W4139

Adaptive Perfusion: A Novel In Vitro Drug Release Testing Method for Complex Drug Products

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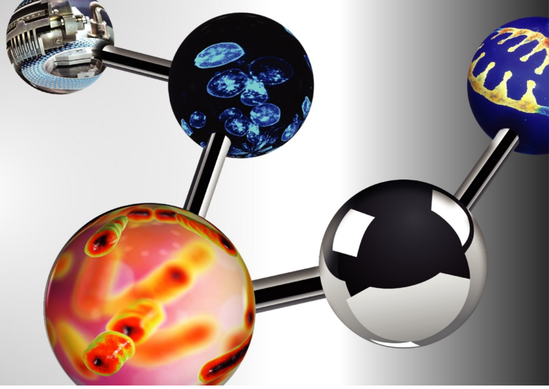

PURPOSE

Drug release testing is critical for evaluating the product quality of drugs. It may be challenging from an analytical perspective to test the drug release of complex drug products containing particulates. An ideal in vitro drug release test (IVRT) should be discriminatory enough to detect the effect of changes in the manufacturing process and of variations in product quality on drug release. However, most of the currently available IVRT methods fail to meet this criterion mainly due to the self-imposed rate-limiting step.

OBJECTIVE(S)

The objective of the current work is to develop a discriminatory new adaptive perfusion (AP) IVRT method, that allows investigation of the rate and extent of drug release from complex particulate formulations.

METHOD(S)

Based on the principle of tangential flow filtration (TFF), the developed AP method uses size-based separation of particulates to simultaneously measure the amount of drug released from and the amount remaining in particulates. Importantly, the TFF filters were pre-conditioned with unique conditioning solutions and processes to improve the reproducibility and robustness. In this study, using difluprednate as a model drug, several micelle and emulsion formulations with known variations were manufactured for testing.

RESULT(S)

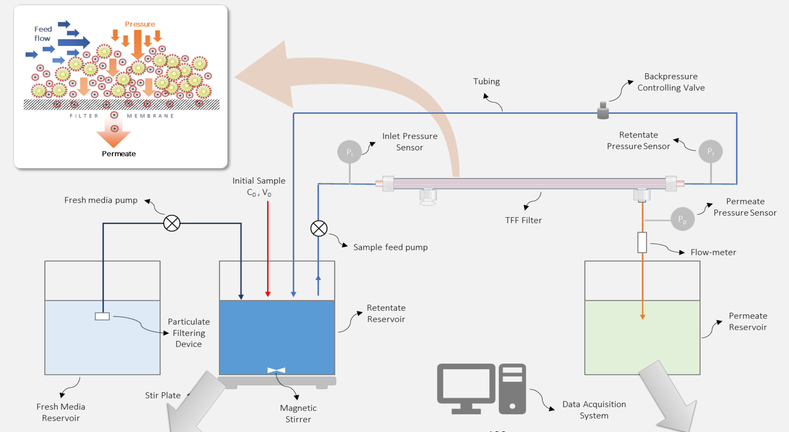

Figure 1. A schematic representation of adaptive perfusion.

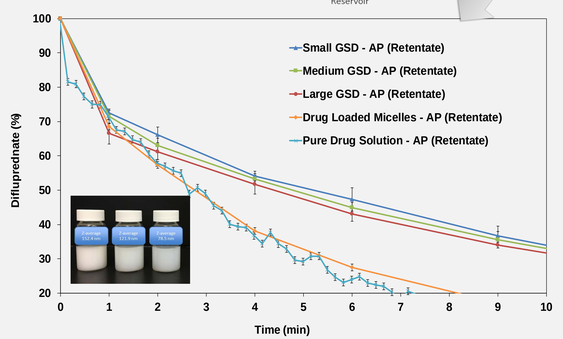

Figure 2. Initial rate of drug removal and the decline of drug concentration in the retentate reservoir using adaptive perfusion (n=3, mean ± sd).

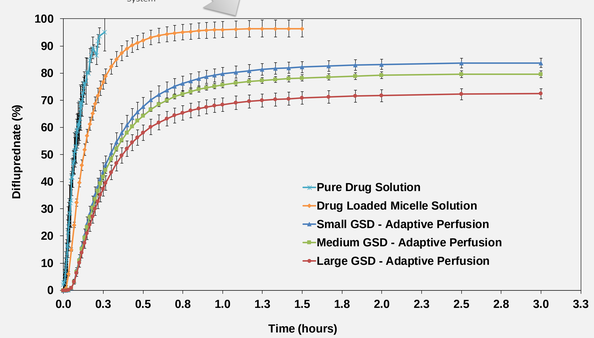

Figure 3. Extent of drug release from the difluprednate nanoemulsions depending on their globule size using adaptive perfusion (n=3, mean ± sd). "GSD" refers to globule size distribution.

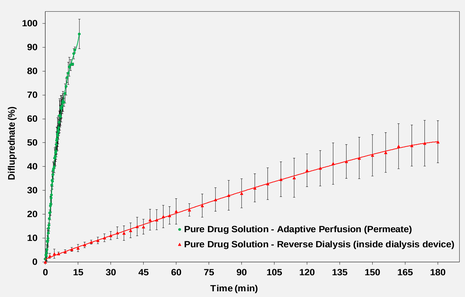

Figure 4. Comparison of rate of drug transfer from pure drug solution between the adaptive perfusion and the reverse dialysis (n=3, mean ± sd).

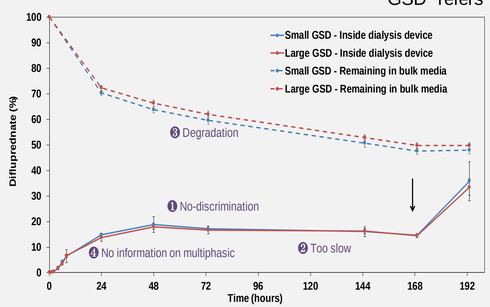

Figure 5. Rate of drug removal and drug release using reverse dialysis (n=3, mean ± sd).

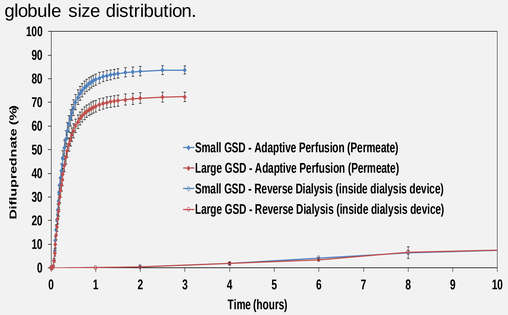

Figure 6. Comparison of extent of drug release (from small and large globule size difluprednate nanoemulsions) between the adaptive perfusion and the reverse dialysis (n=3, mean ± sd).

RESULT(S)

The AP method provided discriminatory drug release profiles for drug in solution, in micelles, and in nanoemulsions of small, medium, and large globule sizes. The drug release obtained using AP method was found to be significantly faster (e.g., minutes rather than hours) with higher extent of release (e.g., >60%) than the release obtained using conventional dialysis method.

CONCLUSION(S)

- The novel AP method provides a new approach to study IVRT from complex formulations.
- The method overcomes the limitation of the traditional IVRT method and provides a variety of tools that may be modulated to control the rate and extent of drug release depending on the type of drug product.
- AP may be used to support bioequivalence and product quality assessment of generic drugs and facilitate drug product development by giving deeper insight into drug release of complex formulations.

ACKNOWLEDGEMENTS

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DISCLAIMER

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.