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

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Introduction

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

Methods

Based on the principle of tangential flow filtration (TFF), the developed AP method uses size-based particulate separation 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 reproducibility and robustness. In this study, difluprednate was selected as a model drug and micelle and emulsion formulations with known variations were manufactured in-house for testing.

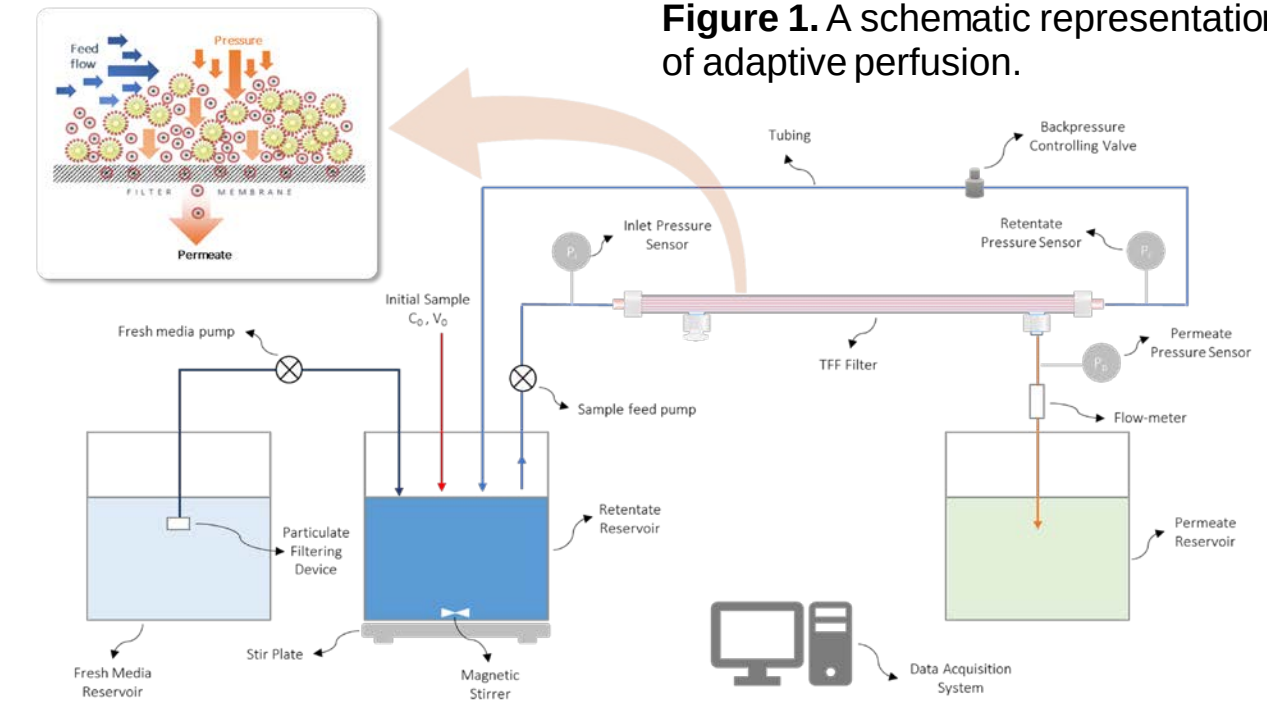


Figure 1. A schematic representation of adaptive perfusion.

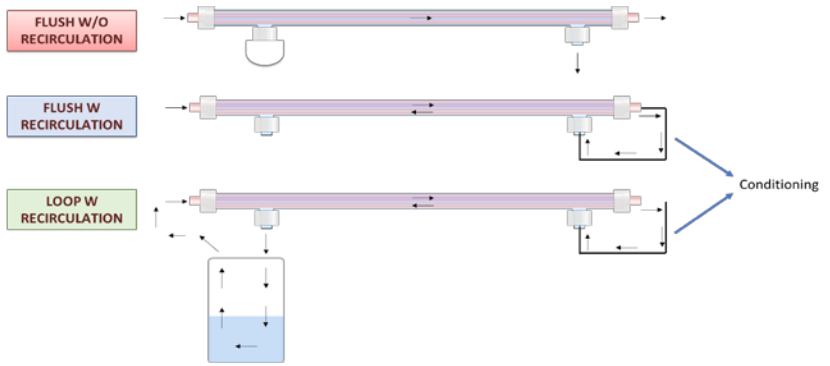
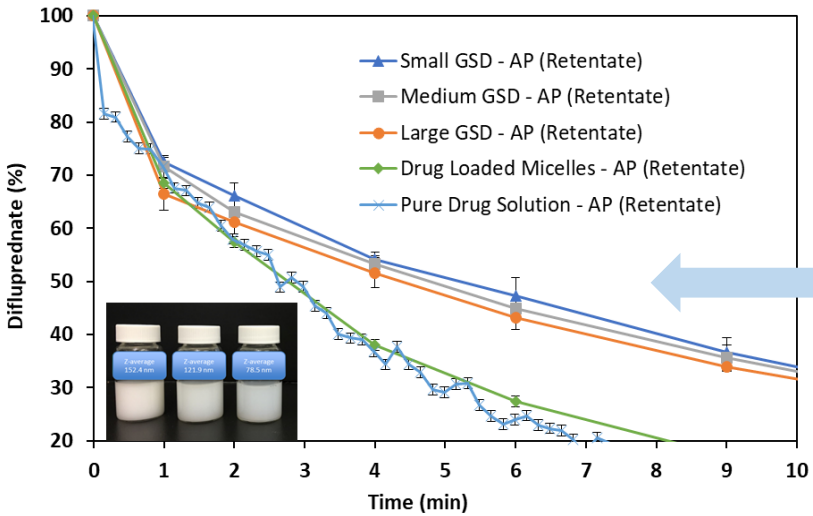
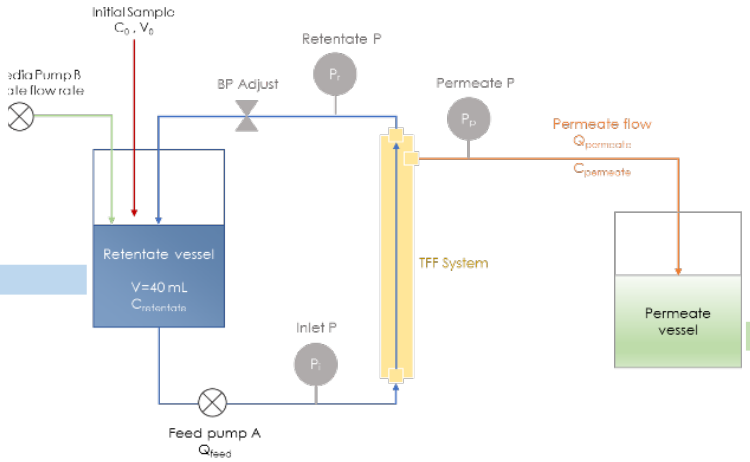


Figure 2. A schematic configuration for different conditioning processes

Results: AP vs. Dialysis





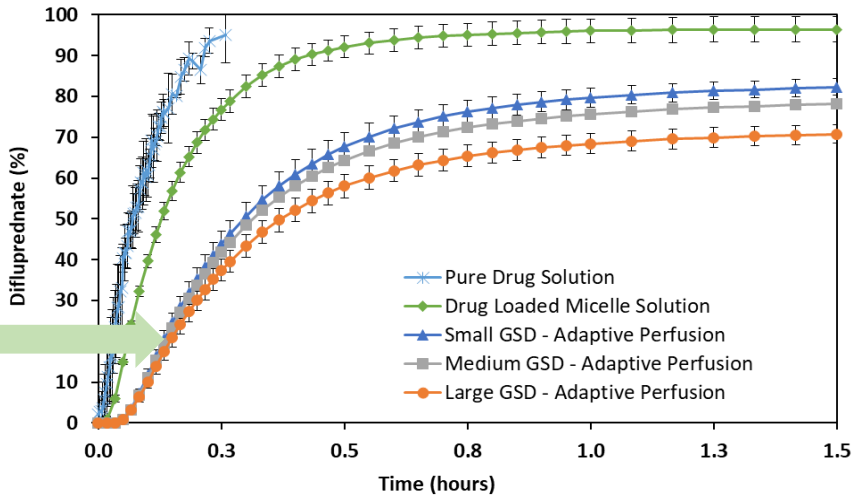
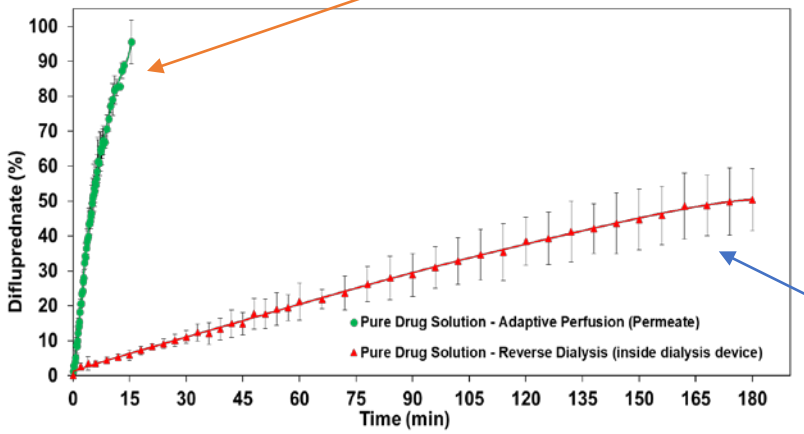
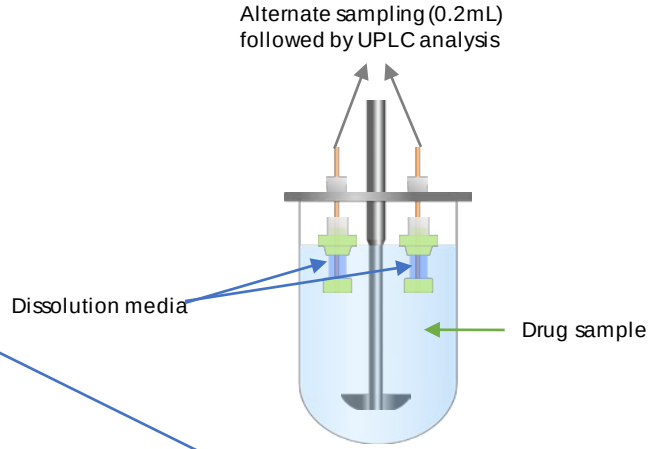


Figure 3. Initial rate of drug removal and the decline of drug concentration in the retentate reservoir for adaptive perfusion. (n=3, mean ± sd)

Figure 4. Extent of drug release from the diflupredate nanoemulsions depending on their globule size for adaptive perfusion. (n=3, mean ± sd)

Adaptive Perfusion (AP)





Dialysis

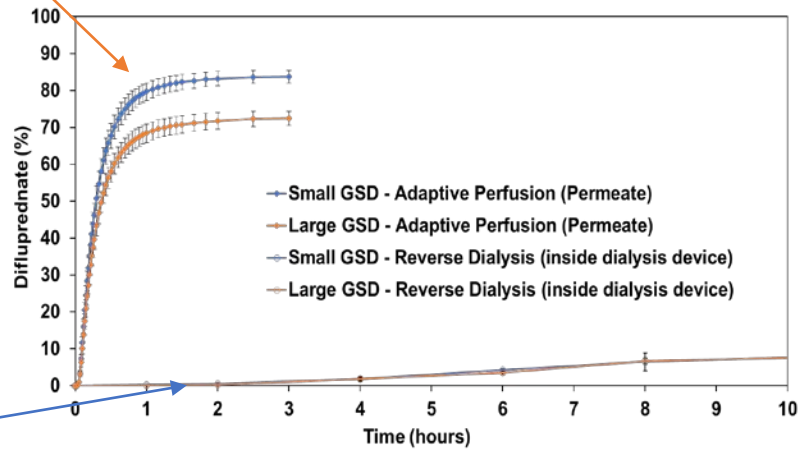


Figure 5. Comparison of rate of transfer from pure drug solution between the adaptive perfusion and the reverse dialysis. (n=3, mean ± sd)

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

Result

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

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Conclusion

The AP method provides a new approach to study in vitro drug release 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 in vitro 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 new drug product development by giving a deeper insight into drug release of complex formulations.

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