A Mechanistic Evaluation of How Metamorphosis of a Topical Dosage Form Impacts Permeation

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PURPOSE

Some topical formulations undergo metamorphosis after application on the skin due to the evaporation of solvents from the formulation, which can dynamically change the thermodynamic activity of the drug in the formulation throughout the time that the formulation is drying on the skin. The thermodynamic activity of a drug can influence both, its release from the formulation and its permeation across the skin - thereby, substantially altering the bioavailability (BA) of the drug product. Fractional solubility (α) is used in the current study as a measure of the thermodynamic activity; the parameter is defined as the ratio of the concentration of drug in the formulation to the saturation solubility of the drug in the same formulation. The objective of the current study was to investigate the impact of changes in the α of a model drug, metronidazole, during metamorphosis, on drug permeation from topical formulations.

METHODS

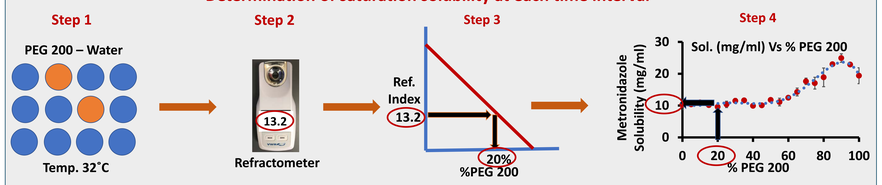
Variations of two binary solvent systems (5 methanol-water systems and up to 5 polyethylene glycol (PEG) 200-water systems) containing different proportions of methanol-water or PEG 200-water were prepared for the studies. Methanol, PEG 200, and water were selected as the solvents because they are not expected to alter the barrier properties of the skin, and methanol is a relatively fast-drying solvent compared to PEG-200.

Infinite dose in vitro permeation tests (IVPT) (n=4 replicates) were performed using the metronidazole binary solvent systems with a drug concentration of 7.5 mg/mL. The infinite dose studies were conducted using 1.13 mL/cm^2 of the metronidazole solution in the donor compartment under occlusion (with parafilm). Finite dose IVPT studies were performed (n=6 replicates) using methanol-water solvent systems (initial α=0.6) and PEG-water solvent systems (initial α=0.7) under un-occluded condition (allowing for evaporation of the solvent system). A 300 µL/cm^2 dose of the metronidazole solution was used in the donor compartment in the case of methanol-water systems and 180 µL/cm^2 was used in the case of the PEG-water systems. Both sets of IVPT studies were conducted using human cadaver skin (donor=1) and static Franz diffusion cells at a skin surface temperature of 32 ± 1°C. The active diffusion area was constant across all studies, throughout the duration of the experiment. Samples were collected at pre-determined time intervals and drug concentration was analyzed using high-performance liquid chromatography (HPLC).

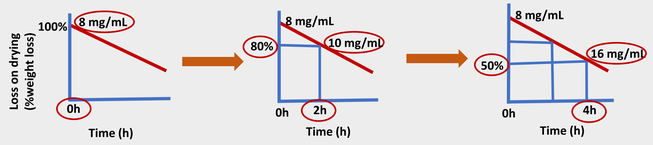
The solvent composition and the drug concentration in the formulation were also evaluated at each predetermined time interval using refractive index measurements and based on solvent loss, respectively. The saturation solubility of the drug at each time point was calculated using polynomial equations derived from empirical solubility data for the two solvent systems. The measured concentration of drug in the formulation at each time point, in conjunction with an understanding of the composition of the solvent system and the corresponding saturation solubility of metronidazole in the solvent system, were utilized to calculate α at each time point. The data were utilized to understand the impact of changes in α on metronidazole flux observed during the IVPT studies.

Data are presented as mean ± standard deviation.

Determination of saturation solubility at each time interval

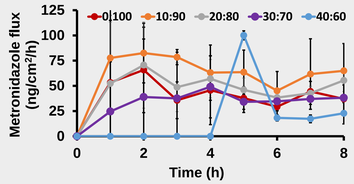


Determination of drug concentration in the donor compartment at each time interval



RESULTS

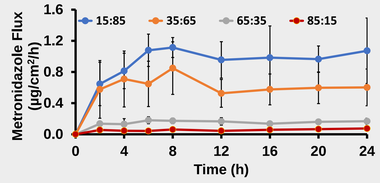
Methanol-Water Binary Solvent System



Methanol:Water	Saturation Solubility (mg/mL)	Concentration (mg/mL)	α	AUC (ng/cm^2)
0:100	10.26	7.5	0.73	339.93±77.67
10:90	8.07	7.5	0.93	518.96±141.96
20:80	9.13	7.5	0.82	394.29±67.76
30:70	11.84	7.5	0.63	280.44±41.27
40:60	16.66	7.5	0.45	151.36±4.60

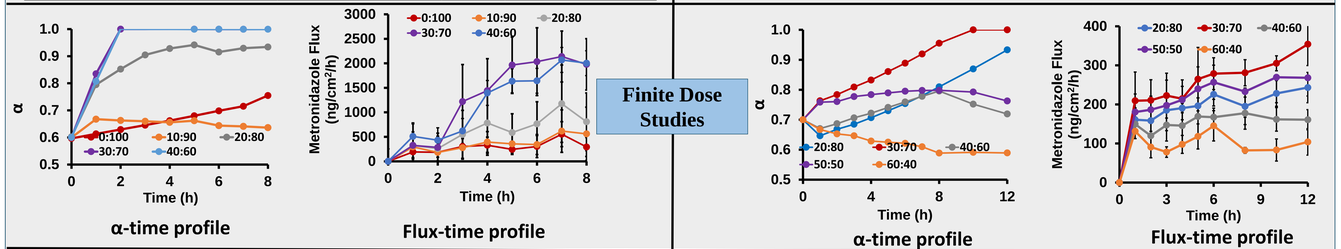
Infinite Dose Studies

PEG 200-Water Binary Solvent System

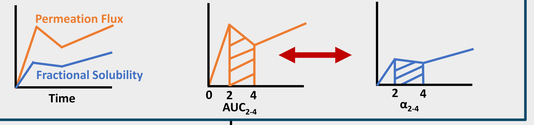


PEG 200:Water	Saturation Solubility (mg/ml)	Concentration (mg/ml)	α	AUC (µg/cm^2)
15:85	10.15	7.5	0.74	22.17±2.66
35:65	11.62	7.5	0.65	14.41±3.11
65:35	14.27	7.5	0.53	3.59±0.38
85:15	22.99	7.5	0.33	1.29±0.30

Finite Dose Studies



Segment-Segment Correlation of Finite Dose Data



CONCLUSION

The results from the current study suggested that the BA of metronidazole appeared to correlate with fractional solubility (α) during the metamorphosis of a formulation. Based on the limited data, it appeared that this correlation may be somewhat stronger in the case of the PEG 200-water systems vs. the methanol-water systems. Additional studies are warranted to understand the mechanistic basis for these observations; our preliminary hypothesis is that a correlation between the BA and α (or differences between formulation variants) may not have been as evident for the methanol-water variants due to the relatively rapid evaporation of methanol from the formulation.

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