

Impact of apparatus and adaptor setups on in vitro drug release of ophthalmic semi-solid drug products

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PURPOSE

In vitro release testing (IVRT) is a useful tool for evaluating drug product quality and performance. For complex formulations such as ophthalmic ointments, there are currently no standardized sample adaptors or drug release apparatus setups for IVRT studies. The aim of this study was to provide a better understanding of the impact of apparatus and sample adaptor setups on IVRT of ophthalmic ointments.

METHODS

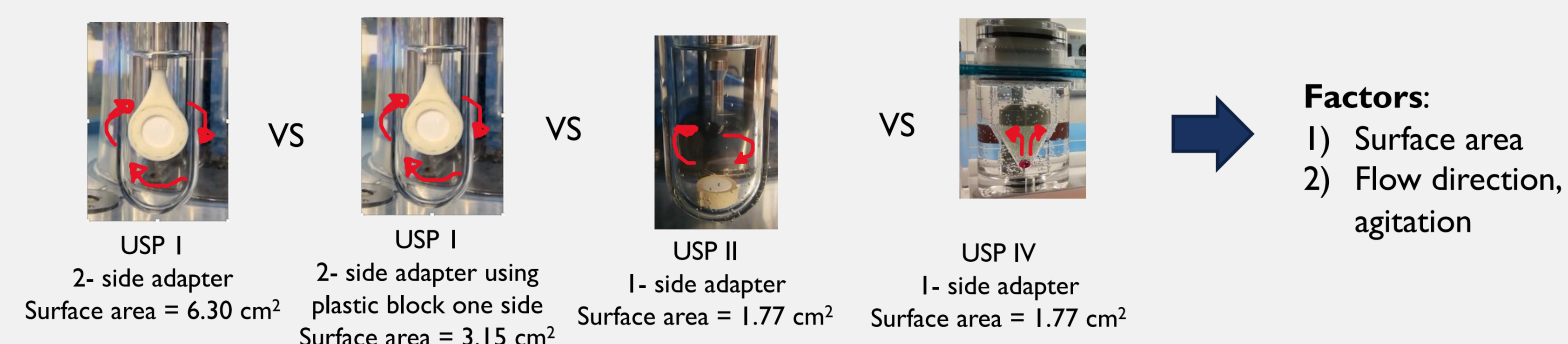
- Dexamethasone (DEX) ophthalmic ointment was selected as a model product. DEX ointment containing 0.2% of DEX, 5% of mineral oil, 0.5% of chlorobutanol, and 94.3% of petrolatum on a w/w basis was prepared using a high shear mixer.
- A novel two-sided adapter was developed to enlarge the release surface area (Figure 1). DEX ointment was placed in one-sided or two-sided release adaptors coupled with 1.2 μm polyethersulfone (PES) membranes, and the drug release was studied in different USP apparatuses (I, II and IV).
- DEX concentrations in the release samples at various timepoints were determined by HPLC analysis. Drug release profiles were plotted as percent cumulative drug release and as surface area normalized cumulative amount against time. Plots of surface area normalized cumulative drug release vs. logarithm of time (or square root of time) was used for linear regression to calculate release rate.



Figure 1 A: Compartments of two-sided semisolid adapter, B: Two-sided semisolid adapter in vessel

RESULTS

Impact of sample adaptor setups



Factors:
1) Surface area
2) Flow direction, agitation

This one-sided adapter and the two-sided semisolid adapter coupled with USP apparatus I were used to investigate the effect of exposed surface area on drug release. The release profiles of dexamethasone ointments using these two adapters are shown Figure 2. Considering the cumulative drug release per area, the release profiles of the two adapter setups were similar (Figure 2A). The percent drug release was directly proportional to the surface area (Figure 2B). The two-sided adapter using membrane showed a higher percent cumulative drug release compared to the one-sided adapter.

Impact of apparatus/flow of medium onto the surface of the ointments

Drug release from USP apparatus II with immersion cells in which the flow of the medium is rotated on the top of the adapter, and USP apparatus IV with a one-sided semisolid adapter in which the flow of the medium is upward facing the adapter, were compared. The results revealed that cumulative drug release amounts per area and percent cumulative drug release obtained from the USP apparatus IV were higher than those of the immersion cells as illustrated in Figure 3A and 3B, respectively. Drug release rates from the USP apparatus IV were also significantly greater than those from USP apparatus II with immersion cells. These results suggested that the agitation flow of USP apparatus IV enhanced the amount of drug release and the release rate.

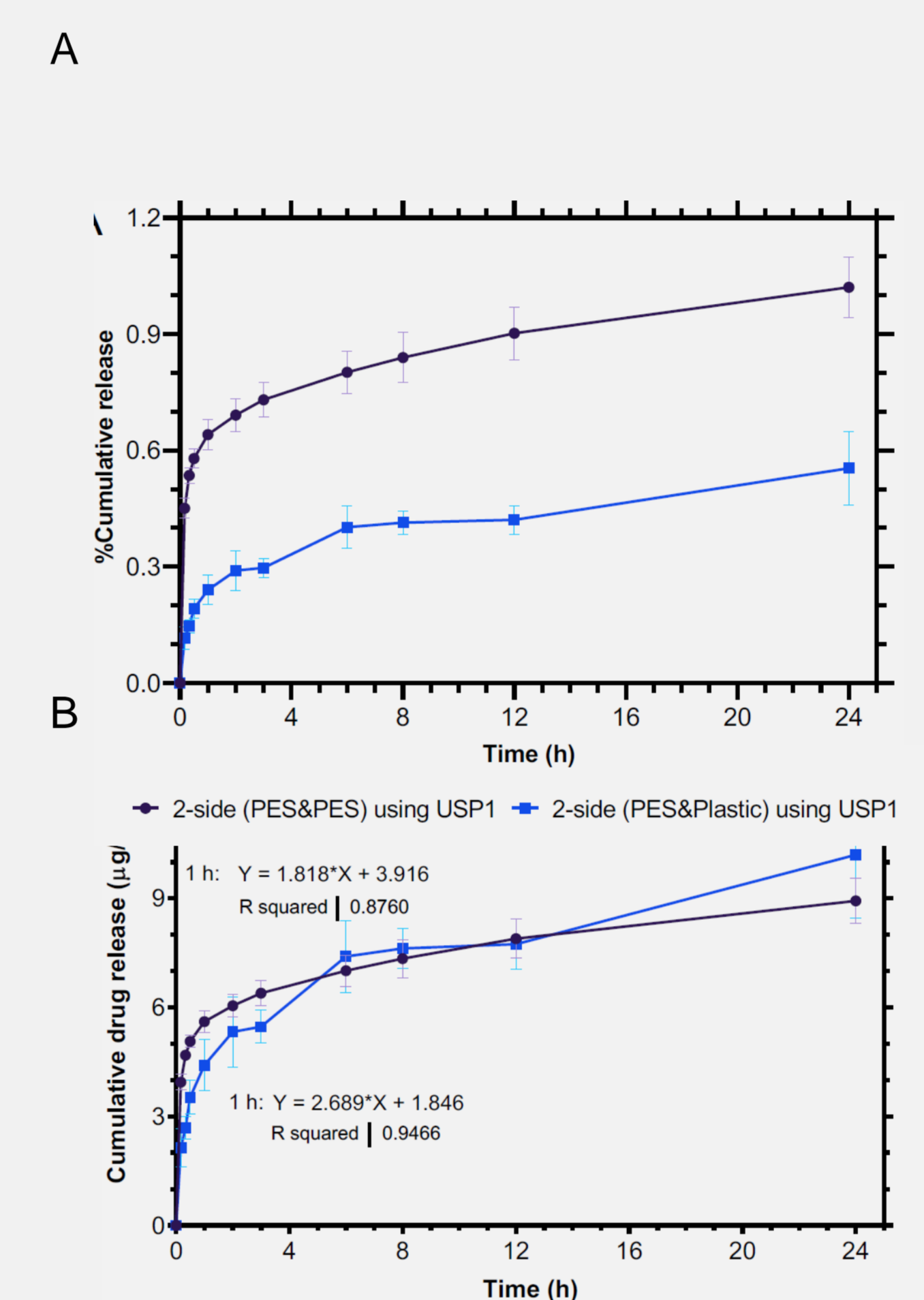


Figure 2 *In vitro* release profiles using PES membrane for both sides of two-sided semisolid adapter and one side with non-permeable plastic membrane in USP apparatus I (mean \pm standard deviation, n=3)

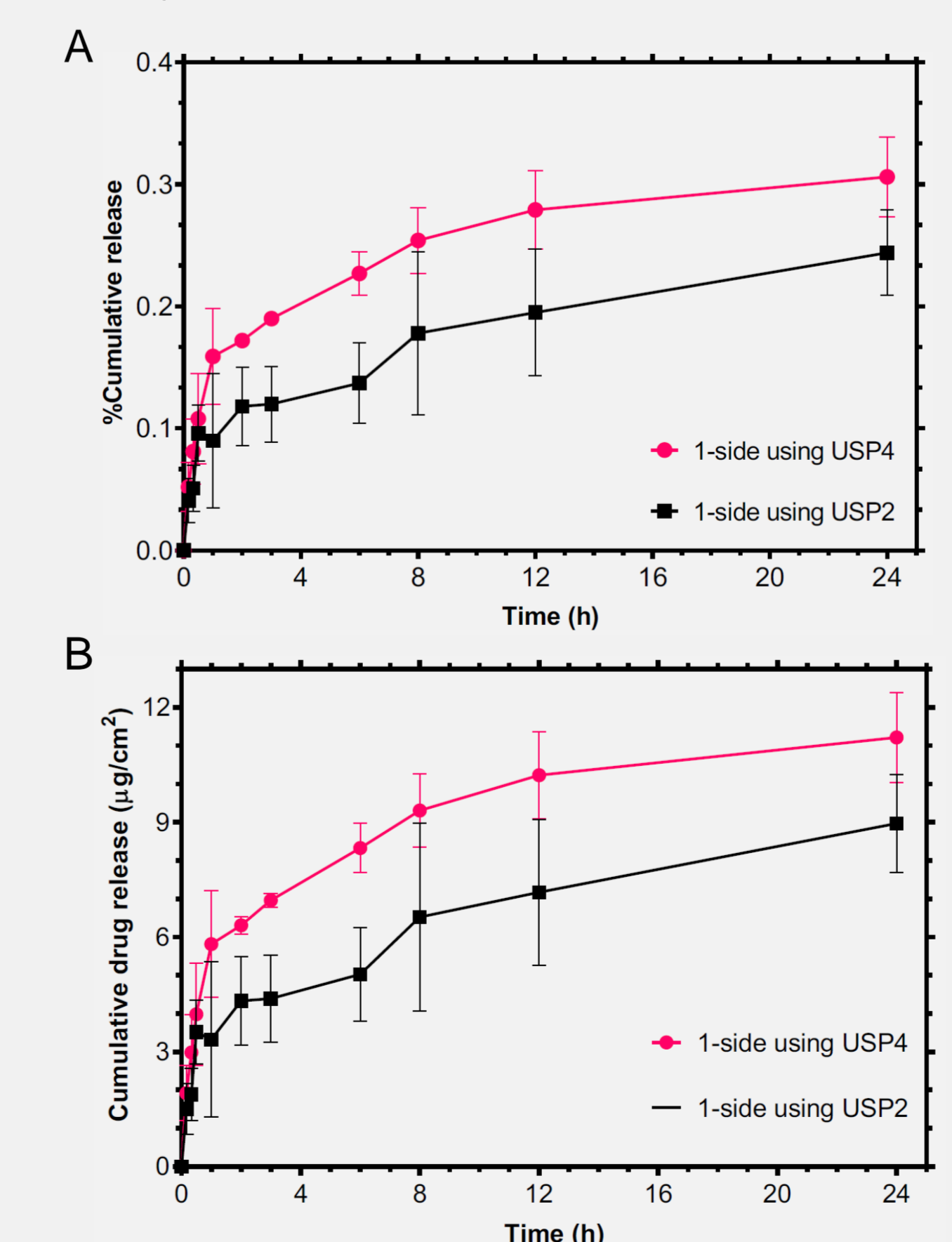


Figure 3 *In vitro* release of dexamethasone using one-sided semisolid adapter in USP apparatuses II and IV (mean \pm standard deviation, n=3)

CONCLUSIONS

- The sample adaptor setups (i.e., 1 sided vs. 2 sided) had a minimal impact on cumulative drug release amount per area or release rate. The exposed surface areas did not significantly affect drug release rate.
- However, release rates obtained using different apparatuses exhibited significant differences, which may be due to different flow properties of the medium on the surface of the ointments/adapters. USP apparatus IV with agitated flow enhanced drug release rates compared with USP apparatus II.
- The results from this study can assist researchers in both the pharmaceutical manufacturing and pharmaceutical research sectors to design an apparatus and sample adaptor setup of IVRT for semisolid drug products.

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