In vitro release and theoretical modeling of a selection of formulations in modified mini-IDR™ holders

E. Ahnfelt, E. Sjögren, N. Axén, and H. Lennnäss

Institution of Pharmacy, Uppsala University, Uppsala, Sweden
emelie.ahnfelt@farmaci.uu.se

ABSTRACT SUMMARY
A novel application of the µDISS profiler™ with modified mini-IDR™ sample holders for drug release profile investigations was developed. Theoretical modeling was applied to the data acquired from the µDISS profiler and analysis of the mechanisms of drug release and the impact of the filter choice, was performed. The method showed promising drug release results from both solutions and from modified release formulations. However, investigations with immediate release tablets illustrate a limitation of the method.

INTRODUCTION
In vitro methods for drug release profiles are important in the drug development process. However, for parenteral modified release (MR) formulations, there is no standardized in vitro method. The µDISS profiler™ with modified mini-IDR™ discs as sample holders might be suitable for such studies, especially when only a small amount of formulation is tested.

The aim of this study was to refine and validate a novel in vitro dissolution method based on the µDISS profiler™, intended for drug release characterization of different parenteral formulations and to characterize the partitioning of the drug to the applied filter.

EXPERIMENTAL METHODS
Modified mini-IDR™ holders were manufactured from magnetic ferritic stainless steel. A small cylindrical cavity (V=21 µl) was drilled centrally in the disc and the formed cavity is the sample reservoir. To constrain the sample to the cavity, the opening was covered with a fine mesh or filter which was held in position with a ring-shaped magnet placed centrally over the cavity opening, on top of the filter. Different filters were tested. The modified sample holder was used together with the standard µDISS profiler™ for drug release profile characterizations of metoprolol and diclofenac in both aqueous solutions and formulations. Three clinically used tablets were tested: Immediate release (IR) Seloken 50 mg, Voltaren T 25 mg and MR Seloken ZOC 100 mg.

To prepare the aqueous solutions, the substance was dissolved in deionized water placed in the sample reservoir, which was covered with a nylon mesh (pore size 150 µm), or a polyvinylidene fluoride filter membrane (pore size 0.45 µm), or with a cellulose based dialysis membrane (pore size 12400 Da, corresponding to approximately 0.003 µm).

The solid formulations were crushed and sieved to achieve a particle size between 0.7 and 1.0 mm to fit into the sample reservoir. The Seloken ZOC MR formulation consists of small pellets, individually coated with a polymer film. The tablet matrix was dissolved in deionized water and the coated pellets (approximate size 0.5 mm) were released. To avoid air bubbles under the filter, both the IR and MR particles were mixed with deionized water just prior to the start of the release test. The slurry was placed in the sample reservoir which was covered with the nylon mesh.

For Seloken ZOC MR, the release tests were performed in deionized water, all other data were acquired in phosphate buffer saline (PBS) at a pH of 7.4. The drug release media was kept constant at 37 °C and the sample holders were rotated at 400 rpm during the tests.

The drug release data was analyzed with theoretical models based on Baker’s and Noyes Whitney’s modifications of Fick’s law of diffusion. Estimations of the parameters k_e (for aqueous solutions), k_d (for IR tablets) and k_f (for MR tablets) (see Figure 1) were performed.

![Figure 1. Schematic illustration of the compartments and the constants used in the drug release modeling. For the aqueous drug solutions, k_e (from Eq. 1) was estimated, for the IR tablets, k_d (from Eq. 2), was estimated and k_f (from Eq. 1) was estimated from the MR tablet.](image-url)
Baker’s equation (Eq. 1) is applicable for drug transport from a reservoir across a filter to a solution.

\[
\frac{dM_t}{dt} = \frac{ADs_k p}{l} M_0 - M_t \quad \text{(Eq. 1)}
\]

M is the absolute cumulative amount of drug released at the time t, A is the surface filter area, D is the diffusivity through the solvent and \( k_p \) is the partitioning constant to the filter with thickness l. \( M_0 \) is the amount of drug in the reservoir at time zero and \( V_r \) is the volume of the drug reservoir. The constant \( k_{film} = \frac{ADs_k p}{l} \) was estimated for Seloken ZOC MR to describe the transport across the polymer coating.

For the solid IR formulations, estimations of \( k_{diss} \) were performed with a modified version of Noyes Whitney’s equation (Eq. 2):

\[
\frac{dM_t}{dt} = M_p^2 k_{diss} (M_s - M_t) \quad \text{(Eq. 2)}
\]

where \( M_p \) is the mass of the solid particles, \( M_p^2 \) is proportional to particle surface area, \( M_s \) is the amount of drug in a saturated solution and \( M_t \) is the absolute cumulative amount of drug released at time t and \( k_{diss} \) is a constant which includes the diffusivity constant for the stagnant layer and the geometrical dimensions of this layer and the release medium.

A statistical ANOVA evaluation of the aqueous solutions \( k_p \)-values over the mesh, filter and membrane were performed.

RESULTS AND DISCUSSION

The release profiles for the aqueous drug solutions are shown in Figure 2. Significant differences in \( t_{max} \) and \( k_p \)-values for metoprolol in aqueous solution were observed for the three filters. For the nylon mesh, \( t_{max} \) and \( k_p \)-values were determined to be 36 sec and 0.68 respectively. For the filter membrane, the values were 3.8 h and 0.0015 respectively and for the dialysis membrane, 9.9 h and 0.00051 respectively.

![Figure 2. The release profiles of metoprolol and diclofenac in aqueous solutions.](image)

Significant differences in \( t_{max} \) and \( k_p \)-value were also observed for diclofenac in aqueous solution for the three filters. For the mesh, \( t_{max} \) and \( k_p \)-value were 40 sec and 0.45 respectively, for the filter membrane 3.3 h and 0.0012, respectively and for the dialysis membrane 6.5 h and 0.00043, respectively.

Release profiles for the formulations are shown in Figure 3. Estimated \( k_{diss} \)-value for Voltaren T was 0.0042 s\(^{-1}\)µg\(^{-2/3}\) and 0.016 s\(^{-1}\)µg\(^{-2/3}\) for Seloken. The estimated \( k_{film} \)-value for Seloken ZOC MR in deionized water as release medium was 0.066 µm\(^{-1}\)s\(^{-1}\).

![Figure 3. Release profiles of commercially available formulations, Seloken, Voltaren T and Seloken ZOC.](image)

\( t_{max} \) increased from seconds to hours when comparing mesh with filter membrane and dialysis membrane. This suggests a correlation between increasing pore size and increasing \( t_{max} \). A decrease in \( k_p \)-values also indicates that a smaller pore size increases the risk of interaction with the filter.

CONCLUSION

The in vitro method can potentially be applied for parenteral formulations such as emulsions, suspensions and liposomes, but should not be used for solid formulations such as the IR tablets in this study. The filter used should preferably be of mesh type, but with small enough pore size to keep the formulation in the sample reservoir. Future research will focus on filter choice and characterization of parenteral MR formulations.

REFERENCES


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