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ANALYTICS

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Special analytics

Insulin Compatibility Studies

Drug Compatibility Study - Customized Solutions for Insulin Pumps

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Introduction

According to a 2021 survey, an estimated 537 million people worldwide suffer from diabetes – a fivefold increase compared to 1980[1] [2]. Despite international efforts, this trend is unlikely to improve significantly in the near future[3]. Consequently, an increasing number of individuals are dependent on diabetes treatment.

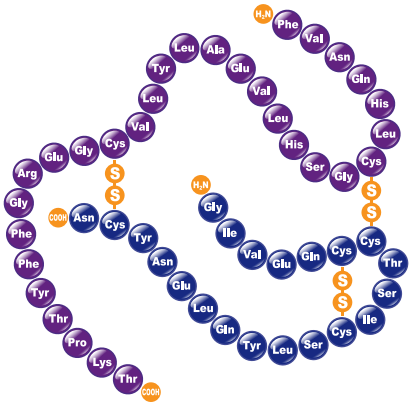
Diabetes is generally classified into Type 1 diabetes ("juvenile diabetes") and Type 2 diabetes ("adult-onset diabetes"). In contrast to Type 2, in which the body is unable to properly utilize its own insulin, patients with Type 1 require exogenous insulin injections to survive, as their bodies no longer produce insulin. Therefore, genetically engineered insulin is administered subcutaneously via an insulin pump for the treatment of Type 1 diabetes.

In 2023, the global market for insulin patch pumps and pumps with infusion sets was estimated at approximately US$ 6 billion[4]. Today, there are numerous manufacturers of insulin pumps – and all of these systems must undergo drug compatibility studies to obtain market approval.

Why are insulin compatibility studies necessary?

In continuous subcutaneous insulin infusion (CSII) therapy for treating Type 1 diabetes, the insulin remains in contact with the reservoir (the insulin storage container) and the infusion pathway (tubing and injection needle) of the insulin pump for extended periods. During this time, the insulin is exposed to various environmental factors. Changes in pH, increased temperatures, vigorous shaking, or contact with the pump materials can potentially lead to chemical or structural modifications of the insulin. These modifications include, for example, the formation of insulin degradation products such as B3- and A21-desamidoinsulin[5], the generation of high-molecular weight insulin (e.g., via covalent dimer formation between A21Asn and B29Lys)[6], or the creation of insoluble aggregates (Figure 1). Furthermore, preservatives (phenol, m-cresol) or other pharmaceutically active substances from the insulin solution (e.g., niacinamide, treprostinil) may be adsorbed by the materials of the infusion pathway (Figure 5). According to current regulatory requirements, the manufacturer must ensure that the insulin pump does not adversely affect the medication in any way[7] [8]. To this end, an in-use simulation is conducted under controlled laboratory conditions that closely mimic actual pump usage, and the insulin product is subsequently analyzed for various parameters.

Figure 1:
Human insulin molecule with the A-chain in blue, the B-chain in violet, and disulfide bridges in yellow. *(image: shutterstock)*



Planning and Execution

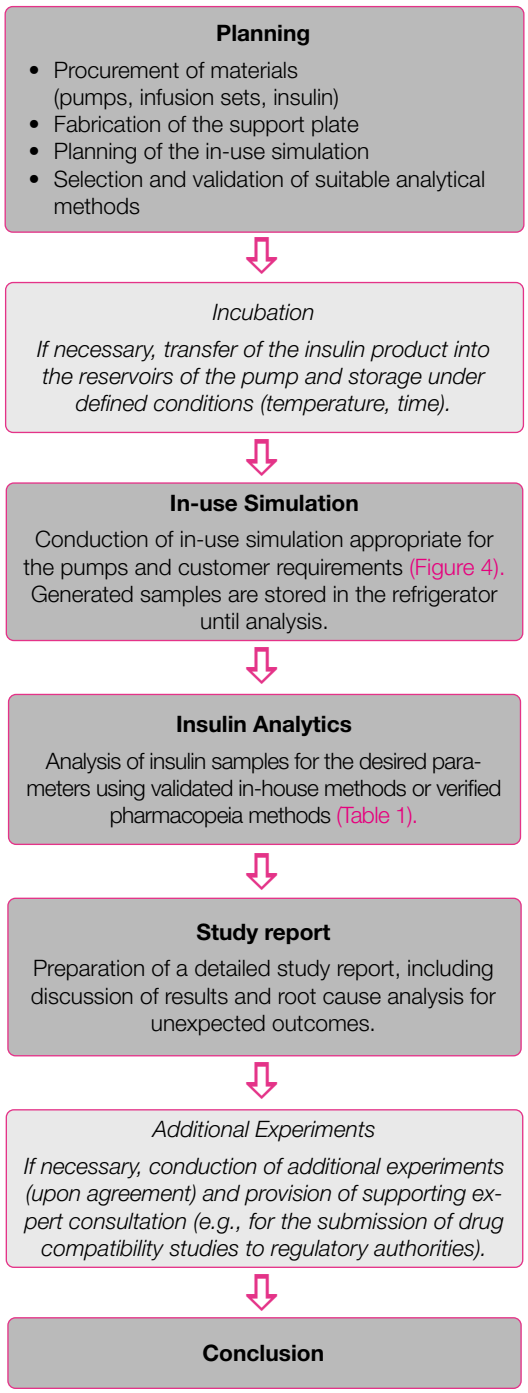
The concept of the drug compatibility study is tailored individually to the respective insulin pump system and its specific requirements (Figure 2).

In the first step, the parameters for conducting the in-use simulation (e.g., flow rate, bolus, temperature, study duration) as well as the selection of appropriate analytical methods are developed in collaboration with the customer.

In a second step, the in-use simulation is carried out under conditions that are as realistic as possible. If necessary, the insulin is transferred into reservoirs and stored under controlled conditions prior to the simulation.

In a third step, the analysis of the generated insulin samples is performed. This analysis employs either validated in-house methods or verified pharmacopoeia methods. If suitable analytical methods are not available for all insulin brands and parameters, additional methods can be implemented and validated at the customer's request.

Figure 2:
Process flow of the insulin compatibility study



The final results, including a discussion and root-cause analysis in the event of unexpected findings, are compiled in a detailed study report. Where possible, we also offer technical support, for example, for submitting the compatibility study to regulatory authorities. During the study, regular updates on the project status are provided and adjustments are made as needed based on mutual agreement.

In-use Simulation

In the in-use simulation, a realistic application of the insulin pump is mimicked under controlled laboratory conditions, representing the usage by a patient. Parameters such as flow rate, bolus, light exposure, shaking, temperature, humidity, study duration, and the choice of the insulin product to be tested can be individually adjusted.

For this purpose, the insulin pumps are filled with insulin or equipped with pre-filled reservoirs. These reservoirs can also be stored for a specified period at controlled temperatures (e.g., 5 °C) prior to the commencement of the in-use simulation, simulating a scenario in which the patient stores the insulin in a refrigerator for an extended period before use. Subsequently, the infusion sets are connected to the insulin pump and the entire system is mounted on a custom-made holding plate (Figure 3).

The prepared insulin pumps are then placed on a horizontal shaker in a climate chamber with controlled lighting (Figure 4). Environmental conditions, which are typical when wearing an insulin pump under clothing, are selected: temperature = 37 °C, relative humidity = 60 %. The patient's daily movement and natural daylight are simulated by shaking (150 rpm) and artificial lighting.

Once the pump flow is initiated, the in-use simulation begins. If desired, the infusion sets can be exchanged during the study to further simulate realistic use. The necessity for a precise in-use simulation is exemplified by the case of the preservative m-cresol, which can be adsorbed by the materials of the infusion pathway, resulting in a very characteristic concentration profile (Figure 5).

Insulin Analytics

Subsequently, the insulin samples from the in-use simulation are analyzed for various parameters to verify the compatibility of the insulin product with the insulin pump system. For parameters such as insulin assay, insulin related substances, high-molecular weight insulin (HMWP), preservatives, niacinamide, and treprostinil, in-house chemical analytical methods or pharmacopoeial methods are available (Table 1). The analysis is carried out using high-performance liquid chromatography coupled with UV detection (HPLC-UV). Physical analytical methods are available for parameters such as pH, visible and sub-visible particles, turbidity, and color. Endotoxin load can also be determined by means of gel-clot technique or quantitative assay.

At the customer's request, analytical methods for additional parameters or other insulin products can also be implemented and validated.

Harmonization of analytical methods

As shown in Table 1, a multitude of different analytical methods are currently required for the analysis of insulin assay, insulin related substances, high-molecular weight insulin, and preservatives. Therefore, Interlabor is working on harmonizing the analytical methods for the various insulin brands. In the future, a total of three analytical methods (insulin assay + related substances, high-molecular weight insulin, preservatives) will be offered, which can be applied to all the aforementioned brands. This approach is expected to drastically reduce both the costs and processing times of insulin drug compatibility studies.

Extractables/Leachables Studies

In addition to the compatibility of the insulin product with the insulin pump system, it is often necessary to demonstrate that no substances are released from the infusion system during pump operation that could contaminate the medication. In these "extractables/leachables" studies (conducted in accordance with ISO 10993), an in-use simulation is also performed and the insulin samples are subsequently analyzed by liquid/gas chromatography coupled with mass spectrometry (UPLC-MS/GC-MS) for the presence of unwanted substances (NIAS = Non-Intentionally Added Substances).

Figure 3:
Setup of the insulin pump with infusion set and glass vial (left) as well as a custom-made holding plate for the insulin pumps (right).

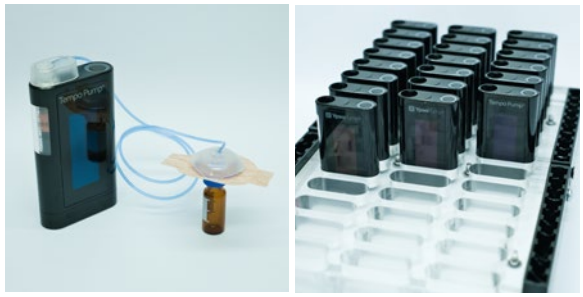


Figure 4:
In-use simulation in the climate chamber with shaking and artificial light (see also cover image)

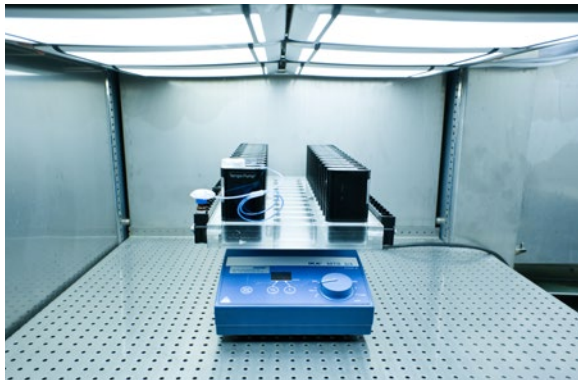


Figure 5:
Determination of m-cresol. In-use simulation of insulin pumps with infusion pathway exchange on day 3 and day 6 (pink) versus storage of an insulin reference under the same conditions (blue).

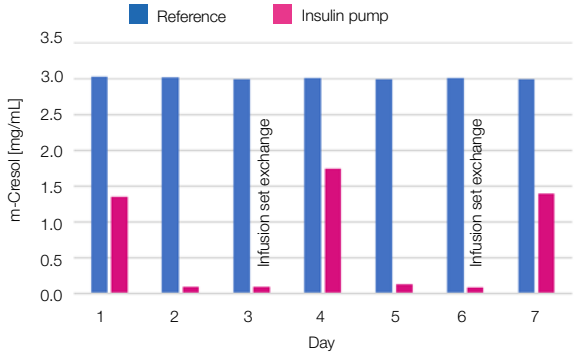


Table 1: Overview of insulin products and analysis parameters

Insulin type	**Aspart**			**Glulisine**	**Lispro**			**Human**
Brand product	Insulin aspart Sanofi®	NovoRapid®	Fiasp®	Apidra®	Humalog®	Insulin lispro Sanofi®	Lyumjev®	Insuman® Infusat
Insulin assay	•		•	•	•		•	•
Insulin related substances					•		•	•
High-molecular weight insulin (HMWP)	•		•	•	•		•	•
Preservatives (phenol, m-cresol)	•	•		•			•	•
Niacinamide[1]	-	-	•	-	-	-	-	-
Treprostinil[2]	-	-	-	-	-	-	•	-
pH value	•							
Endotoxins	•							
Particles (visible and sub-visible)	•							
Turbidity	•							
Colour	•							

• Interlabor • Pharmacopoeia (USP) [1]Niacinamide is only contained in Fiasp® [2]Treprostinil is only contained in Lyumjev®

Such substances can typically include plasticizers from plastic components or constituents of adhesives. Targeted searches for known substances can be performed, or a screening with subsequent database matching can be carried out. For unidentified substances, further structural investigations (e.g., MS/MS analyses) can be conducted if necessary. In collaboration with an external expert, toxicological assessments of the identified substances can also be provided upon request.

Conclusion

With the rising number of Type 1 diabetes patients, infusion systems play a central role in insulin therapy. It is essential to demonstrate the compatibility of the insulin product with the insulin pump system through a drug compatibility study. Interlabor has developed an extensive concept for this purpose:

- Customized planning and execution of drug compatibility studies for insulin pump systems
- Validated analytical methods for various parameters and insulin products
- Capability to develop and validate new methods for additional parameters and insulin products upon request
- Unified, time- and cost-saving analytical methods available from Spring/Summer 2025
- Technical consulting and support for submissions to regulatory authorities
- Regular project updates and a dedicated point of contact

References

[1] International Diabetes Federation, "Diabetes Facts & Figures", 2021, available at: https://idf.org/about-diabetes/diabetes-facts-figures/, accessed on 01.11.2024.

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[3] Ezzati et. al., "Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants", Lancet, 2016, 387:1513-30.

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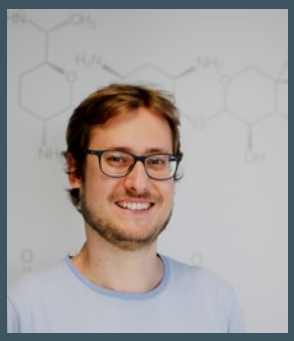

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