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Thermodynamic, Computational Solubility Parameters in Organic Solvents and *In Silico* GastroPlus Based Prediction of Ketoconazole

Sultan Alshehri,* Afzal Hussain,* Mohd Neyaz Ahsan, Raisuddin Ali, and Mohd Usman Mohd Siddique

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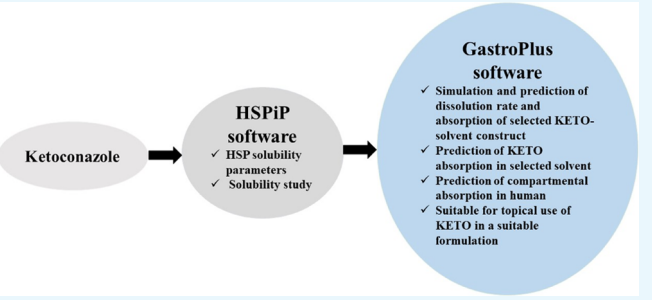
ABSTRACT: The study aimed to select a suitable solvent capable to solubilize ketoconazole (KETO) and serve as a permeation enhancer across the skin. Experimental solubility and Hansen solubility parameters were obtained in ethanol, dimethyl sulfoxide (DMSO), ethylene glycol, oleic acid, span 80, limonene, eugenol, transcutol (THP), labrasol, and propylene glycol. Thermodynamic functional parameters and computational models (van't Hoff and Apelblat) validated the determined solubility in various solvents at T = 298.2 K to 318.2 K and P = 0.1 MPa. The HSPiP software estimated the solubility parameters in the solvents. The maximum mole fractional solubility values of KETO were found to be in an order as oleic acid (8.5×10^{-3}) > limonene (7.3×10^{-3}) > span 80 (6.9×10^{-2}) > THP (4.9×10^{-2}) > eugenol (4.5×10^{-3}) at T = 318.2 K. The results of the apparent thermodynamic analysis confirmed that the dissolution rate was endothermic and entropy driven. The GastroPlus program predicted significantly high permeation of KETO (79.1%) in human skin from the KETO-THP construct as compared to drug solution (38%) and excellent immediate release from THP-solubilized construct (90% < 1 h). Hence, THP could be a better option for topical, transdermal, and oral formulation.



INTRODUCTION

The incidence of fungal infections occurred about 40 million in developing and under developing nations as per global estimates.[1] Chemically, ketoconazole (KETO) is an azole type (±) (*cis*-1-acetyl-4-[4-[2-(2,4-dichlorophenyl-2-(1H-imidazol-1ylmethyl)-1,3-dioxalon-4-yl]methoxy]phenyl]-piperazine) antifungal drug for local and systemic treatments.[2] The empirical molecular formula and molecular weight of KETO are $C_{26}H_{28}Cl_2N_4O_4$ (Figure 1A) and 531.43 g mol^{-1}, respectively.[3] Azole molecules are the first choice option to treat cutaneous and systemic fungal infections. However, the drug possesses poor aqueous solubility (0.04 mg/mL at 25 °C), high partition coefficient (log$P$ = 4.31), and limited oral bioavailability.[3] The drug is reported to treat several cutaneous fungal infections such as (a) onychomychosis (nail fungal infection), (b) psoriasis, (c) dermatitis, and (d) fungal infections (*Candida* species and *Cryptococcus neoformans*) associated with other diseases (human immunodeficiency virus).[4] The poor aqueous solubility challenged the drug for parenteral, oral, and topical delivery to treat these fungal infections. A high oral dose owing to limited aqueous solubility results in dose-related toxic side effects. Therefore, topical and transdermal delivery could be a suitable alternative using a suitable permeation enhancer. Hossin et al. investigated the nail−drug interaction (affinity) using Hansen solubility parameters, which can assist formulation scientists to design a suitable carrier or solvent selection (DMSO, *N*-methyl pyrrolidone, ethanol, and ethylene glycol) for topical application with improved efficacy.[5] Hashemzadeh and Jouyban studied the binary system of ethanol + water mixture for improved solubility of KETO at various temperatures using a Jouyban−Acree model of co-solvency.[2] Moreover, authors reported that KETO exhibited the maximum mole fractional solubility (0.117) at 308.2 K when the mass fraction of ethanol in water was 0.8.[2] They also reported KETO molar solubilities of 1.40×10^{-5} and 2.90×10^{-5} at 293.2 and 308.2 K in water, respectively.[2] Jouyban et al. explored the solubility of KETO in various polyethylene glycol-200 + water binary systems at various temperature range (298.2−318.32 K) wherein the computational models (Jouyban−Acree and van't Hoff models) were the best fit to the experimental solubility data within acceptable range of mean relative deviation (MRD) values.[6] In further development, polyethylene glycols (of various molecular weights such as 200, 400, and 600) were used for the solubility study of KETO as binary as well as ternary with ethanol or water at 298.2 K. Soltanpour and

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Sultan Alshehri [1], Afzal Hussain [1], Mohd Neyaz Ahsan [2], Raisuddin Ali [1], Mohd Usman Mohd Siddique [3]

Affiliations

Affiliations

1 Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.
2 Department of Medical Laboratory Technology University Polytechnic, Birla Institute of Technology, Mesra, Ranchi 835215, Jharkhand, India.
3 Department of Pharmaceutical Chemistry, Shri Vile Parley Kelavani Mandal's Institute of Pharmacy, Dhule 424001, Maharastra, India.

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Abstract

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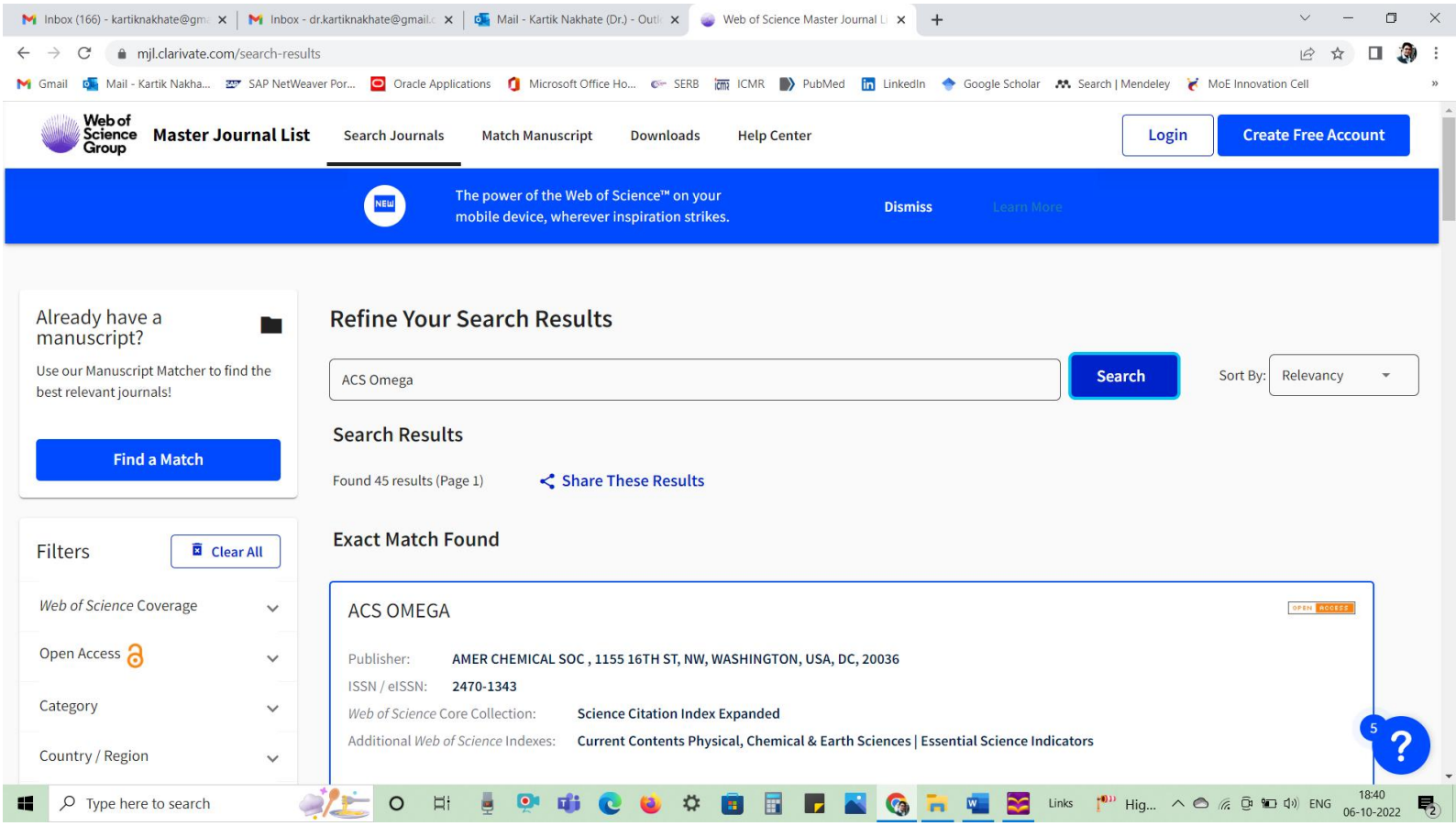
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Inbox - dr.kartiknakhate@gmail.c
Mail - Kartik Nakhate (Dr.) - Outl
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