RESEARCH PAPER

Deep Eutectic Solvents as a Novel Approach for Solubility Enhancement of Hydrochlorothiazide: Development and Evaluation

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ABSTRACT
A significant barrier to the formulation of many medications taken orally is still poor water solubility. Because of its poor water solubility, the thiazide diuretic hydrochlorothiazide (HCTZ) serves as an appropriate model for assessing different solubilisation techniques. In this study, deep eutectic solvents (DESs) made with sucrose, citric acid, or oxalic acid as hydrogen-bond donors (HBDs) and choline chloride as the hydrogen-bond acceptor (HBA) were examined. Fifteen formulations with varying HBA: HBD molar ratios and three DES families were created and compared. Organoleptic evaluation, thermal behaviour, UV spectrophotometric characterisation, solubility, and pH measurement were among the preformulation investigations. A calibration range of 10–50 µg/mL was used to quantify HCTZ at 273 nm. Following the equilibration of surplus medication in distilled water and the produced DES systems, saturation solubility was assessed. The DES formulations improved the solubility of HCTZ to 4.50–11.30 mg/mL, whereas its aqueous saturation solubility was 0.835 mg/mL. DES-S2 (7.60 mg/mL; 9.10-fold enhancement), DES-C2 (11.30 mg/mL; 13.53-fold enhancement), and DES-O2 (9.90 mg/mL; 11.86-fold enhancement) were the best formulations among systems based on sucrose, citric acid, and oxalic acid, respectively. The ideal system was chosen to be DES-C2, which consists of citric acid and choline chloride in a 1:2 molar ratio. While maintaining the main spectrum characteristics of HCTZ, FTIR results showed modifications compatible with changed intermolecular interactions. DSC revealed an altered thermal profile for the physical mixture and a rapid endothermic transition for pure HCTZ at 272.29 °C without any unexpected events suggestive of significant incompatibility. The study finds that the choline chloride–citric acid system is the most promising formulation among those examined and shows that both HBD identity and component ratio affect HCTZ solubilisation.

Key words: citric acid, hydrochlorothiazide, deep eutectic solvents, solubility increase, choline chloride, saturation solubility, FTIR, DSC

1. **How to cite this article:** Anchal Gangwar* Dr. Aseem Tewari Dr. Puspendra Kannojia. Deep Eutectic Solvents as a Novel Approach for Solubility Enhancement of Hydrochlorothiazide: Development and Evaluation. Int J Drug Deliv Technol. 2026;16(80s):1792-1799. DOI: 10.25258/ijddt.16.80s.219.

Introduction

Because a drug's dissolving behaviour can significantly affect the amount accessible for absorption after oral administration, limited water solubility continues to be a significant barrier in pharmaceutical development. Poor water solubility is present in many recently produced medication candidates, which can lead to sluggish dissolution, inconsistent absorption, and decreased oral bioavailability [1-4]. Therefore, improving the solubility and dissolution of medications that are poorly soluble in water continues to be a crucial focus of pharmaceutical research.

A common thiazide diuretic, hydrochlorothiazide (HCTZ) is mainly used to treat oedema and hypertension. Its poor water solubility may limit its dissolution rate and lead to variability in pharmaceutical and biopharmaceutical performance, despite its known therapeutic significance [5–7]. Therefore, a number of formulation strategies have been studied to enhance HCTZ's solubility and dissolving properties [8–11]. Particle-size reduction, solid dispersions, cyclodextrin complexation, surfactant-based systems, lipid-based formulations, self-emulsifying systems, and nanoscale drug-delivery platforms are more general conventional methods for poorly water-soluble medications [2–4,12]. Although these approaches can be effective, their practical application may involve complex processing, the use of multiple excipients, physical stability concerns, or specialized manufacturing requirements.

A new family of multicomponent solvent systems with potential uses in medicine is called deep eutectic solvents (DESs). DESs are typically created by combining two or more highly interacting components, often by hydrogen bonding, which significantly lowers the mixture's melting point in comparison to the constituents' individual melting points [13–15]. A hydrogen-bond acceptor (HBA) and a hydrogen-bond donor (HBD) make up a standard DES, while more intricate multicomponent systems can also be created. The resulting eutectic system's physicochemical properties are significantly influenced by the components' molar ratio and chemical identity [14–16].

Because choline chloride may form eutectic systems with a variety of hydrogen-bond donors, it is one of the most studied HBA components for DES production. The unique solvent characteristics

of choline chloride-based eutectic mixtures were initially shown by Abbott and colleagues, which sparked a great deal of investigation into their basic characteristics and uses [13]. DESs have variable physicochemical properties, including as polarity, viscosity, conductivity, density, thermal behaviour, and solvent capacity, according to later research [14–16]. These characteristics can be significantly altered by changing the identity or molar ratio of the HBA and HBD, offering chances to create solvent environments for particular uses.

The field of eutectic systems was further broadened by the creation of natural deep eutectic solvents (NADESs). Organic acids, sugars, amino acids, and related substances are among the naturally occurring metabolites that make up NADESs [17–20]. The potential application of these systems as alternate and more biocompatible solvent environments has drawn a lot of attention. Drug–solvent interactions and molecular dispersion may be altered by DESs, depending on their composition, which might offer physicochemical conditions that are very different from water and traditional organic solvents [17–20].The ability of DESs to alter the solubility and dissolution properties of substances with poor water solubility is the main factor contributing to their medicinal significance. DES-based systems have the ability to increase a drug's molecular dispersion or solubilisation by fostering positive interactions between the drug and the eutectic mixture's constituents [21, 22]. Nevertheless, not all DES formulations exhibit the same level of solubility augmentation. A drug's affinity for a particular eutectic system can be influenced by a number of factors, including the drug's structure, the identity of the HBA and HBD, their molar ratio, polarity, viscosity, and hydrogen-bonding interactions [14–16,19–22]. Therefore, while creating a DES-based approach for pharmaceutical solubilisation, comparative screening of various DES compositions is crucial. Previous research has shown that altering HCTZ's physical surroundings can enhance its solubility and dissolving properties. To improve the dissolving behaviour of HCTZ, solid-dispersion systems and liquisolid formulations have been studied [8,9]. To increase the drug's solubility and processability, self-emulsifying and other sophisticated formulation techniques have also been investigated [10]. Furthermore, it has been shown that cyclodextrin-based inclusion systems can alter HCTZ's solubility, dissolving behaviour, and medicinal performance [7,11,23,24]. An essential framework for assessing drug–carrier interactions and solubilisation behaviour in such systems has also been made possible by the concepts of phase-solubility analysis [25]. Pharmaceutical companies are nevertheless interested in the systematic comparative assessment of DES composition as a solubilisation method, even though there are numerous ways to increase the solubility of HCTZ. Specifically, changes in the molar ratio of DES components and the hydrogen-bond donor can drastically change the physicochemical environment and, in turn, the system's solubilisation capability.

In order to improve the saturation solubility of HCTZ, the current work assessed deep eutectic solvent systems based on choline chloride. While sucrose, citric acid, and oxalic acid were studied as hydrogen-bond donors, choline chloride was chosen as the hydrogen-bond acceptor. To investigate the impact of HBD identity and composition on the saturation solubility of HCTZ, fifteen DES formulations with various component combinations and molar ratios were created. Differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR) were then used to characterise the optimised formulation. The study's objectives were to offer a targeted physicochemical characterisation of the optimised system and to determine the best DES formulation based on comparative saturation-solubility performance.

2. Materials and Methods

2.1. Materials

The model medication was hydrochlorothiazide. While sugar, citric acid, and oxalic acid were utilised as HBDs, choline chloride was chosen as the HBA. Methanol and distilled water were utilised in the solubility and analytical processes. Hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate, sodium chloride, and potassium bromide were additional laboratory reagents needed for the corresponding experimental procedures.

2.2. Study design

The investigation was organized in four stages:

(i) Preformulation and analytical evaluation of HCTZ and selected components
(ii) Preparation of choline chloride-based DES systems at different molar ratios
(iii) Comparative determination of HCTZ saturation solubility in distilled water and DES systems
(iv) Physicochemical characterization of the selected system using FTIR and DSC.

2.3. Preformulation and analytical evaluation

The drug's organoleptic properties and thermal behaviour were investigated, as were some of its constituent parts. HCTZ was subjected to UV spectrophotometric examination between 200 and 400 nm. For quantitative analysis, the maximum absorption wavelength of 273 nm was determined. The concentration–absorbance relationship was utilised to estimate HCTZ after working standards

in the range of 10–50 µg/mL were examined at 273 nm..

2.4. Preparation of DES systems

The heating and magnetic-stirring procedure was used to develop DES systems. A clear and homogenous system was achieved by carefully weighing predetermined amounts of choline chloride and the corresponding HBD in accordance with the chosen molar ratio, transferring them to a dry, clean container, and gradually heating them to between 70 and 80 °C while continuously stirring them with a magnetic stirrer. After cooling to ambient temperature and being checked for homogeneity and clarity, the systems were kept in airtight containers until they could be assessed further.

Table 1. Composition of the investigated deep eutectic solvent systems.

DES family	Code	Molar ratio
Choline chloride:sucrose	DES-S1	1:1
	DES-S2	1:2
	DES-S3	1:3
	DES-S4	1:4
	DES-S5	2:1
Choline chloride:citric acid	DES-C1	1:1
	DES-C2	1:2
	DES-C3	1:3
	DES-C4	2:1
	DES-C5	2:3
Choline chloride:oxalic acid	DES-O1	1:1
	DES-O2	1:2
	DES-O3	1:3
	DES-O4	2:1
	DES-O5	2:3

2.5. Saturation-solubility study

Establishing equilibrium between dissolved and undissolved HCTZ in distilled water or the corresponding DES was the foundation of the saturation-solubility process. In a properly sealed vial, an excess of around 100 mg of HCTZ was added to 5 mL of test medium. Samples were continuously shaken at 100 rpm for 48 hours while being equilibrated at 25 ± 2 °C. After that, the samples were centrifuged for 15 minutes at 5000 rpm. After collecting clear supernatants, they were filtered through a 0.45 µm membrane filter, appropriately diluted with methanol, and examined using UV–visible spectrophotometry at 273 nm. The solubility enhancement was calculated using the aqueous value as a reference. The equilibrium-based method adheres to the main principle utilised in studies of phase and saturation solubility..

2.6. pH determination

A calibrated digital pH meter was used to measure the pH of prepared systems and specific products. After the electrode response stabilised at room temperature, samples were dissolved or dispersed in distilled water as needed, and the pH was measured.

2.7. FTIR and DSC characterization

The conservation of distinctive absorption characteristics and modifications that would suggest modified intermolecular interactions were evaluated by comparing the FTIR spectra of pure HCTZ, pertinent DES components, the physical mixture, and the HCTZ-loaded DES. The thermal behaviour of pure HCTZ and the chosen HCTZ–component physical combination were compared using DSC.

3. Results

3.1. Preformulation and analytical observations

HCTZ was found to be a fine, crystalline, white, odourless powder that flowed freely. Choline chloride was a white, crystalline substance that was hygroscopic and had a faint, distinct smell. White crystalline solids were obtained from sucrose, citric acid, and oxalic acid. The materials under investigation did not exhibit any anomalous physical properties or visible foreign particles.

At about 273 °C, HCTZ showed thermal behaviour with decomposition. At about 302 °C, choline chloride began to break down. Oxalic acid broke down between 189 and 191 °C, whereas sucrose and citric acid displayed thermal transitions at roughly 186 °C and 153 °C, respectively. Maximum absorption of HCTZ was found at 273 nm in UV analysis, and absorbance gradually rose with concentration throughout the assessed 10–50 µg/mL range.

Table 2. Selected preformulation and analytical findings.

Parameter	Observed result
Appearance of HCTZ	White, odourless, crystalline and free-flowing powder
Thermal behaviour	Approximately 273 °C with decomposition
Maximum absorption wavelength	273 nm

Calibration range	10–50 µg/mL
Aqueous saturation solubility	0.835 mg/Ml

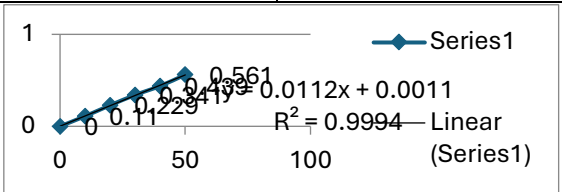

Figure 1. UV calibration curve of hydrochlorothiazide measured at 273 nm.

3.2. Comparative saturation solubility

HCTZ has a saturation solubility of 0.835 mg/mL in pure water. Higher values, ranging from 4.50 to 11.30 mg/mL, were obtained by all 15 DES formulations. The degree of improvement differed between formulations, indicating that the observed solubilisation performance was influenced by both HBD identity and HBA:HBD ratio.

Table 3. Saturation solubility of hydrochlorothiazide in the investigated DES systems.

Formulation	Molar ratio	Solubility (mg/mL)	Enhancement (fold)
DES-S1	1:1	6.10	7.31
DES-S2	1:2	7.60	9.10
DES-S3	1:3	6.90	8.26
DES-S4	1:4	5.20	6.23
DES-S5	2:1	4.50	5.39
DES-C1	1:1	8.20	9.82
DES-C2	1:2	11.30	13.53
DES-C3	1:3	9.40	11.26
DES-C4	2:1	7.50	8.98
DES-C5	2:3	8.90	10.66
DES-O1	1:1	7.70	9.22
DES-O2	1:2	9.90	11.86
DES-O3	1:3	9.10	10.90
DES-O4	2:1	6.70	8.02
DES-O5	2:3	8.30	9.94

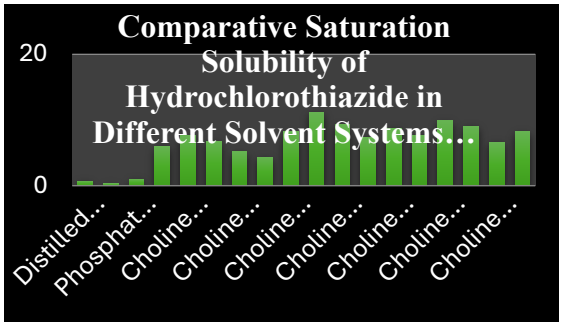

Figure 2. Comparative saturation solubility of hydrochlorothiazide in distilled water and the investigated DES formulations.

3.3. Effect of DES family and molar ratio

DES-S2 (1:2) generated the highest saturation solubility of 7.60 mg/mL and a 9.10-fold boost among the sucrose-based group. There was no further improvement when the proportion of sugar was increased. DES-C2 (1:2) generated the highest solubility of 11.30 mg/mL and a 13.53-fold improvement in the citric acid-based group. At 9.40 mg/mL, DES-C3 (1:3) was the next best formulation; the values for the other compositions were lower.

Significant improvements were also produced by the oxalic acid-based group. The best formulation in this family, DES-O2 (1:2), achieved 9.90 mg/mL and an enhancement of 11.86 times. The 1:2 ratio produced the maximum solubility within each of the three DES families. However, the distinct absolute values achieved with oxalic acid, citric acid, and sucrose show that the HBD's chemical makeup also played a significant role.

Table 4. Comparative performance of the best formulation from each DES family.

System	Best formulation	Ratio	Solubility (mg/mL)	Enhancement
Distilled water	DW	—	0.835	1.00-fold
Choline chloride:sucrose	DES-S2	1:2	7.60	9.10-fold
Choline chloride:citric acid	DES-C2	1:2	11.30	13.53-fold
Choline chloride:oxalic acid	DES-O2	1:2	9.90	11.86-fold

3.4. FTIR characterization

In addition to distinctive bands related to its sulfonamide/sulfone-containing structure, pure HCTZ had a wide absorption area at roughly 3397–3327 cm^{-1} linked to N–H stretching. Vibrations linked to S=O were consistent with strong absorptions in the range of 1122–1024 cm^{-1}. The primary absorption characteristics of the constituents were still discernible in the physical combination, despite broadening in the 3600–3000 cm^{-1} area and slight variations in peak intensity.The O–H/N–H stretching area of the HCTZ-loaded DES showed further broadening, while the carbonyl-related and C–O/C–N regions showed very slight alterations. These observations were consistent with an altered intermolecular environment and possible hydrogen-bonding interactions. Importantly, principal characteristic features of HCTZ remained identifiable and no major new absorption pattern indicative of extensive chemical degradation was observed.

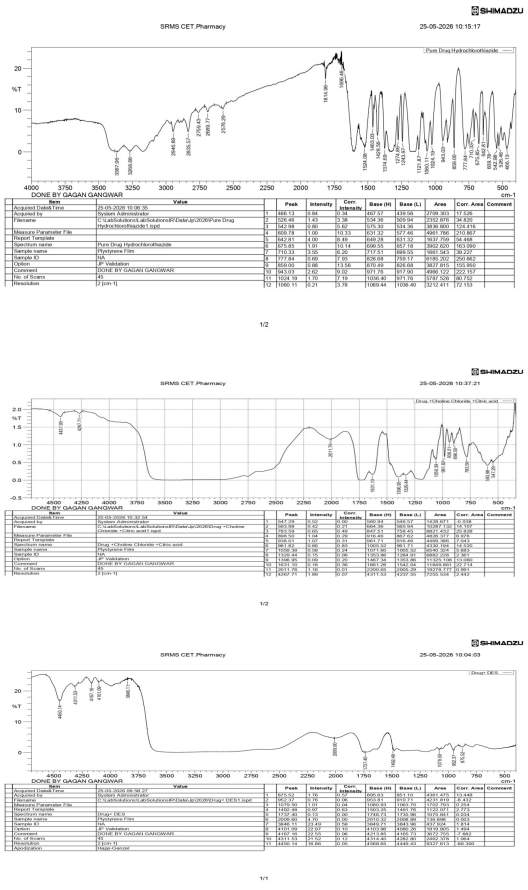

Figure 3. Comparative FTIR spectra of (A) pure hydrochlorothiazide, (B) physical mixture, and (C) HCTZ-loaded DES.

3.5. DSC evaluation

At 272.29 °C, pure HCTZ showed a distinct endothermic transition. A peak area of 523.249 mJ and an associated enthalpy of 153.8967 J/g were observed. The sharp incident matched the pure drug's crystalline thermal behaviour.

There was no discernible endothermic event in the physical mixture of HCTZ, choline chloride, and citric acid that matched the distinctive transition of pure HCTZ. Drug dilution, overlap of component-related transitions, and/or physicochemical interactions between constituents could all be linked to the changed profile. There were no reports of any unexpected, notable thermal events that were very suggestive of significant incompatibility.

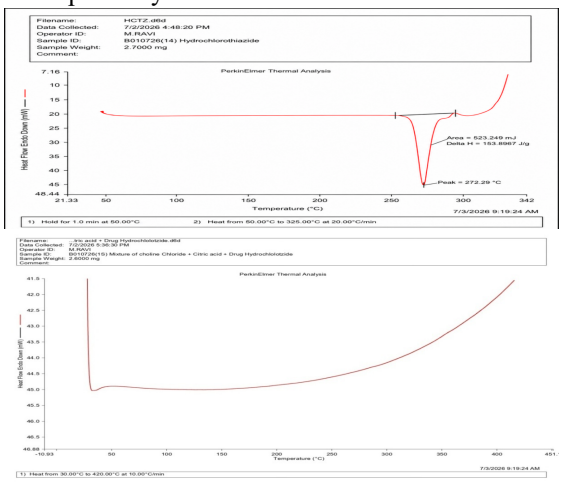

Figure 4. Comparative DSC thermograms of (A) pure hydrochlorothiazide and (B) the HCTZ–choline chloride–citric acid physical mixture.

4. Discussion

The current study shows that, in comparison to distilled water, the generated choline chloride-based DES systems significantly improved the saturation solubility of HCTZ. All 15 DES formulations yielded results ranging from 4.50 to 11.30 mg/mL, while the reference solubility was 0.835 mg/mL. The measured range, which represents an enhancement of 5.39 to 13.53 times, demonstrates that the physicochemical environment produced by the DES systems was significantly different from that of water alone.

The impact of DES composition was a key discovery. Even with similar ratios, the three HBDs did not yield the same results. The oxalic acid family reached 9.90 mg/mL, the citric acid family reached 11.30 mg/mL, and the sucrose-based family reached 7.60 mg/mL. Therefore, one of the main factors influencing HCTZ solubilisation was HBD identity.

The fact that the 1:2 ratio was consistently shown to be ideal within each DES family indicates that, in the compositions under investigation, the equilibrium between choline chloride and HBD produced a more favourable solvent environment than the other ratios. Nevertheless, the disparate results of DES-S2, DES-O2, and DES-C2 demonstrate that solubilisation capacity cannot be predicted only by ratio. The HBD's chemical makeup is still crucial. The increased solubility is in line with the more general justification for using DES as adjustable solvent systems. DESs have the

ability to create vast networks of interactions and environments that can alter the affinity between drugs and solvents. The precise chemical mechanism underlying DES-C2's better performance was not directly determined in this investigation. However, of the compositions examined, the choline chloride–citric acid system produced the most suitable environment for HCTZ, according to the comparative results.

FTIR characterization provides additional context for the solubility findings. Broadening and minor changes in O–H/N–H and related regions were consistent with altered intermolecular interactions and possible hydrogen bonding. At the same time, the retention of principal HCTZ bands provides no evidence from the recorded spectra of extensive chemical modification. The findings therefore support predominantly physicochemical interaction rather than a conclusion of covalent transformation.

A similarly cautious view is supported by the DSC data. While the physical mixture revealed a changed profile and decreased visibility of the pure-drug event, pure HCTZ showed a fast endothermic transition. Such alterations may result from dilution, transition overlap, changed crystallinity, or intermolecular interactions in multicomponent systems. The results were deemed consistent with satisfactory compatibility under the tested settings because no unexpected large thermal event suggestive of obvious incompatibility was seen. Nevertheless, no single interaction mechanism is established by the DSC data alone. The results can also be compared to previous methods of improving HCTZ solubility. It has been shown that altering the drug's physical environment can enhance its solubility or dissolution in solid dispersions, liqui-solid systems, and cyclodextrin complexes. The DES technique has the same general goal but offers more flexibility because the HBA, HBD, and component ratios can be changed to change the solvent's properties.

Even with the favourable comparative solubility results, more research is needed to advance DES-C2. Viscosity, water content, storage stability, reproducibility of the solubility data, dissolving after inclusion into a dosage form, and behaviour after dilution in biologically relevant fluids are all significant factors. The present work primarily establishes comparative saturation-solubility performance and physicochemical observations; it does not directly establish in vivo performance or final dosage-form suitability.

Overall, the screening strategy successfully differentiated the relative performance of 15 DES formulations. DES-C2 emerged as the optimized composition because it produced the highest saturation solubility and enhancement ratio. The convergence of comparative solubility, FTIR, and DSC observations supports its selection for further investigation, while the variation across the three DES families demonstrates the importance of systematic composition screening.

5. Conclusion

When compared to distilled water, the saturation solubility of hydrochlorothiazide was significantly increased by deep eutectic solvents based on choline chloride. Fifteen formulations with oxalic acid, citric acid, or sucrose as hydrogen-bond donors were made and compared. In comparison to the aqueous reference value of 0.835 mg/mL, all DES systems increased HCTZ solubility.

DES-S2 yielded 7.60 mg/mL with a 9.10-fold enhancement, DES-O2 yielded 9.90 mg/mL with an 11.86-fold enhancement, and DES-C2 yielded the highest value of 11.30 mg/mL with a 13.53-fold enhancement. Within each DES family, the 1:2 HBA:HBD ratio yielded the best results; nevertheless, the degree of improvement was highly dependent on the HBD identity. While maintaining the main characteristics of HCTZ, FTIR results showed modified intermolecular interactions. The distinctive transition of pure HCTZ at 272.29 °C was confirmed by DSC, which also revealed a modified physical-mixture profile without an unanticipated large event suggestive of substantial incompatibility. All things considered, the results point to the choline chloride–citric acid system at a 1:2 molar ratio as the most promising formulation studied and encourage more research on stability, viscosity, water content, dissolution performance, and dosage-form development.

Acknowledgement

The authors would like to sincerely thank **BIU College of Pharmacy, Bareilly International University,** for providing the infrastructure, academic support, and laboratory resources needed to complete this research project. Throughout the study, the esteemed faculty members provided invaluable advice, support, and helpful recommendations, for which the authors are grateful. The authors further thank the laboratory staff for their assistance and collaboration in the fabrication of deep eutectic solvent systems, solubility investigations, and hydrochlorothiazide physicochemical characterisation. The authors would like to express their sincere gratitude to everyone who helped to successfully complete this research project, whether directly or indirectly.

Conflict of Interest: The authors declare that they have no conflict of interest.

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