Application note 501/15

A novel in vitro model for subcutaneous injection

Introducing Pion Scissor

Pion Scissor is a new instrument designed to simulate the physiological conditions of the hypodermis, to be used as an in vitro model of the physical behaviour of biopharmaceutical formulations undergoing subcutaneous (SC) injection.

Often biopharmaceuticals are formulated under non-physiological conditions with the aim of improving stability and prolonging shelf-life. Biopharmaceuticals intended for SC injection are typically formulated at low pH to mitigate decomposition, and in the presence of various stabilising agents and excipients[1].

Upon injection a biopharmaceutical moves from formulation conditions to a homeostatic environment and there are various physical and chemical stresses associated with this transition, which may be detrimental to PK. These include:

- Temperature, pressure and pH transitions
- Changes in formulation composition due to loss of excipients
- Non-specific interactions with the extracellular matrix (ECM).

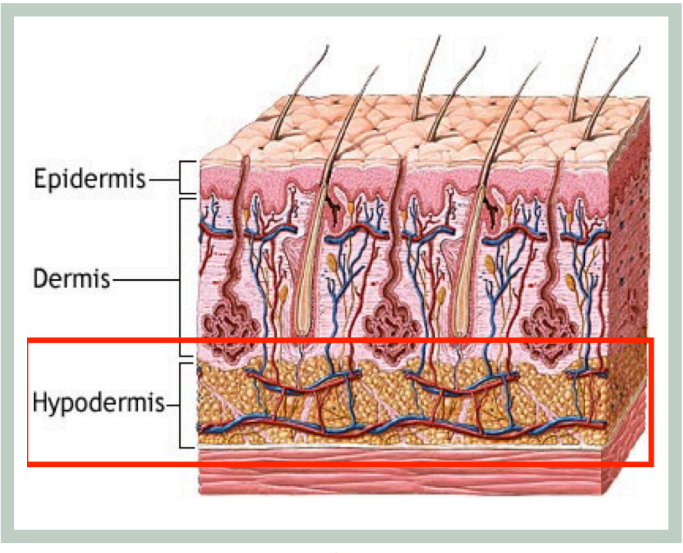

Fig. 1 Diagram of the subcutaneum[2]

Fig. 2 Pion Scissor, a novel instrument for in vitro testing of biopharmaceutical formulations

Limitations with current testing protocols

Currently too little is understood about the physical behaviour of biopharmaceutical formulations post-injection and understanding how the various transitional stresses affect a formulation may be key to improving efficacy. It is widely recognised that site-to-site and patient-to-patient variability is seen in the bioavailability of many biopharmaceuticals, and that no animal model correlates to bioavailability observed in man. It is also known that the conditions and characteristics of physical and chemical environments of the injection site are species specific. It is therefore the case that no *in vivo* model satisfactorily predicts behaviour of a formulated biopharmaceutical upon administration.

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A novel in vitro method for SC injection

Simulating SC injection

Pion Scissor provides a new tool for investigating bioavailability under simulated physiological conditions.

In order to mimic these conditions, Pion Scissor incorporates the following:

- Dynamic pH control and monitoring
- Carbonate-based interstitial fluid (ISF) buffer system
- Simulated ECM
- Temperature control
- Simulated systemic circulation

Samples are manually injected into a cartridge that is pre-loaded with ingredients to simulate the ECM. Turbidity and pH are monitored inside the cartridge. To simulate the passage from the injection site to the systemic circulation, materials can diffuse through the membranes in the cartridge walls into a ISF buffer system maintained at 34°C (skin temperature), from which aliquots can be collected for determination of concentration.

These data allow users to identify any possible interactions between the biopharmaceutical and the ECM.

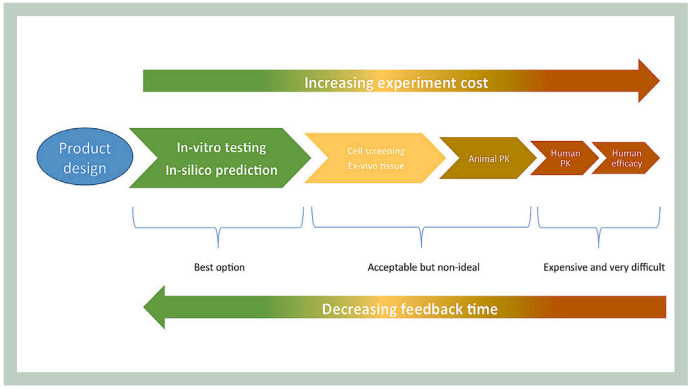

Fig. 3 Pion Scissor feedback loops[3]

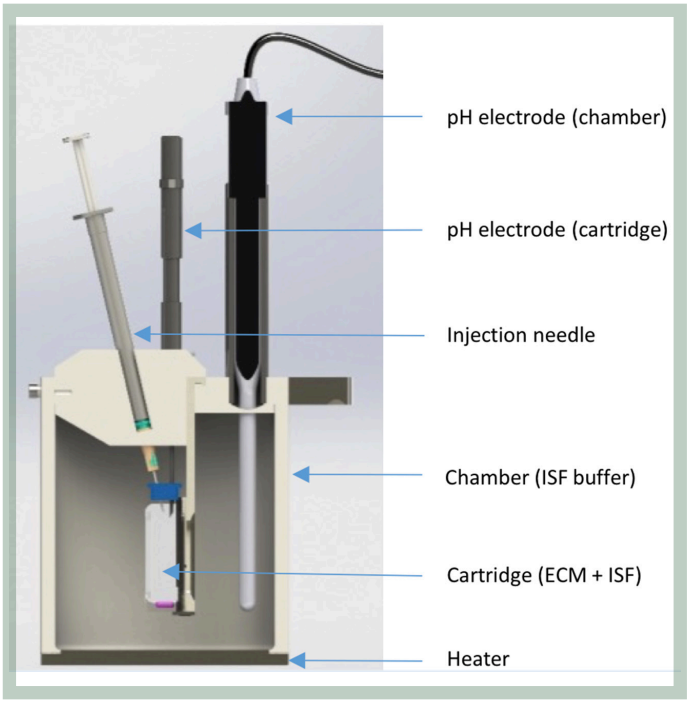

Fig. 4 Pion Scissor: schematic

Aims

Pion Scissor has the potential to expedite the product development cycle and reduce the cost associated with clinical trials. It will allow scientists to identify areas of best performance *in vitro* when employing DoE approaches which will result in quicker lead identification by enhancing the product knowledge base and facilitating rational formulation design. This will reduce the need for clinical trials on all but the most promising test candidates.

REFERENCES

1) Kinnunen, H; Mrsny, R. Journal of Controlled Release, March 2014

2) http://owh.adam.com/pages/guide/reftext/ html/skin_sys_fin.html (A.D.A.M.)

3) http://www.bath.ac.uk/pharmacy/research/ research-in-medicines-design/ Adapted from University of Bath (UK)

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