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The Impact of the Metamorphosis of Topical Formulations on Bioavailability

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PURPOSE

Some topical formulations undergo metamorphosis after application on the skin due to an evaporation of solvents from the formulation. Such evaporation of solvent results in a dynamic change in the thermodynamic activity of the drug in the formulation. The thermodynamic activity of the drug can influence both the release of drug from the formulation and its permeation across the skin, thereby modulating the bioavailability (BA) of the drug from the formulation. The goal of this project was to develop an experimental model to study the impact of changes in the thermodynamic activity of a drug in a formulation over time on drug delivery. Such a model can enable us to better understand the impact of the evaporation of the solvent system on the BA of topical formulations. Metronidazole (0.5% w/w) solubilized in an aqueous formulation was used as a model system to understand the role of evaporation (and the corresponding change in thermodynamic activity) on the release and permeation of drug from the formulation.

METHODS

The model system was designed such that the drug concentration, and therefore the (thermodynamic) activity coefficient of the drug, increased as the solvent evaporated - without leading to substantial changes in the viscosity of the formulation, which could otherwise be a confounding factor during the evaluation of diffusion/permeation. The active diffusion area was also held constant throughout the duration of the experiment. An aqueous solution of metronidazole (5 mg/mL) was used for the drug release and drug permeation studies.

In vitro release test (IVRT) studies were conducted using Franz diffusion cell apparatus under finite and infinite dose conditions at 32 ± 1°C (n=6). The observed changes in the rate of drug release from the metronidazole formulation due to corresponding changes in the solvent system and the drug concentration in the donor compartment are expected to be gradual, slow and prolonged. Therefore, a modified membrane system consisting of a saran membrane with an aperture of 0.031 cm^2 on top of a dialysis membrane (MWCO – 1kDa) was designed for the evaluation of the release kinetics. Infinite dose studies were conducted using 2 mL of the metronidazole solution in the donor compartment under occlusion (with parafilm), whereas finite dose studies were conducted using 300 µL of the metronidazole solution in an unoccluded condition (allowing for evaporation of the solvent system). Samples were collected from the receiver chamber every half an hour for the first 3 hours and replaced with fresh receiver medium. The samples were analyzed by UV spectroscopy using a Synergy H1 microplate reader. The drug concentration in the donor compartment was also determined by removing 2 µL of drug solution every half hour from the donor chamber during a finite dose study, and at the end of the study for an infinite dose study.

In vitro permeation studies (IVPT) were performed using human cadaver skin to quantify the impact of changes in the thermodynamic activity of drug in the formulation on drug permeation across skin under finite and infinite dose conditions. The experimental conditions were identical to the in vitro release studies, except that human cadaver skin was used instead of the membrane system, and the study was conducted for 24 hours (n=6). The concentration of drug in the receiver and donor compartments was analyzed using HPLC.

Data are represented as mean ± standard deviation (SD).

RESULTS

In Vitro Release Test (IVRT)

Figure 1: Metronidazole concentration in the donor compartment vs. time from finite volume IVRT (n=6)

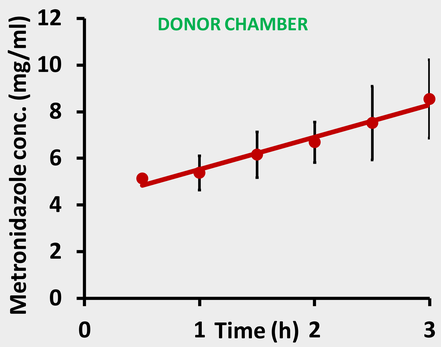
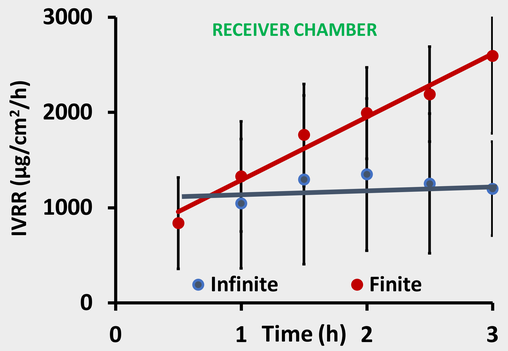


Figure 2: Metronidazole in vitro release rate (IVRR) vs time profiles from finite and infinite volume IVRT (n=6)



In Vitro Permeation Test (IVPT)

Figure 3: Metronidazole concentration in the donor compartment vs time from finite and infinite volume IVPT (n=6)

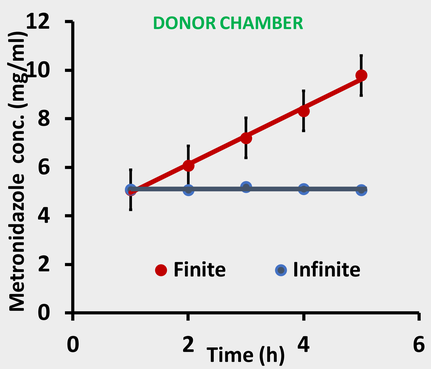


Figure 4: Metronidazole flux vs time profiles from finite and infinite volume IVPT (n=6)

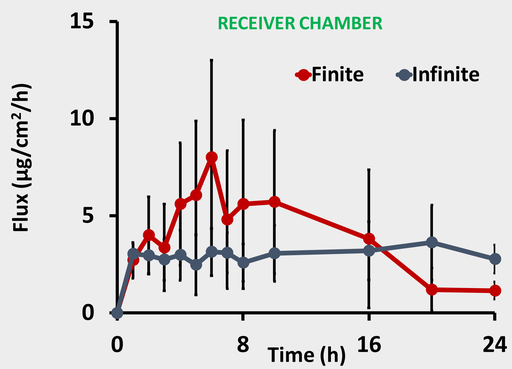


Table 1: Peak flux and cumulative permeation of metronidazole during IVPT

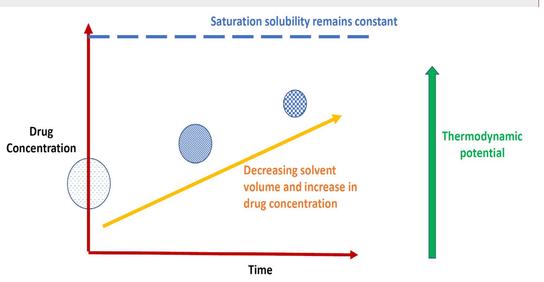
	Finite Volume Study	Infinite Volume Study
J_{max} (µg/cm²/h)	7.14 ± 1.56	5.09 ± 0.52
AUC(µg/cm²)^	91.99 ± 53.87	72.64 ± 22.29

^Expressed as area under the amount permeated vs. time curve

CONCLUSION

The results of this study illustrate that in the case of a single-phase aqueous system wherein the drug is present at a concentration below the saturation solubility, evaporation of the solvent leads to an increase in the (thermodynamic) activity coefficient of drug in the formulation, which in turn results in an increase in the release as well as the permeation of the drug over time. The role of viscosity was negligible in the current study, since the viscosity of the system did not change with the evaporation of the solvent.

Figure 5. Evaporative metamorphosis of a single solvent drug solution



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