25W0200

In vitro study of Lidocaine and Enoxaparin subcutaneous formulations performance using Sirius Scissor

ANA INES MELEIRO, NUNO MADEIRA DO O, KARL BOX

Sirius Analytical Instruments

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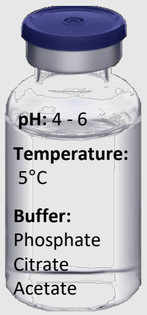
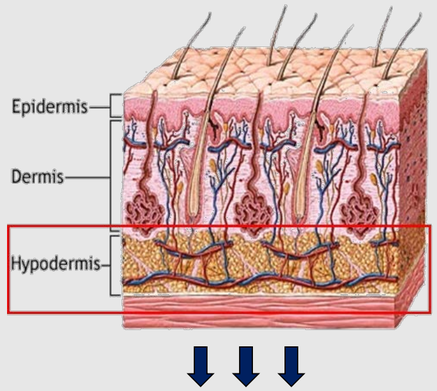




pH: 7.35 – 7.4

Temperature: 34°C

Interstitial fluid: Bicarbonate based

Extracellular matrix (ECM):
- Hyaluronic acid
- Collagen
- Fibronectin
- Chondroitin sulphate

Aggregation of the API leading to precipitation

Low bioavailability

API does not diffuse from the injection site

PURPOSE

Compared with IV, the subcutaneous route is more comfortable for patients and more cost effective for health systems. For this reason, it is important to have a better understanding of the behaviour of these formulations and to carry out a better formulation screening, development and a more rational approach to the development of new therapies.

Sirius Scissor is an instrument that gives insight on formulation fate after subcutaneous injection. It mimics the injection site with respect to its physiological parameters and tissue composition and is therefore a helpful tool when developing new formulations. Previous studies showed a correlation between Scissor and *in vivo* data for biopharmaceuticals formulations. So far, data generated using Scissor does not include non-protein molecules.

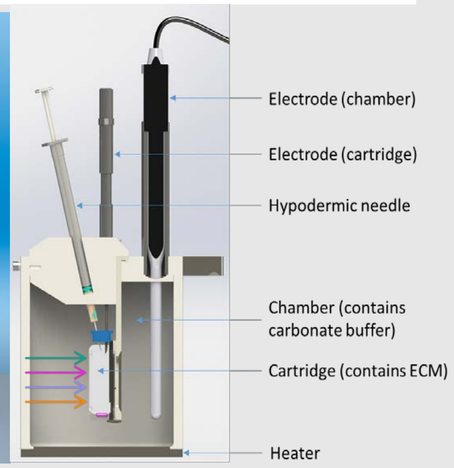
Lidocaine and Enoxaparin are among the most important medications needed in a basic health system and are part of the WHO Model List of Essential Medicines. Both can be administered subcutaneously and the work here described relates to their release rate, and physical behaviour upon injection using Sirius Scissor. The data collected during this study could be compared with previously described *in vivo* data and allow for the establishment of *in-vivo in-vitro* correlation

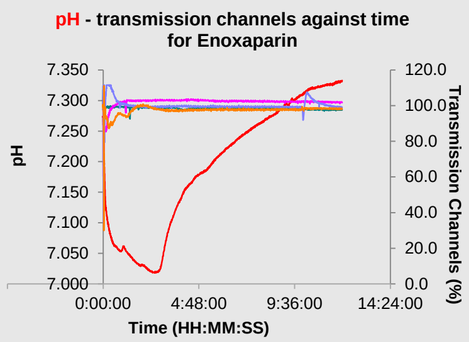
METHOD

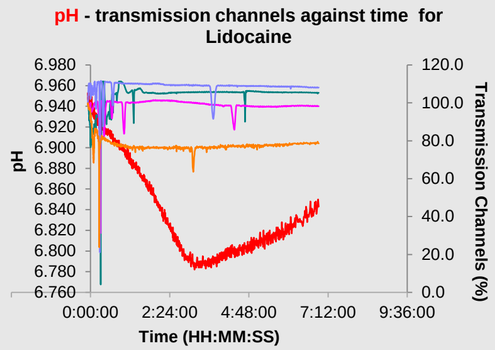
Sirius Scissor is an instrument that gives insight on formulation fate after subcutaneous injection. It mimics the injection site with respects to its physiological parameters and tissue composition and is therefore a helpful tool when developing new formulations.

Both Lidocaine (in house formulation: lidocaine hydrochloride, 10 mg/mL; 0.3 mg/mL NaCl. pH 5) and Enoxaparin (commercial formulation) were injected into Sirius Scissor cartridge containing a simulated extracellular matrix (ECM). Scissor monitors pH and light transmission through the cartridge which is of particular importance in case the formulation precipitates upon injection. In a situation where a drug precipitates after injection, the precipitated material blocks the light pathway causing a decrease in light transmission. Measurements of the pH throughout the assay allow to understand how the APIs diffuse from the injection site.

During the assay both the API and the excipients diffuse out of the cartridge through a customised dialysis membrane to an outer chamber containing a bio-relevant buffer (always under sink conditions). From this outer chamber samples were collected within a time span similar to the *in vivo* release profile of these drugs and analysed through offline RP_HPLC.



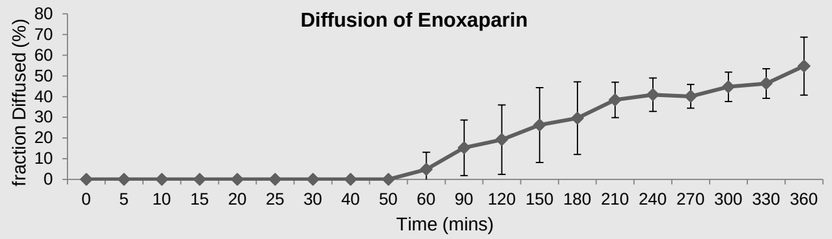


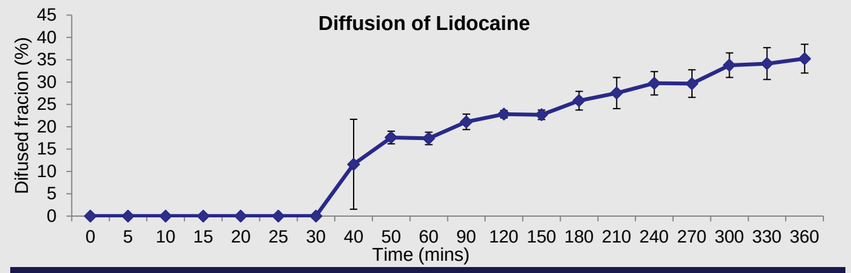


RESULTS

Using Sirius Scissor it was possible to evaluate the behaviour of both Lidocaine and Enoxaparin formulations in an *in vitro* subcutaneous environment. None of the formulations showed precipitation upon injection (as shown by the light transmission obtained during the assay).

It was possible to observe a decrease in the pH after the injection related to the lower pH of the formulations (5-7) comparing to the pH of the ECM (7.4). As Lidocaine and Enoxaparin are fast acting drugs, 6 hours assays were suitable to capture the drug release profile in a subcutaneous simulated environment. Offline RP_HPLC analysis of the samples collected during the assay revealed the fraction diffused across the membranes. The onset time obtained for Enoxaparin allows the establishment of a favourable IVIVC between Sirius Scissor and the in vivo human data described previously (maximum plasma activity: 3h). This is not possible for Lidocaine as there is no *in vivo* data for an in house formulation.





CONCLUSION

Lidocaine and Enoxaparin showed that Sirius Scissor is a useful tool for the study of non-protein formulations subcutaneously administered.

Sirius Scissor provides essential information about the fate of a formulation after injection in the ECM. It is a useful tool when developing new formulations and has the potential to help researchers with the increasing demand for subcutaneous formulations. Furthermore, it may help to reduce the number of *in vivo* experiments in animal models as they have a poor IVIVC with formulations designed for subcutaneous administration.