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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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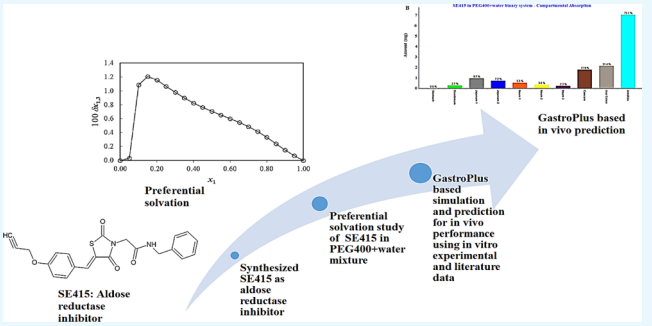
ABSTRACT: (*Z*)-*N*-Benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide (SE415) is a novel aldose reductase inhibitor used in the management of diabetes mellitus (DM) and associated complications. Herein, the drug was solubilized (mole fraction solubility) in a "PEG 400 (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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isopropyl alcohol, and polyethylene glycol 400 (PEG 400)] have been reported to exhibit improved aqueous solubility, resulting from the preferential solvation of various semipolar and/or hydrophobic compounds.[4−6] PEG 400 is a well-established water-soluble and biocompatible organic solvent intended for oral and parenteral drug delivery as a carrier or solvent. Busulfex and Robaxin are commercially available parenteral products containing PEG (polyethylene glycol) as much as 67% v/v and 50% v/v, respectively.[7] Hence, PEG 400 may be considered as a suitable solvent for SE415 selection in the current study.

Considering the reported % *I* (percent inhibition) value (~8.8 at 10 μM concentration) of SE415 to inhibit aldose reductase, a random oral dose of 10.0 mg was used for the prediction study using GastroPlus (predictive software in human and animal models).[3] The dose can also be delivered using the {PEG 400 (1) + water (2)} cosolvent mixture for oral or subcutaneous (sub-Q) delivery.

The phenomenon of preferential solvation is common to implement in the pre-formulation stage of research and development at the laboratory level or industrial platform. To understand the mechanisms involved in the drug dissolution, the functional dissolution thermodynamic parameters and preferential solvation process were studied in the aqueous the binary cosolvent mixture.[8−11] Generally, the dissolution behavior of a drug is important to study for drug-purification, pre-formulation, and drug delivery for expected *in vivo* performance. Moreover, the equilibrium solubility is critical at the industrial scale as the physicochemical properties of the drug impact the pharmacokinetics profile of a designed dosage form intended for oral, parenteral, and sub-Q administration.[12] An equilibrium solubility data permit the estimation of the preferential solvation parameters of the drug by the solvent components of the aqueous mixture system. These parameters served as a powerful tool to understand the primary molecular interactions involved in the dissolution process in the mixed cosolvent system.[9,10]

We aimed to investigate the preferential solvation parameters of SE415 in the (PEG 400 + water) cosolvent system using the experimental solubility data at 298.15 K in the (PEG 400 + water) systems. The equilibrium solubility study of SE415 was carried out in neat solvents (PEG 400 and water) and at various mass ratios of PEG 400 to water (from 0.0 to 1.0). The preferential solvation parameters of SE415 by each solvent component of the (PEG 400 + water) mixture have not been investigated so far. Therefore, we proposed to evaluate the impact of each component of the mixture system on drug solubilization and subsequently estimated the preferential solvation parameters of the drug in the proposed binary system that conformed to PEG 400 and water. The synthesized compound is novel with potential aldose inhibitory activity as reported before.[3] Therefore, several physicochemical properties and *in vivo* data have not been reported so far. Finally, GastroPlus software allowed us to predict the dissolution process, *in vivo* absorption, and the regional absorption of SE415 from various (nine) segments of the gastrointestinal tract (GIT) (human) using a conventional suspension and (PEG 400 + water) construct under fast conditions.

2. MATERIALS AND METHODS

2.1. Materials. PEG 400, acetonitrile, and methanol were procured from Sigma-Aldrich (Mumbai, India), CDH, and Spectrochem (India), respectively. Sodium acetate and acetic acid were procured from Sigma-Aldrich, Mumbai, India. The acetate buffer was freshly prepared for dissolution and analytical studies. Solvents were of analytical reagent grade (AR). Millipore water was used as an aqueous medium for varied PEG 400 to water ratio in the mixture.

2.2. Methods. *2.2.1. Analytical Method.* The drug was assayed using a high-performance liquid chromatography (HPLC) analytical tool (Agilent, 1200 series, California, USA). The process of analysis was conducted using a C_{18} column (250 mm × 4.6 mm, 5 μm) coupled (isocratic mode) with a UV detector at 357 nm. The freshly prepared mobile phase was composed of acetonitrile (ACN), methanol, and water containing acetate buffer (1% v/v) in a 70:20:10 v/v/v ratio, respectively, with a final pH of 6.5.[13] Analysis was conducted at a flow rate of 1.0 mL/min and an operating temperature of 298 K. The sample (20 μL) was injected to run over a time period of 10 min. A standard calibration curve was prepared in the working concentration range of 1.0−100.0 μg/mL in the mobile phase (Figure S1). The obtained regression coefficient (r^2) value was 0.999. The lower limit of quantification and lower limit of detection values were estimated as 1.5 μg/mL and 0.5, respectively. Experiments were conducted in triplicate for mean and standard deviation (SD).

2.2.2. HSPiP Software: Prediction of Solubility Parameters and Physical Properties of SE415. The existing interaction forces between a solute and solvent are dispersion, polarity (solute and solvent), and hydrogen bond formation, which are considered the driving factors during the mixing/dissolution process. The Hansen solubility HSPiP software (version 5.02.6) was applied to predict prime solubility parameters and physicochemical properties of SE415 and solvents. The formula "$C_{22}H_{18}N_2O_4S$" and CCC(=O)NCC1=CC=CC=C1O=C2NC(=O)C(/S2)=C/C3=CC=C(OCC#C)C=C3, are the molecular formula and SMILE text form of SE415, respectively. These three-dimensional HSP (Hansen solubility) parameters are based on the polarity of the compound (dipole−dipole interaction) expressed as "δ_p", dispersion (δ_d), and hydrogen bonding interaction (δ_h). Moreover, the sum of these parameters is related to the sum of total cohesive force energy of a solute among the inner atoms, and the total sum (δ_t) depends upon the divided individual components (eq 1).[14]

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

It is noteworthy that the maximized solubility of a compound in a specific solvent is usually obtained when the values of "δ_{ps}" (polarity solubility parameter of a compound) and "δ_{pv}" (polarity solubility parameter of a solvent) are approximately close or the difference of these values becomes zero [$\Delta(\delta_{ps} - \delta_{pv}) = 0$].[15] The idea of solubility parameters were first discovered by Hildebrand and Scott by considering the solute behavior in a particular solvent. Hildebrand and Scott were the first investigators who considered the cohesive energy (cause of attractiveness) of a solid compound in a specific solvent at a particular temperature. This energy was an accountable factor to dissociate ions or molecules or atoms from the parent one (related with the solubility parameters).[16] Notably, the principle of Hildebrand can be implemented to a simple homogeneous mixture commonly used pharmaceutical formulation such as aqueous-based parenteral and oral products. HSPiP software provided the molecular volume,

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ACS Omega 2022, 7, 1197−1210

log(K_{ow}), density, molecular weight, and the value of refractive index of PEG 400 and water.

2.2.3. Solubility Assessment. The solubility values (mole fraction) of SE415 in several binary systems were estimated at various mass ratios (0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.0) of "PEG 400 + water" at T = 298.15 K and 0.1 MPa following the reported method.[5,17−19] Briefly, an accurately weighed amount of SE415 was added into a glass container containing the mixture of {PEG 400 (1) + water (2)}. The glass container was properly capped and tightened before placing in the waterbath shaker maintained at 298 K for 40 h. The shaker was allowed to run until saturation was achieved. The transfer of the drug was continued to achieve an equilibrium. After equilibrating for 40 h, the glass container was centrifuged (5000 rpm for 10 min) to obtain a clear solution of the drug dissolved in the supernatant and the insoluble drug settled at the bottom.[17] The supernatant was taken for estimation of the drug from each specific ratio (dissolved) using a validated HPLC method (λ_{max} of 357 nm). The analysis was replicated (n = 3) for the average and SD values during statistical analysis. The experimental mole fraction solubility (x_e) was calculated as (eq 2)

$$x_e = \frac{\left(\frac{m_e}{M_e}\right)}{\left(\frac{m_e}{M_e}\right) + \left(\frac{m_{solv}}{M_{solv}}\right)} \tag{2}$$

where m_e and M_e are the mass and the molar mass of SE415, respectively. Similarly, the values of m_{solv} and M_{solv} represent the mass and the molar mass of the solvent, respectively.

2.2.4. Preferential Solvation Study. In general, drug solubilization in a particular solvent is a result of various forces working together. These forces are collectively called as molecular interactions and estimated using several experimental and theoretical models. These models deliver informative parameters to understand the molecular interactions taking place within the solvation shell of the dissolved solute in the solvent. These interactions can be accounted as (a) specific interactions (electron donor−acceptor and H-bonding interactions) and (b) non-specific interactions (polarity and polarizability interactions).[18] Moreover, any variation in the solvent composition leads to the deviation in the "solute−solvent" and "solvent−solvent" interactions occurring in the mixed system as function of the composition and the explored temperature. Maximum dissolution of a drug in the binary mixture can be used to investigate the information about the preferential solvation phenomenon in the mixture.[18] Theoretically, a preferential solvation is defined as a phenomenon wherein the proportion of a solvent (binary system) in the vicinity of a solute differentiates from the static proportion in the bulk. A principle predicted that a cohesive solvent−solvent interaction force (attractiveness force) can be disrupted in the solute molecule vicinity other than the solvent(s)/polymers.[18,19]

In various literature studies, experimental and theoretical models have been published to resolve the issue of the preferential solvation phenomenon. These models involve the quasi-lattice-quasi chemical theory, Kirkwood−Buff theory, the solvent exchange model, and the dielectric enrichment of the competitive preferential solvation theory.[18] Few solute-related molecular behaviors such as diffusion, reactivity, and chemical shift are directed by the distinct component of the mixed solvents.[5] In this study, the parameters of preferential solvation for SE415 by PEG 400 (1) in the binary {PEG 400 (1) + water (2)} mixtures can be defined as (eq 3)

$$\delta x_{1,3} = x_{1,3}^{L} - x_1 = -\delta x_{2,3} \tag{3}$$

$x_{1,3}^{L}$ and x_1 are the local mole fraction of PEG 400 (1) (as the prime component of the polymeric mixed solvent mixture) in the vicinity of SE415 (3) and the bulk mole fraction of PEG 400 (1) in the initial (PEG 400 + water) solvent mixture without SE415, respectively. The value of $\delta x_{1,3}$ decides the probable chance of preferential solvation of SE415 either by PEG 400 (1) or water (2). The positive ($\delta x_{1,3} > 0$) and negative ($\delta x_{1,3} < 0$) values of $\delta x_{1,3}$ indicate the preferential solvation of SE415 by PEG 400 and water, respectively. The PEG 400 local composition ($x_{1,3}^{L}$) and bulk composition (x_1) can be integrated with the thermodynamic parameter (Gibbs free energy, G) using inverse Kirkwood−Buff integrals.

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \tag{4}$$

where

$$G_{1,3} = RT\kappa_T - \bar{V}_3 + x_2 \bar{V}_2 D/Q \tag{5}$$

$$G_{2,3} = RT\kappa_T - \bar{V}_3 + x_1 \bar{V}_1 D/Q \tag{6}$$

With the correlation volume (V_{cor}) as

$$V_{cor} = 2522.5 \cdot \{r_3 + 0.1363 \cdot (x_{1,3}^{L} \bar{V}_1 + x_{2,3}^{L} \bar{V}_2)^{1/3} - 0.085\}^3 \tag{7}$$

In eqs 4 and 5, κ_T indicates the isothermal compressibility of the {PEG 400 (1) + water (2)} mixture estimated as an additive property using the mixture composition and the reported values of κ for the neat components. The values of $\bar{V}_1$, $\bar{V}_2$, and $\bar{V}_3$ are the partial molar volume of PEG 400 (1), water (2), and SE415 (3) in the mixtures, respectively. The D value refers to the derivative function of the standard Gibbs free energies of transfer of SE415 (3) from water (2) to the (PEG 400 + water) system with respect to the solvent mixture composition without SE415. The Q value represents the second derivative function of the excess molar Gibbs free energy of mixing of two solvents (1 and 2) with respect to the water proportion in the mixture.

$$D = \left(\frac{\partial \Delta_{tr} G^{o}_{3,2\rightarrow 1+2}}{\partial x_1}\right)_{T,p} \tag{8}$$

$$Q = RT + x_1 x_2 \left(\frac{\partial^2 G^{Exc}_{1+2}}{\partial x_2^2}\right)_{T,p} \tag{9}$$

Notably, the value of the molecular radius of SE415 can be calculated using eq 10, where N_{Av} and r_3 are the Avogadro number and the molecular radius, respectively.

$$r_3 = \left(\frac{3 \cdot 10^{21} V_3}{4\pi N_{Av}}\right)^{1/3} \tag{10}$$

Moreover, the definitive correlation volume requires iteration because of its dependency on the local mole fraction of PEG 400 and water around SE415. This iteration is conducted by replacing $\delta x_{1,3}$ and V_{cor} in eqs 2, 3 and 6 to re-estimate the value of $x_{1,3}^{L}$ until a non-variant value of V_{cor} is achieved.

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ACS Omega 2022, 7, 1197−1210

Finally, a classical MS simulation (computational analysis) was performed for the SE415, PEG 400, SE415 + PEG 400, and SE415 + PEG 400 + water system. The software identified prime functional groups that serve as the H-bonding acceptor and H-bonding donor for SE415 and PEG 400. This software-based simulation predicted the H-bonding-based interaction responsible for preferential solvation. This rough estimation also predicted surface propensity and its impact on surface tension (conjugate base nature of SE415 due to the acidic alkyne H atom) in the water system.

2.2.5. In Vitro Dissolution Study in Buffer Solution. For the comparative study, the SE415-loaded binary mixture and SE415 suspension containing an equivalent concentration of the drug were subjected for the dissolution study using apparatus I (basket type). The suspension was formulated using a suspending agent (Na-CMC, carboxymethyl cellulose sodium salt) to investigate the *in vitro* drug dissolution study. Briefly, the prepared suspension (10 mg/g) was transferred into a capsule. The capsule was used for the dissolution study in PBS as the dissolution medium (500 mL). The capsule was placed in a basket to prevent floating on the surface. The study was performed at 298 K under constant stirring (100 rpm). Sampling was conducted at varied time points (0.0, 0.5, 1, 2, 4, 8, and 12 h), followed by replacing the equal volume with a fresh medium. The withdrawn sample was filtered and analyzed using a UV−vis spectrophotometer at 357 nm (U-1800, spectrophotometer, Kyoto, Japan). The experiment was performed three times for the mean and SD values.

2.2.6. GastroPlus-Based Prediction Studies. It is required to simulate the *in vitro* dissolution behavior of the drug in buffer with the *in vivo* performance in the human subject. Therefore, GastroPlus simulation and prediction software (GastroPlus, version 9.7, Simulation Plus, Inc., Lancaster, USA) is a suitable tool for this purpose using experimental *in vitro* data, which provides the physicochemical profile of the drug or related derivative if available and the software dictated data. The tool is simple, versatile, and US FDA approved for preliminary screening at the industrial scale for various pharmaceutical products to predict *in vivo* performance, population pharmacokinetics, and parameter sensitivity assessment (PSA) analysis in human, rodents, primates, and animals under fast conditions. The program is widely applied at the industrial scale and approved by the regulatory agency (US FDA) to expedite the approval process and reduce the cost burden of clinical investigation in humans for a new formulation. There are three tabs in the program such as a (a) compound tab, (b) physiological tab, and (c) pharmacokinetics tab. The compound tab and pharmacokinetics tab require various physicochemical parameters related to the drug, and the pharmacokinetics profile of the drug in the targeted animal model.[20] The ACAT (advanced compartmental absorption and transit model) model was used to predict the pharmacokinetics parameters using *in vitro* solubility data for batch and population studies. PSA analysis provides information about the critical factors having a great impact on PK parameters (area under the curve, time to reach maximum drug concentration, and the maximum drug concentration in the plasma), dissolution process, drug absorption, drug access to portal vein, hepatic circulation, and so on. Both ACAT and ADMET (ADMET predictor model) models were used to predict oral absorption of the drug by the nine compartments (stomach, duodenum, jejunum-1, jejunum-2, ileum-1, ileum-2, ileum-3, caecum, and ascending colon) of the GIT.[20] This regional absorption indicates the prime site of the drug absorption after oral administration using a specific dosage form and selected dose. Notably, the change of the physicochemical properties of the investigated drug in the fast compound tabs will change the percent value of regional absorption predicted by GastroPlus prediction software.

2.2.7. Calculation and Software: a Statistical Analysis. GastroPlus (version 9.7, Simulation Plus, Inc., Lancaster, USA) and HSPiP (version 5.02.6, USA) software were used for the prediction study of biopharmaceutical/pharmacokinetics parameters in humans and three-dimensional HSPs of SE415 and solvents, respectively. Statistical data were calculated to test the data using "Kruskal−Wallis analysis" and "Denn's test". A value was statistically considered significant at $p < 0.05$ in this study. All experimental studies were replicated ($n = 3$) for mean and SD.

2.2.8. Solubility Calculations Using Cosolvency Models. The generated solubility data of SE415 is fitted to the common cosolvency models. The first model is the combined nearly ideal binary solvent/Redlich−Kister (CNIBS/R−K) model (Acree, 1992), which expresses the relation between the solute solubility with respect to solvent composition at an isothermal condition and presented as

$$\log C_m = w_1 \log C_1 + w_2 \log C_2 + w_1 \cdot w_2 \sum_{i=0}^{2} A_i \cdot (w_1 - w_2)^i \quad (11)$$

in which C_m, C_1, and C_2 are the solubility values in the mixed solvents and in the mono-solvents 1 and 2, and A_i terms are the model parameters computed by the linear regression of ($\log C_m - w_1 \log C_1 - w_2 \log C_2$) against $w_1 \cdot w_2$, $w_1 \cdot w_2 \cdot (w_1 - w_2)$, and $w_1 \cdot w_2 \cdot (w_1 - w_2)^2$.[21,22] The second model, as a non-linear model, is the modified Wilson model, which calculates the solubility data in binary solvent mixtures at a given temperature and presented as

$$-\log C_m = 1 - \frac{w_1(1 + \log C_1)}{w_1 + w_2\lambda_{12}} + -\frac{w_2(1 + \log C_2)}{w_1\lambda_{12} + w_2} \quad (12)$$

where λ_{12} and λ_{21} are the model coefficients that are computed by the non-linear analysis.[23] In addition to these correlative models, there are some pre-trained models to predict the solubility of a drug in (PEG 400 + water) mixtures. The simplest predictive model is the trained version of the log-linear model of Yalkowsky and is presented as

$$\log C_m = \log C_2 + w_1(0.68 + 0.88 \log P) \quad (13)$$

which requires the aqueous solubility of the drug and its log P value (=2.87 for SE415).[24] The next model is the trained version of the Jouyban−Acree model, which is represented as

$$\log C_{m,T} = w_1 \log C_{1,T} + w_2 \log C_{2,T} + \frac{394.82 w_1 \cdot w_2}{T} - \frac{355.28 w_1 \cdot w_2 (w_1 - w_2)}{T} + \frac{388.89 w_1 \cdot w_2 (w_1 - w_2)^2}{T} \quad (14)$$

in which $C_{m,T}$, $C_{1,T}$, and $C_{2,T}$ are the solubility of SE415 in the mixed and mono-solvents 1 and 2 at temperature T (expressed in kelvin).[25] Equation 15 is trained using the experimental

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Table 1. Summary of HSPs ($MPa^{1/2}$) of SE415 and Solvents along with Other Predictive Physicochemical Properties of SE415

parameters	SE415	PEG 400[a]	water	propylene glycol	NMP
δ_d	19.6	15.1	15.5	16.8	18.0
δ_p	7.9	6.8	16	10.4	12.3
δ_h	9.2	7.9	42.3	21.3	7.2
δ_t	23.0	18.4	47.8	29.8	21.8
mol. vol ($cm^3 \cdot mol^{-1}$)[b]	258.4	635.6		74.3	99.7
mol. wt ($g \cdot mol^{-1}$)[c]	406	420	18	76.1	99.1
density ($g \cdot cm^{-3}$)	1.25	1.3	1	1.024	1.03
enthalpy of fusion ($kJ \cdot mol^{-1}$)	63.74	30.56		8.81	8.28
R (space parameter)		6.76	14.71	14.34	8.35

[a]PEG 400 = polyethylene glycol 400. [b]Mol. vol = mol volume. [c]Mol. wt = molecular weight; NMP = *N*-methyl-2-pyrrolidone.

solubility of various drugs in (PEG 400 + water) mixtures; however, no solubility data of SE415 were used in its training process. The solubility of SE415 in the mono-solvents at each temperature of interest is required as the input data for this model.[25] A more general model was trained using the experimental solubility data of various drugs dissolved in different cosolvents + water solvent systems employing the HSPs (for numerical values, see Table 1) and the basic form of the Jouyban−Acree model. The Jouyban−Acree−Hansen model is

$$\log C_{m,T} = w_1 \log C_{1,T} + w_2 \log C_{2,T} + \left(\frac{w_1 w_2}{T}\right) \{0.606\delta_{p_3}(\delta_{p_1} - \delta_{p_2})^2 + 0.013\delta_{h_3}(\delta_{h_1} - \delta_{h_2})^2\} + \left(\frac{w_1 w_2 (w_1 - w_2)}{T}\right)\{-8.696\delta_{d_3}(\delta_{d_{,1}} - \delta_{d_2})^2 + 0.376\delta_{p_3}(\delta_{p_1} - \delta_{p_2})^2 + 0.013\delta_{h_3}(\delta_{h_1} - \delta_{h_2})^2\} + \left(\frac{w_1 w_2 (w_1 - w_2)^2}{T}\right)\{9.277\delta_{d_3}(\delta_{d_{,1}} - \delta_{d_2})^2 - 0.461\delta_{p_3}(\delta_{p_1} - \delta_{p_2})^2 + 0.017\delta_{h_3}(\delta_{h_1} - \delta_{h_2})^2\} \quad (15)$$

in which the subscripts 1−3 means solvents 1 and 2 and the solute and the other symbols were already defined. Equation 15 requires the solubility data in the mono-solvents and the computed HSPs of the solvents and the solute and its expected prediction error is ∼34%.[26]

The accuracy of the solubility correlations/predictions is assessed by computing the mean percentage deviation (MPD) of the calculated and experimental solubility data using

$$\text{MPD} = \frac{100}{N}\sum_{1}^{N}\frac{|\text{calculated} - \text{experimental}|}{\text{experimental}} \quad (16)$$

where N is the number of data points in each set.

3. RESULTS AND DISCUSSION

3.1. HSPs of SE415 and Solvents. We aimed to investigate the biocompatible and approved (US FDA) cosolvent for the maximized solubilization of SE415 in the explored binary system, followed by studying preferential solvation by the cosolvent in the same binary mixture. As we discussed before, the synthesized compound (SE415) was poorly soluble in water, which is hurdle for a formulation scientist to translate into a suitable parenteral dosage form, oral solution, and subcutaneous delivery. Considering the chemical structure and estimated HSP solubility parameters, there may be probable chance of interaction with the cosolvents (PEG 400, PG, and NMP) bearing functional groups capable of forming hydrogen bonding, polar interaction, and substantial dispersion. Prior to the solubilization study, SE415 and explored solvents possessing more chance of solubilization were identified in HSPiP software by analyzing the values of three-dimensional HSPs (δ_d, δ_p, and δ_h). Aftermath of analysis, PG, NMP, and PEG 400 were predicted as the most suitable cosolvents based on the values of δ_d, δ_p, and δ_h, as shown in Table 1. The estimated values of δ_d, δ_p, and δ_h were found to be 19.6, 7.9, and 9.7 for SE415, respectively. Similarly, the values of δ_d, δ_p, and δ_h were observed to be 15.1, 6.8, and 7.9 $MPa^{1/2}$ for PEG 400. Thus, δ_p (6.8 $MPa^{1/2}$), δ_d (15.1 $MPa^{1/2}$), and δ_h (7.9 $MPa^{1/2}$) values of PEG 400 are closely related to the values of δ_d, δ_p, and δ_h of SE415, as shown in Table 1. This may be prudent to correlate that PEG 400 has a maximum dispersion potential, polarity-mediated interaction, and hydrogen-bonding-based interaction for facilitated preferential solvation with the cosolvent of SE415 leading to better miscibility as compared to NMP and PG. Furthermore, the δ_h values for SE415 and PEG 400 were 9.7 and 7.9, respectively, which indicated the lowest value of the difference ($\Delta\delta_h$) (9.7−7.9 = 1.8). This further supported the rationalized reason for improved solubilization of SE415 by the cosolvent in PEG 400 *via* the H-bonding-mediated interaction. This may be attributed to the presence of the acidic hydrogen functional group (acidic propylene) in the drug (Figure 1A).

It is apparent that a slight difference in the "$\Delta\delta_p$" value (between SE415 and the solvents may result in maximum solubility/miscibility in that type of the solvent. Therefore, considering the determined values of $\Delta\delta_p = (\delta_{ps} - \delta_{pv})$ such as 1.1, 2.5, and 4.6 $MPa^{1/2}$ for PEG 400, PG, and NMP, respectively, suggested that PEG 400 could be the most suitable cosolvent for SE415 solubilization at an explored temperature as compared to PG and NMP. Comparing the value of $\Delta\delta$ of NMP (4.6 $MPa^{1/2}$) among the investigated solvents, it is quite clear that NMP showed poor aqueous solubility due to the maximum difference value of the solubility parameter. Likewise, the values 1.8 and 1.1 $MPa^{1/2}$ were determined as $\Delta\delta_h$ and $\Delta\delta_p$, respectively, for SE415 in PEG 400 as the lowest values among them for maximum solubility/miscibility.[27−31] These calculated values further supported the rationalized selection of PEG 400 for the preferential solvation study in the binary mixture with water. Hence, PEG 400 was selected to investigate the solubility and preferential solvation of SE415 in varied mass ratios of PEG 400 to water following the reported method.[15]

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ACS Omega 2022, 7, 1197−1210

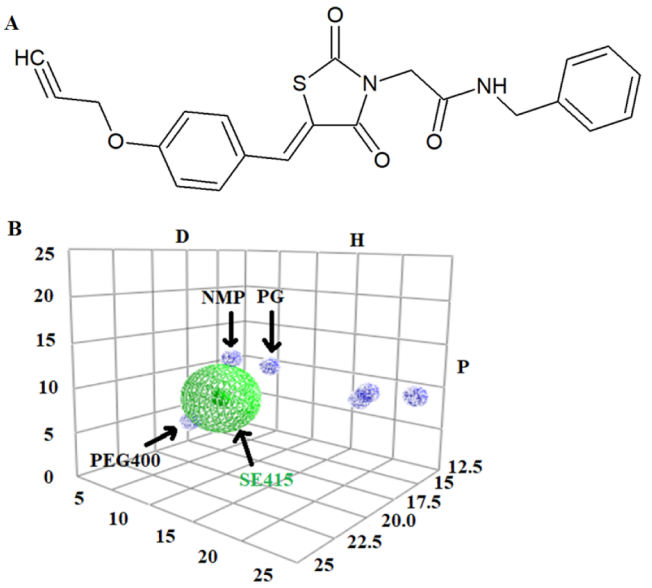

Figure 1. (A) Molecular structure of (*Z*)-*N*-benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide (3), expressed as SE415, and (B) Hansen solubility sphere of SE415 and various suggested solvents with varied distance (space parameter, *R*) from the center of SE415 sphere (green solid sphere). Blue spheres are the selected solvents possessing a maximum interaction (in terms of space parameter, *R*) with SE415.

In general, several related physicochemical parameters of a solute help to understand the miscibility behavior and dissolution process. These parameters were molecular weight (MW), density, molar volume (*V*), and molar enthalpy of fusion (H_f) estimated using HSPiP software. The estimated values of molecular weight (MW), density, molar volume (*V*), and H_f were 406 g·mol^{-1}, 1.25 g·cm^{-3}, 258.4 cm^3·mol^{-1}, and 63.74 kJ·mol^{-1}, respectively, for SE415. The same values were also estimated for the solvents, and the results are presented in Table 1.

In Figure 1B, we depicted the solubility sphere of SE415 in different solvents and the green dot at the center indicates the location of the solute followed by "*R*" as the radius of the sphere and termed as the "space parameter".

The values of "*R*" as the space parameter for PEG 400, PG, water, and NMP are provided in Table 1. The values of R for NMP and PEG 400 are approximately close to each other and near the sphere.[27−29] Thus, PEG 400 could be the most suitable solvent for the SE415 preferential solvation study.

3.2. Mole Fraction Solubility, Hildebrand Solubility, and Thermodynamics Parameters. The main problem was poor aqueous solubility, which further challenged a formulation scientist, researcher, and scientist working in a related domain at the pre-formulation stage for successful drug delivery to the patients. Therefore, it was of utmost need to investigate a suitable co-solvent assisting the solvation behavior in water. Therefore, the current study emphasized us to investigate the mechanistic perspective of the preferential solvation phenomenon in the {PEG 400 (1) + water (2)} mixture, followed by estimating related parameters. The HSPiP software predicted PEG 400 as a suitable solvent for SE415 solubility/miscibility based on the HSPs and "*R*" values. Moreover, PEG 400 is widely used as a cosolvent in parenteral formulation for improved aqueous solubility of poor soluble drugs. It has low polarity (dielectric point ∼ 14.1 unit) as compared to water (dielectric point ∼ 81.0 unit) and anticipated to increase aqueous solubility of a lipophilic drug by lowering the polarity of the PEG−water mixture system to such a level that closely reflects the dielectric constant value of the drug.[31,32]

Considering the structural analysis, low aqueous solubility of SE415 can be correlated with the heterocyclic aromatic rings (Figure 1A) which may further lead to limited intestinal absorption after oral administration. The result of the drug solubility is demonstrated in the {PEG 400 (1) + water (2)} cosolvent mixture, as depicted in Figure 2A. The solubility values (mole fraction) of SE415 in neat PEG 400 (neat w_1 = 1.0) and pure water (w_1 = 0.0) were found to be 7.26 × 10^{-7} and 2.83 × 10^{-3} at 298.15 K, respectively. Overall, the values of mole fraction solubility of SE415 were observed to be

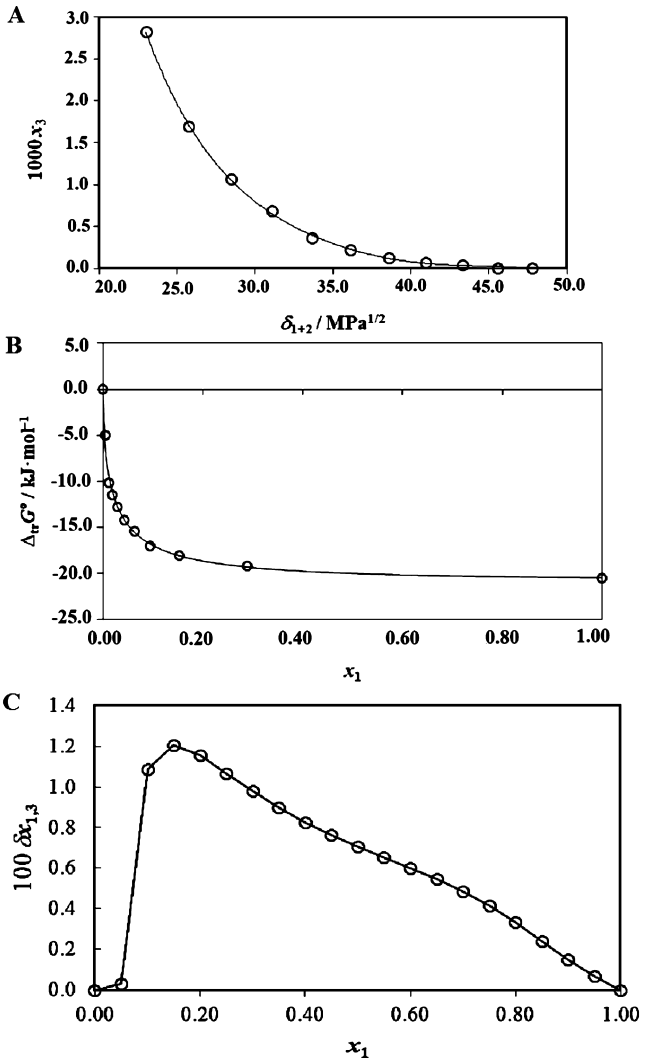

Figure 2. (A) Mole fraction solubility of (*Z*)-*N*-benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide (3) as the function of the Hildebrand solubility parameters of the {PEG 400 (1) + water (2)} cosolvent mixtures at 298.15 K, (B) Gibbs energy of transfer of (*Z*)-*N*-benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)-benzylidene)thiazolin-3-yl)}acetamide (3) from neat water (2) to {PEG 400 (1) + water (2)} mixtures at 298.15 K, and (C) values of $\delta x_{1,3}$ of (*Z*)-*N*-benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)-benzylidene)thiazolin-3-yl)}acetamide (3) in the {PEG 400 (1) + water (2)} mixture system at 298.15 K.

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ACS Omega 2022, 7, 1197−1210

increased with the increasing concentration of PEG 400 in the mixture ratio (as shown in Figure 2A). As described before, the explored cosolvent has already been commercialized for the delivery of a poor soluble drug for oral, parenteral, and topical dosage forms due to biocompatibility and safety concern among US FDA recommended excipients (FDA Inactive excipients database, 2021). Figure 2A illustrates the solubility behavior of SE415 as the function of the polarity of (PEG 400 + water) cosolvent mixtures, as shown in the Hildebrand solubility parameter (δ_{1+2}). In case of the liquid mixtures, the values of δ_{1+2} are estimated using the Hildebrand parameters of individual neat solvents such as neat PEG 400 (δ_1 = 20.77 $MPa^{1/2}$) and neat water (δ_2 = 47.8 $Mpa^{1/2}$), and the volume fraction of each components of the mixture.[33] In this mathematical calculation, the volume fraction was assumed as the volume fraction additivity, as revealed in eq 2.[27−29] Moreover, the density of the (PEG 400 + water) cosolvent mixture system was obtained from our previous papers.[19,34,35]

$$\delta_{1+2} = \sum_{i=1}^{2} f_i \delta_i \tag{17}$$

It is quite clear that the substantial solvation/solubility of the present model drug was achieved in neat PEG 400, as shown in the curve graph (Figure 2A) by considering the entire polarity range (δ_1 = 9.9 $Mpa^{1/2}$). The literature suggested that a solute reveals maximized solubility/miscibility when the values of δ_d, δ_p, and δ_h of HSPs and the Hildebrand solubility parameters are the same and the resulting difference between the solute and the solvent becomes zero (δ_p of solute−δ_p of solvent = 0).[19,34,35] Thus, the value of δ_3 of SE415 in the investigated (PEG 400 + water) cosolvent mixture would be 23.0 $MPa^{1/2}$ for maximum solubility, which is evidenced with the approximate value obtained from the Fedors' method (Table 1, δ_3 = 31.11 $MPa^{1/2}$). Notably, a small significant difference (10.34 $MPa^{1/2}$) might be due to the PEG 400-mediated solvation process in the PEG 400-rich ratio of the (PEG 400 + water) mixture in the Fedors' method. As described previously, PEG 400 is a basic solvent, which may enhance the drug's preferential solvation by PEG 400 due to the drug acting as Lewis acid possessing a phenolic functional group in the molecular structure. The finding could be correlated to a previous report with a similar observation using PEG 400, ethanol, and PG.[35]

In general, HSPs, the thermodynamic functional parameters, and computational models are commonly used to understand the mechanism of the dissolution process. There are several established thermodynamic functional parameters such as standard dissolution enthalpy ($\Delta_{soln}H^\circ$), standard dissolution Gibbs energy ($\Delta_{soln}G^\circ$), and standard dissolution entropy ($\Delta_{soln}S^\circ$) for the solubilization/miscibility of a compound in a specific solvent. The zero or negative value of $\Delta_{soln}G^\circ$ indicates the spontaneous mixing/dissolution process in the solvent or mixed system. Moreover, the −ve and +ve values of $\Delta_{soln}H^\circ$ signifies an endothermic and exothermic dissolution/mixing process, respectively.[19] The results of apparent thermodynamic parameters ($\Delta_{soln}G^\circ$) of SE415 in all mass ratios of the (PEG 400 + water) cosolvent mixture is calculated using eq 3, as shown in Table 3.

$$\Delta_{soln}G^\circ = -RT \ln x_3 \tag{18}$$

It is clear from the result presented in Table 3 that the negative values of $\Delta_{soln}G^\circ$ in all mixture ratios indicated the spontaneous dissolution process of SE415. Moreover, the value of $\Delta_{soln}G^\circ$ is favorable {less positive value (15.77 kJ·mol^{-1}) in the neat PEG 400} for preferential solvation and facilitated dissolution of SE415 due to an increased content of PEG 400 in the higher ratios.

3.3. Preferential Solvation. The modeling of the solubility data using thermodynamic parameters is very desirable to a solid−liquid equilibrium.[36] Thermodynamic parameters are commonly used to explain the mechanistic approach of drug solubilization in a particular solvent or solvent mixture. The values of Gibbs free energy as the preferential solubility parameters of SE415 in a {PEG 400 (1) + water (2)} mixed system are presented in Tables 3 and 4. All values of Gibbs free energy transfer of SE415 from pure water (2) to the {PEG 400 (1) + water (2)} mixtures ($\Delta_{tr}G^\circ_{3,2\rightarrow1+2}$) have been observed as negative in Table 3, which indicates the affinity of SE415 with PEG 400 at the studied temperature. There may be a probable chance of increment in the partial molar volume change of the solvent/cosolvent and water at varied temperatures (data not given). Moreover, the Gibbs free energy transfer behavior is illustrated in Figure 2B at 298.15 K. The values of $\Delta_{tr}G^\circ_{3,2\rightarrow1+2}$ were observed to be changed from a low negative value (−1.81 kJ·mol^{-1}) to high negative value (−15.33 kJ·mol^{-1}), as shown in Table 3. These values were calculated from mole fraction solubility data. Notably, the negative values of $\Delta_{tr}G^\circ_{3,2\rightarrow1+2}$ were found to be significantly increased with an increased content of PEG 400 in the (PEG 400 + water) cosolvent mixture. Therefore, the maximum negative value of Gibbs energy of transfer of SE415 from water to the (PEG 400 + water) mixture was found to be −15.33 kJ·mol^{-1} (Table 3). Thus, the value of $\Delta_{tr}G^\circ_{3,2\rightarrow1+2}$ parameter in neat PEG 400 was found to be nearly 8.33 folds higher than this parameter obtained at w_1 = 0.1 (x_1 = 0.0198). The values of $\Delta_{tr}G^\circ_{3,2\rightarrow1+2}$ were calculated using the following equation.

$$\Delta_{tr}G^\circ_{3,2\rightarrow1+2} = RT \ln\left(\frac{x_{3,2}}{x_{3,1+2}}\right) \tag{19}$$

Additionally, the $\Delta_{tr}G^\circ_{3,2\rightarrow1+2}$ values were correlated with the coefficients of the quotient-polynomial model, as expressed in eq 19. The calculated values of coefficients were found to be a = 0.15, b = 4.22, c = −106.92, d = 16.95, and e = −347.49, with a regression coefficient (r^2) value of 0.980, typical error = 0.809, and F = 146.7.

$$\Delta_{tr}G^\circ_{3,2\rightarrow1+2} = \frac{a + cx_1^{0.5} + ex_1}{1 + bx_1^{0.5} + dx_1} \tag{20}$$

Thus, the D values were calculated from the first derivative of the respective polynomial model, as reported in Table 4. Moreover, the values of $\bar{V}_1$, $\bar{V}_2$, $RT{\cdot}\kappa_T$, and Q were obtained from the reported literature for the studied {PEG 400 (1) + water (2)} cosolvent mixture system.[34] The value of the molar volume of SE415 was calculated using the Fedors method (258.4 $cm^3{\cdot}mol^{-1}$, Table 2) despite the composition of the mixture system. Notably, the values of $G_{1,3}$ and $G_{2,3}$ were observed as negative in all explored compositions, suggesting a good affinity of SE415 with both solvents: PEG 400 and water. This may be due to polar interaction, dispersion behavior, and hydrogen bonding of the drug with water, followed by the facilitated interaction by PEG 400 working as a cosolvent in the mixture. This can be further explained based on the proportion of PEG 400 in the mixture where the values of free

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Table 2. Summary of Internal Energy, Molar Volume, and the Hildebrand Solubility Parameters of (*Z*)-*N*-Benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide (3) as per Fedors' Method

functional groups	number	$\Delta U°$/kJ·mol^{-1}	$V°$/cm^3·mol^{-1}
$-CH_2-$	3	14.82	48.3
$-CH=$	1	4.31	13.5
$>C=$	1	4.31	−5.5
$HC\equiv$	1	3.85	27.4
$-C\equiv$	1	7.07	6.5
phenylene	1	31.90	52.4
ring closure ≥ 5	1	1.05	16.0
phenyl	1	31.9	71.4
−O−	1	3.35	3.8
−CO−	1	17.4	8.10
−CONH−	1	33.5	9.5
−CON<	1	29.5	−7.7
−S−	1	14.15	12.0
	Σ	197.11	258.4
	$\delta_3 = (197.11/258.4)^{1/2} = 27.62$ MPa$^{1/2}$		

Gibbs energy of transfer of SE415 from pure water to the mixture was found to be substantially increasing with the increasing content of PEG 400 in the mixture (Table 3). The value of Gibbs energy of transfer of SE415 in neat PEG 400 was relatively high as compared to any composition of the mixture.

The value of the solute radius (r_3) was estimated to be 0.468 nm, as calculated from eq 9. The value of V_{cor} was iterated three times using eqs 2, 3, and 6 to achieve the values reported in Table 4. Table 4 provides the preferential solvation parameters of SE415 (3) by PEG 400 molecules, expressed as $\delta x_{1,3}$.

From Table 4 and Figure 2C, it is quite obvious that the $\delta x_{1,3}$ values of SE415 (3) varying non-linearly with the proportional increase of PEG 400 (1) in the mixture at a fixed temperature, which may further increase or decrease at varied temperatures for comparative investigation. Additionally, the addition of PEG 400 (1) into water (2) makes the values of $\delta x_{1,3}$ of SE415 (3) positive in all compositions of the mixture ranging from $x_1 = 0.0$ (neat water) to 1.0 (neat PEG 400). In these contexts, the local mole fraction of PEG 400 (1) in the vicinity of SE415 (3) is profoundly greater than the ones in the bulk of the binary mixture without SE415. Notably, the maximum positive value of $\delta x_{1,3}$ was achieved at $x_1 = 0.15$ ($\delta x_{1,3} = 1.21 \times 10^{-2}$), which corroborates the true preferential solvation effect of PEG 400 molecules on SE415.[37] The solvent is basic in nature for solvation of SE415 (3), and SE415 may behave as a Lewis acid for concentration-dependent solubilization by PEG 400 in the mixed system. The improved preferential solvation of SE415 by PEG 400 might be correlated with the hydrogen bond formation polar interaction, reduced surface tension, increased wettability through PEG 400, and facilitated dispersion. Kamlet and Taft reported facilitated solubilization through the hydrogen bond acceptor count responsible for hydrogen bond formation-mediated solubilization.[38] It is quite clear from Figure 2C that the drug is preferentially solvated by PEG 400 as indicated above, which may be due to the Lewis acid behavior of SE415 in front of the unshared electron pairs on oxygen atoms of PEG 400.

The improved preferential solvation by PEG 400 in the binary mixture can be correlated to the acceptor and donor functional groups present in the compound. These groups are responsible for hydrogen bonding formation and subsequently increased solubility in the binary mixture. Therefore, this was justified by MD simulation software. The result showed that SE415 possessed three acceptor groups (red net sphere) and one donor group (blue net sphere), as shown in Figure 3A. Similarly, PEG 400 was found to have several acceptor and acceptor−donor groups, as revealed in Figure 3B. The interaction simulation result showed a good interaction between SE415 and PEG 400 (Figure 3C). Moreover, the binary mixture (PEG 400 + water) exhibited preferential solvation by PEG 400 in the presence of water as a result of various hydrogen bonding (dotted lines) interactions with the compound (Figure 3D). Chemically, the SE415 compound may exhibit slight acidic nature due to the acidic alkyne H-atom. Therefore, a typical snapshot box (Figure 3D) indicated solubilized SE415 in bulk rather the surface-active property in water.[39]

3.4. *In Vitro* Drug Dissolution at Physiological pH. The SE415-loaded suspension and binary mixture {(PEG 400 + water) construct} were prepared and subjected for dissolution in PBS solution. The result of SE415-loaded suspension exhibited that 21.0% drug was dissolved over a period of 12 h at room temperature, as shown in Figure 4A, as calculated

Table 3. Summary of Apparent Thermodynamic Properties of (*Z*)-*N*-Benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide in {PEG 400 (1) + Water (2)} Cosolvent Mixtures at 298.15 K

w_1[a]	f_1[a]	x_1[a]	$\delta_{(1+2)}$[b]	x_3	$\Delta_{soln}G°$/kJ·mol^{-1}	$\Delta_{tr}G°_{3,2\rightarrow1+2}$/kJ·mol^{-1}
0.00	0.0000	0.0000	47.80	7.26×10^{-7}	35.04	0.00
0.10	0.0898	0.0050	45.57	5.34×10^{-6}	30.10	−4.95
0.20	0.1817	0.0111	43.29	4.39×10^{-5}	24.87	−10.17
0.30	0.2757	0.0189	40.96	7.45×10^{-5}	23.56	−11.48
0.40	0.3719	0.0292	38.58	1.27×10^{-4}	22.23	−12.81
0.50	0.4704	0.0431	36.13	2.21×10^{-4}	20.87	−14.17
0.60	0.5713	0.0633	33.63	3.68×10^{-4}	19.60	−15.44
0.70	0.6745	0.0951	31.07	6.91×10^{-4}	18.04	−17.00
0.80	0.7804	0.1527	28.45	1.07×10^{-3}	16.97	−18.07
0.90	0.8888	0.2885	25.76	1.70×10^{-3}	15.82	−19.23
1.00	1.0000	1.0000	23.00	2.83×10^{-3}	14.55	−20.49

[a] w_1, f_1, and x_1 are the mass, volume, and mole fractions of PEG 400 in the {PEG 400 (1) + water (2)} mixtures free of (*Z*)-*N*-benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide (3). [b] δ_{1+2} is the Hildebrand solubility parameter of {PEG 400 (1) + water (2)} mixtures free of SE415 at 298.15 K.

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ACS Omega 2022, 7, 1197−1210

Table 4. Few Properties Associated with the Preferential Solvation of (*Z*)-*N*-Benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide in {PEG 400 (1) + Water (2)} Mixtures at 298.15 K

x_1[a]	D (kJ·mol^{-1})	$G_{1,3}$ (cm^3·mol^{-1})	$G_{2,3}$ (cm^3·mol^{-1})	V_{cor} (cm^3·mol^{-1})	$100\delta x_{1,3}$
0.00	−817.56	−6218.1	−257.3	1025	0.00
0.05	−70.80	−650.8	−656.1	1421	0.03
0.10	−28.65	−386.9	−544.2	1832	1.09
0.15	−15.74	−317.4	−477.8	2151	1.21
0.20	−9.97	−290.3	−437.1	2443	1.15
0.25	−6.87	−277.4	−410.8	2722	1.07
0.30	−5.02	−270.5	−393.2	2992	0.98
0.35	−3.81	−266.4	−381.3	3255	0.90
0.40	−2.98	−264.0	−373.4	3512	0.83
0.45	−2.39	−262.4	−368.5	3763	0.76
0.50	−1.96	−261.4	−365.7	4010	0.71
0.55	−1.63	−260.7	−364.7	4251	0.65
0.60	−1.37	−260.2	−365.0	4488	0.60
0.65	−1.17	−259.8	−366.0	4719	0.55
0.70	−1.00	−259.6	−367.0	4946	0.48
0.75	−0.87	−259.3	−367.1	5167	0.41
0.80	−0.76	−259.0	−364.9	5383	0.33
0.85	−0.67	−258.6	−359.4	5593	0.24
0.90	−0.59	−258.1	−350.3	5799	0.15
0.95	−0.53	−257.7	−338.3	6000	0.07
1.00	−0.47	−257.3	−324.9	6196	0.00

[a] x_1 is the mole fraction of PEG 400 (1) in the {PEG 400 (1) + water (2)} mixtures free of (*Z*)-*N*-benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide (3).

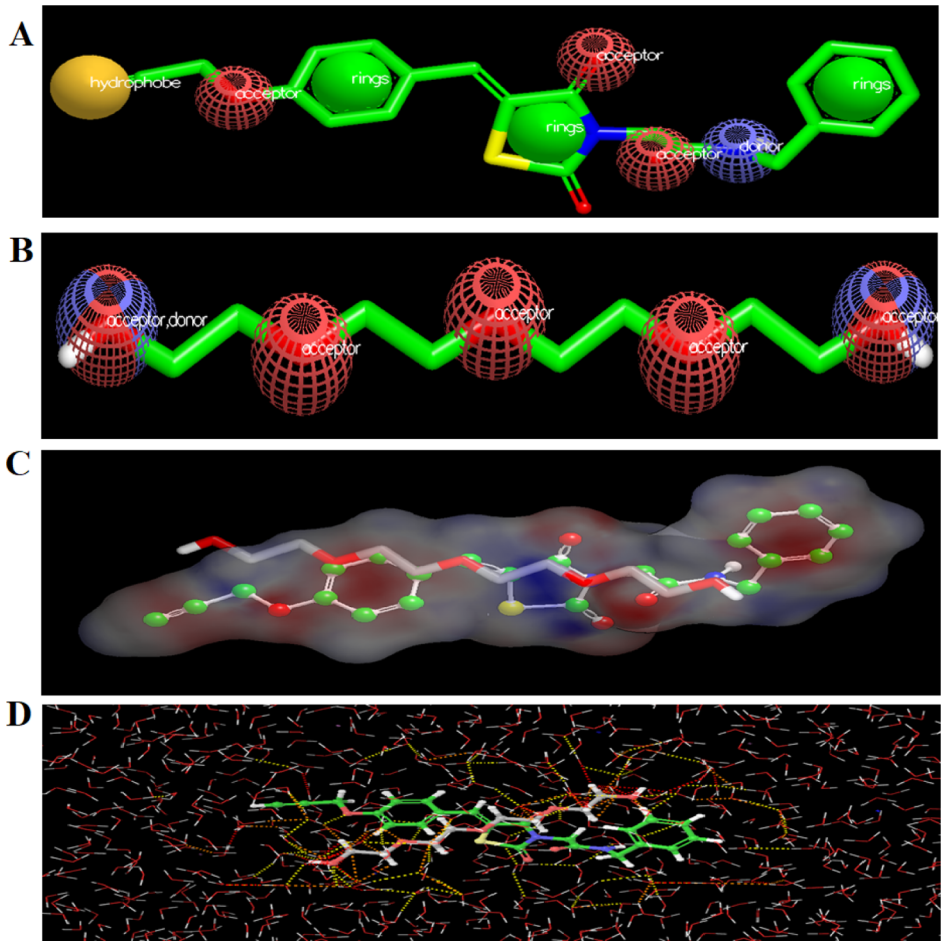

Figure 3. Typical Pharmacophoric features of (A) SE415, (B) PEG 400, and (C) electrostatic surface potential diagram of SE415 and PEG 400, and (D) interactions between SE415 and the binary mixture (PEG 400 + water).

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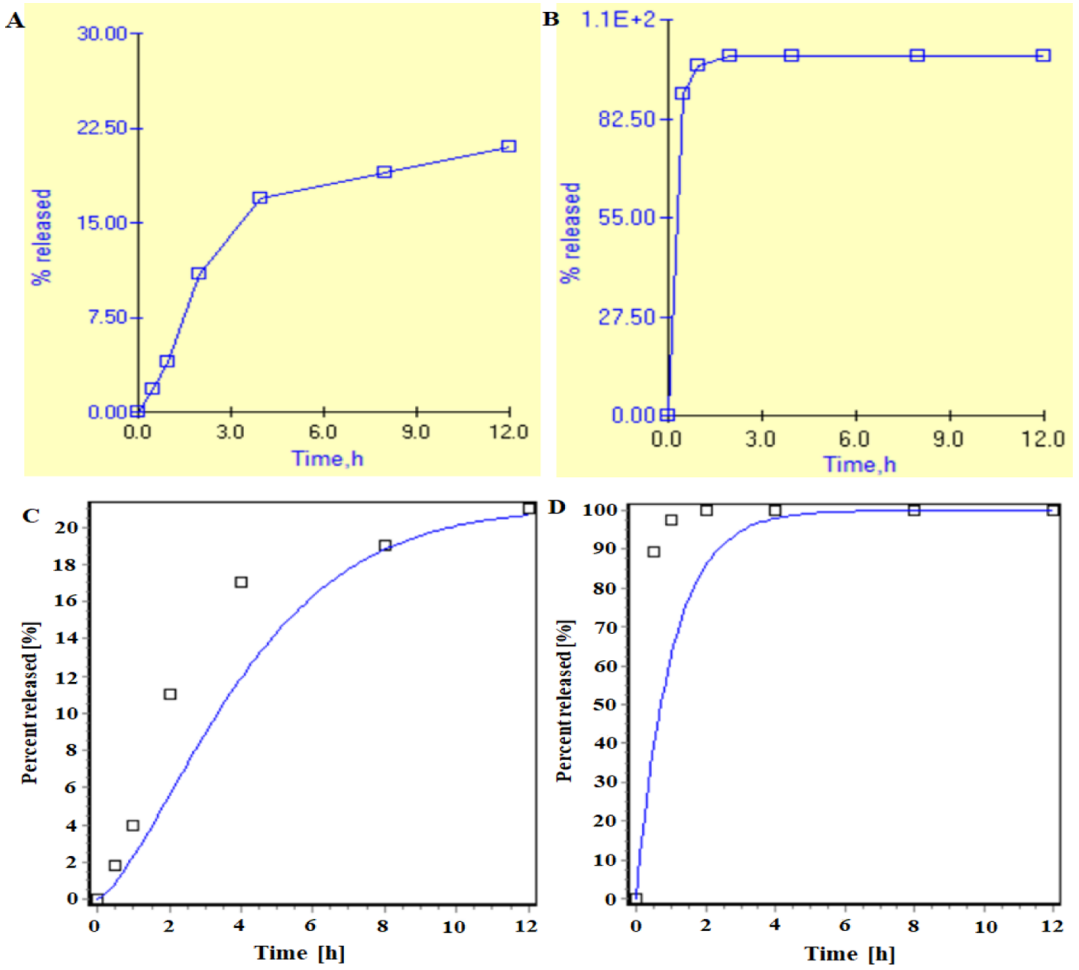

Figure 4. *In vitro* drug dissolution of the SE415 suspension and SE415-loaded (PEG 400 + water) mixed binary system in PBS (pH 7.4): (A) *in vitro* release profile of SE415 suspension, (B) *in vitro* release profile of the SE415 ferrying (PEG 400 + water) mixed binary system, (C) fitting Weibull function of SE415 suspension, and (D) fitting Weibull function of the SE415-loaded (PEG 400 + water) binary mixed system.

using GastroPlus program. Similarly, Figure 4B shows the release profile (89.0% within 5 min) of the SE415-loaded (PEG 400 + water) mixture in the same release medium and experimental conditions. Figure 4C,D illustrated the Weibull fit model applied for the SE415 and SE415-binary system, respectively. The simulation of experimental and predicted release pattern, which was in good agreement with the best fit of the applied model (Weibull model as a flexible model with great potential to be fitted over range of release pattern), as evidenced with the regression coefficient value (r^2) of 0.90. The shape factor (β, a characteristic parameter of the release curve) of the Weibull function parameter (favorable model sensitive to the range of release data) was found to be 1.44, suggesting the sigmoidal ($\beta > 1$) release pattern from suspension in PBS (Figure 4C). Figure 4C exhibits the result of single Weibull fit analysis on release behavior and the model predicted a release percentage of 23.34%, lag time of 0.55 min, and an AIC (akaike information criterion) value of 0.85. Likewise, Figure 4D reveals the result of single Weibull fit analysis on release behavior ($\beta = 1.0$) and the model predicted an exponential release percentage of 99.8%, lag time of 0.1 min, and an AIC (akaike information criterion) value of 0.91. The low value of dissolution can be correlated with the poor aqueous solubility in the aqueous medium.

3.5. *In Silico* GastroPlus Software-Based Prediction: a Comparative Prediction. The software allowed us to predict some physicochemical properties and *in vivo* pharmacokinetic parameters based on the input parameters (Table S1). The GastroPlus program was used to predict several physicochemical properties, dissolution pattern, and degree of *in vivo* absorption performance in humans under fast conditions. Thus, HSPiP software-based predicted values (particle density, enthalpy of fusion, and log *P*), GastroPlus default values (permeability coefficients, dosing volume, and pK_a), and experimentally obtained data (aqueous solubility and PEG 400 based solubility) of the SE415 suspension and SE415-loaded (PEG 400 + water) construct were used to run the prediction program (Table S1). The novel compound SE415 was poorly soluble in water, and there is no *in vivo* data available in animals and humans so far. Therefore, software was used to compare the dissolution rate and the absorption profile of this drug in humans after oral administration using suspension and binary (PEG 400 + water) mixed system in humans (fast condition).[20] Interestingly, the dissolution rate and *in vivo* absorption of SE415 loaded in the binary mixture of the (PEG 400 + water) system were predicted relatively higher as compared to the suspension in humans (Figure 4A,B). In case of the SE415-loaded suspension, the predicted absorbed value was approximately 5.0 mg after 12 h, whereas the

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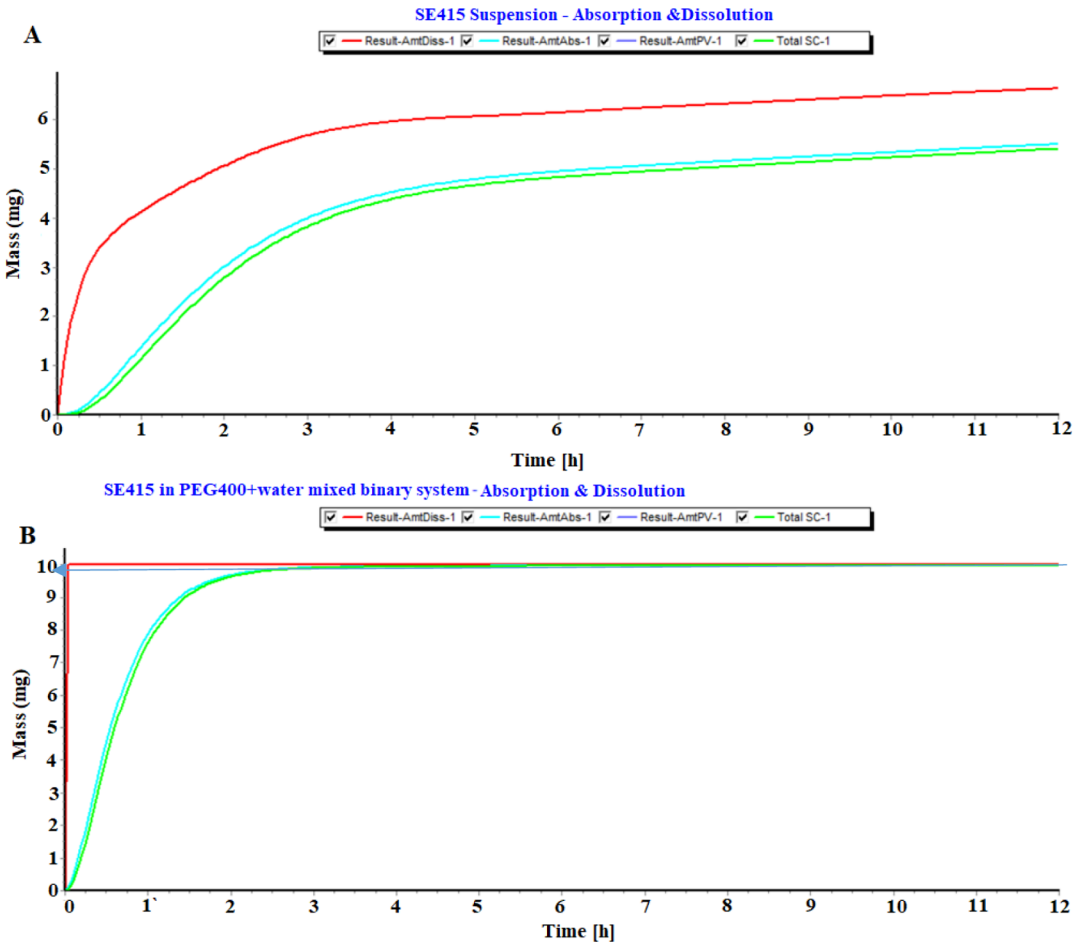

Figure 5. GastroPlus-based prediction of (a) suspension for *in vitro* dissolution and *in vivo* absorption (humans) under fast conditions and (b) solubilized SE415 in the binary system *in vitro* dissolution and *in vivo* absorption (humans) under fast conditions at 10 mg dose.

predicted dissolved amount was about 6.4 mg in the fast condition (Figure 5A). In contrast, the predicted dissolution value was approximately 9.9 mg after 5 min, whereas the predicted absorbed amount of the SE415-loaded (PEG 400 + water) construct was about 9.78 mg (Figure 5B). This means that the dissolution and absorption processes were modified by constructing a binary system with improved solubilization of the SE415 compound, as evidenced in predicted values.[20]

Anatomically, the GIT is composed of several segments such as the stomach, duodenum, small intestine, large intestine, and colon. The upper and middle regions of the GIT are considered a suitable and prime site for the absorption of the drug, water, and electrolytes.[19,20] The present software was used to predict the extent of the absorption of SE415 suspension and SE415-loaded binary PEG 400 + water system through the nine regional compartments of the GIT. The results of regional compartmental absorption of both formulations have been illustrated in Figure 6A,B. The GastroPlus program predicted approximately 22.8 and 70.1% as the total absorption through the GIT of humans from the suspension and the binary system, respectively (Figure 6A,B). Moreover, Figure 6 predicts that the prime sites of the drug absorption such as the duodenum, jejunum, ileum, and the distal region which relates to its poor acidic nature (acetylene functional group) and ionized form in the strong acidic medium of the stomach (pH ∼ 1−2).[19,20] This may be a reason for zero absorption from the stomach in both formulation (Figure 6). In this way, the software allowed us to hypothesize that the dissolved form of SE415 in the (PEG 400 + water) binary mixture can improve *in vivo* absorption and subsequently oral bioavailability in the fast condition as compared to the conventional suspension in the human body. This may be prudent to correlate the regional absorption values with the improved dissolution, as predicted in Figure 4. Thus, the drug absorption (9.9 mg) within the reduced time period (5 min) as compared to suspension indicated improved solubilization of SE415 by PEG 400 mediated due to the preferential solvation phenomenon.[35] Conclusively, SE415 solubilization in the (PEG 400 + water) mixture can be a suitable alternative for enhanced bioavailability after oral or subcutaneous delivery to the conventional suspension form.[35]

3.6. Solubility Correlation/Prediction. The solubility data of SE415 in (PEG 400 + water) at 298.15 K was fitted to the CNIBS/R−K model, and the obtained model was

$$\log C_m = w_1 \log C_1 + w_2 \log C_2 + 2.831(w_1 \cdot w_2) - 3.205(w_1 \cdot w_2(w_1 - w_2)) + 2.604 (w_1 \cdot w_2(w_1 - w_2)^2) \quad (21)$$

which correlated the solubility data with the MPD of 9.6%.[40−42] The trained version of the modified Wilson model is

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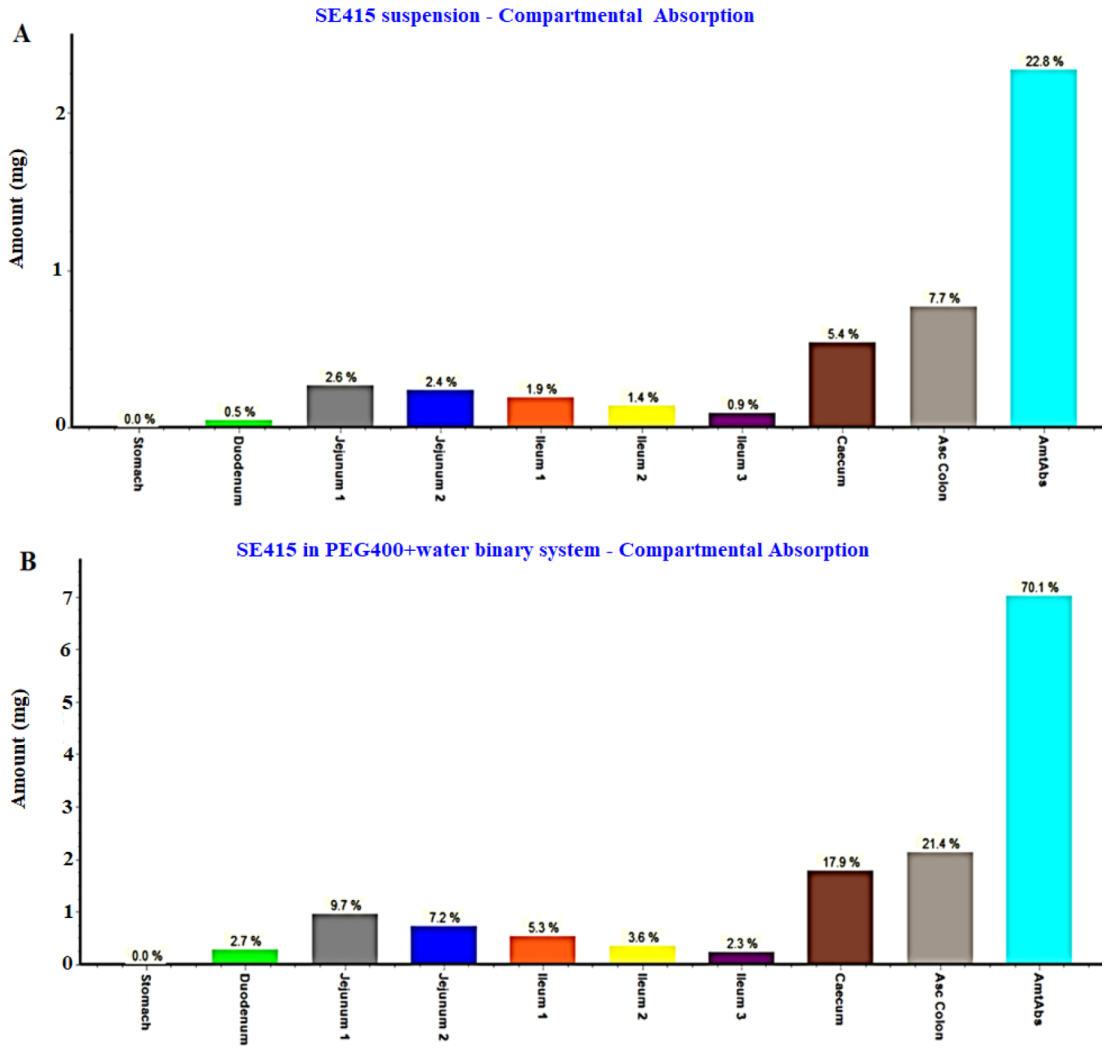

Figure 6. GastroPlus-based prediction of (A) regional compartmental absorption of SE415 suspension under fast conditions in humans and (b) regional compartmental absorption of SE415 in the (PEG 400 + water) mixed system (fast condition) in humans at an oral dose of 10 mg.

$$-\log C_m = 1 - \frac{w_1(1 + \log C_1)}{w_1 + 0.366w_2} + \frac{w_2(1 + \log C_2)}{2.736w_1 + w_2} \quad (22)$$

which correlated the solubility data with an MPD of 24.7%. As noticed in Section 2.2.8, the solubility of SE415 could be predicted using previously trained models employing the experimental solubility data of other drugs. The obtained MPD values for eqs 12−14 were 72.5, 38.8, and 36.3%, respectively. Equation 14 requires only the solubility data in the mono-solvents at each temperature of interest and could be considered as a generally trained model. When the solubility data of SE415 in any neat solvent were measured, its solubility in the aqueous binary mixture could be predicted using eq 14 and the expected prediction error is ∼34%, which is a reasonable prediction error.

4. CONCLUSIONS

SE415 is a poor water-soluble aldose reductase inhibitor. In this study, we highlighted the mechanistic understanding of the dissolution process by biocompatible PEG 400 in the (PEG 400 + water) cosolvent mixture using HSPs, Kirkwood−Buff integrals, and thermodynamic functional parameters for solubility. Chemically, SE11 is (*Z*)-*N*-benzyl-2-{2,4-dioxo-5-(4-prop-2-yl-1-yloxyl)benzylidene)thiazolin-3-yl)}acetamide possessing the acetylene group (slight acidic). HSPs of SE415 and PEG 400 suggested that the preferential drug solubilization may be due to the combined impact of hydrogen bonding, dispersion, and polarity difference parameters. MD simulation supported the H-bonding group-based interaction for solvation of SE415 in the binary mixture. Moreover, the preferential solvation phenomenon was explained by estimating Hildebrand solvation parameters of SE415 by PEG 400 in the (PEG 400 + water) cosolvent mixture. The result showed that the values of Gibbs energy of transfer of SE415 by PEG 400 from water to the (PEG 400 + water) mixture were found to be decreased with increased concentration of PEG 400 in the mixture. Moreover, the positive values of $\delta x_{1,3}$ confirmed the preferential solvation of SE415 by PEG 400 in the (PEG 400 + water) cosolvent mixture. *In vitro* dissolution showed a poor release profile at physiological pH due to poor aqueous solubility. Finally, *in silico* GastroPlus program predicted relatively an improved *in vitro* dissolution process, *in vivo* absorption, and maximized regional absorption of SE415 in the binary system as compared to suspension. Thus, SE415 can be maximally solubilized in the binary (PEG 400 + water) mixed system, and the mixture can improve the oral absorption of SE415 in the fast physiological condition on humans to control systemic DM and associated complications..

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c05788.

Input parameter details for the drug from the literature and experimental and by-default values before *in silico* prediction using GastroPlus simulation and prediction program including the physicochemical properties of the compound, *in vitro* study findings, and formulation-related information as per the desired goal; calibration of the drug using the HPLC method over the given concentration range in the mobile phase (PDF)

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Author Contributions

A.H.: conceptualization, software, writing—original draft preparation; M.A.A.: software, validation: data curation and reviewing; O.A.: conceptualization and writing—original draft preparation; A.S.A.A.: validation, data curation, and reviewing; A.A.: data curation, resources, and reviewing; A.A.: data curation, resources, and reviewing; F.M.: analysis and software; M.U.M.S.: conceptualization and software; W.E.A.Jr.: analysis and data curation; and A.J.: data curation, drafting, and formal review. All authors have read and agreed to the published version of the manuscript.

Notes

The authors declare no competing financial interest.

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