Supersaturation and Trans-membrane Flux Behavior of Meloxicam Solid Dispersions

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INTRODUCTION

This study was aimed at comparing the supersaturation ability of Soluplus® and Kollidon® VA 64 with low soluble compound Meloxicam as a model drug by using real time concentration monitoring and dissolution – permeability setup.

MATERIALS AND METHODS

Soluplus®, Kollidon® VA64, Kolliphor® TPGS and meloxicam (API, Figure 1) were obtained from BASF Corporation. The amorphous solid dispersions (ASD) were prepared on Thermo Fisher Pharma 11 mm co-rotating twin screw equipment operating at 155 °C with feed rate of 1.25 kg/hour and with screw speed of 150 rpm.

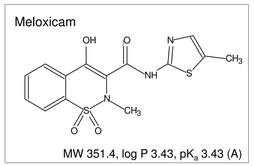

Figure 1. Structure and physicochemical properties of Meloxicam, a model drug used in this study.

The following formulations were studied:

a) Untreated Meloxicam
b) 15% Meloxicam/85% Soluplus
c) 15% Meloxicam/85% Kollidon VA64
d) 15% Meloxicam/72.5% Kollidon VA64/12.5% Kolliphor TPGS
e) XRD and DSC data (not presented) for the ASD with 15% load of API showed that VA 64 Formulation had some crystalline material present in the mixture while Soluplus ASD contained only amorphous material.

The µFLUX™ device is an add-on option to the µDISS Profiler™ instrument (Pion Inc.) consisting of four pairs of temperature controlled side-by-side permeability chambers mounted on top of the stirring platform. The Revision 2 of the device was used in the study with available permeation area 1.54 cm^2. Each pair (Figure 2) consists of a donor and an receiver compartment separated by a filter-supported membrane. GIT-optimized artificial membrane (Double-Sink™ PAMPA[1]) was used in this study. The donor compartment was filled with 16 mL of the media of interest. For this study the receiver compartment contained Acceptor Sink Buffer at pH 7.4 (ASB-7.4, Pion Inc). The integrated fiber-optic UV probes were positioned in the donor and receiver compartments allowing real time concentration monitoring in all chambers.

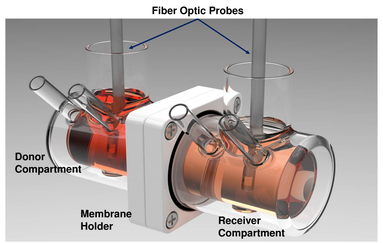

Figure 2. A schematic showing a pair of the donor and receiver chambers. FO probes attached to the µDISS Profiler monitor concentrations in the donor (left) and receiver (right) compartments. The chambers can be separated by PAMPA, cell-based (Caco-2 or MDCK), dialysis, or other types of membranes mounted in the Membrane Holder.

The dissolution media for this study was SGF with no pepsin (pH 1.6). All measurements were performed at ambient temperature.

Flux Measurements

Flux (J) of a drug through a biological membrane is defined as the amount of drug crossing a unit area perpendicular to its flow per unit time. In the one-dimension steady-state approximation it may be expressed through the effective permeability coefficient P_e and concentration $c(t)$ in the donor compartment as follows

$$J(t) = \frac{dm}{A \cdot dt} = P_e \cdot c(t) \qquad (1)$$

In the µFLUX device, where area A is known (1.54 cm^2) and the rate of appearance of material $\frac{dm}{dt}$ can be determined at any time point by continuously monitoring the concentration in the receiver compartment, the flux can be easily determined.

RESULTS AND DISCUSSION

Dissolution of Different Formulations of Meloxicam

Dissolution of Meloxicam and its formulations were performed in 20 mL of SGF media using several different loads of material. Figure 3 shows an example of concentration profiles for different forms of Meloxicam. As evident from Figure 3, a, solubility of untreated API was about 0.7 µg/mL. Averaging this data with the other replicate yielded value 0.74±0.05 µg/mL. Analysis of dissolution profile[2] revealed that "effective spherical particle size" for untreated meloxicam powder was ~ 16 µm.

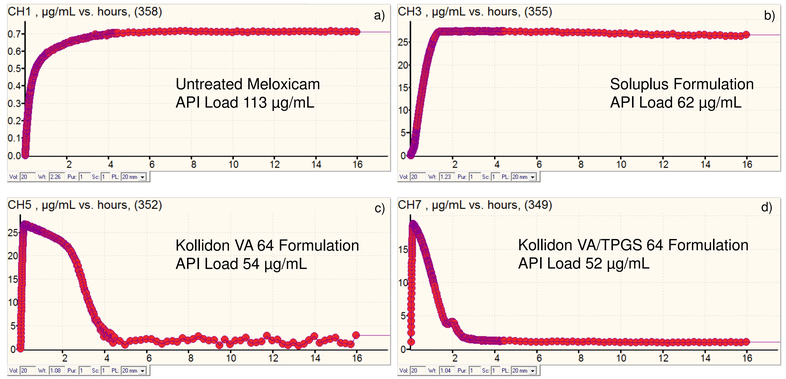

Figure 3. Examples of dissolution – precipitation profiles (µg/mL versus hours) for Untreated Meloxicam (a), Soluplus Formulation (b), VA 64 Formulation (c) and VA 64/TPGS Formulation (d). Assays were performed in 20 mL of SGF medium.

Kinetic solubility of Meloxicam from ASD formulations were dependent on the load the formulations. For example, solubility of Meloxicam from Soluplus ASD reached 27 µg/mL with 413 µg/mL load of Soluplus Formulation (62 µg/mL of API, Figure 3, b) and it was 50 µg/mL when 693 µg/mL load of the same formulation was introduced (104 µg/mL of API, not shown). Similar effect was observed for Kollidon VA64 Formulation and to a lesser extend for Kollidon VA 64/TPGS Formulation. Such dependence on the load could be explained by the increase in the background level of formulation ingredients with the change of the load.

Soluplus Formulation stayed supersaturated over 16 hours of the experiment while both Kollidon VA64 and Kollidon VA64/Kolliphor TPGS Formulations precipitated (with different rate) after initial supersaturation phase.

Flux of Meloxicam from Untreated Powder and Formulations

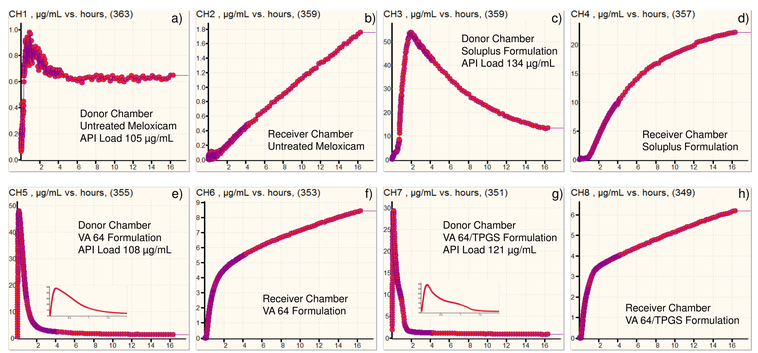

Figure 4. Concentration – time profiles of meloxicam (µg/mL vs. hr) in donor compartments a), c), e), g) and receiver chambers b), d), f), h) in the µFLUX assay. Inserts in e) and g) zoom in into first 2 hours of the assay to highlight peculiarities of supersaturation phase for corresponding formulations.

Figure 4 a), c), e) and g) show concentration – time profile in the donor compartment for untreated Meloxicam (a) and its ASD formulations. As evident from Figure 3 c), Soluplus formulation precipitated unlike in the case of a simple dissolution experiment (Figure 3, b), however, the rate of precipitation was much slower than for other formulations being consistent with so-called parachute supersaturation behavior.

Figure 4 b), d), f) and h) show concentration – time profile in the receiver chambers corresponding to the donor compartments shown to the left of them. Except for untreated Meloxicam, where Flux was low, but almost constant over the course of the experiment, the flux from ASD formulations was changing drastically following their supersaturation – precipitation profile in the donor. This is demonstrated in Figure 5 where flux values were calculated based on 50 moving time points using Equation (1).

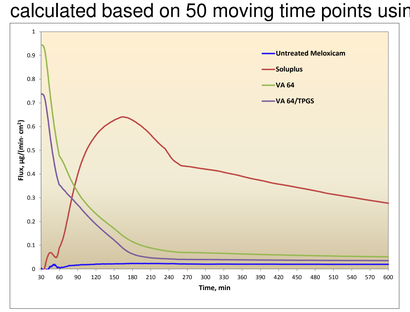

Figure 5. Flux change over time for Meloxicam and its formulations.

It could be seen from Figure 5 that Kollidon VA 64 and Kollidon VA64/Kolliphor TPGS formulations had the highest initial flux. However, due to their relatively quick precipitation in the donor the flux from Soluplus formulation kept increasing and surpassed the flux from both Kolliphor VA 64 and Kolliphor VA64/Kolliphor TPGS formulations after about 90 min. The lower initial flux from Soluplus formulation could also be caused by relatively large particle size for this ASD formulation.

Area under concentration versus time profile (AUC) in the receiver compartment is suggested to be a parameter that can differentiate formulations when flux is changing during the course of the experiment. This parameter could provide insight into what formulation has a better chance to improve *in vivo* performance of the drug product. Figure 6 visualizes AUC for studied formulations for the initial 240 min time period.

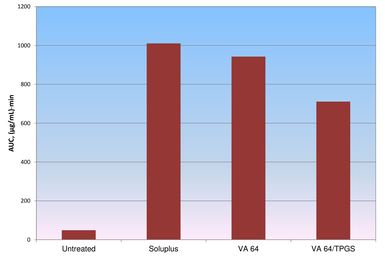

Figure 6. Area under the concentration versus time curves in the receiver chambers for untreated Meloxicam and its formulations.

CONCLUSIONS

- All studied formulations improved Meloxicam flux through artificial membranes.
- Soluplus Formulation maintained longer supersaturation comparing to other formulations that could translate into superior pharmacokinetic behavior of such formulation especially if particle size could be further reduced.
- Area under concentration profile in the receiver compartment could be suggested as a useful parameter particularly for cases when flux is changing significantly over time.
- Dissolution experiments alone cannot correctly predict the *in vivo* response to formulations due to the peculiar interplay of solubility and permeability in complex media.

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