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Validation of an automated method for compounding monoclonal antibody patient doses: case studies of Avastin® (bevacizumab), Remicade® (infliximab) and Herceptin® (trastuzumab)

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Introduction

Automated robots have come to the market as an alternative for manual compounding of drugs for IV administration.
According to the Summary of Product Characteristics (SPC), Monoclonal antibodies (mAbs) require gentle swirling to aid reconstitution (if lyophilized powder) and drawing into a syringe should be done slowly to avoid aggregation
Robotic procedure might harm delicate substances such as monoclonal antibodies (mAbs).

Objective

To assess whether a fully automated robotic procedure can achieve similar quality compared to manual compounding of mAbs patient doses.

Methods (I)

Robot and swirling protocol definition
The robot selected for the study was the i.v.STATION® (Bolzano, Italy, www.health-robotics.com). Swirling protocols visually identical to manual hand movements were programmed. A minimum of stress was pursued by visual inspection of drug glass vials filled with water.

Procedures to solubilize Remicade® and Herceptin®
For Remicade® and Herceptin®, three scenarios are compared: manual reconstitution according to the SPC (3 vials procedure I), robotic reconstitution in analogy with the manual procedure (3 vials procedure II), and a vigorously shaking worst-case scenario (1 vial procedure III).
The final concentration was 10 mg/ml for Remicade® and 21 mg/ml for Herceptin®.

Stress by aspiration and dispense
For all three mAbs, 1 ml was aspirated and dispensed one, five and fifteen times rapidly through a BD 18G 2" 1.2x50mm needle using a 20 ml B. Braun Omnifix syringe.

Methods (II)

Analytical methods
Five analytical techniques were used for protein characterization at Therapeomic Inc, Basel, Switzerland.
UV-Vis absorbance and 90° light scatter (LS) for qualitative information on aggregation state. Intrinsic fluorescence emission (IFE) (Trp, Tyr) provides information on conformation, aggregation state, and chemical degradation if in proximity to the intrinsic fluorophores. Nile Red fluorescence microscopy to assess size and shape of micrometer-sized aggregates. Field Flow Fractination (FFF) to determine molecular weight/size by static light scattering suitable to characterize loose aggregates.

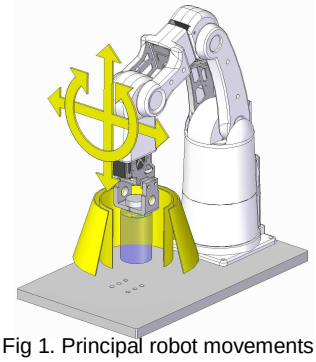


Fig 1. Principal robot movements

Results (I)

Four different principal robotic movements were programmed: (I) linear, (II) arch, (III) cone, and (IV) circle movement (Figure 1). Robotic solubilization with two arches, ten cones and two arches resulted reproducibly in a clear homogenous solution for both Remicade® and Herceptin®.

The worst-case scenario (procedure III, red line) showed changes in the aggregation state for all analytical methods except for intrinsic fluorescence emission (Figure 2, results shown for Herceptin®). No aggregation was detected for the vials reconstituted by manual solubilization procedures according to the SPC and by the automated method using the robotic system.

For all three mAbs under study, increasing numbers of aggregates were observed with increasing numbers of aspiration/dispense (AD) cycles (1, 5 and 15x).

Results (II)

Fig 2. UV-Vis, 90° LS, IFE and NR results for solubilization procedures and the effect of aspiration/dispense cycles for Herceptin®

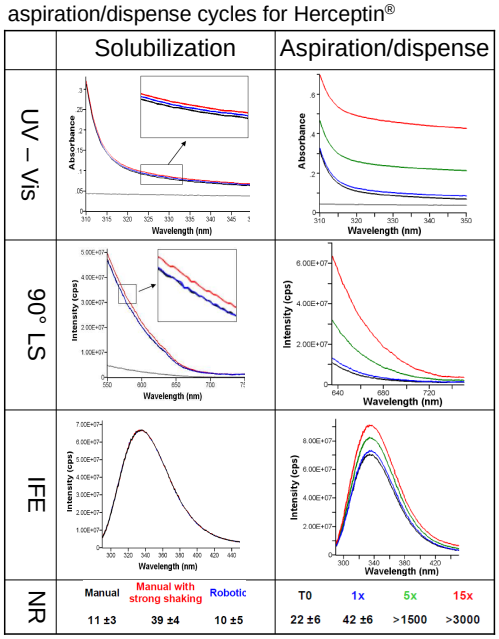


Fig 3. FFF results for the effect of 0, 1, 5, and 15 AD cycles for Herceptin®. Black, blue, green, and red represent respectively 0, 1, 5, and 15 cycles.

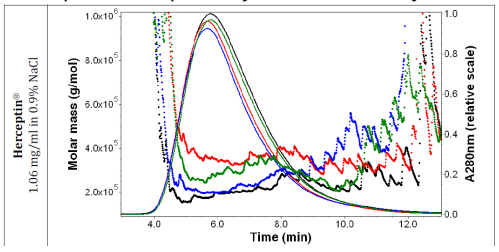
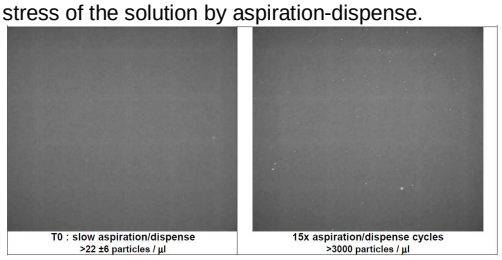


Fig 4. NR analysis of Herceptin® before and after stress of the solution by aspiration-dispense.



Conclusion

Robotic compounding of mAbs is feasible if programmed exactly according to the SPC. Robotic compounding of mAbs can be used to achieve reproducible high-quality compounding for delicate formulations.

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