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

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Abstract

Background: Measuring drug release from complex products that contain particulates (such as emulsions, micelles, suspensions, liposome, drug-protein complexes) can be analytically challenging but is considered a critical test of product quality. An ideal in vitro drug release test (IVRT) should be able to detect critical manufacturing process changes as well as variations in the product quality and performance. However, most of the currently available IVRT methods fail to meet that need, mostly due to self-imposing rate limiting step (e.g., membrane diffusion).

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

Methodology: Based on the principle of tangential flow filtration (TFF), the developed AP method uses size-based particulate separation to simultaneous measure the amount of drug released from and amount remaining in formulation 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 various micelle and emulsion formulations were manufactured in-house and used as testing samples.

Results: 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 profile obtained using AP method was found significantly faster (e.g., minutes rather than hours) and higher (e.g., >60%) than the release obtained using conventional dialysis method.

Conclusion: The 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 can be modulated to control the rate and extent of drug release depending on the type of drug product. AP may serve as a useful tool to support bioequivalence assessment for generic products as well as serve as a quality control test to ensure batch-to-batch consistency. Such methods can also facilitate new drug product development by providing a better understanding of drug release, especially for complex formulations.

Introduction

Adaptive perfusion (AP) is a novel drug release testing method, suitable for evaluation of drug release for a variety of complex formulations. This method can overcome the limitations of existing technologies and excels at detecting and discriminating against critical manufacturing process changes as well as variations in the product quality and performance.

Materials and Methods

AP operates based on the tangential flow filtration principle (Figure 1). The testing sample (i.e., difluprednate in solution, in micelles, and in emulsions) was directed to flow through a TFF filter (MicroKros 100kD MWCO, 20 cm^2, Repligen) and subjected to a pressure-driven filtration process, wherein a portion of the fluid (permeate) containing components smaller than the pores passed through the TFF filter into the permeate reservoir. The remaining fluid (retentate), which contained the larger retained components, was circulated back to the feed reservoir (also known as the retentate reservoir). Returned fluid was concurrently diluted with the fresh media to compensate for the loss of volume. This kept the total sample volume constant in the feed reservoir (40 mL) and maintained the sink conditions. Samples in both permeate and retentate reservoir were analyzed by ultra-performance liquid chromatography (UPLC). Conventional reverse dialysis was also performed to compare with AP method. To demonstrate the discrimination capability of the adaptive perfusion method, pure drug, micelle solution, and three difluprednate nanoemulsions (small, medium, and large globule size distribution (GSD) were evaluated and compared to the conventional dialysis technique (results are shown in Figures 2-6).

Results and Discussion

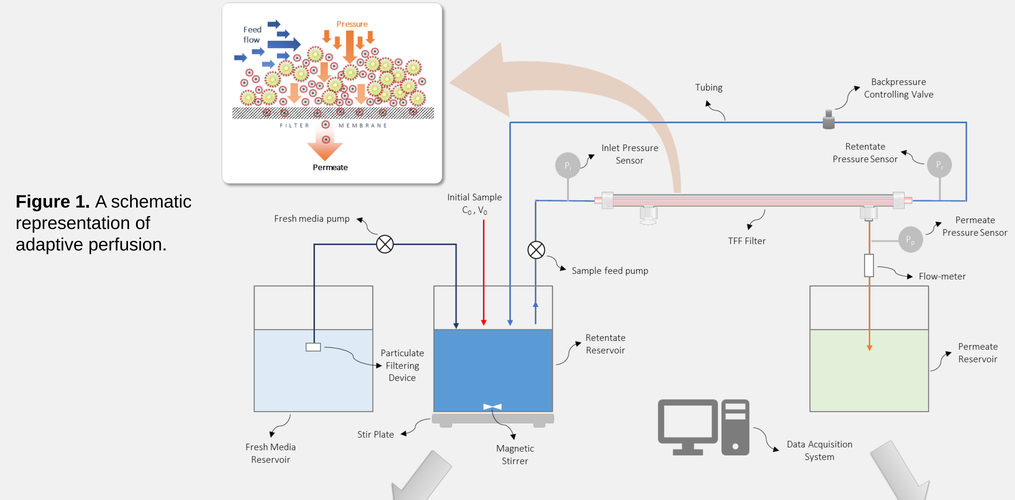

Figure 1. A schematic representation of adaptive perfusion.

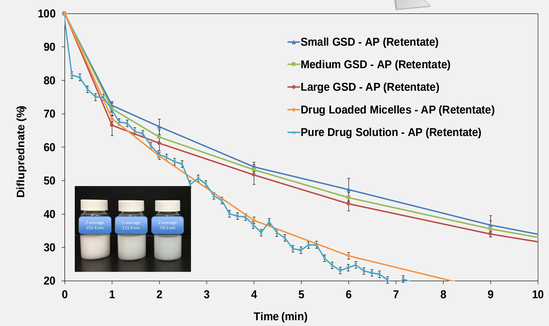

Figure 2. Initial rate of drug removal and the decline of drug concentration in the retentate reservoir for adaptive perfusion (n=3, mean ± sd).

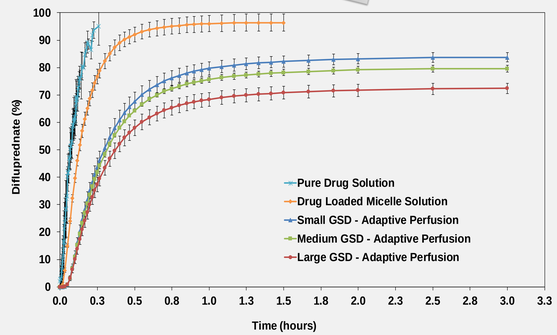

Figure 3. Extent of drug release from the difluprednate nanoemulsions depending on their globule size for adaptive perfusion (n=3, mean ± sd).

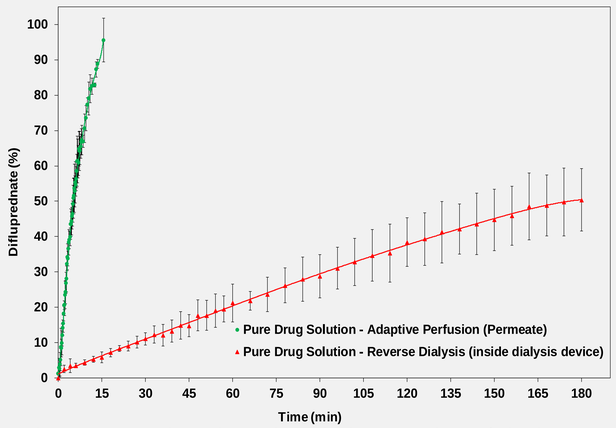

Figure 4. Comparison of rate of transfer from pure drug solution between the adaptive perfusion and the reverse dialysis (n=3, mean ± sd).

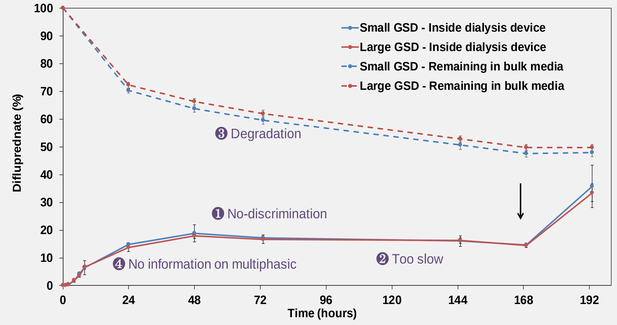

Figure 5. Rate of drug removal and drug release for reverse dialysis (n=3, mean ± sd).

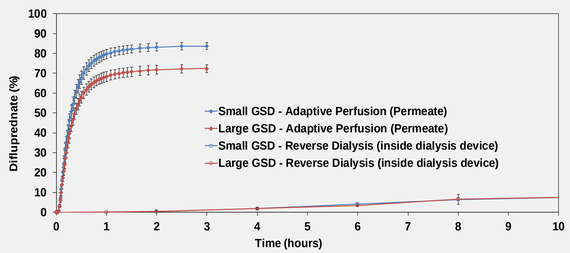

Figure 6. Comparison of extent of drug release (from small and large difluprednate nanoemulsions) between the adaptive perfusion and the reverse dialysis(n=3, mean ± sd).

Conclusion

Adaptive perfusion enabled analysis of correlation between a critical quality attribute (e.g., GSD) of the formulation and its performance attribute (i.e., release characteristics). This novel filtration-based technique, free from the constraints of rate-limiting factors such as diffusion, has a potential to be extended further to analyze the impact of variations in manufacturing process on the drug distribution and release characteristics of complex drug products.

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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.