localized accumulation. These results indicate that NFI device can deliver drugs efficiently into the subcutaneous tissue while maintaining tissue integrity. Moreover, this NFI device exhibited negligible drug adsorption, indicating favorable physicochemical compatibility.

Conclusion: These findings provide direct evidence supporting the applicability of NFI technology for the SC delivery of biopharmaceuticals and highlight the potential of the NFI devices as a practical and effective alternative to conventional needle-based injection methods. In addition, this comprehensive evaluation of NFI devices provides fundamental insights for the translational application of NFI devices as a practical alternative to needle-based injections.

Keywords: needle-free injectable device, insulin, ovalbumin

Introduction

Needle-based injections remain the standard method for administering drugs and are indispensable for delivering different biopharmaceuticals, including insulin, vaccine antigens, and therapeutic antibodies.[1,2] However, conventional needle-based injections have several challenges. Patients often experience pain and needle-related anxiety during administration.[3,4] Moreover, both healthcare workers and patients are at risk of needlestick injuries and subsequent infections, and careful disposal of used needles is required to prevent such incidents.[5,6] These issues represent significant barriers to treatment adherence, particularly for individuals requiring self-injection at home.

https://doi.org/10.2147/MDER.S582443
Received: 9 December 2025
Accepted: 19 February 2026
Published: 7 March 2026

Needle-free injectable (NFI) devices have been developed since around 1940.[7] NFI devices generate fine fluid jets under high pressure, enabling drug administration without penetrating the skin with a needle.[8] Therefore, NFI devices can reduce injection pain and alleviate psychological distress in patients with trypanophobia, while eliminating the risk of needlestick injuries.[7–9] Several NFI devices have been applied for subcutaneous (SC) administration of several biopharmaceuticals, including insulin, vaccines, and antibodies.[10–13] From a clinical and translational perspectives, factors such as ease of patient self-administration, reproducibility of injection, and consistency of across devices are also important considerations for the broader adoption of NFI technologies. Evidence that drug delivery performance is reliable and comparable to established injection methods is regulatory evaluation of NFI devices.

Several studies have described the physical principles and clinical applications of NFI devices. Pharmacokinetic data of specific biopharmaceuticals administered using specific NFI devices are sometimes compared with those from conventional needle-based injections to validate the suitability of drug administration via NFI devices as a drug delivery system (DDS).[13] However, few comprehensive studies have quantitatively evaluated and compared the pharmacological performance of multiple biopharmaceuticals delivered by the specific NFI device with those delivered by conventional injections. Furthermore, NFI-based jet injection delivers the formulation under high pressure and may differ from needle-based SC injection in terms of local tissue distribution, dispersion patterns, or immunological responses.

Therefore, we aimed to provide direct evidence supporting the utility of NFI technology compared with conventional needle-based administration. We evaluated the performance of a novel NFI device (Figure 1) by comparing the in vivo hypoglycemic effects of insulin and vaccination efficacies of model antigen (ovalbumin [OVA]) following SC administration. Successful SC delivery was confirmed using Evans blue dye. Furthermore, drug adsorption to the device was quantitatively assessed. These results demonstrated that the NFI device is a promising alternative to conventional needle-based injection systems for the SC delivery of biopharmaceuticals.

Materials and Methods

In vivo Hypoglycemic Effect After Insulin Injection

All animal experiments in this study were performed in accordance with the guidelines approved by the Ethics Committee for Animal Care and Use of Kumamoto University (Approval ID: A2022-060, A2024-035). Phosphate-buffered saline (PBS) containing human insulin was administered to 10-week-old Wistar rats at a dose of 2 U/kg (100 μL) using either the NFI device (SAIJECT®, SAIJECT Co., Ltd., Tokyo, Japan, Taisei Kako Co., Ltd., Osaka, Japan) with 200 N jet (spring) pressure or a conventional syringe. Next, blood samples were collected from the jugular vein, and the serum glucose levels were measured using the Glucose CII-Test kit (Fujifilm Wako Pure Chemical Corporation, Osaka, Japan).

Antigen-Specific Antibody Production After OVA Injection

PBS (100 μL) containing OVA (100 μg) and adjuvants (aluminum hydroxide [Alum, 1 mg] or (K3)-CpG-ODN [0.1 mg]) were administered to 10-week-old Wistar rats using either a NFI device with 200 N jet (spring) pressure or a conventional syringe. Blood samples were collected from the jugular vein 14 days after the initial administration,

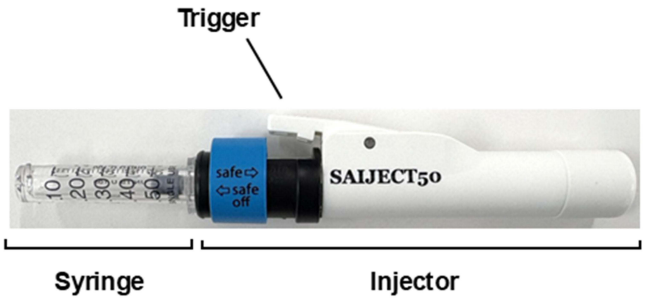

Figure 1 Structure of the NFI device.

and a booster dose containing the same amount of OVA and adjuvants was administered. Blood samples were collected 7 days after the boost administration. Antigen-specific antibodies (total IgG) in blood were quantified using an enzyme-linked immunosorbent assay (ELISA). Briefly, OVA (10 μg/mL) was coated onto each well of a 96-well half-area plate, and 50 μL of serially diluted serum from each rat was added. Horseradish peroxidase (HRP)-conjugated anti-IgG antibody (Abcam; Tokyo, Japan; 1:4000 dilution; 50 μL), 3,3',5,5'-Tetramethylbenzidine (TMB) peroxidase substrate/peroxidase substrate solution B (1:1 mixture; 50 μL), and 1 M H_2SO_4 (50 μL) were used for detection. The absorbance was measured using a microplate reader (sample: 450 nm; reference: 540 nm). The antigen-specific antibody titers were determined based on the corresponding dilution series.

Evans Blue Penetration Study

PBS (100 μL) containing Evans blue (500 μg) was administered to porcine skin (Funakoshi Co., Ltd., Tokyo, Japan) using a NFI device with 200 N jet (spring) pressure. The treated skin was embedded in an optimal cutting temperature compound and flash-frozen on dry ice. Frozen sections were cut at 50 μm using a cryostat and observed using a BIOREVO BZ-9000 microscope (Keyence; Osaka, Japan).

Protein Adsorption

PBS (500 μL) containing insulin (0.29, 0.725, or 1.45 mg/mL) or OVA (1.0, 2.0, or 4.0 mg/mL) was loaded into the syringes of the NFI device. The syringes were maintained at 25°C for 2 h. Subsequently, the absorbance of the samples at 280 nm was measured using a glass cuvette and a NanoPhotometer C40 (WAKENYAKU Co., Ltd., Kyoto, Japan).

Statistical Analysis

The data of hypoglycemic acid and protein adsorption are expressed as the mean ± standard deviation. Data distribution was assessed for approximate normality. Statistical significance was defined at a risk rate of less than 5% and determined using Student's *t*-test (for two-group comparison) or Scheffe's test (for multiple-group comparison). Antibody production data are presented as geometric mean ± 95% confidence interval on the log scale, and statistical analyses were performed on log-transformed values. Sample sizes were determined based on variability observed in preliminary or previously reported data to allow detection of biologically meaningful differences. Although formal power calculations were not performed, the experimental design considered effect size and data variability.

Results and Discussion

The hypoglycemic effect in Wistar rats was investigated (Figure 2) to evaluate the in vivo pharmacological activity of insulin delivered by the NFI device. A rapid decrease in serum glucose levels was observed following the administration of insulin via both NFI device and conventional SC injection. The serum glucose levels reached nadir values within 1–2 h. The time–course profiles and recovery dynamics demonstrated negligible differences between the two methods, with no statistically significant differences at any time point. These results suggest that NFI device delivers insulin with efficacy and biological activity comparable to those of the conventional needle-based SC injection, ensuring systemic absorption without compromising pharmacological function. Thus, the high-pressure jet of NFI device during injection hardly induces significant structural damage or denaturation of the biopharmaceutical.[14–16] Previous studies reported that insulin or nanosuspension formulations injected via NFI devices were absorbed more rapidly.[10,17] In contrast, the NFI device offers the advantage of delivering insulin equivalent to conventional SC administration.

Next, the vaccination efficacy of antigens delivered using the NFI device was evaluated to investigate whether NFI device can deliver macromolecular vaccine antigens (Figures 3 and 4). We quantified antigen-specific antibody titers (total IgG) by ELISA (Figure 3) after administration of a combination of OVA, the model antigen, and adjuvant Alum to Wistar rats using either the NFI device or a conventional syringe. The administration of antigen via the NFI device produced antibodies comparable to those achieved by conventional needle-based SC injection, both before and after the booster administration. Furthermore, the administration of OVA with the (K3)-CpG-ODN adjuvant via NFI device caused higher vaccination efficacy than with Alum (Figure 4). Thus, the NFI device may serve as an effective vaccination device with efficacy comparable to that of conventional SC injection. In addition, the findings indicate that NFI device can

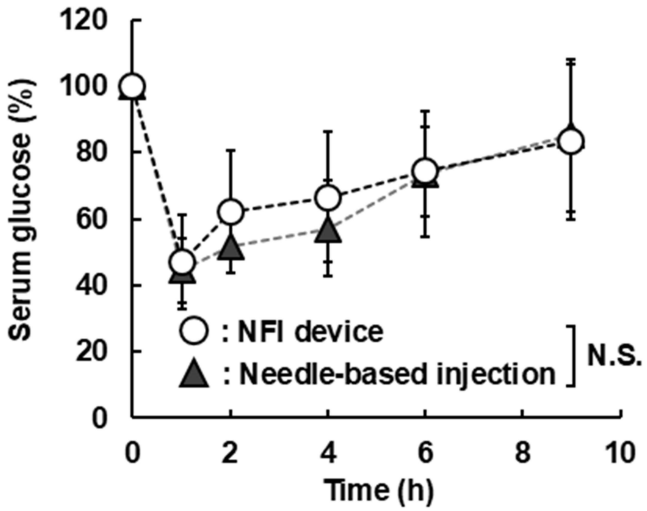

Figure 2 Serum glucose levels in Wistar rats after insulin injection via NFI device or a conventional needle-based SC injection. Each point represents the mean ± standard deviation (n = 7–8 rats).
Abbreviation: N.S., Not significant.

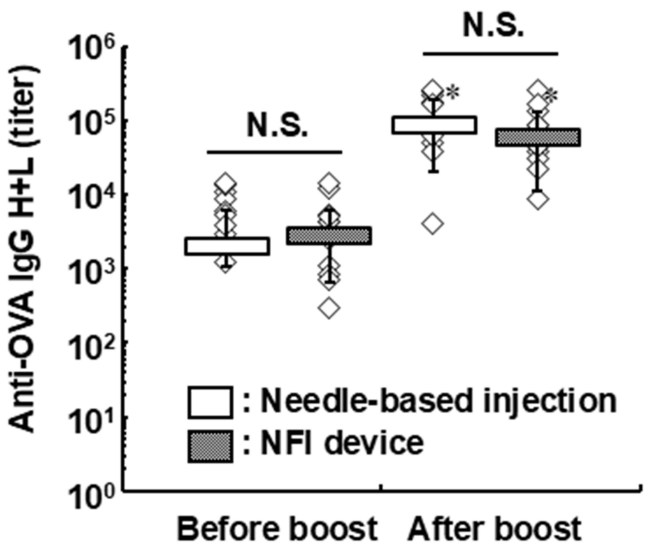

Figure 3 Anti-OVA total IgG production after OVA + Alum injection via NFI device or a conventional needle-based SC injection. Each value represents the geometric mean ± 95% confidence interval (n = 10–11 rats). *$p < 0.05$ versus Before boost.
Abbreviation: N.S., Not significant.

deliver antigen to antigen-presenting cells (APCs) such as macrophages, B cells, and dendritic cell, which are abundant in the dermal and subcutaneous regions.[18–20] Further studies of local immune responses may provide insights into the efficacy and underlying mechanisms of vaccination with antigen delivered via NFI device. In particular, investigating antigen delivery via NFI may clarify whether this delivery method enhances antigen uptake by specific APCs in the injected tissues and whether it acts like adjuvants. Long-term evaluation of antibody titers could provide deeper insights by enabling an assessment of not only vaccination efficacy but also immune memory formation and sustained antibody production.

The physical mechanism of drug delivery by the NFI device was visualized by studying the penetration of Evans blue dye after injection. Evans blue dye was administered into porcine skin using the NFI device, and its distribution was observed to assess local tissue dispersion following administration. As shown in Figure 5, Evans blue was broadly distributed throughout the dermis and subcutaneous tissue. Negligible skin perforation, leakage, or localized

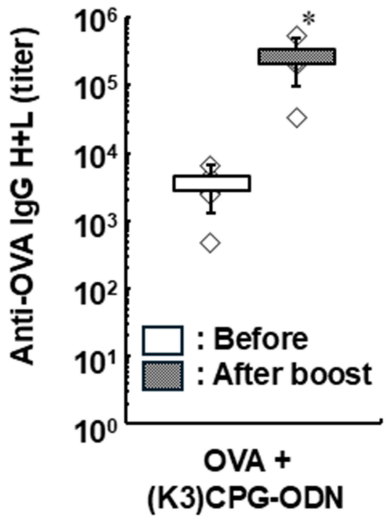

Figure 4 Anti-OVA total IgG production after OVA + K3(CpG-ODN) injection via NFI device or a conventional needle-based SC injection. Each value represents the geometric mean ± 95% confidence interval (n = 6 rats). *$p < 0.05$ versus Before boost.

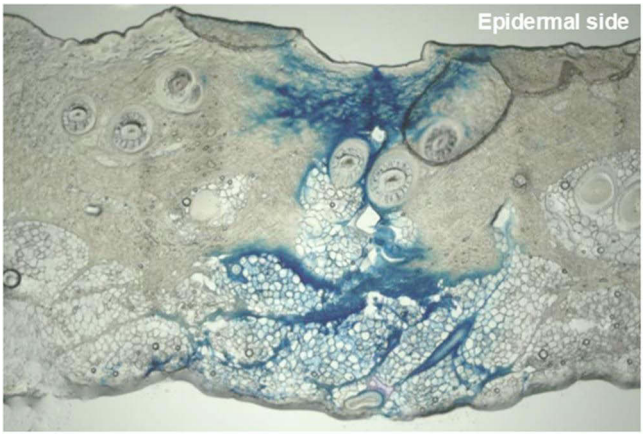

Figure 5 Microscopic observation of Evans blue penetration into porcine skin after injection via NFI device.

accumulation was observed. These results indicate that NFI device can deliver drugs efficiently into the subcutaneous tissue while maintaining tissue integrity. This mechanism possibly supports equivalent or enhanced pharmacological effects and offers potential patient benefits, including reduced pain and minimized risk of internal bleeding.[7–9]

Finally, protein adsorption onto the internal surface of the NFI device was assessed using insulin and OVA (Table 1). Adsorption was negligible for both insulin and OVA, indicating that the device exhibits high material compatibility and is suitable for repeated use with sensitive biopharmaceutical formulations.

Table 1 Protein Adsorption to the NFI Device

	Concentration (mg/mL)	Adsorption (%)
Insulin	0.29	−3.03 ± 1.29
	0.73	−0.04 ± 0.12
	1.45	−1.40 ± 0.40

(*Continued*)

https://doi.org/10.2147/MDER.S582443

Table 1 (Continued).

	Concentration (mg/mL)	Adsorption (%)
OVA	1.00	1.78 ± 5.02
	2.00	−2.32 ± 2.42
	4.00	−1.06 ± 0.09

Notes: Each value represents the mean ± standard deviation of 3 experiments. Adsorption (%) was expressed as the percentage decrease in concentration from the protein solution prior to adsorption. Therefore, negative adsorption data indicates that the absorbance of the protein solution after adsorption treatment was slightly higher than that of the control.

These findings should be interpreted in light of the design and scope of the present study. Animal studies in this study were not conducted under randomized or blinded conditions, and formal equivalence or non-inferiority statistical frameworks were not applied. The evaluations were performed in a limited number of model drugs and animal models, and the influence of species differences and individual variability cannot be completely excluded. Within these defined boundaries, however, the results establish an important foundation for the continued development of NFI-based delivery systems. Future studies will be required to support clinical translation, including systematic assessment of long-term safety, dosing reproducibility, and device performance consistency under conditions relevant to patient use. Moreover, expanding evaluation to additional biopharmaceutical classes such as therapeutic antibodies, protein complexes, and emerging molecular modalities to determine the general applicability of jet-based SC delivery.

Nevertheless, the comprehensive data presented here demonstrate that NFI injection can achieve SC delivery performance comparable to conventional needle-based injection while preserving drug integrity. These results showed the potential utility of further optimization for NFI systems as alternative platforms for biopharmaceutical delivery.

Conclusion

We evaluated the novel NFI device as an alternative to conventional needle-based SC injection for the administration of biopharmaceuticals. The pharmacological activities of insulin and OVA delivered via NFI device were comparable to those achieved by needle-based SC injection. The administration of Evans blue dye using the NFI device to porcine skin demonstrated that the device can deliver drugs broadly within the subcutaneous tissue. Furthermore, the NFI device demonstrated negligible drug adsorption. These results provide direct evidence supporting the utility of NFI device for SC administration of biopharmaceuticals within the scope of short-term pharmacological and immunological evaluations in animal models and suggest their potential as a novel DDS approaches. In addition, this comprehensive evaluation of NFI devices provides fundamental insights for the further development and evaluation of NFI-based delivery platforms for biopharmaceuticals, particularly in contexts where reduced injection burden and improved patient acceptability are desirable.

Acknowledgments

This work was funded by Taisei Kako Co., Ltd. The authors would like to acknowledge Ms. Arina Ishimatsu for technical support.

Disclosure

Kensuke Taniguchi and Taiji Horita are employees of Taisei Kako Co., Ltd. The authors report no other conflicts of interest in this work.

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