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Preferential Solvation Study of the Synthesized Aldose Reductase Inhibitor (SE415) in the {PEG 400 (1) + Water (2)} Cosolvent Mixture and GastroPlus-Based Prediction

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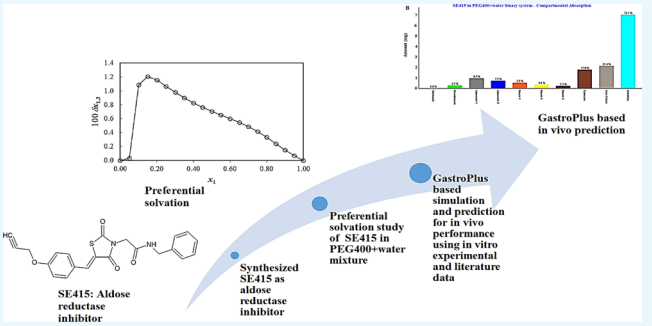
ABSTRACT: (*Z*)-*N*-Benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide (SE415) is a novel aldose reductase inhibitor used in the management of diabetes mellitus (DM) and associated complications. Herein, the drug was solubilized (mole fraction solubility) in a "PEG 400 (polyethylene glycol 400) + water" mixture of various ratios at 298.15 K. We reported the preferential solvation of SE415 by PEG 400 using Kirkwood−Buff integrals, the thermodynamic functional parameter, *in vitro* dissolution, and GastroPlus-based predictions for *in vivo* performance. The result of Hansen solubility parameter analysis suggested PEG 400 as a suitable solvent for SE415 solubilization at 298.0 K, followed by prediction of several physicochemical properties. In the preferential solvation study, the molar volume, Hildebrand solubility parameters, and the molecular radius of SE415 were estimated as 258.4 $cm^3 \cdot mol^{-1}$, 27.62 $MPa^{1/2}$, and 0.468 nm, respectively, using Fedors' method. The inverse Kirkwood-Buff integrals indicated that the preferential solvation of SE415 by PEG 400 occurred in all studied ratios of the (PEG 400 + water) mixtures. The maximum value ($\delta x_{1,3} = 1.21 \times 10^{-2}$) of the preferential solvation of SE415 by PEG 400 was achieved at $x_1 = 0.15$. Then, using GastroPlus software, the maximum dissolution, improved *in vivo* oral absorption, and high regional compartmental absorption (total 99.0%) of SE415 in humans were predicted. Finally, the solubility data were correlated/predicted using various cosolvency models with satisfactory results. Thus, the binary cosolvent system can be a promising approach for enhanced oral absorption in controlling DM and associated complications in humans.



1. INTRODUCTION

Diabetes mellitus (DM) is a global health challenge as it is a complex metabolic disease (lack of insulin or insulin resistance) leading to high morbidity and mortality in developed nations. The aldose reductase (AR) is a key enzyme (cytoplasmic aldo-keto-reductase) of the polyol pathway that controls the critical factors involved in the onset, progression, and related DM complications (retinopathy, nephropathy, and neuropathy).[1] The enzyme has been targeted for developing various AR inhibitors and is reported with challenged therapeutic effectiveness. Few commercial drugs (lidorestat, zopolrestat, fidarestat, and tolrestat) have been withdrawn from the market due to their low pharmacokinetics profile (due to their ionizable −COOH functional group).[2] Therefore, the newly synthesized potential benzylidine thiazolidinedione derivative, namely, (*Z*)-*N*-benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide (SE415), has been reported to target AR for managing long-term DM and associated complications. Moreover, the compound (SE415) is a potent PPARγ (peroxisome proliferator-activated receptor gamma) modulator and AR inhibitor (dually active) (Siddique *et al.*, 2021).[3] In this study, SE415 is a chemically non-carboxylic acid inhibitor (*N*-substituted thiazolidinedione derivative) of the AR enzyme for dual functionality.[3] The drug "SE415" ($C_{22}H_{18}N_2O_4S$) possessed poor water solubility (0.0059 mg/mL, at normal temperature and pressure, and pH 7.4) and adequate molar mass (406.0 $g \cdot mol^{-1}$) and molar volume (258.4 $cm^3 \cdot mol^{-1}$).[3] The drug showed poor water solubility, which forced us to investigate a suitable co-solvent for maximized co-solvency and subsequently good dissolution rate in the phosphate buffer saline (PBS).

Several water-soluble solvents [ethanol, *N*-methyl-2-pyrrolidone (NMP), propylene glycol (PG), ethylene glycol (EG),

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Abstract

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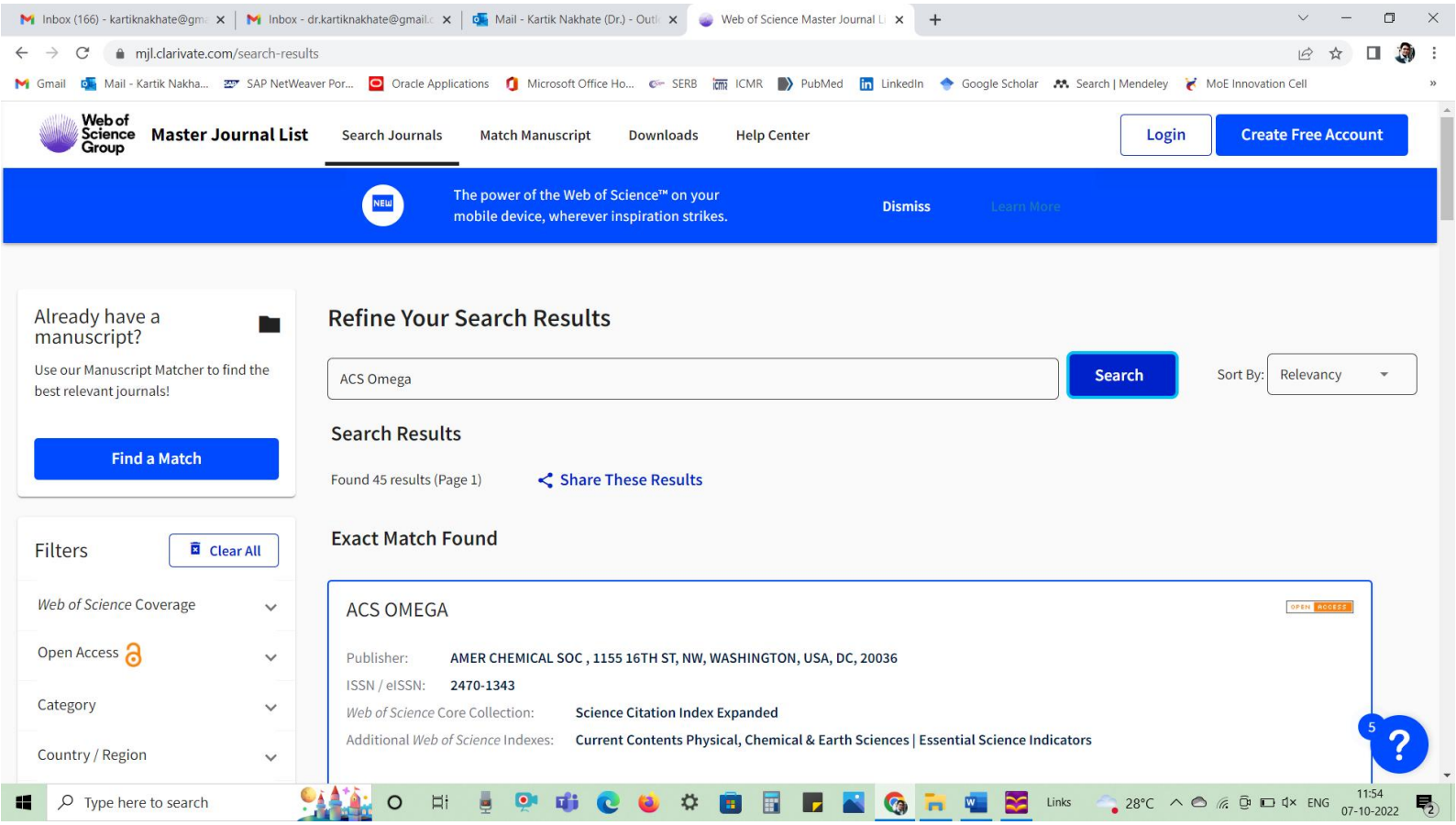
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