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Cocrystals of Hydrochlorothiazide: Solubility and Diffusion/Permeability Enhancements through Drug−Coformer Interactions

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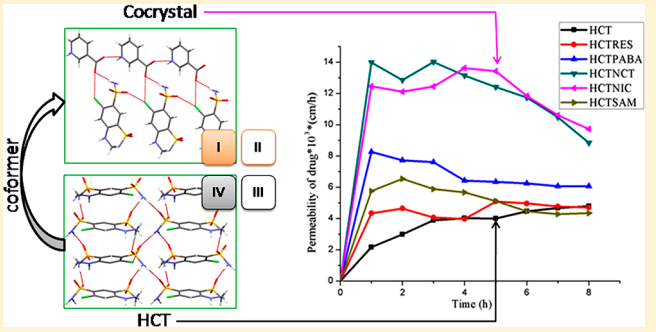
Supporting Information

ABSTRACT: Hydrochlorothiazide (HCT) is a diuretic and a BCS class IV drug with low solubility and low permeability, exhibiting poor oral absorption. The present study attempts to improve the physicochemical properties of the drug using a crystal engineering approach with cocrystals. Such multicomponent crystals of HCT with nicotinic acid (NIC), nicotinamide (NCT), 4-aminobenzoic acid (PABA), succinamide (SAM), and resorcinol (RES) were prepared using liquid-assisted grinding, and their solubilities in pH 7.4 buffer were evaluated. Diffusion and membrane permeability were studied using a Franz diffusion cell. Except for the SAM and NIC cocrystals, all other binary systems exhibited improved solubility. All of the cocrystals showed improved diffusion/membrane permeability compared to that of HCT with the exception of the SAM cocrystal. When the solubility was high, as in the case of PABA, NCT, and RES cocrystals, the flux/permeability dropped slightly. This is in agreement with the expected interplay between solubility and permeability. Improved solubility/permeability is attributed to new drug−coformer interactions. Cocrystals of SAM, however, showed poor solubility and flux. This cocrystal contains a primary sulfonamide dimer synthon similar to that of HCT polymorphs, which may be a reason for its unusual behavior. Hirshfeld surface analysis was carried out in all cases to determine whether a correlation exists between cocrystal permeability and drug−coformer interactions.



KEYWORDS: *cocrystal, diffusion, flux, heterosynthons, permeability, solubility*

INTRODUCTION

Large numbers of lipophilic compounds are emerging from drug discovery research programs.[1,2] During drug design, lipophilicity is often increased in order to improve the affinity and selectivity of the drug candidate. Such compounds may exhibit poor aqueous solubility, leading to low oral absorption. Oral absorption is a function of dissolution across barrier tissue, such as small intestinal cells.[3] Drugs or drug candidates with low solubility and low permeability are classified as BCS (Biopharmaceutics Classification System) class IV drugs.[4] Such molecules often fail to proceed to advanced stages of research and development. It is also known that more favorable physicochemical properties are necessary for lower-potency lead compounds.[3] To improve oral bioavailability, formulations have been developed using surfactants, liposomes, and microencapsulation as well as nanoparticle-based methods.[5] However, many of these formulations are often not a viable option during large-scale manufacturing, and some of them are even unstable during storage. Structural modification through crystal engineering is an emerging method for improving biopharmaceutical properties and may be done by either (i) replacing ionizable/or nonionizable groups, (ii) increasing lipophilicity, (iii) replacing polar groups; (iv) reducing hydrogen bonding and polarity, (v) reducing size, or (vi) adding a non polar side chain.[6−8] Crystal engineering has been used extensively in tuning the physicochemical properties of drug candidates.[9−13] This method has been shown to be effective in addressing problems of low aqueous solubility/permeability of drug-like substances.[9] It is known that highly soluble coformers may lead to solubility enhancement in the cocrystal form of a poorly soluble drug.[14−16] However, examples related to permeability enhancement using cocrystals are scarce in the literature.[9] Permeability of drugs, however, has been improved through the use of coformers/excipients such as lactic acid, tartaric acid, fumaric acid, and glutaric acid (higher lipophilicity of the acids).[17−19] Caffeine and ascorbic acid, when used as coformers, are known to help in crossing the blood−brain barrier.[20,21] These coformers are applicable not only to molecules of a specific physical and chemical nature but also to

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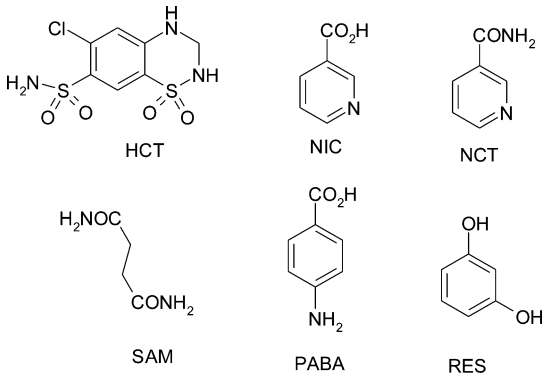
a wide range of crystalline materials. A comprehensive knowledge of the drugs at the molecular level is often required to determine the appropriate approach toward improving solubility and permeability during drug development.

Hydrochlorothiazide (HCT; Scheme 1), a diuretic drug, acts by inhibiting the ability of the kidney to retain water. It is a BCS class IV drug with low aqueous solubility (0.7 g/L) and low permeability (Caco-2 permeability: −6.06). The crystal structure of HCT was studied by Dupont and Dideberg.[22] The molecule exhibits low bioavailability (65%). Previous studies on HCT cocrystals[23] have shown improved aqueous solubility when biologically safe coformers such as 4-amino-benzoic acid, nicotinamide, nicotinic acid, succinamide, and resorcinol are used. The present study is an attempt to utilize cocrystallization methods to modify solubility and diffusion/membrane permeability of HCT at physiological pH. In vivo absorption of molecules can be predicted based on measurements of permeability. Pade et al.[24] first introduced the parallel artificial membrane permeation assay (PAMPA) in 1998. Considerable progress has been made in predicting the oral fraction of molecules absorbed based on permeability values obtained from Caco-2 or PAMPA methods.[25−27] It is also possible to obtain a preliminary and comparative idea of diffusion/membrane permeability by the use of a simple diffusion cell. In this study, we have used a simple Franz diffusion cell[28,29] to compare the diffusion as well as membrane permeability of HCT and its cocrystals. The rationale for measuring absorption with in vitro techniques is based on the fact that absorption rates are determined by passive diffusion through the nonliving system. The measurements are a relative method and provide a comparative assessment for formulation.

Scheme 1. Chemical Structures of the Drug and Coformers Used To Make Cocrystals



MATERIALS AND METHODS

Hydrochlorothiazide (mp 269−272 °C) was obtained from Sigma-Aldrich Chemicals, Bangalore, India, and used directly for experiments without further purification. All other reagents were purchased from commercial sources and were used directly. Melting points were measured on a Büchi melting point apparatus (Sigma-Aldrich, Bangalore, India). Water filtered through a double-distilled water purification system (Siemens, Ultra Clear, Germany) was used in all solubility/permeability experiments. Powder X-ray diffraction (PXRD) data was recorded using a Philips X'pert Pro X-ray powder diffractometer equipped with a X'cellerator detector at room temperature with the scan range 2θ = 5 to 40° and step size 0.017°. X'Pert HighScore Plus was used to compare the experimental PXRD pattern of the HCT cocrystals with the calculated lines from the crystal structure; see Figure S1, Supporting Information. Solid-state grinding, solution crystallization, and slurry methods in polar solvents such as MeOH and CH_3CN were used to obtain cocrystals.

Preparation of HCT Cocrystals. *HCT−NIC (1:1).* 100 mg HCT (0.33 m mol) and 41.0 mg NIC (0.33 m mol) were ground in a mortar and pestle for 15 min in the presence of a few drops of MeOH, and the ground mixture was crystallized from MeOH to obtain single crystals. Colorless needle crystals were harvested after 3 to 4 days (mp 258−262 °C). The yield of all cocrystals varied between 90 and 95%.

HCT−NCT (1:1). 100 mg HCT (0.33 m mol) and 41.4 mg NCT (0.33 m mol) were ground in a mortar and pestle for 15 min in the presence of a few drops of MeOH, and the ground mixture was crystallized from MeOH to obtain single crystals. Colorless plate crystals were grown after 3 to 4 days (mp 173−175 °C).

HCT−SAM (1:0.5). 100 mg HCT (0.33 m mol) and 20.2 mg SAM (0.33 m mol) were ground in a mortar and pestle for 15 min in the presence of a few drops of MeOH, and the ground mixture was crystallized from MeOH to obtain single crystals. Colorless block crystals were obtained after 3 to 4 days (mp 235−238 °C).

HCT−PABA (1:2). 100 mg HCT (0.33 m mol) and 92.1 mg PABA (0.67 m mol) were ground in a mortar and pestle for 15 min in the presence of a few drops of MeOH, and the ground mixture was crystallized from MeOH to obtain single crystals. Colorless rod crystals were obtained after 3 to 4 days (mp 176−178 °C).

HCT−RES (1:1). 100 mg HCT (0.33 m mol) and 37.0 mg resorcinol (0.33 m mol) were ground in a mortar and pestle for 15 min in the presence of a few drops of MeOH. No single crystals could be grown (mp 173−177 °C).

Solubility Study. The absorption coefficient of each HCT cocrystal was measured using the slope of absorbance vs concentration of the five known concentrated solutions in pH 7.4 phosphate buffer and measurements were done at 317−318 nm on a PerkinElmer UV−vis spectrometer. The solubility of each solid was measured at 1 h and also 4 h using the shake-flask method.[30]

Diffusion Study. The diffusion studies of HCT and its cocrystals were carried out using the modified Franz diffusion cell apparatus through a dialysis membrane (MW 14000 Da, Himedia, India). The use of the Franz diffusion cell to assess skin permeability has evolved into a major area of research, and this method can provide preliminary information on the relationship among the skin/membrane, the drug, and its formulation.[28,29] Franz cells are individually hand-blown diffusion cells made of two borosilicate glass components. The upper part may be called the cell cap, cell top, donor chamber, or donor compartment. The lower portion is generally called the body of the cell and is sometimes referred to as the receptor chamber. The upper surface of the cell body and the mating lower surface of the donor chamber are together known as the joint. The membrane through which the permeation or transport is being studied is placed in the middle of the joint and held in place with a clamp. The orifice of a Franz cell is the area to which the donor and receptor chambers are exposed. In the case of blown-glass diffusion cells, this area is circular. When referring to a Franz cell, the size of the cell is

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the orifice diameter of the joint at the mating surface and is not the outer diameter of the joint.

The dialysis membrane was pretreated with 10% of $NaHCO_3$ at 70 °C for 20 min to remove traces of sulfides, followed by 10 mM of EDTA at 70 °C for 20 min to remove the traces of heavy metal and 20 min of treatment with deionized water at 70 °C to remove glycerine. The treated dialysis membrane was mounted in vertical static diffusion cells with an effective surface area of 4.15 cm^2. The donor compartment contained 50 mg of the drug and its respective cocrystals, and these were suspended in 2 mL of distilled water. The receptor compartment was filled with 125 mL of phosphate buffer (pH 7.4), maintained at room temperature, and bubbles were removed. Receptor solution was magnetically stirred at 45 ± 5 rpm to ensure medium homogeneity throughout the duration of the experiment. An aliquot of 2 mL of the sample was withdrawn from the receptor compartment at predetermined time intervals and replaced with fresh medium. Diffusion study of HCT and its cocrystals was carried out in triplicate. Samples were analyzed by UV−vis spectrophotometer at a λ_{max} of 317 nm after suitable dilution.

Permeability Measurements. The concentration of each cocrystal and the API were measured at 1 h intervals for 8 h during the diffusion experiment in pH 7.4 phosphate buffer medium and recorded at 317 nm using a UV−vis spectrometer.

RESULTS AND DISCUSSION

Recent studies have shown that an interplay exists between solubility and permeability when using solubility-modifying formulations.[31,32] Solubility-enhancing formulations can lead to unexpected effects on the overall absorption of molecules. The reasons for such behavior are not unexpected since solubility enhancement is carried out using polarity-enhancing formulations. The use of polar components is accompanied by a lowered partition coefficient and a subsequent reduction in membrane permeability. Overall absorption is a product of solubility (concentration at the site of absorption) and membrane permeability (diffusion through gastrointestinal membrane), and this may be a predictor of the in vitro bioavailability of a drug.[3,4] To understand the effects of chemical and structural modification on solubility and permeability properties of HCT, a crystal engineering approach is used that results in supramolecular heterosynthons between the drug and coformers. The BCS class IV drug HCT is known to have low solubility and permeability and hence is thought to be a good candidate for physicochemical property improvement using cocrystallization methods. Thus, cocrystallized HCT was subjected to studies of solubility and membrane permeability using a Franz diffusion cell.

Structural Studies of Cocrystals of HCT. A single-crystal X-ray diffraction (SCXRD) study of the cocrystals of HCT has been carried out by Sanphui and Rajput.[23] The authors prepared multicomponent cocrystals of HCT with nicotinic acid, nicotinamide, succinamide, 4-aminobenzoic acid, and resorcinol (Scheme 1) as coformers using liquid-assisted grinding. Spectroscopic and SCXRD studies carried out by the authors showed that the N−H···O sulfonamide catemer synthons found in the stable polymorph of pure HCT are replaced by drug−coformer heterosynthons in the cocrystals.

Solubility Studies. Buffered solubility, also termed apparent solubility, refers to the solubility at a given pH and usually neglects the influence of salt formation with counterions of the buffering system on the measured solubility value. Figure 1 summarizes the solubility values of the HCT cocrystals in pH 7.4 buffer. Solubility of HCT increases from 840 mg/L in water[23] to 994 mg/L in pH 7.4 buffer. Except for nicotinic acid and succinamide cocrystals, all other cocrystals showed improved solubility, which is possibly related to an increase in polarity of the cocrystals. Solubilities of coformers NIC, NCT, and RES were plotted against corresponding cocrystal solubilities (Figure S4, Supporting Information). Coformer solubilities do not show a clear correlation with cocrystal solubilities.

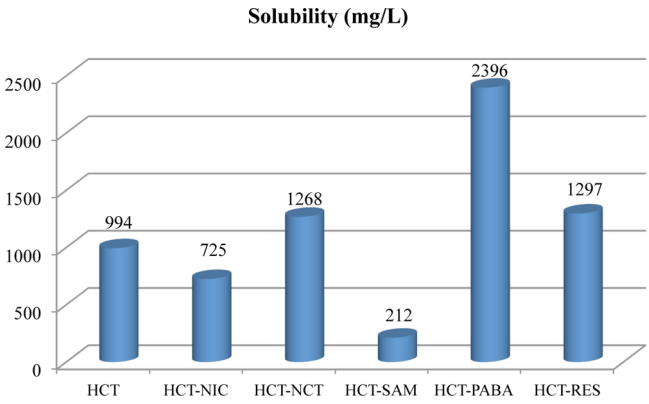

Figure 1. Solubility of HCT and cocrystals in pH 7.4 buffer.

Permeability/Flux of Cocrystals. Cocrystallization affects the permeability of an API since it may lead to changes in polarity of the relevant chemical entity. Flux of a drug is defined as the amount of solid moving through a membrane of certain cross-sectional area over a given period of time.[33] Diffusion/permeability studies of HCT and its cocrystals were carried out using Franz diffusion cells with a polymeric membrane. Generally, for highly permeable drugs (BCS classes I and II), the transport of the solid from the donor to the acceptor compartment causes a first-order decrease of the drug's concentration in the donor chamber and simultaneously leads to an increase in its concentration in the acceptor chamber.[33] The transport pattern changes in a class IV drug due to lowered solubility and permeability. In the present study, diffusion of the drug throughout the membrane was measured at 1 h intervals for 8 h. Figure 2a−c shows plots of the cumulative amount diffused, flux, and permeability of API/cocrystals against time. Figure 2a shows that the cumulative amount of API/cocrystal diffused increases slowly with time, except for NIC/NCT cocrystals, where a sharper rise ensues. These two cocrystals showed maximum diffusion at about 6 h. The plot of flux (Figure 2b) suggests a sharp rise in absorption of the drug within an hour, after which steady state is observed. The figure suggests that the amount of drug flux is higher in cocrystals than the API, except for SAM cocrystals, which exhibit a small initial increase that levels off after 4 h. It can be seen that the initial rate of flux/permeability of HCT−SAM cocrystals is higher than that of HCT, but after 5 to 6 h, diffusion drops slightly. Similarly, permeation behavior of HCT and cocrystals is observed (Figure 2c) and resembles the flux plots. From the plots in Figure 2a,b, a qualitative order of diffusion may be stated as follows: HCT−NIC > HCT−NCT > HCT−PABA > HCT−RES ≈ HCT > HCT−SAM. Log $D_{pH\ 7.4}$ of coformers were plotted against permeabilities of cocrystals, but no clear correlation was found.

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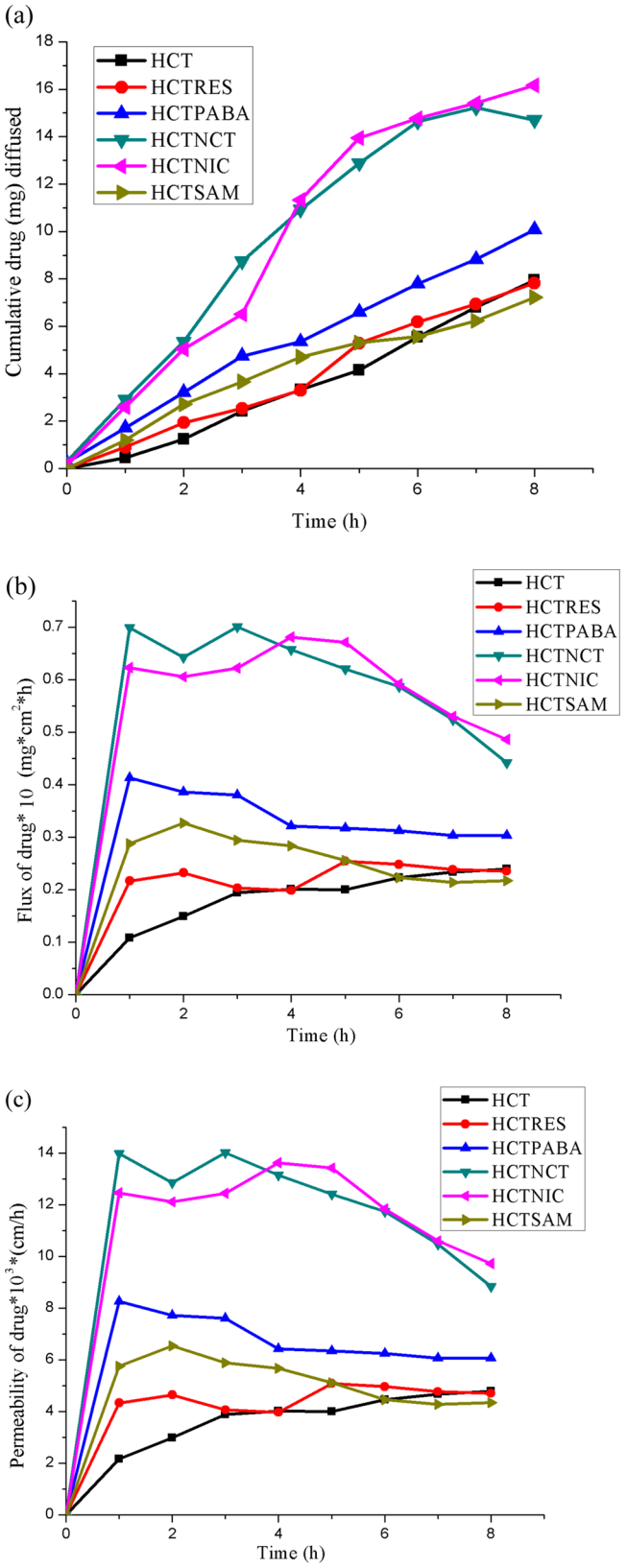

Figure 2. (a) Cumulative amount of HCT and the cocrystals diffused vs time plot. (b, c) Plots of flux/permeability of the cocrystals with respect to time.

Diffusion, by definition, is the random movement of molecules through a domain and is driven by a concentration gradient. Any compound applied to either a tissue or an artificial membrane will have a lag time, the time it takes to permeate through the membrane and diffuse into the receptor fluid and then finally reach a steady state of diffusion. The lag time is the period during which the rate of permeation across the membrane is increasing. The mass of cocrystal permeated was found to be higher than the drug in this time. No appreciable difference is observed in the lag time among the cocrystals and the drug. Steady state is reached when there is a consistent, unchanging movement of the permeant through the membrane. Steady state is reached in about 1 h for HCT and its cocrystals. The amount of time it takes to achieve steady state will depend on several factors, such as the permeability of the tissue or membrane being used, the properties of the compound itself, and, finally, the flow rate of the receptor fluid if flow-through diffusion cells are being used. Figure 3a,b

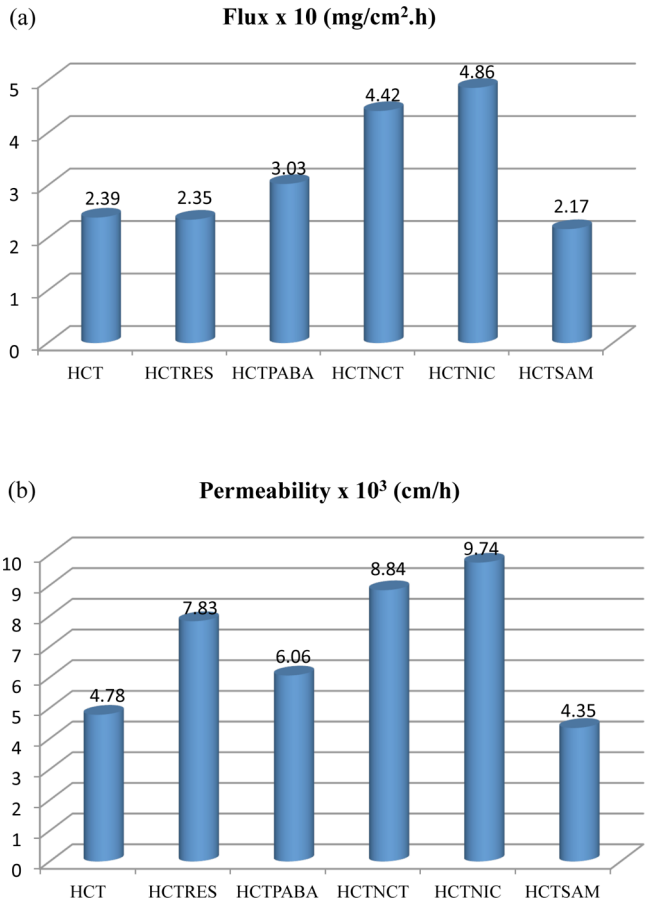

Figure 3. (a) Flux and (b) permeability of HCT and cocrystals measured at 8 h indicate the superiority of most of the cocrystals over the drug.

shows flux and permeability of the API and cocrystals reached after 8 h. In the plots, it can be seen that the parameters are higher than the API (except for HCT−SAM). The plots clearly show that cocrystallization has enhanced the permeation/flux/mass transport of HCT across an artificial membrane compared to that of the pure drug. The permeability at 6 h has almost tripled in HCT−NCT compared to that of the parent drug (Figure 2b,c).

Solubility−Permeability Product. In vitro solubility and permeability determination can help in the prediction of the in vivo bioavailability of a drug molecule.[34] Figure 4 shows the interplay between solubility and permeability values of

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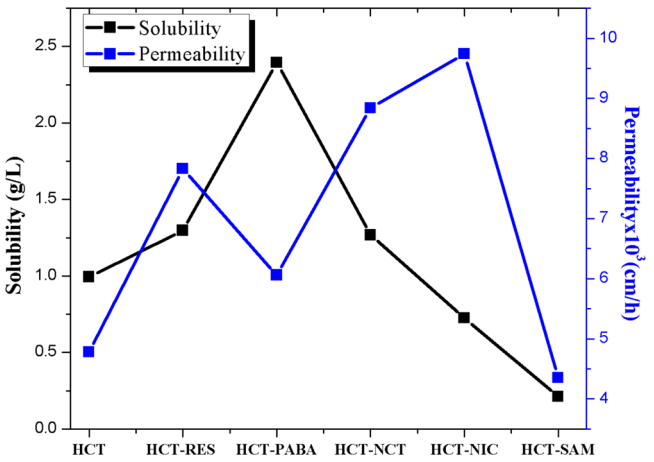

Figure 4. Permeability−solubility interplay in cocrystals of HCT.

cocrystals of HCT. Permeability values are higher for all of the cocrystals when compared to that of the parent drug except for HCT−SAM. Cocrystals with NCT have higher solubility (1.3 fold) and permeability (1.8 fold) compared to those of HCT and hence the product is high (Figure 5). PABA cocrystals

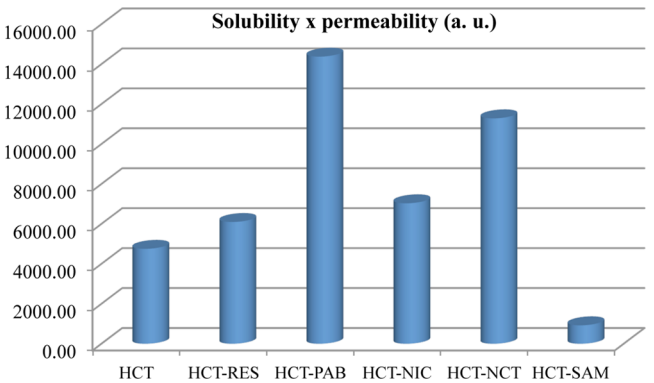

Figure 5. Product of solubility and permeability in HCT and cocrystals.

exhibited the highest solubility (2.4 fold) with a slight drop in permeability (1.3 fold) and hence the product is the highest (Figure 5). The HCT−NIC cocrystals showed the highest permeability (2 fold), but they exhibited lower aqueous solubility and hence the product for the cocrystal drops compared to that of PABA cocrystals. Thus, cocrystallization has been shown to enhance permeability in all of the cocrystals relative to the API (except HCT−SAM) in the diffusion cell study, and most of the cocrystals also exhibit solubility enhancement (except NIC and SAM cocrystals). SAM cocrystals behaved unusually, and both permeability and solubility values drop.

Permeability Studies of HCT−NIC Physical Mixture. To understand the difference in permeation rates of a cocrystal and a physical mixture of drug and coformer, an experiment was conducted on a drug−coformer mixture. The permeability of a physical mixture of HCT and nicotinic acid was measured in the Franz cell (Figure S6, Supporting Information). The UV spectrum of NIC showed peaks at 208 and 263 nm. The UV absorbance of the permeated mixture shows four peaks (~202, 226, 272, 317). With increasing the time from 2 to 8 h, it can be seen that a new peak appears at 311 nm and that the peak becomes slightly stronger, indicating the slow permeation of HCT into solution. At the same time, the absorption at 208 nm, corresponding to NIC, blue shifts and disappears. The blue shift and disappearance of the band are not easy to explain, but it is likely that NIC is forming a new complex with time. The experiment clearly indicates slow appearance of the HCT peak with time and with the blue shift and disappearance of the NIC peak.

Structure−Permeability Correlation. It is often difficult to correlate physicochemical properties (such as solubility/permeability) with crystal structure.[35,36] Permeability experiments on HCT cocrystals indicate that most of the cocrystals exhibited improved permeability compared to the API, but solubility drops for SAM and NIC cocrystals (Figures 1 and 3). If we carefully examine the crystal structure of the HCT polymorphs, then we can see that forms I and II consist of a primary sulfonamide catemer and secondary sulfonamide dimer synthons, respectively; see Figure S2, Supporting Information. In cocrystals of HCT−NIC and HCT−NCT, the sulfonamide dimer/catemer synthons are not observed (Figure 6 a,b). We suggest that in these cocrystals the absence of sulfonamide synthons leads to enhanced permeability. It can be seen that all of the cocrystals (except for HCT−SAM) exhibit an increase in permeability. Permeability drops slightly for the soluble cocrystals, such as HCT−RES and HCT−PABA (Figure 3). In the case of HCT−PABA cocrystals, there are discrete intermolecular hydrogen bonds between primary sulfonamide NH and secondary sulfonamide sulfonyl groups, which may explain its intermediate permeability (Figure 6e). The PABA cocrystal consequently shows a drop in membrane permeability, although this is still higher than that of the drug itself (Figure 3). HCT−SAM cocrystals comprise primary sulfonamide dimers (Figure 6c) that are similar to HCT polymorphs, and this may be the reason for its low solubility and permeability. It is generally expected that the permeability of a drug depends upon the hydrophobic interactions on the crystal's surface, which may interact with the nonpolar cell membranes during diffusion. However, we have found that not only the heterosynthons between the drug (sulfonamide) and the coformers but also combined hydrophobic ($\pi\cdots\pi$/H$\cdots\pi$) and hydrophilic (N/O$\cdots$H) interactions may play a role in improving the permeability of the drug.

Hirshfeld Surface Analysis. Hirshfeld surfaces are a reflection of intermolecular interactions in a novel visual manner.[37,38] The surfaces provide features characteristic of different interactions that are represented by color mapping of a variety of functions. It provides a visualization of a molecule within its environment, and the decomposition of this surface provides a molecular fingerprint that leads to an understanding of intermolecular interactions. In the present study, a Hirshfeld surface analysis (using Crystal Explorer, version 3.1) was carried out for HCT and its cocrystals to attempt to determine whether a correlation exists between the intermolecular interactions and the permeability data. Thus, 2D Hirshfeld surface finger plots of HCT and cocrystals with all types of noncovalent interactions are displayed in Figure S3, Supporting Information. The histogram (Figure 7) indicates that both polar (H$\cdots$O, H$\cdots$N) and nonpolar interactions (C$\cdots$C, C$\cdots$H, C$\cdots$all) together contribute to the diffusion/permeation of the drug cocrystals. If we consider the total percentage of polar/apolar interactions (as mentioned in the histogram), then there is a rough correlation with the permeability × solubility of the HCT cocrystals. The order of intermolecular contacts (%),

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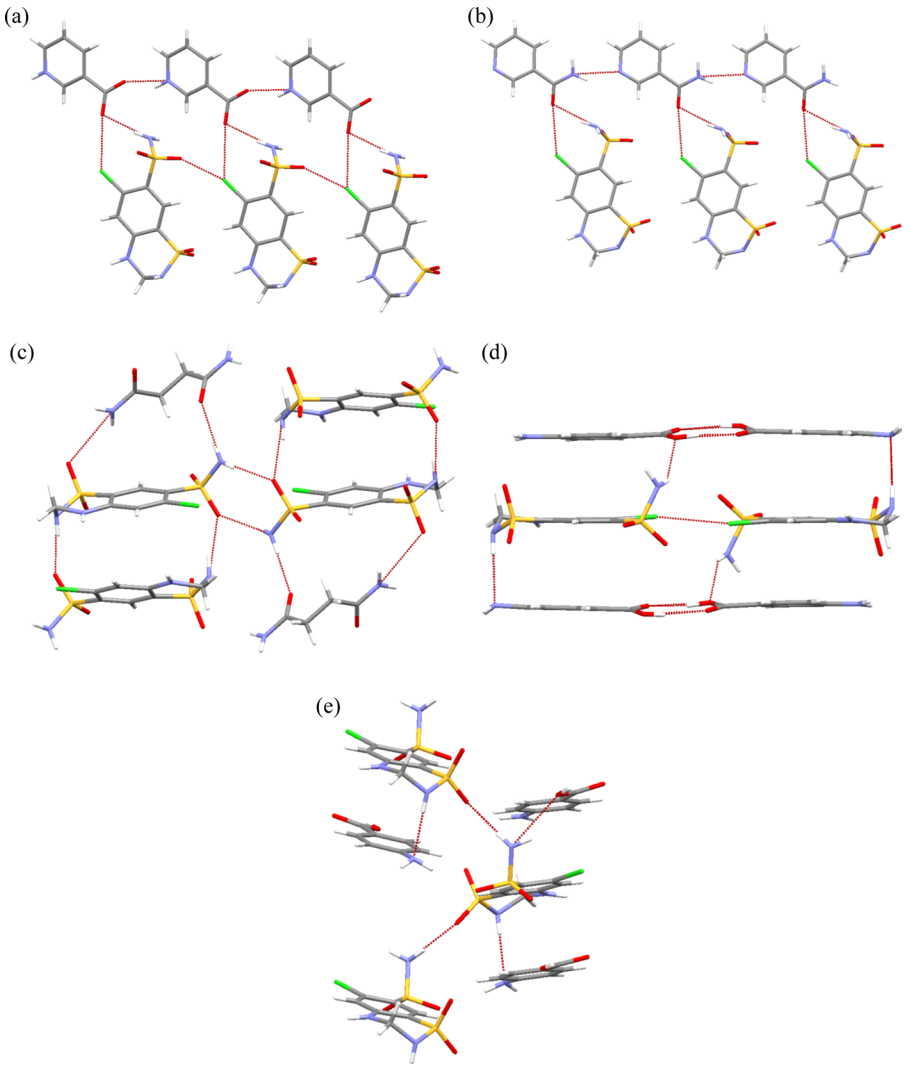

Figure 6. Heterosynthons formed between HCT and coformers: (a) HCT−NIC, (b) HCT−NCT, (c) HCT−SAM, and (d, e) HCT−PABA cocrystals.

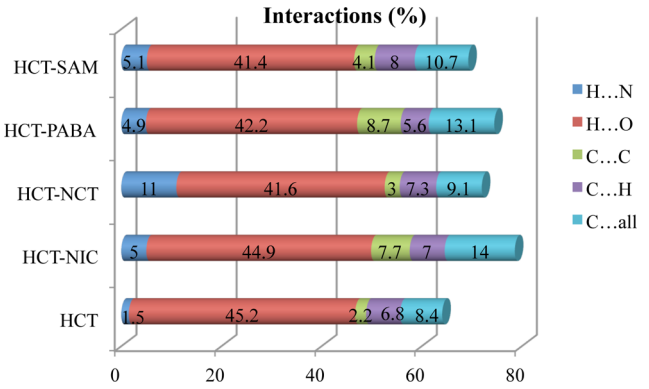

Figure 7. Contributions of the percentage of intermolecular contacts to the Hirshfeld surface area in HCT and its cocrystals. Percentages are given on the histogram only for the major atom type/atom type contacts.

HCT−NIC (78.6) > HCT−PABA (74.5) > HCT−NCT (72.0) > HCT−SAM (69.3) > HCT (64.1), is approximately in the order of (solubility × permeation) of the HCT and cocrystals.

CONCLUSIONS

Hydrochlorothiazide (HCT) is a BCS class IV drug with low solubility and permeability. The present study is an attempt to improve the physicochemical properties of HCT by cocrystallization methods. A number of biologically safe coformers are used to form cocrystals of the API, and solubility and diffusion/permeability are studied. Except for SAM and NIC, all cocrystals exhibited enhanced solubility, and this is attributed to a possible polarity increase caused by cocrystallization. Flux/permeability studies of the HCT cocrystals in a Franz diffusion cell showed enhanced flux/permeability in almost all cases except for the succinamide cocrystal. The solubility increase is accompanied by a drop in permeability and points to a trade-off between solubility and permeability. Modification of the sulfonamide synthon of HCT is a reason for the improved permeability of the cocrystals. The product of solubility and permeability (proportional to bioavailability) is higher for all of the cocrystals except for the succinamide cocrystals. Although an interplay between solubility and permeability is seen in the cocrystals, the product of the two is higher in most of the cocrystals than in the API itself. A Hirshfeld surface analysis was carried out and shows a correlation between drug−coformer

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interactions (heterosynthon) of the cocrystals and the permeability × solubility values.

■ ASSOCIATED CONTENT

Supporting Information

PXRD pattern comparisons, crystal structures of HCT polymorphs, and 2D fingerprint of Hirshfeld surface analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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