Understanding excipient effect *in vitro* using the Pion Scissor

Showcasing how the subcutaneous injection site simulator (Scissor) can be used to screen excipients to better understand their impact on formulations designed for subcutaneous delivery.

The subcutaneous (SC) route of administration has gained much interest in recent years, showing higher levels of patient compliance than current IV methods and giving a cost-effective alternative for health organisations. For this reason, a better understanding *in vivo* of the behaviour of these types of formulations is essential for more insightful development and application of these drugs in the future.

Scissor (Subcutaneous Injection Site Simulator) is an instrument that successfully mimics in vitro the SC environment, providing important information about the fate of a formulation upon subcutaneous injection. It simulates the SC injection site with respects to its physical, chemical, and physiological parameters. Previous studies using Scissor have revealed a correlation between Scissor and in vivo data for biopharmaceutical formulations.

Scissor can also distinguish between different formulations of the same API. This is particularly important as it allows the user to assess which excipients are important in promoting the stability of the API upon injection their effect in the formulation's performance.

METHOD

Solu-Cortef® (Hydrocortisone sodium succinate) is a corticosteroid used for several different conditions. Amongst those, Solu-Cortef® can also be used as an emergency therapy for patients with Addison's disease. It is usually administered via the IV or IM routes but more recently clinicians have been studying the possibility of administering it subcutaneously.

In this work we analysed three different formulations of Solu-Cortef® (Table I): two of the formulations were prepared in house (commercial formulation with added excipients) and the third was the commercial form only.

The diffusion of the API from the injection site was modelled using KinetDS using the Hill equation and it is based on the average release (n=3).

Figure 1. ScissorN1, the subcutaneous injection site simulator.

Table 1. Compositions of the different formulations analysed

Formulation number	pH	Formulation Composition/ Excipients
1	6.8	Commercial formulation (CF)
2	7.0	CF + 5% PEG 400 + 150 mM Mannitol
3	7.2	CF + 2% PEG 400 + 400 mM Mannitol + 150 mM NaCl

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RESULTS

Results show that the transmission throughout the assay was kept constant at around 100% indicating that the three formulations analysed are stable under conditions of the human body (100% transmission assumes a completely clear cartridge and 0% transmission a completely blocked one).

The diffusion profiles of the three different formulations is markedly different (Fig.3). The commercial formulation (black) presents has the lowest %diffused and the longest onset time. From the other two formulations, the highest PEG 400/lowest Mannitol concentrations (blue) resulted in the highest %diffused. The onset time for the two prepared formulations does not differ substantially though the commercial formulation seems to have a slower onset time.

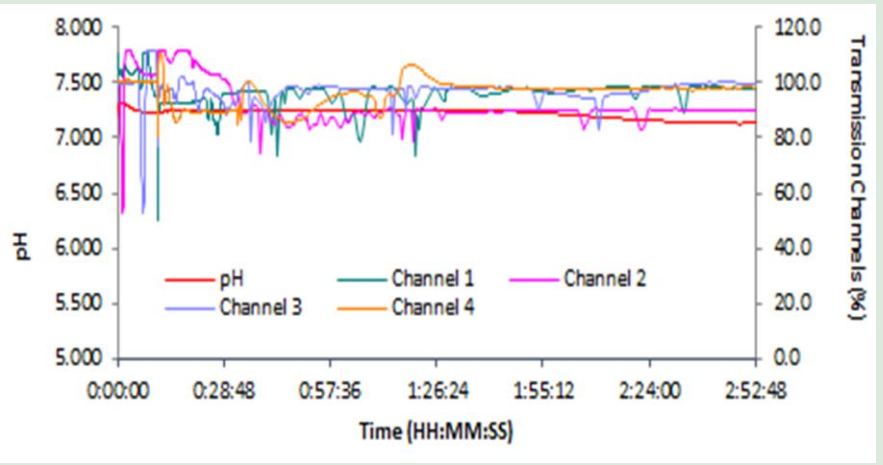

Figure 2. Typical transmission data for Solu-Cortef®

Modelled results shown in figure 4 (averages) also display a clear difference between the release profiles of the three formulations. The addition of different excipients to the commercial formulation has successfully changed the profile of diffusion as well as the max release obtained over the 3-hour experiment.

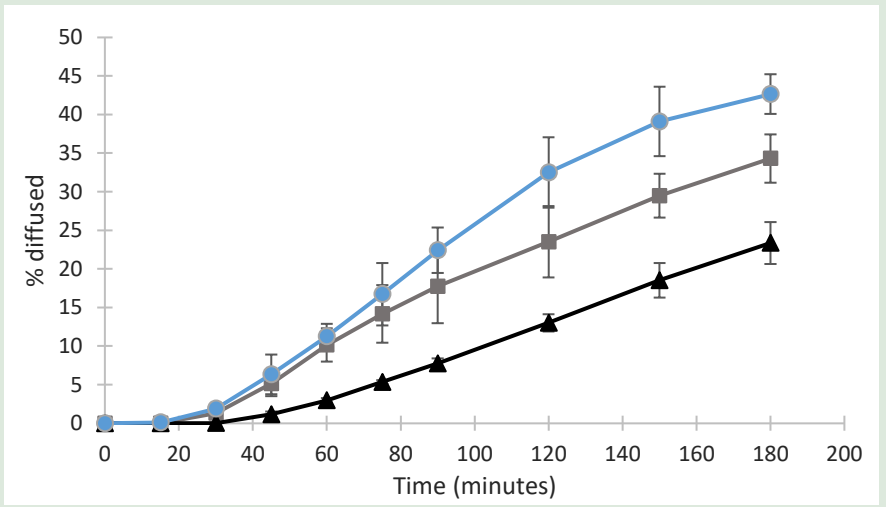

Figure 3. Diffusion of the three different formulations on Scissor (average ± SD). Black: formulation 1; Blue: formulation 2; Grey: formulation 3.

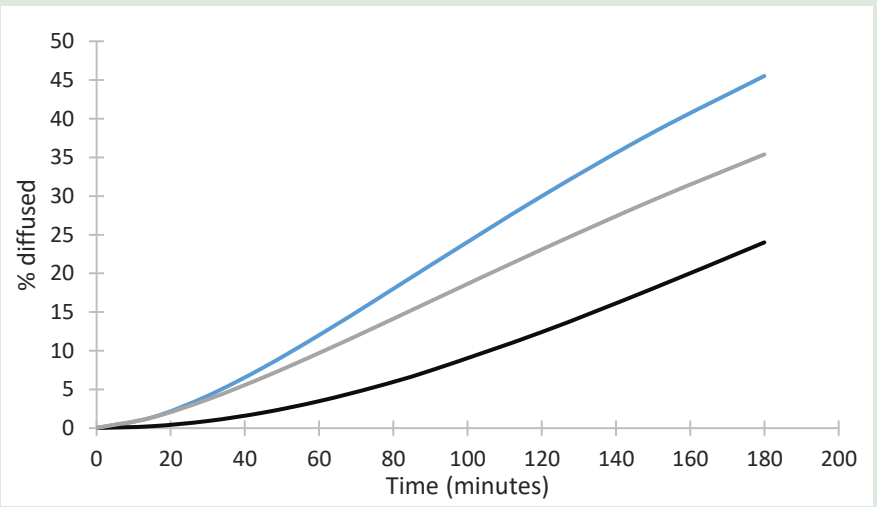

Figure 4. Average diffusion of the three different formulations when modelled as explained in the method. Black: formulation 1; Blue: formulation 2; Grey: formulation 3

VALIDATION

Despite the data obtained with non-protein formulations, Scissor's initial validation was carried out using antibodies. Four different antibodies with known %bioavailability at t = 6h (in humans) were analysed in Scissor used for the same length of time. The composition of the Extracellular Matrix (ECM) was varied in order to obtain the highest in vivo in vitro correlation.

Results show that an artificial ECM containing 10 mg/ml of HA provided the highest correlation with human in vivo bioavailability, with an IVIVC of 90%[1].

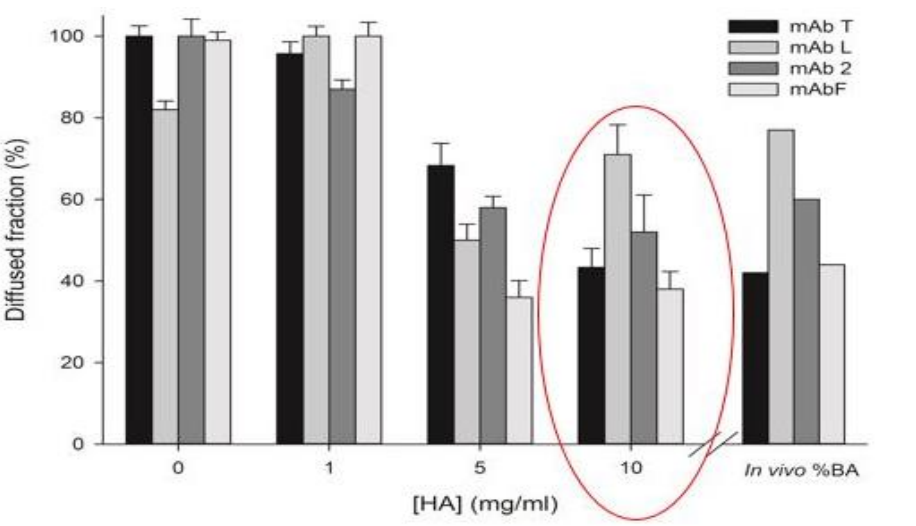

Figure 5. Comparison between the data obtained with Scissor and the human bioavailability of the four antibody formulations analysed.

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[1]Kinnunen, H. M. *et al. J Contr Rel* (2015) 214, 94- 102

DEPOT BEHAVIOUR

Scissor also has the capacity to monitor the behaviour of a depot (non-protein formulation) being formed in the subcutaneous space (Fig.6). In addition to the collection of images, the transmission data can also be collected during the length of the experiment.

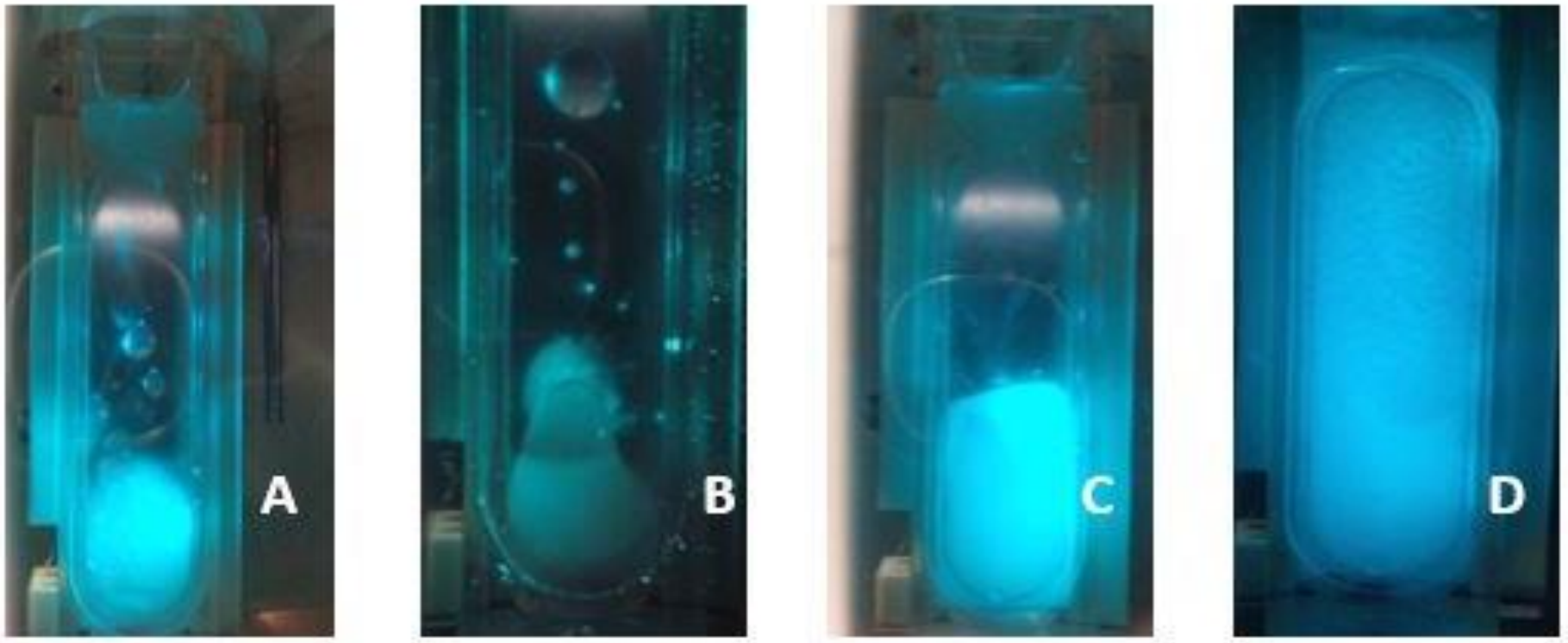

Figure 6. Physical changes of a non-protein subcutaneous formulation over time. A: 20 minutes after injection; B) 5h; C) 6h; D) 24h after injection

CONCLUSIONS

Scissor is an effective platform to test subcutaneous formulations in vitro.

The different Solu-Cortef® formulations analysed exhibited different release profiles, indicating that the instrument is capable of rank-order and differentiate between formulations of non-protein molecules.

Moreover, Scissor allows for the establishment of IVIVC as demonstrated by the work carried out with antibodies.

Whether for assessing the stability upon injection of a formulation, to evaluate the performance of a subcutaneous formulation to extrapolate the in vivo behaviour of a product, Scissor is extremely useful and optimising and accelerating the product development process.

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