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Preferential solvation study of (*Z*)-*N*-benzyl-2-{5-(4-hydroxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetamide (3) in {NMP (1) + Water (2)} co-solvent mixture and GastroPlus software based *in vitro* simulation

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ABSTRACT

(*Z*)-*N*-benzyl-2-{5-(4-hydroxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetamide (3) (SE11) is a newly synthesized benzylidine thiazolidinedione to inhibit aldose reductase (AR) to control Diabetes Mellitus (DM) and related complications. This reported compound exhibits poor water solubility and based on Hansen solubility parameter (HSP) considerations NMP (*N*-methyl-2-pyrrolidone) is expected to be a suitable co-solvent. SE11 was soluble in various ratios of (NMP + water) mixture at 298.15 K. Moreover, preferential-solvation (PS) of SE11 by the mixed components was investigated (thermodynamic functional parameters and Kirkwood-Buff integrals) followed by *in-vitro* dissolution, and simulation (GastroPlus) of dissolution data for the best fit of Weibull model. Hansen solubility parameters (HSP) analysis suggested NMP as the most relevant solvent for SE11 solubility at 298 K and predicted physicochemical properties. In PS, the molar-volume (214.0 $cm^3 \cdot mol^{-1}$), Hildebrand solubility parameter (31.11 $MPa^{1/2}$), and molecular-radius (0.44 nm) of SE11 were calculated. The inverse Kirkwood-Buff integral computational analysis showed that the PS of SE11 through NMP was found in all explored ratios. The highest value ($\delta x_{1,3} = 0.67 \times 10^{-2}$) of PS was obtained at x_1 = 0.60–0.65 in NMP. Finally, the GastroPlus software simulated *in vitro* dissolution profile and the impact of shape factor on release behaviour followed by computational assessment. Hence, the explored binary mixture can be used as a suitable approach to treat systemic DM.

1. Introduction

The pathological polyol pathway of Diabetes mellitus (DM) and associated complications (nephropathy, retinopathy, and neuropathy) is associated with cytoplasmic aldo–keto-reductase enzyme (aldose reductase). Aldose reductase (AR) is a prime target for various newly developed AR inhibitors to control the progression of DM [1]. Several AR inhibitors have been reported with limited clinical efficacies, withdrawal from marketing, and poor PK (pharmacokinetic) profiles (due to ionizable carboxylic functional group) such as lidorestat, zopolrestat, fidarestat, and tolrestat [2]. Therefore, the potential compound "(*Z*)-*N*-benzyl-2-{5-(4-hydroxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetamide (SE11)" as an effective benzylidine thiazolidinedione derivative was previously synthesized (Fig. 1) and reported to AR enzyme to cure chronic diabetes mellitus (DM) and related issues [3]. Notably, SE11 was dually active, PPARγ-modulator, and potent AR inhibitor [3]. Pharmaceutically, SE11 ($C_{19}H_{16}N_2O_4S$) is associated with limited aqueous solubility (0.0034 $mg \cdot mL^{-1}$ as experimental value), molar mass of

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