A Mechanistic Evaluation of the Impact of Formulation Viscosity and Fractional Solubility on Drug Release and Permeation

S. Ajjarapu[1], S. Rangappa[1], P. Ghosh[2], M. Kelchen[2], S. G. Raney[2], EE Ureña-Benavides[3], H. Maibach[4], S. Narasimha Murthy[1]

[1]Department of Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi, Oxford, MS 38677
[2]Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993
[3]Department of Chemical Engineering, The University of Mississippi, Oxford, MS 38677
[4]School of Medicine, The University of California at San Francisco, San Francisco, CA 94143

aaps 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

Fractional solubility (α) of a drug in a formulation is defined as the ratio of the concentration of drug in the formulation to the saturation solubility of the drug in the same formulation. Fractional solubility is used in the current study as a measure of the thermodynamic activity, one of the main driving forces that impacts the release of drug from the formulation, and thereby the amount of drug that is available for permeation. The viscosity of a formulation can also impact the diffusion of the drug within the formulation and thereby the release of the drug from the formulation. Differences in inactive ingredients between topical dermatological formulations can simultaneously impact both the fractional solubility as well as the viscosity of the formulation. Therefore, the objective of the current study was to mechanistically understand the impact of differences in α and viscosity on drug release and permeation by systematically varying formulation composition.

METHODS

Metronidazole was selected as the model drug for the study. Different metronidazole topical formulations were prepared using polyethylene glycol (PEG 200) and water-based binary systems.

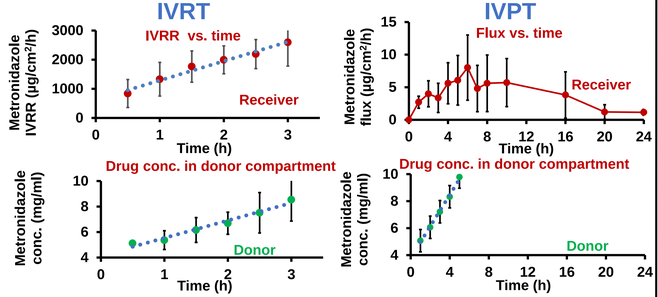
The release and skin permeation of metronidazole from various topical formulations were evaluated using an in vitro release test (IVRT) and an in vitro permeation test (IVPT) under both finite and infinite dose conditions. For the infinite dose studies, 1.13 mL/cm^2 of each metronidazole formulation was applied to the donor compartment under occlusion (with parafilm), whereas for the finite dose studies, 300 µL of each metronidazole formulation was applied under unoccluded conditions (allowing for evaporation of the solvent system). A static Franz diffusion apparatus was used for all studies and the active diffusion area remained constant throughout the studies. The IVRT studies were conducted using a modified membrane system consisting of a polyethylene membrane with an aperture of 0.031 cm^2 on top of a dialysis membrane (molecular weight cutoff – 1 kDa) at 32 ± 1°C (n=6) for the evaluation of the release kinetics. Samples were collected at pre-determined time intervals from the receiver chamber and analyzed using ultraviolet spectroscopy and a Synergy H1 microplate reader. The experimental conditions for the IVPT studies were identical to the IVRT studies except that human cadaver skin from one donor (New York Firefighters Skin Bank) was used instead of the synthetic membrane system and the study was conducted for 24 hours compared to 3 hours (n=6 replicates). The concentration of drug in the receiver compartment was analyzed using high-performance liquid chromatography (HPLC).

Four different study conditions (described within the Results section) were utilized to systematically evaluate the impact of α and viscosity on release and permeation of metronidazole from the formulations. Data are presented as mean ± standard deviation.

	α	Viscosity	Formulation	Dose
Case 1	Varying	Constant	Aqueous drug solution, 5 mg/mL	Finite
Case 2	Varying	Varying	Different PEG-water systems, 7.5 mg/mL	Infinite
Case 3	Constant	Constant	Aqueous drug solution, 5 mg/mL	Infinite
Case 4	Constant	Varying	Different PEG-water systems with the same fractional solubility (α=0.5)	Infinite

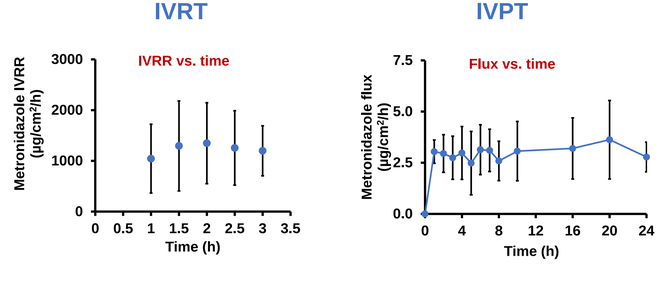
RESULTS

Case 1 : Finite Dose
Formulation: Aqueous drug solution, 5 mg/mL
Varying α while the viscosity of the formulation remained constant



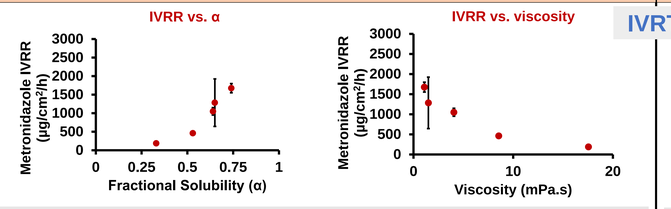
Metronidazole in vitro release rate (IVRR) by an IVRT and flux (IVPT) increased with increase in fractional solubility, when viscosity of the formulation remained constant

Case 3 : Infinite Dose
Formulation: Aqueous drug solution, 5 mg/mL
α and viscosity of the formulation remained constant



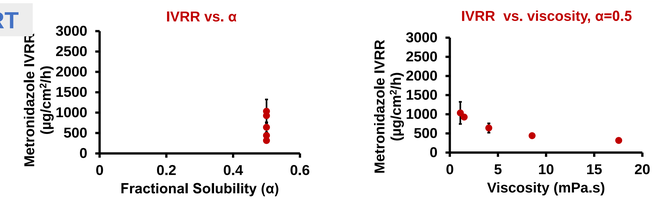
Metronidazole IVRR (IVRT) and flux (IVPT) remained constant when fractional solubility and viscosity of the formulation remained constant

Case 2 : Infinite Dose
Formulation: Different PEG-water compositions, 7.5 mg/mL
Varying α and viscosity of the formulation simultaneously

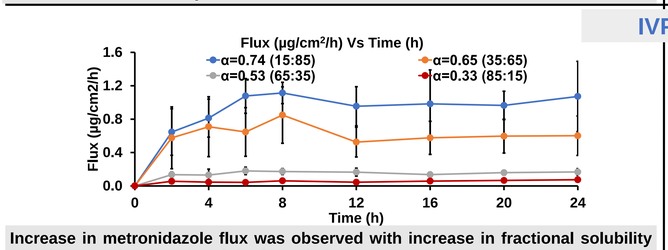


Increase in metronidazole IVRR was observed with increase in fractional solubility and decrease in viscosity of formulations

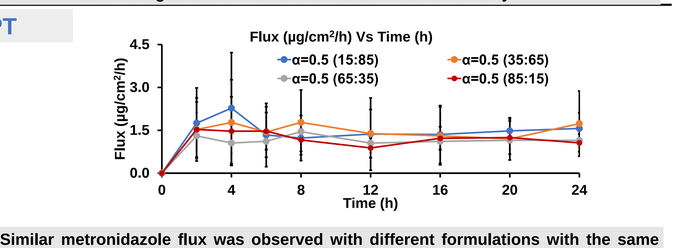
Case 4 : Infinite Dose
Formulation: Different PEG-water compositions, same fractional solubility (α=0.5)
Varying the viscosity of the formulation when α remained constant



Decrease in metronidazole IVRR was observed with increase in viscosity of formulations although formulations had same fractional solubility



Increase in metronidazole flux was observed with increase in fractional solubility and decrease in viscosity of the formulation



Similar metronidazole flux was observed with different formulations with the same fractional solubility, but different viscosities.

	α	Viscosity	IVRR	IVRR correlates with		IVRR Determining Factor	Flux correlates with		Flux Determining Factor
				α	Viscosity		α	Viscosity	
Case 1	Varying	Constant	Increased with α	Yes	Viscosity did not change	α	Yes	Viscosity did not change	α
Case 2	Varying	Varying	Increased with α	Yes	Yes	Inconclusive	Yes	Yes	Inconclusive
Case 3	Constant	Constant	No change with α	Yes	Yes	Inconclusive	Yes	Yes	Inconclusive
Case 4	Constant	Varying	No change with α	No	Yes	Viscosity	Yes	No	α

CONCLUSION

Drug release from topical formulations is governed by several factors, including the thermodynamic activity of the drug in the formulation and the viscosity of the formulation. The results from the current study suggest that when formulations have comparable viscosity, the α, which was used as a measure of the thermodynamic activity of the drug in the formulation, may play a dominant role in controlling the rate of release of metronidazole from topical formulations and thereby the amount of drug that is available for permeation. When there are differences in viscosity across formulations, the results suggest that drug release may be substantially influenced by viscosity, however, α may continue to play a role in controlling the permeation of metronidazole from topical formulations into and across skin.

FUNDING

This project was supported by the U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) through Grant 1U01FD006507. The views expressed in the poster are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

THE UNIVERSITY of MISSISSIPPI SCHOOL OF PHARMACY

FDA U.S. FOOD & DRUG ADMINISTRATION

Contact Information:
S. N. Murthy Group
http://home.olemiss.edu/~murthy
Email ID: murthy@olemiss.edu
Phone No.: 662-915-5164