Application note 502/15

In vitro study of subcutaneous injection of two insulin formulations using Pion Scissor to assess physical behaviour and release rate

Insulin

Insulin is a peptide hormone produced in the pancreas. It is used to regulate blood glucose levels by promoting the absorbance of glucose from the blood stream and inhibiting the production of glucose by the liver.

Sufferers of type 1 diabetes are unable to produce insulin to regulate blood glucose levels. Sufferers of type 2 diabetes typically either do not respond to insulin (also known as insulin resistance) or do not produce enough insulin. As part of their diabetes management programs, both groups may be required to self-administer insulin, although this is most commonly associated with those suffering from type 1.

Insulin Formulations

In order to regulate their blood glucose levels, diabetes patients are prescribed a variety of different insulin formulations which need to be administered at different times during the day.

There are many different types of insulin formulations but the most common categories are 'fast acting' and 'slow acting'. As a general rule, fast acting insulin formulations should be injected before a meal and are designed to be absorbed quickly into the blood stream to give a quick boost to insulin levels in order to cope with the increased blood glucose levels after eating. Slow-acting insulin formulations should be injected once or twice a day and are designed to be absorbed slowly and give a safe background level of insulin throughout the day.

Pion Scissor

Pion Scissor is a novel instrument designed to simulate the physical behaviour of biopharmaceutical formulations post-injection. It uses a cartridge loaded with a simulated extracellular matrix (ECM) suspended in an interstitial fluid (ISF) buffer. The formulation is injected into the cartridge using the same delivery system used for human administration, and the pH and light transmittance are used to assess the fate of the biopharmaceutical. Dialysis membranes in the cartridge walls allow sample to diffuse into the ISF buffer. Aliquots of the ISF buffer are removed for analysis by HPLC to assess the rate of diffusion.

Fig. 1 Two insulin formulations; InsumanRapid (fast acting) and InsumanBasal (slow acting)

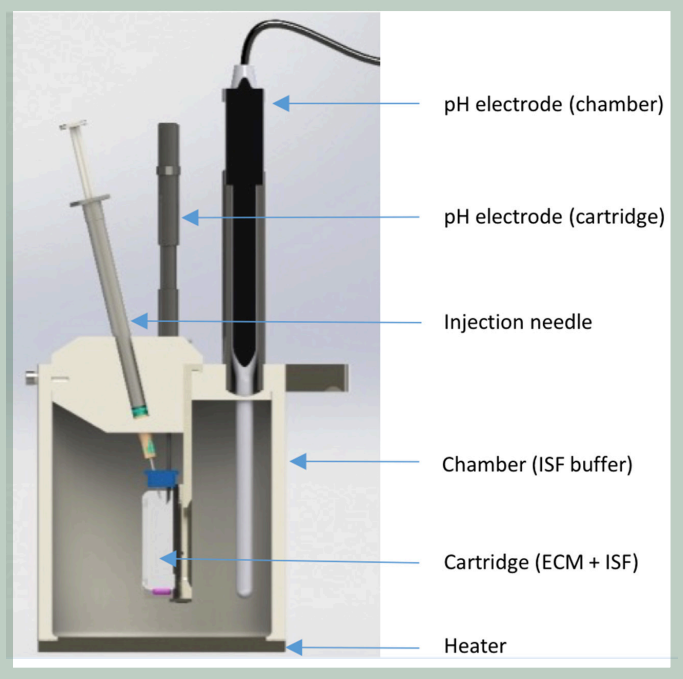

Fig. 2 Schematic of Pion Scissor

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Experimental

Insuman Rapid and Insuman Basal were supplied by AAH Pharmaceuticals Ltd. (Coventry, UK). Insuman Rapid was supplied as a 100 IU/mL solution and Insuman Basal was supplied as a 100 IU/mL suspension.

The cartridge was loaded with the simulated ECM and left suspended in the ISF buffer to allow pH of the ECM to adjust to pH 7.4 and the temperature to 34°C. The ISF buffer was maintained at pH 7.4 by sparging with CO_2 gas. Both the ECM and the ISF buffer were stirred using a built-in magnetic follower to ensure good mixing. Once the pH of the ECM and the ISF buffer had stabilised a reference sample was removed from the ISF buffer and the light transmittance and pH electrode of the cartridge were calibrated.

0.5 mL of formulation was introduced by hypodermic needle to the cartridge. Light transmission and pH inside the cartridge were monitored. Aliquots of ISF buffer were collected at specific time points throughout the experiments and analysed offline by HPLC to determine % diffused.

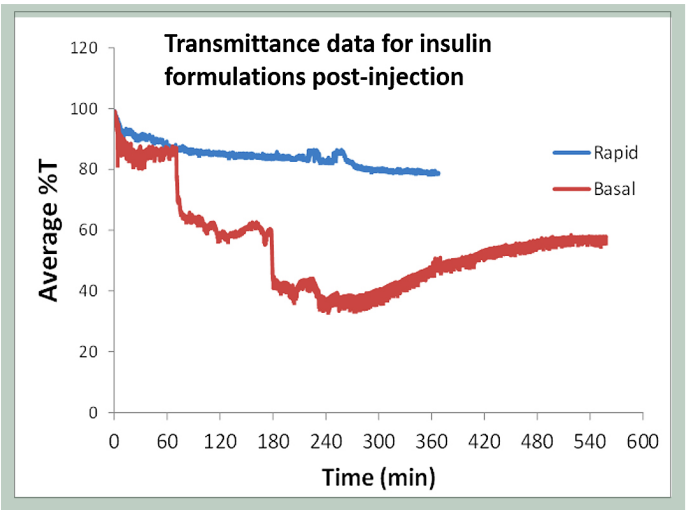

Fig. 3 Light %T of Insuman Rapid and Basal

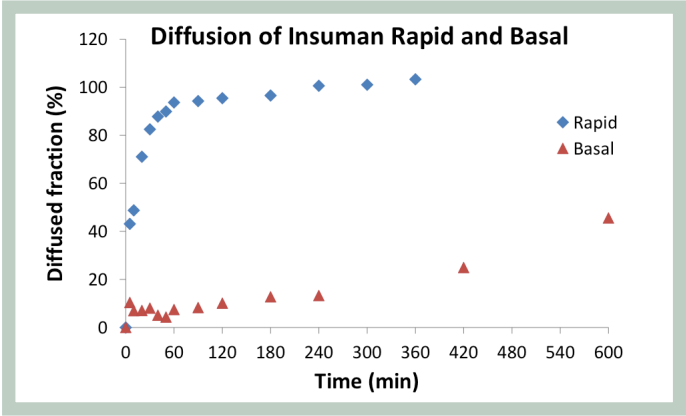

Fig. 4 Fraction appearing in ISF buffer (data by HPLC)

Results and Discussion

Light transmittance data (Fig. 3) demonstrate that Insuman Rapid remains in solution throughout the assay, as shown by the near-constant transmittance around 100%. Insuman Basal is a suspension and the particles cause the light to be obscured. Transmission initially drops, but slowly recovers as the insulin dissolves and diffuses into the ISF buffer. The pH (not shown) also drops after injection but slowly increases as the insulin moves into the ISF.

HPLC data (Fig. 4) show how almost all of the Insuman Rapid has diffused out of the ECM within 60 minutes of injection. Insuman Basal took markedly longer, achieving approximately 50% diffused after 10 hours. The release rates of the two formulations align strongly with the published PK properties of the formulations (Fig. 5).

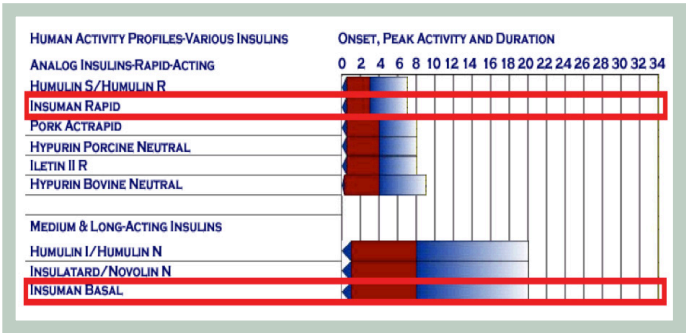

Fig. 5 PK of Insuman Rapid and Basal

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