Automated Adaptive Perfusion: A Novel *In Vitro* Release Testing System for Complex Drug Products

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PURPOSE

Drug release testing is critical for evaluating the product quality of drugs. An ideal in vitro drug release test (IVRT) should be discriminatory enough to detect the effect of changes in the manufacturing process and or variations in product quality on drug release. However, from an analytical perspective, it can be challenging to accurately measure the drug release from complex drug products containing sub-micron particulates, such as micelles, emulsions, liposomes, and nano-suspensions. Often, a semi-permeable membrane such as dialysis membrane is needed to retain the particles while allowing the released drug to diffuse across the membrane. Yet, the process of diffusion highly depends on the drug concentration gradient and may become the rate-limiting step if the rate of drug release from particles approaches or becomes faster than the rate of diffusion across the membrane.

Recently, a novel IVRT method using adaptive perfusion (AP) has been developed that overcomes the limitations of measuring drug release through conventional dialysis diffusion systems[1]. Drug release profiles obtained using AP IVRT is significantly faster (e.g., minutes rather than hours) and higher (e.g., >60%) than the release obtained using dialysis method (Figure 1). An advantage of AP IVRT is that the method conditions (e.g., filter MWCO, feed flow rate, applied backpressure, rate of dilution and medium volume) can be modulated to control the rate and extent of drug release. However, setting and controlling these parameters can give rise to a labor-intensive manual process.

OBJECTIVE

To develop a fully automated AP system (Figure 2) to improve accuracy of the existing AP method and reduce the manual labor required to set-up and run an experiment.

METHOD

The new AP IVRT method is based tangential flow filtration (TFF) and uses size-based separation of particulates. It can simultaneously measure the amount of drug released and the amount of drug remaining in particulates. In this study, a system control program was developed using LabVIEW (National Instruments, TX, U.S.) to achieve the automation of the AP method. The automated system was validated by testing several diflupredate emulsion formulations with different globule size distribution (GSD) which were manufactured via different processes. The result generated with the new method was compared with the results obtained with the manual AP method.

RESULTS

The drug release profile obtained using the new automated AP IVRT method was found to have similar results (e.g., releasing rate and releasing extent) compared with results from the previous manual AP method (Figure 3). The customized LabVIEW control system (Figure 4) maintained constant retentate volume with high precision and accuracy through a feedback control algorithm (Figure 5). The automation function also led to less experimental time (8% less) and significantly simplified steps (75% less) compared with the previous manual AP method (Figure 6).

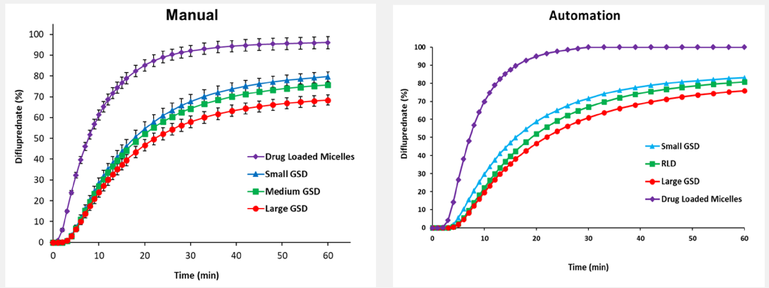

Figure 3. Similar permeate results from the automated AP system (n=1) compared with the previously manual AP method (n=3, mean ± sd). "GSD" refers to globule size distribution. "RLD" refers to reference listed drug.

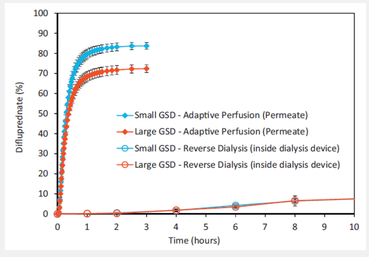

Figure 1. Comparison of extent of drug release (from small and large globule size diflupredate nanoemulsions) between the AP and the reverse dialysis (n=3, mean ± sd)[1].

Feedback-control between the retentate volume and the flow rate of the feeding pump (right).

Multiple solvents for automatic pre-experimental and post-experimental conditioning process.

Figure 2. The setup of the automated AP IVRT system.

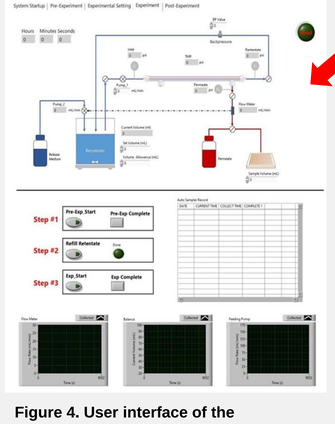

Figure 4. User interface of the automated AP system

Figure 6. Operational step comparison between manually AP method and automated AP method.

Procedure	Manual	Automation
New Fiber Washing	17 Steps	2 Steps
Pre-Experiment	20 Steps	3 steps
Experiment	75 Steps	24 steps
Post-Experiment	14 Steps	2 steps

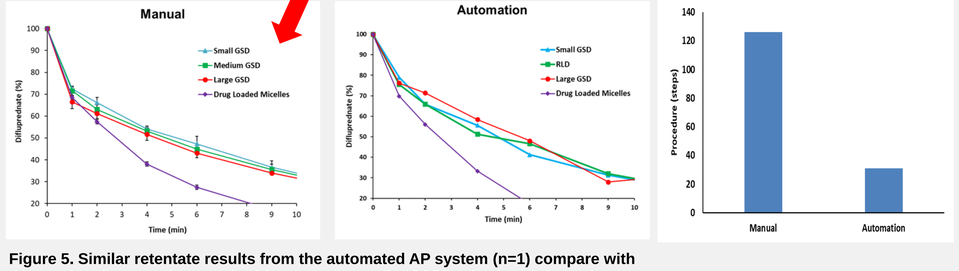

Figure 5. Similar retentate results from the automated AP system (n=1) compare with the previously manual AP method (n=3, mean ± sd). "GSD" refers to globule size distribution. "RLD" refers to reference listed drug.

CONCLUSIONS

- The automated AP system simplified the operational procedures, reduced the personnel burden, and offers more reliable control mechanism compared to the previously reported AP method.[1]
- Notably, the new automated AP improves the operation of AP, which paves the way for routine use of the AP method for IVRT studies of complex formulations.
- The automated AP method 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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REFERENCE(S)

1. Patel D, Zhang Y, Dong Y, Qu H, Kozak D, Ashraf M, Xu X. Adaptive perfusion: An in vitro release test (IVRT) for complex drug products. Journal of Controlled Release. 2021 May 10;333:65-75.

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