ABSTRACT: This present study investigated the effect of Captisol, a chemically modified cyclodextrin, on the in vitro dissolution of glimepiride. We prepared glimepiride–Captisol complexes of different mass ratios (1:1, 1:2, and 1:3 w/w) by a physical mixing or freeze-drying technique, and found that complexation with Captisol enhanced the water solubility of glimepiride. Molecular docking and dynamic simulation predicted complex formation; at the same time, Fourier transform infrared spectroscopy, differential scanning calorimetry, powder X-ray diffractometry, and scanning electron microscope indicated molecular interactions that support complexation. We also found that an inclusion complex was better than a physical mixture in enhancing the complexation of glimepiride with Captisol and enhancing water solubility. Phase solubility study of the glimepiride–Captisol complex showed an $A_1$-type profile, implying the formation of a 1:1 inclusion complex. The study also revealed that pH influenced the stability of the complex because the stability constant of the glimepiride–Captisol complex was higher in distilled water of pH $\sim$6.0 than in phosphate buffer of pH 7.2.

INTRODUCTION

Glimepiride (Figure 1) is a long-acting, second-generation sulfonylurea drug indicated for type 2 diabetes mellitus. The drug is poorly water-soluble, which limits its bioavailability and, ultimately, efficacy, and therefore creates a critical need to enhance the water solubility of the drug. In this regard, there are intensive efforts to apply solubility enhancement techniques such as encapsulation within cavitands to improve glimepiride solubility. Well-known cavitands are cyclodextrins (Figure 1), which encapsulate poorly water-soluble drugs within their hydrophobic cavity and, through their hydrophilic exterior, enhance water solubility. Ammar’s group, for instance, designed different drug–cyclodextrin–polymer ternary systems to enhance the solubility of glimepiride, and Uekama’s group integrated cyclodextrin into drug carriers to improve the solubility of the drug. In the ternary system, the cyclodextrin forms both inclusion and noninclusion complexes with glimepiride, leading to an increase in the drug’s solubility. Depending on the concentration of cyclodextrin in the system, aggregates of 1:1 or 1:2 glimepiride–cyclodextrin inclusion complexes are assembled, which can further solubilize the drug via noninclusion complexation or micelle-like structure.

The structure of the cyclodextrin plays a critical role in drug solubilization. Uekama’s group found that glimepiride forms more water-soluble complexes with $\alpha$- and $\beta$-cyclodextrins than with $\gamma$-cyclodextrin, implying that structural and functional modifications could fine-tune drug solubilization properties. Sulfoluylether-$\beta$-cyclodextrin (SBE-$\beta$-CD) (Figure 1) typifies a chemically modified cyclodextrin with improved solubility and reduced systemic toxicity. Recently, Captisol, a chemically modified $\beta$-cyclodextrin (Figure 1), was designed to maximize safety and enhance drug solubility, stability, and bioavailability. Preclinical and clinical evaluations suggest that Captisol is less toxic than $\beta$-cyclodextrin and provides more interactions to enhance water solubility of poorly water-soluble drugs. These superior properties have triggered an interest in using Captisol to solubilize and stabilize poorly water-soluble drugs. Here, we hypothesize that Captisol complexes glimepiride within the hydrophobic cavity to enhance the drug’s solubility in aqueous media.

The goal of this study is to test the hypothesis by formulating a glimepiride–cyclodextrin solid dispersions, physical mixture and inclusion complex, and then study the drug’s solubility. The solid dispersions were prepared using freeze-drying and physical mixing techniques. We carried out phase solubility studies to understand how temperature and pH affect the solubility of the glimepiride–Captisol inclusion complex. We also conducted molecular docking and simulation experiments to predict complex formation and stability. Powder X-ray diffractometry
in the acidic hydrochloric acid or slightly alkaline phosphate buffer, respectively, enhancing drug solubilization. A more likely explanation, however, is that at these conditions, acid or alkaline hydrolysis of the drug occurs, resulting in drug degradation and ultimately lowering the concentration. Indeed, literature precedence suggests that glimepiride degrades under acidic or alkaline conditions, lowering drug concentration. Given the likely degradation of the drug at acidic pH, we decided to evaluate the thermodynamic parameters for glimepiride–Captisol interactions and phase solubility studies only in distilled water (pH 6) and phosphate buffer (pH 7.2). On the other hand, we attributed the negligible effect of temperature on the saturation solubility of glimepiride (Table 1) to the inherent complexity in the relationship between hydrophobic effect and temperature. Indeed, considering that hydrophobic effect exerts its most substantial effect around 20 °C and then decreases above and below this temperature, we expected the solubility of glimepiride at 10 and 35 °C to differ slightly.

Captisol Enhances Water Solubility of Glimepiride. We prepare glimepiride–Captisol solid dispersion by physically mixing the powdered form of both compounds to form a physical mixture or freeze-drying a homogeneous solution of both compounds to form an inclusion complex. In both approaches, different glimepiride/Captisol mass ratios (1:1, 1:2, and 1:3 w/w) were obtained by varying the mass of Captisol in the solid dispersion. The water solubility of glimepiride in the physical mixture and inclusion complex was compared with that of the pure drug to obtain a solubility enhancement factor, which is the ratio of the amount of glimepiride that dissolves from the physical mixture or inclusion complex into distilled water to that from the pure drug. In distilled water, the enhancement factor increases, indicating that Captisol enhances the water solubility of glimepiride. Also, glimepiride solubility increases with mass ratio because a 1:3 ratio yielded over 1-fold increase in enhancement factor (Figure 2). For instance, in the inclusion complex, no significant increase was observed at a 1:1 ratio, but ~2-fold and ~3-fold increases in enhancement factor were found at ratios of 1:2 and 1:3, respectively (Figure 2). We found that increasing the amount of Captisol in the physical mixture or inclusion complex increases the drug solubility in distilled water (Table 2) and that the enhancement factor of inclusion complexes was better than that of physical mixtures. Our finding concurs with a previous report that shows the superiority of the Captisol inclusion complex over a physical mixture in enhancing water solubility of hydrophobic drugs such as

Table 1. Saturation Solubility of Glimepiride in Different Media and Various Temperatures

| Solutions                        | 10 °C  | 35 °C  |
|----------------------------------|--------|--------|
| distilled water                  | 0.53   | 0.56   |
| phosphate buffer (pH 7.2)        | 0.49   | 0.49   |
| hydrogen chloride acid buffer (pH 1.2) | 0.26   | 0.27   |

Figure 2. Solubility enhancement factors of glimepiride in physical mixtures and inclusion complexes in distilled water.
ibuprofen. Also, our observation that the dissolution of glimepiride increases with the concentration of the cyclodextrin agreed with a previous report.

Phase Solubility Profiles Indicate an $A_1$-Type Glimepiride–Captisol Inclusion Complex and a Strong Interaction between both Compounds. Intrigued by the ability of Captisol to enhance the water solubility of glimepiride, we investigated the binding constants between the two compounds using phase solubility profiles in distilled water and phosphate buffer (pH 7.2) at 10 and 35 °C. The solubility profiles were obtained by plotting the molar concentration of glimepiride against that of Captisol. According to Higuchi’s phase solubility profile classification, a solubility phase is an $A_1$-type if the drug solubility increases linearly with the concentration of Captisol in the solvent. In this study, the linearity of the curves and values of the slope, which are less than one (Figure 3), suggests that the drug exhibited an $A_1$-type behavior. The increase in drug solubility with Captisol agrees with previous findings and is consistent with the solubility enhancement nature of cyclodextrin derivatives.

Table 3 shows the apparent stability constants and other thermodynamic parameters for interactions of Captisol with glimepiride at various temperatures. The stability constant ($K_c$) was calculated from the slope and intercept of the phase solubility diagram (Figure 3), which depends on the molecular weight and binding capacity of the drug and Captisol. The $K_c$ of glimepiride in phosphate buffer was 3 and 73 M$^{-1}$ at 10 and 35 °C, respectively (Table 3). As the value of $K_c$ lies between 50–2000 M$^{-1}$ at 35 °C, we inferred that Captisol interacts with the drug to improve the physical and chemical characteristics of the latter. We found the change in Gibbs free energy ($\Delta G$) to be negative for all the samples, implying that complexation between Captisol and glimepiride was spontaneous, which concur with previously reported interactions between $\beta$-cyclodextrin and ibuprofen or ketoprofen.

We also evaluated $K_c$ of glimepiride in distilled water and obtained values of 29 and 83 M$^{-1}$ at 10 and 35 °C, respectively. At 35 °C, these values lie between the 50–2000 M$^{-1}$ range, indicating that the interactions in Captisol are sufficient to solubilize the drug. Again, the negative $\Delta G$ values confirm the spontaneity of the binding interaction between Captisol and glimepiride, while the positive values of the change in enthalpy ($\Delta H$) indicate that the interaction was endothermic. The positive values of entropy change ($\Delta S$) (Table 3) imply increased disorderliness, presumably due to enhanced dis-
solution of the glimepiride in Captisol, and also support the spontaneous of the drug–Captisol interaction, as evidenced by the negative ΔG values.25

A previous study of inclusion complexes of various cyclodextrins with the hydrophobic drug, naproxen, showed that under acidic conditions, the unionized form of the drug forms a more stable complex with the negatively charged cyclodextrin compared with the ionized form.26 In this study, we assumed that the negatively charged Captisol formed a more stable complex with unionized or partially positively charged glimepiride in distilled water (∼pH 6) than its negatively charged form in phosphate buffer (pH 7.2). Indeed, at pH 7.2, a negatively charged glimepiride electrostatically repels the negatively charged Captisol, whereas at pH 6, a slightly positively charged drug electrostatically attracts and complexes the negatively charge Captisol.

**Molecular Docking and Molecular Dynamics Simulation Support Formation of Inclusion Complex.** We conducted molecular docking of pure glimepiride with β-cyclodextrin using MOE 2019.01 to understand the binding affinity and stability of the inclusion complex. We used β-cyclodextrin for the docking experiment because Captisol is a modified β-cyclodextrin but most importantly is a proprietary compound with undisclosed structure. The energy minimized structure obtained from the docking experiment predicts that β-cyclodextrin can encapsulate glimepiride within its hydrophobic cavity (Figure 4). The experiment also predicts the formation of the van der Waals energy, electrostatic energy, polar solvation energy, SASA energy, and overall binding energies (Table 4).

**Figure 4.** β-cyclodextrin–glimepiride docked inclusion complex. Blue molecule denotes glimepiride, and orange molecule denotes β-cyclodextrin.

| parameters                        | values     |
|-----------------------------------|------------|
| van der Waals energy (kJ/mol)     | −127.21 ± 5.78 |
| electrostatic energy (kJ/mol)     | −4.92 ± 0.55 |
| polar solvation energy (kJ/mol)   | 24.88 ± 1.25 |
| SASA energy (kJ/mol)              | −12.14 ± 0.44 |
| binding energy (kJ/mol)           | −119.52 ± 5.49 |

**Solid-State Analyses Show that Glimepiride Interacts with Captisol.** To substantiate the results of the computer simulation that indicate that Captisol interacts with glimepiride, we used SEM, FTIR, PXRD, and DSC for solid-state analyses of the physical mixture and freeze-dried inclusion complex. SEM images revealed solid-state glimepiride and Captisol as flake-shaped and spherical materials, respectively (Figure 5). The morphologies of the inclusion complex and the physical mixture differ considerably due to differences in processing procedures (Figure 5). For instance, we observed drug residues on the surface of the physical mixture, which contrasts with the inclusion complex, where none was present on the surface (Figure 5), probably as a result of encapsulation with the hydrophobic core. The FTIR spectra of glimepiride and Captisol showed the expected absorption bands and a shift in bands of the physical mixture, probably because of the interaction between the two compounds (Figure 6). For the inclusion complex, some characteristic bands of Captisol and glimepiride were absent; for example, the band at 3284 cm⁻¹ (N=H stretching) associated with glimepiride was not observed (Figure 6). Previously, FTIR confirms the formation of an inclusion complex,29 and we infer from the results of this study that the observed changes in the FTIR spectrum of glimepiride and Captisol in the inclusion complex support the formation of drug complexation.

The PXRD diffractogram of the glimepiride was sharp and intense, confirming the expected crystallinity of the drug, while that of Captisol was broad, indicating amorphousness (Figure 7). The diffractogram of the physical mixture (mass ratio of 1:3) showed peaks that were characteristic of glimepiride, although many peaks shifted while some were absent. The diffractogram of inclusion complexes (mass ratio of 1:1) was broad, and the characteristic crystalline peaks of glimepiride were absent, presumably due to the encapsulation of glimepiride within the hydrophobic cavity of Captisol. A previous report shows that drugs encapsulated with cyclodextrin lose their crystallinity; for instance, pimozide was found to lose its crystallinity in a β-cyclodextrin-poly(vinylpyrrolidone) inclusion complex, resulting in an enhanced water solubility.30 We also performed DSC analyses to probe the interactions between glimepiride and Captisol. The thermogram (Figure 8) of glimepiride shows an endotherm at 211 °C and enthalpy of fusion (ΔHf) of 88 J/g while that of Captisol showed an endotherm at 265 °C. The thermogram of the physical mixture exhibited the typical endotherms of glimepiride and Captisol. We attributed the endotherm at ~210 °C to complexation between the drug and Captisol. In the thermograms of the inclusion complexes, the glimepiride endotherm disappeared, suggesting that the drug was encapsulated in the cavity of Captisol.
In Vitro Dissolution Study Shows that Captisol Enhances Water Solubility of Glimepiride. We evaluated the in vitro dissolution of glimepiride from the pure powdered form, physical mixture, and inclusion complex at physiological pH (7.2) and temperature (37 °C) conditions. We found that the drug in physical mixtures dissolved faster than in the pure form, with almost 44% of glimepiride being solubilized within 90 min (Figure 9). The drug in the inclusion complex had the fastest dissolution rate, with 100% of the drug being solubilized within 90 min. We attribute the enhanced water solubility of the drug in the physical mixture and inclusion complex to Captisol, which enhances the wettability of glimepiride through the formation of a hydrodynamic film around the drug particles, or solubilization of Captisol within the microenvironment, as demonstrated with acyclovir−hydroxypropyl-β-cyclodextrin complex.31 Previous studies have shown that water solubility of drugs is higher in inclusion complexes than in physical mixtures or pure drugs.30 We attributed the slow dissolution of glimepiride from the inclusion complexes within the first 20 min to the fractional entrapment of glimepiride molecules inside the cyclodextrin cavity.

In conclusion, we prepared glimepiride−Captisol solid dispersions by a freeze-drying or physical mixing technique to increase the water solubility of the hydrophobic type 2 diabetes drug, glimepiride. Captisol is a modified β-cyclodextrin with a hydrophobic cavity that can encapsulate and solubilize glimepiride and a hydrophilic exterior that ensures that the encapsulated drug is homogeneously dispersed in an aqueous medium. Our molecular docking experiment predicts that β-cyclodextrin encapsulates and stabilizes glimepiride. Empirical data from PXRD, DSC, SEM, and FTIR confirm that Captisol interacts with glimepiride. Indeed, PXRD indicates that Captisol encapsulates glimepiride because the characteristic crystalline peaks of the drug disappear upon the formation of the inclusion complex. These interactions and encapsulation phenomenon enhance the water solubility of the drug. Indeed, in vitro dissolution experiments show that the water solubility of glimepiride in the physical mixture and inclusion complex was higher than that in the pure drug. Overall, our results show that Captisol can enhance the water solubility of hydrophobic drugs to improve their bioavailability.

MATERIALS AND METHODS

Materials. Glimepiride and Captisol were a gift from Indoco Remedies Ltd., Baddi, Katha, Himachal Pradesh, India, and CyDex Pharmaceuticals Inc., Kansas, USA, respectively. Other reagents and solvents were of analytical grade and used without any further purification.

Determination of Saturation Solubility of Glimepiride. To determine the saturation solubility of glimepiride, we added an excess amount of glimepiride to 20 mL of an appropriate medium (pH 7.2 phosphate buffer, pH 1.2 hydrochloric buffer, or distilled water) maintained at 10 °C or 35 °C and stirred continuously with a magnetic stirrer.15 After equilibrium, the sample was centrifuged, and the supernatant was recovered by filtration. The filtrates were diluted, and their absorbances were monitored using a UV spectrophotometer at a wavelength of 228 nm while the drug concentration was obtained from a standard curve.

Preparation of Physical Mixtures of Glimepiride with Captisol. Different mass ratios (1:1, 1:2, and 1:3 w/w) of glimepiride and Captisol were mixed and homogenized by triturating using a mortar and pestle for 30 min.32 The mass of Captisol was varied while that of glimepiride was kept constant.

Preparation of Inclusion Complexes of Glimepiride and Captisol Using Freeze-Drying. The inclusion complexes were prepared by dissolving the glimepiride and Captisol at different mass ratios (1:1, 1:2, and 1:3) in water to form a homogeneous mixture. Briefly, the weighted glimepiride was added to water and stirred, and then the weighted Captisol was...
added to the solution and stirred for 24 h using a magnetic stirrer. The solution was filtered, and the filtrate was freeze-dried at −40 °C under vacuum for 12 h until a dried powder was obtained.33

Drug Content Determination. The drug contents in the physical mixtures and inclusion complexes were determined according to the previously described method.34 Briefly, 10 mg of physical mixture or inclusion complex was added into 10 mL of DMF/water solvent (1:1, v/v) to dissolve both the free and complexed glimepiride. Then, the solutions were stirred, centrifuged for 10 min at 4000 rpm, filtered, and then diluted, and the drug content was quantified at 228 nm using a UV spectrophotometer (UV Shimadzu 1800, India).

Phase Solubility Study. The experiment was carried out at 10 or 35 °C in pH 7.2 phosphate buffer or distilled water18 and with different molar concentrations of glimepiride and Captisol. A phase solubility diagram was constructed using the molar concentration of glimepiride against that of Captisol.22 Using the following equation,12,15,26,35 the apparent stability (binding) constants (Kc) of different glimepiride–Captisol complexes were calculated by:

Figure 6. FTIR spectra of (a) glimepiride, (b) Captisol, (c) glimepiride–Captisol 1:1 physical mixture, (d) glimepiride–Captisol 1:1 inclusion complex, (e) glimepiride–Captisol 1:2 physical mixture, (f) glimepiride–Captisol 1:2 inclusion complex, (g) glimepiride–Captisol 1:3 physical mixture, and (h) glimepiride–Captisol 1:3 inclusion complex.
where \( S_0 \) (intrinsic solubility) is the intercept of the phase solubility curve and denotes the saturation solubility of glimepiride in distilled water or phosphate buffer without Captisol at different temperatures and the "slope" denotes the slope of the straight line.

The complexation efficiency (CE) was calculated from the phase solubility diagram:

\[
CE = S_0 K_c
\]

Change in enthalpy (\( \Delta H \)) of complexation was calculated using Van’t Hoff’s equation:

\[
\log \frac{K_2}{K_1} = \frac{\Delta H(T_2 - T_1)}{2.303RT_2T_1}
\]

where \( K_2 \) and \( K_1 \) are the stability constants at \( T_2 \) and \( T_1 \) temperatures, respectively, and the temperatures were in Kelvin.

The changes in Gibbs free energy (\( \Delta G \)) and entropy (\( \Delta S \)) due to complexation were determined from the following equations:

\[
K_c = \frac{\text{slope}}{S_0(1 - \text{slope})}
\]

Figure 7. Powder X-ray diffractogram of (a) pure glimepiride, (b) Captisol, (c) glimepiride–Captisol 1:1 physical mixture, (d) glimepiride–Captisol 1:3 physical mixture, (e) glimepiride–Captisol 1:1 inclusion complex, and (f) glimepiride–Captisol 1:3 inclusion complex.

Figure 8. DSC curves of glimepiride, Captisol, physical mixtures, and glimepiride–Captisol inclusion complexes.
$$\Delta G = -2.303RT \log K$$  \hspace{1cm} (4)\\
$$\Delta S = \frac{(\Delta H - \Delta G)}{T}$$  \hspace{1cm} (5)

where R is the gas constant \((R = 8.314 \text{ J/mol/K})\), and \(K\) is apparent stability constant from eq 1.

**Molecular Docking Studies of Glimepiride–β-Cyclodextrin Complexes.** The molecular docking experiments were carried out using the Chemical Computing Group’s Molecular Operating Environment (MOE) software (MOE 2019.01). The 3D chemical structure of the glimepiride was downloaded from the PubChem database portal. Both glimepiride and β-cyclodextrin underwent energy minimization until an RMSD gradient of 0.05 kcal mol\(^{-1}\) Å\(^{-1}\) was obtained. Amber10: EHT force field was employed to calculate the partial charges. We used Triangle matcher as the ligand placement method and London Dg scoring as Rescoring for docking studies. The GBVI/WSA Dg scoring function was used throughout. In all, 30 molecular dynamics performed for each complex. All other options were kept on by default values.

**Scanning Electron Microscopy.** The surface morphologies of the pure glimepiride, physical mixture, and inclusion complex were analyzed using a scanning electron microscope (TM3030 Plus). The powdered samples were mounted on an aluminum stub using double-sided adhesive carbon tapes and then coated with platinum under low pressure to make them electrically conductive. The images of the samples were taken at an excitation voltage of 10 kV.

**Fourier Transform Infrared Spectroscopy.** The analysis was performed on a Fourier transform infrared spectrophotometer (Bruker) to determine functional groups of glimepiride, Captisol, physical mixture, and inclusion complexes. The powdered sample was mixed with the KBr powder of infrared grade at 1% and pressed into a disc using a hydraulic press. Powder X-ray Diffraction Analysis. The powdered sample was analyzed using (XPERT-3) with a Cu Kα radiation source of an accelerating voltage of 40 kV and a current of 30 mA \((\lambda = 1.5406 \text{ Å})\). The experiment was carried out at room temperature. The scan range was over the 2θ angle range of 3 to 50°, and the scan step time was 0.5 s.

**Differential Scanning Calorimetry.** The analysis was done by heating 3 mg of each sample from 25 to 300 °C at a heating rate of 10 °C/min under ultrahigh purity nitrogen gas

Figure 9. Dissolution profiles of glimepiride from the physical mixture (PM in orange), inclusion complex (FD in gray), and pure drug (in blue) in phosphate buffer (pH 7.2) at 37 °C.
flowing at 150 mL/min. The experiment was performed using DSC thermograms (STAR® SW 12.10).

In Vitro Dissolution of Glimepiride from the Pure Drug, Physical Mixtures, and Inclusion Complexes. The dissolution was assessed using the USP apparatus II (paddle method) (in vitro dissolution apparatus, Lab India DS 8000). The experiment was performed for the pure drug, physical mixtures, and inclusion complexes in a dissolution vessel containing pH 7.2 phosphate buffer at a temperature of 37 °C. At different time intervals (10, 20, 40, 60, and 90 min), 1 mL of sample was withdrawn and subsequently replaced with the freshly prepared dissolution medium to maintain the sink condition. The withdrawn samples were then filtered using Whatman filter paper no. 1, and the filtrates were diluted with the dissolution medium and analyzed for drug concentration using a UV spectrophotometer at 228 nm.

AUTHOR INFORMATION

Corresponding Authors

Christian Agatemor — Department of Biomedical Engineering, School of Medicine, Johns Hopkins University, Baltimore 21231, United States; Email: cagatem1@jhmi.edu

Kajal Ghosal — Dr. B. C. Roy College of Pharmacy and AHS, Durgapur 713206, India; orcid.org/0000-0001-6392-2182; Email: kajal.ghosal@gmail.com

Authors

Arpita Pal — Dr. B. C. Roy College of Pharmacy and AHS, Durgapur 713206, India

Sudeep Roy — Department of Biomedical Engineering, Faculty of Electrical Engineering and Communication, Brno University of Technology, 61600 Brno, Czech Republic

Akhil Kumar — Department of Biotechnology, CSIR-CIMAP Kukrail Picnic Spot, Lucknow 226015, India

Syed Mahmood — Department of Pharmaceutical Engineering, Faculty of Chemical and Process Engineering Technology and Centre of Excellence for Advanced Research in Fluid Flow (CARIFF), University Malaysia Pahang, Gambang 26300, Malaysia

Nasrin Khodapanah — Faculty of Engineering Technology, University Malaysia Pahang, Gambang 26300, Malaysia

Sabu Thomas — International and Inter-University Center for Nanoscience and Nanotechnology (IUCNN), Mahatma Gandhi University, Kottayam 686560, Kerala, India

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c01228

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the Dr. B. C. Roy College of Pharmacy and Allied Health Sciences and Dr. Meghnad Saha Sarani of the Bidhan Nagar, Durgapur 713206, West Bengal, India for providing the infrastructural and research facilities. We thank Indoco Remedies Ltd., Baddi, Katha, Himachal Pradesh, India, and CyDex Pharmaceuticals Inc., Kansas, USA, for the gift of Glimepiride and Captisol, respectively.

REFERENCES

(1) Davis, S. N. The Role of Glimepiride in the Effective Management of Type 2 Diabetes. J. Diabetes Complications 2004, 18, 367–376.

(2) Sharma, D. Solubility Enhancement Strategies for Poorly Water-Soluble Drugs in Solid Dispersions: A Review. Asian J. Pharm. 2016, 7, 24–30.

(3) Khadka, P.; Ro, J.; Kim, H.; Kim, I.; Kim, J. T.; Kim, H.; Cho, J. M.; Yun, G.; Lee, J. Pharmaceutical Particle Technologies: An Approach to Improve Drug Solubility, Dissolution and Bioavailability. Asian J. Pharm. Sci. 2014, 9, 304–316.

(4) Davis, M. E.; Brewster, M. E. Cyclodextrin-Based Pharmaceutics: Past, Present and Future. Nat. Rev. Drug Discovery 2004, 3, 1023–1035.

(5) Guyot, M.; Fawaz, F.; Bildet, J.; Bonini, F.; Lagueny, A.-M. Physicochemical Characterization and Dissolution of Norflaxacin/Cyclodextrin Inclusion Compounds and PEG Solid Dispersions. Int. J. Pharm. 1995, 123, 53–63.

(6) Paulidou, A.; Maffeo, D.; Yannakopoulou, K.; Mavridis, I. M. Similar Modes of Inclusion in Complexes of β-Cyclodextrin with Sulfonylurea Hypoglycemic Drugs. Cryst. Eng. Comm. 2010, 12, 517–525.

(7) Iwata, M.; Fukami, T.; Kawashima, D.; Sakai, M.; Furuishi, T.; Suzuki, T.; Tomono, K.; Ueda, H. Effectiveness of Mechanochemical Treatment with Cyclodextrins on Increasing Solubility of Glimepiride. Die Pharmazie: Int. J. Pharm. Sci. 2009, 64, 390–394.

(8) Ammar, H. O.; Salama, H. A.; Ghorab, M.; Mahmoud, A. A. Formulation and Biological Evaluation of Glimepiride—Cyclodextrin—Polymer Systems. Int. J. Pharm. 2006, 309, 129–138.

(9) Ammar, H. O.; Salama, H. A.; Ghorab, M.; Mahmoud, A. A. Inclusion Complexation of Glimepiride in Dimethyl-β-Cyclodextrin. Asian J. Pharm. Sci. 2007, 2, 44–55.

(10) Ammar, H.; Salama, H.; Ghorab, M.; Mahmoud, A. Implication of Inclusion Complexation of Glimepiride in Cyclodextrin—Polymer Systems on Its Dissolution, Stability and Therapeutic Efficacy. Int. J. Pharm. 2006, 320, 53–57.

(11) Aldawarsi, H.; Altaf, A.; Banjar, Z.; Okubo, M.; Ishara, D.; Anraku, M.; Hirayama, F.; Uekama, K. Combined Use of Cyclodextrins and Hydroxypropylmethylcellulose Stearoyl Ether (Sanglose®) for the Preparation of Orally Disintegrating Tablets of Type-2 Antidiabetes Agent Glimepiride. J. Inclusion Phenom. Macrocyclic Chem. 2014, 80, 61–67.

(12) Brewster, M. E.; Vandecruys, R.; Peeters, J.; Neeskens, P.; Verreck, G.; Loots, T. Comparative Interaction of 2-Hydroxypropyl-β-Cyclodextrin and Sulfobutylether-β-Cyclodextrin with Itraconazole: Phase-Solubility Behavior and Stabilization of Supersaturated Drug Solutions. Eur. J. Pharm. Sci. 2008, 34, 94–103.

(13) Lockwood, S. F.; O’Malley, S.; Mosher, G. L. Improved Aqueous Solubility of Crystalline Astaxanthin (3, 3′-dihydroxy-β, B-carotene-4, 4′-dione) by Captisol® (Sulfobutyl Ether B-β-cyclodextrin). J. Pharm. Sci. 2003, 92, 922–926.

(14) Rowe, E. S.; Rowe, V. D.; Biswas, S.; Mosher, G.; Insisienmay, L.; Ozias, M. K.; Gralinski, M. R.; Hunter, J.; Barnett, J. S. Preclinical Studies of a Kidney Safe Ionotonic Contrast Agent. J. Neuroimagiong 2016, 26, 511–518.

(15) Das, S. K.; Kahali, N.; Bose, A.; Khanam, J. Physicochemical Characterization and in Vitro Dissolution Performance of Ibuprofen-Captisol®(Sulfobutylether Sodium Salt of β-CD) Inclusion Complexes. J. Mol. Liq. 2018, 261, 239–249.

(16) Singh, R.; Chen, J.; Miller, T.; Bergren, M.; Mallik, R. Solution Stability of Captisol-Stabilized Melphalan (Evomela) versus Propylene Glycol-Based Melphalan Hydrochloride Injection. Pharm. Dev. Technol. 2018, 23, 1024–1029.

(17) Fukuda, M.; Miller, D. A.; Peppas, N. A.; McGinity, J. W. Influence of Sulfobutyl Ether β-Cyclodextrin (Captisol®) on the Dissolution Properties of a Poorly Soluble Drug from Extrudates Prepared by Hot-Melt Extrusion. Int. J. Pharm. 2008, 350, 188–196.

(18) Beig, A.; Agbaria, R.; Dahan, A. The Use of Captisol (SBE7-β-CD) in Oral Solubility-Enabling Formulations: Comparison to HP-β-CD and the Solubility–Permeability Interplay. Eur. J. Pharm. Sci. 2015, 77, 73–78.

(19) Szostak, M.; Yao, L.; Day, V. W.; Powell, D. R.; Aubé, J. Structural Characterization of N-Protonated Amides: Regioselective N-Activation of Medium-Bridged Twisted Lactams. J. Am. Chem. Soc. 2010, 132, 8836–8837.
(20) Naveed, S.; Qamar, H.; Jawaid, W.; Bokhari, U. Effect of Acid, Base and Time on Different Brands of Glimepiride. *Open Access Lib. J.* 2014, 1, 1–5.

(21) Schellman, J. A. Temperature, Stability, and the Hydrophobic Interaction. *Biophys. J.* 1997, 73, 2960–2964.

(22) Higuchi, T. K. A. C. A Phase Solubility Technique. *Adv. Anal. Chem. Instrum.* 1965, 4, 117–211.

(23) de Miranda, J. C.; Martins, T. E. A.; Veiga, F.; Ferraz, H. G. Cyclodextrins and Ternary Complexes: Technology to Improve Solubility of Poorly Soluble Drugs. *Brazilian J. Pharm. Sci.* 2011, 47, 665–681.

(24) Mura, P.; Faucci, M. T.; Parrini, P. L.; Furlanetto, S.; Pinzauti, S. Influence of the Preparation Method on the Physicochemical Properties of Ketoprofen—Cyclodextrin Binary Systems. *Int. J. Pharm.* 1999, 179, 117–128.

(25) Landsberg, P. T. Can Entropy and “Order” Increase Together? *Phys. Lett. A.* 1984, 102, 171–173.

(26) Loftsson, T.; Brewster, M. E.; Masson, M. Role of Cyclodextrins in Improving Oral Drug Delivery. *Am. J. Drug Delivery* 2004, 2, 261–275.

(27) Mohapatra, R.; Mallick, S.; Nanda, A.; Sahoo, R. N.; Pramanik, A.; Bose, A.; Das, D.; Pattnaik, L. Analysis of Steady State and Non-Steady State Corneal Permeation of Diclofenac. *RSC Adv.* 2016, 6, 31976–31987.

(28) Kumari, R.; Kumar, R.; Lynn, A.; Open Source Drug Discovery Consortium. G_mmpbsa A GROMACS Tool for High-Throughput MM-PBSA Calculations. *J. Chem. Inf. Model.* 2014, 54, 1951–1962.

(29) Venuti, V.; Cannavà, C.; Cristiano, M. C.; Fresta, M.; Majolino, D.; Paolino, D.; Stancanelli, R.; Tommasini, S.; Ventura, C. A. A Characterization Study of Revesantral/Sulfobutyl Ether-β-Cyclodextrin Inclusion Complex and in Vitro Anticancer Activity. *Colloids Surf., B* 2014, 115, 22–28.

(30) Bera, H.; Chekuri, S.; Sarkar, S.; Kumar, S.; Murva, N. B.; Mothe, S.; Nadinpalli, J. Novel Pimozide-β-Cyclodextrin-Polyvinylpyrrolidine Inclusion Complexes for Tourette Syndrome Treatment. *J. Mol. Liq.* 2016, 215, 135–143.

(31) Nair, A. B.; Attimarad, M.; Al-Dhubiab, B. E.; Wadhwa, J.; Harsha, S.; Ahmed, M. Enhanced Oral Bioavailability of Acyclovir by Inclusion Complex Using Hydroxypropyl-β-Cyclodextrin. *Drug Deliv. 2014*, 21, 540–547.

(32) Badr-Eldin, S. M.; Elkheshen, S. A.; Ghorab, M. M. Inclusion Complexes of Tadalafil with Natural and Chemically Modified β-Cyclodextrins I: Preparation and in-Vitro Evaluation. *Eur. J. Pharm. Biopharm.* 2008, 70, 819–827.

(33) Kiran, T.; Shastr, N.; Ramakrishna, S.; Sadanandam, M. Surface Solid Dispersion of Glimepiride for Enhancement of Dissolution Rate. *Int. J. Pharm. Tech. Res.* 2009, 1, 822–831.

(34) Pokharkar, V.; Khanna, A.; Venkatpurwar, V.; Dhar, S.; Mandpe, L. Ternary Complexation of Carvedilol, β-Cyclodextrin and Citric Acid for Mouth-Dissolving Tablet Formulation. *Acta Pharm. 2009*, 59, 121–132.

(35) Loftsson, T.; Brewster, M. E. Cyclodextrins as Functional Excipients: Methods to Enhance Complexation Efficiency. *J. Pharm. Sci.* 2012, 101, 3019–3032.

(36) Berendsen, H. J. C.; van der Spoel, D.; van Drunen, R. GROMACS: A Message-Passing Parallel Molecular Dynamics Implementation. *Comput. Phys. Commun.* 1995, 91, 43–56.

(37) Lindahl, E.; Hess, B.; Van Der Spoel, D. GROMACS 3.0: A Package for Molecular Simulation and Trajectory Analysis. *Mol. Model. 2001*, 7, 306–317.

(38) Wang, R.; Zhou, H.; Siu, S. W. I.; Gan, Y.; Ouyang, D. Comparison of three molecular simulation approaches for cyclodextrin-ibuprofen complexation. *J. Nanomater.* 2015, 2015, 193049.

(39) Syukri, Y.; Fernenda, L.; Utami, F. R.; Qiftayati, I.; Kusuma, A. P.; Istikharah, R. Preperation And Characterization Of B-Cyclodextrin Inclusion Complexes Oral Tablets Containing Poorly Water Soluble Glimipiride Using Freeze Drying Method. *Indones. J. Pharm.* 2015, 26, 71.

(40) Heng, D.; Cutler, D. J.; Chan, H.-K.; Yun, J.; Raper, J. A. What Is a Suitable Dissolution Method for Drug Nanoparticles? *Pharm. Res. 2008*, 25, 1696–1701.