Evaluation of Water Activity (a_w) as a Critical Quality Attribute of Topical Dosage Forms

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INTRODUCTION

- Water activity (a_w) is the measure of thermodynamic energy of water present in a pharmaceutical system. It is denoted as the ratio of partial vapor pressure of water present in system **(ρ)** to the vapor pressure of pure water **($ρ_0$)**. Pure water possess water activity of 1.
- Dissolved or suspended chemical species has the potential to associate with water molecules which in turn would affect its thermodynamic potential of the solvent represented as 'a_w'.

OBJECTIVES

- The main objective of this study was to investigate the effects of water activity (a_w) of a topically applied vehicle on the drug permeation across the skin.
- A related objective was to investigate the mechanistic effects of a_w on skin hydration and barrier properties.

EXPERIMENTAL DESIGN

For the investigation of mechanistic effects, a simple topical vehicle of varied a_w (0.97 - 0.42) was formulated using deionized water with caffeine (as a model drug). Drug transport studies were performed using Franz diffusion cells across synthetic membranes (cellulosic and silastic) and porcine epidermis to study the effect of a_w on drug permeation. Dye diffusion test was undertaken to elucidate the effects of vehicle viscosity and water activity on solute diffusivity. Theoretical and experimental modeling were performed to relate the effects of water activity on caffeine diffusion coefficient. Thermogravimetry analysis was performed to determine the drying rate of water activity vehicles. The effect on skin hydration was investigated by placing vehicles of varied a_w on porcine skin equilibrated with ambient environmental conditions (22°C/50% RH) and monitoring the changes in skin hydration gravimetrically. The effects of these vehicles on (hydration-related) changes in the morphology of the skin barrier were investigated by histological evaluation. The effect of humectant (propylene glycol) on drug permeation from low water activity vehicle and associated changes in skin barrier morphology was investigated was investigated.

RESULTS

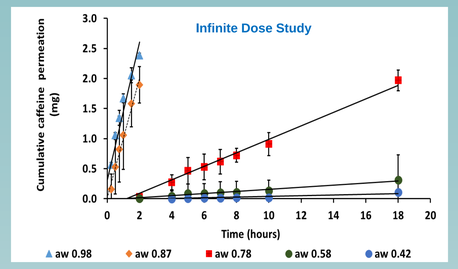


Figure 1: Effect of water activity on caffeine permeation across cellulose membrane (n=6).

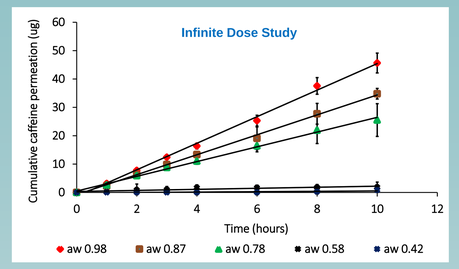


Figure 2: Effect of water activity on caffeine permeation across silicone membrane (n=6).

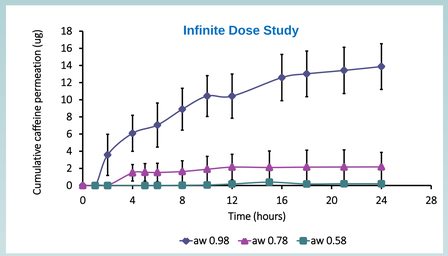


Figure 3: Effect of water activity on caffeine (log p -0.79) permeation across porcine epidermis under infinite dosing condition (n=6).

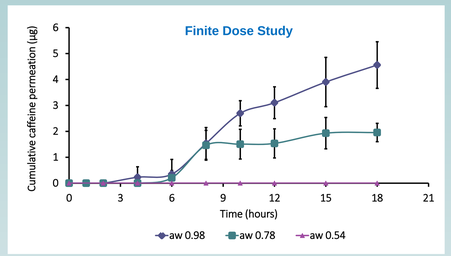


Figure 4: Effect of water activity on caffeine (log p -0.79) permeation across porcine epidermis under finite dosing condition (n=6).

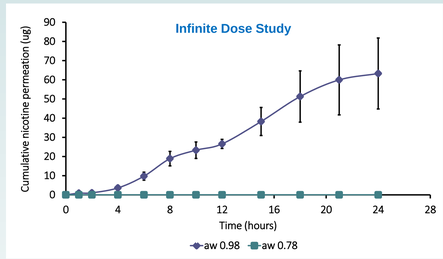


Figure 5: Effect of water activity on nicotine (log p 1.17) permeation across porcine epidermis (n=6).

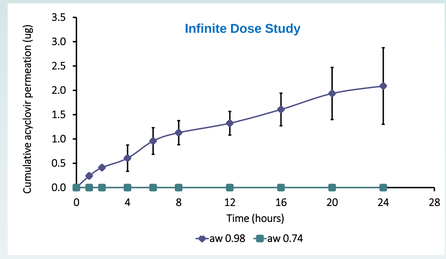


Figure 6: Effect of water activity on acyclovir (log p -1.56) permeation across porcine epidermis (n=6).

Solubility of caffeine was found to be ~15 mg/mL in all water activity vehicles

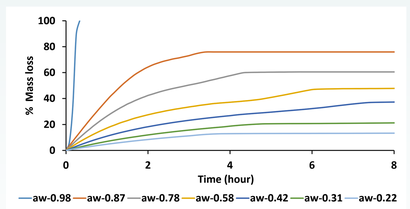
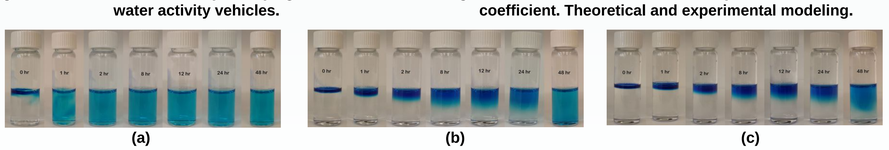


Figure 7: Effect of water activity on drying rate of various water activity vehicles.

Vehicle water activity (a_w) (at 22° C)	Viscosity of water activity vehicles (cP) (at 22° C)	Caffeine diffusion coefficient as a function of viscosity of vehicle(Stokes-Einstein eqn.) (cm^2/s)	Experimental values for caffeine diffusion coefficient from transport studies across cellulose membrane (porous membrane) (cm^2/s)
0.98	0.89	7.15×10^{-6}	2.89×10^{-9}
0.87	1.23	5.17×10^{-6}	5.58×10^{-10}
0.78	1.95	3.26×10^{-6}	3.07×10^{-11}
0.54	2.75	2.31×10^{-6}	2.84×10^{-11}
0.42	3.64	1.75×10^{-6}	1.46×10^{-11}

Figure 8: Effect of vehicle water activity on caffeine diffusion coefficient. Theoretical and experimental modeling.



(a) (b) (c)

Figure 9a: Time lapse observation of solute (methylene blue) diffusion in different a_w vehicles: (a)0.98 (b)0.78 (c) 0.42

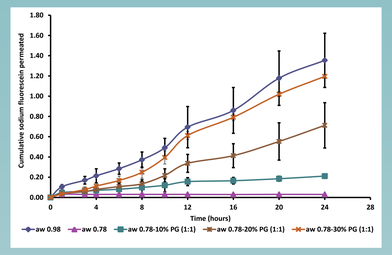


Figure 10: Effect of propylene glycol on sodium fluorescein permeation from a_w 0.78 vehicle across porcine epidermis (n=6).

Pre-treatment Mode	Apparent water content (% w/w of tissue)
Baseline	37.77 ± 6.44
a_w 0.98	50.28 ± 2.32
a_w 0.78	22.85± 4.77
a_w 0.54	17.40 ± 7.89

Figure 11: Effect of vehicle water activity on hydrodynamics of porcine epidermis (n=6).

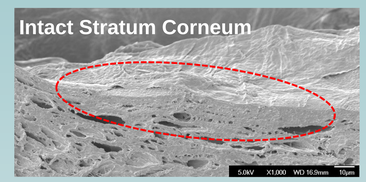


Figure 12: Representative SEM picture of human cadaver skin treated with water (a_w 0.98).

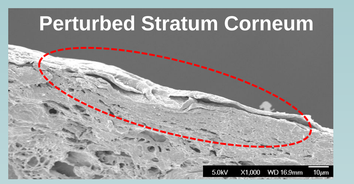


Figure 13: Representative SEM picture of human cadaver skin treated with a_w 0.78 vehicle.

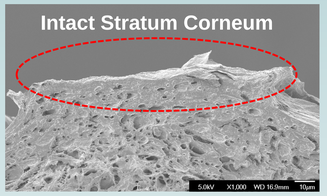


Figure 14: Representative SEM picture of human cadaver skin treated with propylene glycol and a_w 0.78 vehicle (1:1).

CONCLUSION

Drug permeation/diffusion across the skin and membrane barriers from a topically applied vehicle was influenced by water activity of the solution. Drug permeation across the membrane barriers was not enhanced despite higher drug thermodynamic activity (~15 mg/mL) in low water activity vehicles. Based upon the results, water activity appears to be a potentially critical quality attribute of topical semisolid dosage forms, as it could potentially influence the drug release from formulation as well as the permeation of the drug across the skin. Vehicles with a lower a_w were also found to alter the hydrodynamics of skin which could be one of the mechanisms leading to the observed effect.

Acknowledgement

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