Characterizing the Solvation Characteristics of Deep Eutectic Solvents Comprised of Active Pharmaceutical Ingredients as Hydrogen Bond Donor and/or Acceptor

Muhammad Qamar Farooq,[1,2] Nabeel Mujtaba Abbasi,[1,2] Emily A. Smith,[1,2] Jacob W. Petrich,[1,2] and Jared L. Anderson[1,2,*]

[1]*Ames Laboratory—USDOE, 311 Iowa State University, Ames, Iowa 50011 USA*

[2]*Department of Chemistry, Iowa State University, 2415 Osborn Drive, Ames, Iowa 50011, USA*

***Corresponding Author:** andersoj@iastate.edu

Abstract

The formation of eutectic mixtures from active pharmaceutical ingredients (APIs) has emerged as an effective technique to develop liquid pharmaceutical formulations. API-based deep eutectic solvents (DESs) enhance the water solubility of APIs and avoid their recrystallization. The physico-chemical properties of API-DESs can be easily modulated by judicious selection of a hydrogen bond acceptor (HBA) or hydrogen bond donor (HBD) excipient that is mixed with the API. Solvation properties of API-DESs can help in understanding the role of ionic and non-ionic excipients towards the overall solvation interactions of these DESs. In this study, the solvation characteristics of three subclasses of API-DESs containing API-HBAs, API-HBDs, or API-HBAs and API-HBDs are investigated. Inverse gas chromatography is employed to study solute-solvent interactions of a variety of probe molecules for twenty different API-DESs. Among the API-DESs comprised of API-HBAs and carboxylic acid or diol-based HBDs, DESs containing diol-based HBDs exhibited stronger dipolar, hydrogen bond basicity, and hydrogen bond acidity interactions compared to carboxylic acid-based HBDs. No significant differences were observed in the solvation properties of DESs comprised of API HBAs and API HBDs. API-DESs comprised of the choline chloride HBA and API-HBDs exhibited stronger hydrogen bond acidity and dipolarity and weaker dispersive-type interactions among the DESs evaluated in this study. An in-depth evaluation of solvation properties for these DESs is important to completely exploit their potential in separation science as well as the fields of biomaterial science, pharmaceutical chemistry, and biotechnology.

Keywords: Solvation interactions; Inverse gas chromatography; Active pharmaceutical ingredients; Liquid drug formulations; Eutectic mixtures; Deep eutectic solvents.

Introduction

Active pharmaceutical ingredients (APIs) are considered as the backbone of the pharmaceutical industry. Improving the efficacy and formulation of approved drugs is among one of the major goals within the pharmaceutical industry.[1] More than 40% of approved drugs are considered poorly soluble in water, which limits their permeability and bioavailability.[2] Moreover, crystallinity and polymorphism of solid APIs are also limiting factors in their delivery.[3,4] The development of liquid formulations of APIs has emerged as an effective technique to overcome challenges associated with solid APIs.[5] One strategy to develop liquid forms of APIs is the synthesis of ionic liquids (ILs, molten organic salts with melting point <100 °C) using anionic and cationic active ingredients.[6–8] For example, an IL comprised of lidocaine (a local anesthetic) cation and docusate (a laxative) anion has shown curative effects of both components.[6] Similarly, ranitidine docusate was reported to avoid ranitidine polymorphism.[6] However, one of the major challenges of using API-based ILs is that every combination of cation and anion is a novel material and requires detailed toxicological studies before its use in any application. Toxicity studies of ILs have reported poor biodegradability, low sustainability, and high toxicity.[9,10] Eutectic mixtures and deep eutectic solvents (DESs) are considered as advantageous alternatives to API-ILs. In the formation of eutectic mixtures of APIs, the structural integrity of APIs is not compromised as there is no chemical reaction involved in their preparation.[4,5]

DESs have garnered a lot of interest from the scientific community owing to their enormous potential in numerous applications including biocatalysis,[11] carbon dioxide capture,[12] extraction of natural products,[13] and pharmaceutical drug formulations.[5,14] DESs are prepared by the combination of a hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD).[15] The hydrogen bonding interactions among the HBA and HBD result in DESs with a decreased melting point of the mixtures and often governs their physico-chemical properties.[16] The structural tunability, one-step solvent-free preparation, low cost, broad liquid range, low toxicity, and high biodegradability of DESs makes them advantageous solvents for a plethora of applications.[13,17]

API-based DESs are an emerging class of DESs classified as type VI DESs by Rahman et al.[18] It is important to note that the eutectic mixtures of APIs have been known long before the coinage of the term deep eutectic solvents by Abbott et al.[19,20] API-based DESs (also known as therapeutic DESs) require at least one API in their formulation and the API can act either as the HBA or the HBD or both in the DES chemical structure.[5] The preparation of DESs using APIs presents a novel approach for the development of new liquid API formulations. The physico-chemical properties of API-DESs can be easily tailored by carefully choosing the appropriate HBAs and HBDs.[21] API-DESs overcome the drawbacks and limitations of solid drugs by enhancing their solubility in aqueous media, increasing their stability and bioavailability, and improving their permeation as well as their therapeutic activity.[14,22] API-DESs have also been used as porosity enhancers in supercritical fluid sintering,[23] starting materials for the production of biopolymers,[24] and in tissue engineering.[25,26]

The API-DES prepared by mixing lidocaine and prilocaine in a 1:1 molar ratio (known as EMLA, Eutectic Mixture of Local Anesthetics) was the first eutectic mixture to be commercialized and is one of the most widely used topical anesthetics.[20] The combined analgesic effect of EMLA was observed to be higher than either of the individual components.[20] Another study reported a 12.7 fold enhancement in the solubility of ibuprofen when it was in the form of the ibuprofen:thymol API-DES (26.8±2.62 mg/mL) compared to ibuprofen powder (2.1±0.23 mg/mL) in a phosphate buffer saline solution.[27] Moreover, despite the poor solubility of aspirin in water, the eutectic mixture of choline chloride ($[Ch^+][Cl^-]$):Aspirin was reported to be completely miscible with water.[5] Additionally, the API-DES comprised of osthole and paeonol results in higher water solubility, better permeation behavior, and increased bioactivity compared to the pure individual components.[28]

Characterizing the solvation interactions (i.e., dipolarity/polarizability, dispersion, hydrogen bonding, n-π, and π-π interactions) is of utmost importance to fully exploit the designer aspects of API-DESs where the API can be employed as HBA, HBD, or HBA and HBD, and to understand the complex interplay between the HBA and HBD in API-DESs. Several studies have reported the preparation and applications of API-DESs using different APIs such as aspirin, ibuprofen, lidocaine, and prilocaine with excipients (molecules that deliver the active ingredient to active site[29]) like carboxylic acids, long-chain alcohols, and choline chloride.[5,19,30] However, studies that evaluate their polarity and intermolecular solvation interactions are very limited.[31,32,33]

Single polarity scales such as Reichardt's polarity index and nile red polarity scale have been used for DESs.[31,32,33] Kamlet-Taft parameters have also been employed to separately quantify the dipolarity/polarizability (π^*), hydrogen bond accepting ability (β), and hydrogen bond donating ability (a).[31] Saha et al. evaluated solvatochromic parameters of the $[Ch^+][Cl^-]$:Aspirin DES at various temperatures ranging from 25-45 °C and observed no significant difference in polarity.[31] The normalized polarity (E_T^N) values of $[Ch^+][Cl^-]$:Aspirin and $[Ch^+][Cl^-]$:2Glycerol DESs were reported to be 0.518 and 0.530, respectively.[31] Although the two DESs have different HBDs where aspirin possesses acetyl and carboxyl functional groups and glycerol has three alcohol functional groups, no significant difference between their polarities was observed. Similarly, another study reported the E_{NR} values of perillyl alcohol:camphor and perillyl alcohol:menthol DESs to be 52.56 and 52.27 kcal mol^{-1}, respectively.[33] The polarity values obtained by solvatochromic probes often fall within a very narrow range and are unable to differentiate among individual solvation interactions for DESs that have varied chemical makeup and composition. Therefore, a more detailed examination of DES solvation properties is required to aid in their rational design and to evaluate the contribution of APIs as well as the excipients towards overall solvation properties.

In our previous studies, we demonstrated that inverse gas chromatography (IGC) using the Abraham solvation parameter model is an effective technique to quantitatively measure individual solvation interactions of DESs.[34,35,36] Solute-solvent interactions such as dispersive interactions, hydrogen bond basicity, hydrogen bond acidity, dipolarity/polarizability, n-π and π-π interactions are measured through the chromatographic retention of probe molecules when the DES serves as the chromatographic stationary phase.[34] In this study, the solvation interactions of twenty different API-DESs were analyzed for the following three sub-classes of API-DESs: (a) DESs that are comprised of API-based HBAs mixed with carboxylic acid and diol-based HBDs, (b) DESs prepared by mixing two different APIs with each other at a given molar ratio, and (c) DESs composed of alkyl ammonium halide salt HBAs and API-based HBDs. The DESs were systemically chosen to carefully investigate differences in their solvation behavior when the API acts as the HBA, HBD, or both HBA and HBD. Moreover, the APIs are mixed with several different types of HBDs (when API is the HBA) and HBAs (when API is acting as the HBD) to examine their effect on the physico-chemical properties of API-DESs. Insights into solvation properties can guide the rational design of API-DESs and aid in deciphering the contribution of individual HBA or HBD towards the overall solvation behavior of these solvents. An enhanced understanding of API-DESs solvation characteristics can help in developing a molecular model that can be used to interpret the behavior of API-DESs in various applications including biomaterial science,[24] tissue engineering,[25,26] drug delivery,[37] and chemical separations.[38]

Experimental

Materials, DES preparation, and characterization

A comprehensive list of the compounds used for the preparation of API-DESs and the probe molecules employed in IGC measurements is provided in the supporting information (SI) and all abbreviations are defined in Figure 1. Deuterated dimethyl sulfoxide (d_6-DMSO) and chloroform ($CDCl_3$) used for NMR characterization of DESs were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). Deactivated capillary (5 m × 250 μm) was obtained from MEGA (Legnano, MI, Italy) and used as received for the preparation of all chromatographic columns evaluated in this study.

All DESs examined in this study have been previously reported and employed in various applications.[4,5,22,30,39] DESs investigated in this study (Figure 1) were prepared by using the heating and stirring method.[15] Firstly, all reagents were dried in a vacuum oven at room temperature for 24 hours. The appropriate amount of HBA and HBD was weighed carefully in a 20 mL vial containing a magnetic stirrer. The vial was then heated for three hours at 60 ℃ to obtain a uniform and homogenous mixture of the API-DES.

The water content of the prepared DESs was measured by a Metrohm 831 Karl Fischer coulometric titrator and the data is provided in Table S1. Differential scanning calorimetry (DSC) measurement were carried out by using a DSC Q2000 calorimeter (TA instruments) for those API-DESs whose melting points are not reported in the literature. API-DES samples were cooled from 40 to -120 ℃ at a rate of 20 ℃/min and then heated to 80 ℃ at the same rate. The melting point and/or glass transition temperatures for all DESs are provided in Table S2. The ^{13}C and ^{1}H NMR spectra for all DESs are provided in the supporting information.

Chromatographic column preparation using DESs

Chromatographic columns were prepared by coating a thin layer of DES on the inner wall of five-meter deactivated fused silica capillaries using the static coating method. All DESs (except those that contain $[Ch^+][Cl^-]$ HBA) were dissolved in dichloromethane to prepare a coating solution (0.32% w/v) that produced an approximate film thickness of 0.20 µm. The $[Ch^+][Cl^-]$-based DESs were dissolved in a mixed solvent containing 5% (v/v) methanol and 95% (v/v) dichloromethane due to their low solubility in dichloromethane. All columns were conditioned after coating at 60 °C for 30 min under a constant flow of helium. Column efficiencies were determined by injection of naphthalene (1 mg/mL) at 60 ℃ and were observed to be greater than 1500 plates/meter.

For the IGC study, all probe molecules were dissolved in dichloromethane at a concentration of 1 mg/mL. A total of 42 probe molecules (shown in Table S3) were employed. The probe molecules were injected separately at 40, 50, and 60 ºC. GC measurements were carried out using an Agilent Technologies 7890B gas chromatograph equipped with a flame ionization detector (GC-FID). Helium was used as a carrier gas at a flow rate of 1 mL/min. The injector and detector temperatures were maintained at 150 °C. A split ratio of 20:1 and an injection volume of 1 µL was employed. A flow rate of 25 mL/min was used for the helium makeup gas and the air flow was held at 400 mL/min. The dead volume of the column at each temperature of 40, 50, and 60 ºC was measured using propane. Multiple linear regression analysis and statistical calculations were performed using the program Analyze-it (Microsoft, USA). Figure S1 shows a typical regression line for the Lid:Ibuprofen DES at 50 ℃ consisting of all probe molecules with a correlation coefficient (R) value of 0.99.

Results and Discussion

This study examines the solute-solvent interactions of API-based DESs using IGC. The chromatographic retention of various probe molecules is related to the individual solvation interactions of the API-DESs by using a linear free energy relationship, such as the Abraham solvation parameter model, represented by Equation 1.

$$\text{Log } k = c + eE + sS + aA + bB + lL \quad (1)$$

In equation 1, k is the retention factor of probe molecules determined from their retention time and the column dead volume. The solute descriptors (E, S, A, B, and L) are specific for each probe molecule and have been previously reported by Abraham et al.[40] The E-term describes the excess molar refraction measured from the solute's refractive index, S represents the dipolarity/polarizability, *A* is a measure of the hydrogen bond acidity, *B* describes the hydrogen bond basicity, and *L* is the solute-gas hexadecane coefficient at 298 K. The system constant *e* represents the n-π and π-π interactions of the solvent, *s* is a measure of dipolarity/polarizability of the solvent, *a* describes the hydrogen bond basicity, *b* defines the hydrogen bond acidity, and *l* measures dispersive interactions of the DES stationary phase.

To evaluate the solvation interactions of DESs using IGC, it is important that the integrity of the thin stationary phase film coated on the inner wall of capillary be maintained. Therefore, inlet and detector temperatures of 150 °C were employed to allow sufficient volatilization of the probes. Solvation interactions were measured at 40 °C, 50 °C, and 60 °C, as temperatures exceeding 60 °C resulted in disruption of the DES film and variations in the retention time of probe molecules upon repeated injections. To ensure the soundness of the models and allow comparison of solvation interactions with varying temperature, these temperatures were studied for all DESs, as shown in Tables 1-3. Figure 2 shows a comparison of system constants for selected DESs from each subclass of API-DESs, where Atr:2DecA DES, Lid:2DecA DES, and Lid:2OctD DES consist of API HBAs, Lid:Ibuprofen DES and Lid:Prilocaine DES are API:API DESs, and 7[N_{8881}^{+}][Cl^{-}]:3Ibuprofen DES, [Ch^{+}][Cl^{-}]:2Aspirin DES, and [Ch^{+}][Cl^{-}]:Resorcinol DES possess API HBDs. Figure 2 shows that solvation interactions of DESs can be controlled by varying the HBA or the HBD of the API-DESs.

System constants of API-DESs comprised of API HBA

DESs comprised of API-based HBAs (lidocaine and atropine) were mixed with various carboxylic acids featuring long alkyl chain substituents and diol-based HBDs. The alkyl chain length, nature of the functional group, and molar ratio of HBDs were systematically varied to evaluate their effects on the solvation properties of these DESs. Among the eleven DESs evaluated in this subclass, DESs **1** and **7** show the effect of varying the API-HBA on the solvation interactions. DESs **3** and **4** are comprised of long alkyl chain carboxylic acid HBDs (stearic acid and linoleic acid) to evaluate their effect on dispersive interactions. DESs **6-8** contain different molar ratios of decanoic acid HBD and DESs **9-11** are comprised of varying molar ratios of octane diol HBD to study the effect of molar ratio on the solvation properties of DESs. System constants of DESs comprised of API-HBAs (**DESs 1-11**) are shown in Table 1.

Dipolar interactions (*s*-term) ranged from (1.17±0.05) to (1.65±0.06) at 50 °C. The highest dipolarity/polarizability was observed for the Lid:OctD DES and the lowest for the Atr:2DodA DES. Increasing the molar ratio of decanoic acid HBD from 1 to 3 (**DES 6-8)** resulted in weaker dipolar interactions of DESs from (1.55±0.06) to (1.20±0.05) at 50 °C. A similar trend was observed for the Lid:OctD DESs (**DES 9-11)** as well, where the molar ratio of the octanediol HBD was increased from 1 to 3. Overall, DESs comprised of diol-based HBDs exhibited stronger dipolar interactions compared to carboxylic acid HBDs featuring long alkyl chain substituents in this class of API HBA-based DESs.

The hydrogen bond basicity (*a*-term) was observed to range from (2.90±0.08) to (3.89±0.10) at 50 °C for DESs comprised of lidocaine and atropine API-HBAs. Atropine-based DESs exhibited relatively stronger hydrogen bond basicity compared to their analog lidocaine-based DESs. For example, the *a*-term at 50 °C was (3.33±0.08) for the Atr:2DecA DES compared to (3.01±0.09) for the Lid:2DecA DES. The difference in hydrogen bond basicity can be justified through the chemical structures of atropine and lidocaine in which atropine contains three oxygen atoms and one nitrogen atom that can act as hydrogen bond acceptors, resulting in stronger chromatographic retention of acidic probes. Lidocaine, on the other hand, contains two nitrogen atoms and one oxygen atom capable of interacting with acidic analytes. The hydrogen bond basicity of DESs containing the octanediol HBD was higher compared to the carboxylic acid-based HBDs. For example, the *a*-term for the Lid:3OctD DES was (3.89±0.10) compared to that of (3.04±0.08) for the Lid:3DecA DES at 50 °C. The hydrogen bond basicity of DESs comprised of lidocaine HBA and decanoic acid HBD (**DES 6-8**) was observed to decrease from (3.56±0.10) to (3.21±0.08) at 40 °C when the molar ratio of decanoic acid HBD was increased from 1:1 to 1:3, respectively. A similar trend has been previously reported for other monocarboxylic acid-based HBDs, where the *a*-term decreased from (8.11±0.08) to (7.13±0.15) at 40 °C when the molar ratio of HBD was increased from 1:1 to 1:2 in the case of the $[N_{4444}^{+}][Cl^{-}]$:octanoic acid DES.[34] An opposite trend was observed when octanediol was employed as the HBD and lidocaine as HBA. In this case, the hydrogen bond basicity increased from (4.01±0.11) to (4.22±0.10) at 40 °C when the molar ratio of HBD was increased from 1:1 to 1:3. This increase in hydrogen bond basicity is also consistent with previously reported results for diol-based HBDs.[35] For example, the *a*-term of $[Ch^{+}][Cl^{-}]$:1,4-butanediol increased from (4.96±0.11) to (5.13±0.12) at 40 °C when the molar ratio was increased from 1:1 to 1:3.[35]

Dispersive interactions (*l*-term) were observed to be higher for this sub-class of API-DESs compared to conventional ammonium and choline-based DESs.[34,35] The *l*-term ranged from (0.77±0.01) to (0.87±0.01) at 60 °C and the highest dispersive interactions were observed for the Lid:SteA DES (0.87±0.01) containing the stearic acid HBD. Moreover, increasing the molar ratio of decanoic acid HBD from 1 to 3 (**DES 6-8**) did not result in significant changes in dispersive interactions. The *l*-term was observed to be (0.84±0.01) at 50 °C for all three DESs (**DES 6-8**). Similarly, no significant difference in dispersive interactions was observed upon varying the molar ratio of the octanediol HBD from 1 to 3 (**DES 9-11**) with the *l*-term ranging from (0.77±0.01) to (0.79±0.01). This is consistent with a previously reported trend for DESs comprised of the trihexyl(tetradecyl)phosphonium chloride HBA and octanoic acid HBD. The *l*-term (0.81±0.02) was the same for the $[P_{66614}^{+}][Cl^{-}]$:Octanoic acid DES as well as the $[P_{66614}^{+}][Cl^{-}]$:2Octanoic acid DES.[34] This demonstrates that for DESs capable of undergoing strong dispersive interactions, increasing the molar ratio of HBD does not play a significant role in increasing the dispersive interactions.

Values for the hydrogen bond acidity (*b*-term) were positive for DESs containing more than 1 molar equivalent of octanediol HBD, such as Lid:2OctD (0.12±0.07 at 50 °C) and Lid:3OctD (0.24±0.08 at °C) (**DESs 10 and 11**). Interactions of Lid:OctD DESs (1:2 and 1:3) can be associated with the presence of two hydroxyl functional groups on both terminal ends of the alkyl chain, that are capable of strong interactions with basic probe molecules. For example, the retention factors of *N*,*N*-dimethylformamide (*N*,*N*-DMF) and *N*,*N*-dimethylacetamide (*N*,*N*-DMAC) were 20.54 and 54.64, respectively, for the Lid:2OctD DES compared to 9.16 and 21.58 for the Atr:2C10A DES, as shown in Table 4. No significant n-π and π-π interactions (*e*-term) were measured for this sub-class of API-DESs.

These results demonstrate that stronger dispersive interactions can be attained by employing HBDs featuring long alkyl chain substituents along with the API-based HBAs. The increase in molar ratio of HBD in the DESs comprised of API-HBAs can result in stronger (using octanediol HBD) or weaker (using decanoic acid HBD) hydrogen bond basicity interactions. API-DESs containing diol-based HBDs result in higher dipolarity and hydrogen bond acidity compared to carboxylic acid-based HBDs.

Solvation interactions of DESs comprised of API HBA and HBD

Preparation of DESs by mixing two different active pharmaceutical ingredients (API:API DESs) is an effective route to produce dual function liquid formulations of APIs and to overcome challenges associated with the polymorphism and crystallization of these materials.[28] In this subclass of API-DESs, lidocaine as HBA was mixed with different API-based HBDs such as ibuprofen, tetracaine, prilocaine, and vanillin. The four API-based HBDs employed in this subclass of DESs were structurally unique and possessed different functional moieties. Ibuprofen HBD contained carboxylic acid functional group, tetracaine amine and carboxylate functionalities, prilocaine amine and amide functional groups, and vanillin possessed carboxyl, hydroxyl, and ether functional groups in its chemical structure. The system constants for these DESs (**DESs 12-15**) are shown in Table 2.

All four API:API DESs exhibited strong dispersive-type interactions (*l*-term), dipolarity (*s*-term), and hydrogen bond basicity (*a*-term). The *l*-term values for these API:API DESs were relatively higher compared to conventional choline and ammonium halide-based DESs.[34,35] For example, the Lid:Tetracaine DES resulted in a *l*-term value of (0.82±0.01) compared to that of (0.43±0.02) for the $[Ch^+][Cl^-]$:Resorcinol DES. The dipolarity values of the API:API DESs were higher than the DESs comprised of API-HBAs and carboxylic acid HBDs, with *s*-term values ranging from (1.64±0.06) to (1.80±0.07) at 50 °C, where the Lid:Prilocaine DES exhibited the strongest dipolar interactions. The hydrogen bond basicity (*a*-term) ranged from (3.18±0.09) to (3.27±0.10) for this class of API:API DESs. These values are lower than previously reported conventional choline and ammonium halide-based DESs containing a free halide anion capable of undergoing strong interactions with acidic analytes.[34,35] The presence of hydrogen bond donating (-NH, -OH, -COOH) and hydrogen bond accepting ($-NR_2$, -OR) moieties on both components of the API:API DESs result in strong intermolecular interactions between both components and lower hydrogen bond basicity for the DES.

The API:API DESs offer different interactions with the probe molecules compared to the API-HBD-based and API-HBA-based DESs. Figure 3 shows a chromatographic separation comparison of 12 probe molecules using the Atr:2DecA (API-HBA DES), Lid:Ibuprofen (API:API DES), and $[Ch^+][Cl^-]$:2Aspirin (API-HBD DES). The analyte elution order and separation selectivity vary among different DESs due to their different solvation interactions. The two non-ionic DESs, Atr:2DecA DES and Lid:Ibuprofen DES, resulted in stronger retention of alcohols compared to the ionic $[Ch^+][Cl^-]$:2Aspirin DES. Basic probe molecules including *N*,*N*-DMF and *N*,*N*-DMAC exhibited very strong retention on the $[Ch^+][Cl^-]$:2Aspirin DES. The Lid:Ibuprofen DESs offers the strongest retention of long alkyl chain haloalkanes compared to the other two DESs.

Comparison of DESs containing ionic HBA and API HBD

API-DESs can also be prepared by mixing ionic excipients (employed as HBAs) with the API-HBDs. Five different DESs were analyzed in this sub-class where API-based HBDs were mixed with ionic excipients to evaluate the effect of ionic HBAs on solvation interactions. The system constants of DESs **16-20** are shown in Table 3. $[Ch^+][Cl^-]$ is one of the most commonly used HBAs for the preparation of DESs due to its low molar enthalpy of fusion, low cost, and biodegradability.[4] The $[N_{8881}{}^+][Cl^-]$ HBA was also used to evaluate the effect of varied alkyl chain length of ionic excipient on the solvation properties of API-DESs. Four HBDs mixed with the $[Ch^+][Cl^-]$ HBA possessed the carboxylate (aspirin), hydroxyl (resorcinol), carboxylic acid (phenyl acetic acid), and amide (acetaminophen) functional groups to understand their effects on solvation properties. Interactions by non-bonding and π-electrons were found to be significant in three of the choline-based DESs, including, $[Ch^+][Cl^-]$:Resorcinol (0.32±0.08 at 50 °C), $[Ch^+][Cl^-]$:Phenyl AA (0.22±0.06 at 50 °C), and $[Ch^+][Cl^-]$:Acetaminophen (0.21±0.08 at 50 °C).

Previously, Martins et al. compared the role of ionic and non-ionic excipients towards the formation of API-based DESs and observed a higher melting point depression in systems involving the non-ionic excipients compared to the ionic excipients.[4] The solvation properties of the API-HBD based DESs were significantly different from the other two subclasses of DESs evaluated in this study. The dipolarity value (*s*-term) of $7[N_{8881}^+][Cl^-]$:3Ibuprofen was higher than the previously discussed API-HBA-based and API:API DESs and observed to be (1.87±0.07) at 50 °C. Dipolar interactions were strongest in the DESs comprised of $[Ch^+][Cl^-]$ HBA and API-based HBDs and ranged from (2.21±0.07) to (2.27±0.07) at 50 °C. Differences among the dipolarity of the four $[Ch^+][Cl^-]$ HBA-based DESs were not significant, indicating that the relative increase in dipolarity compared to other sub-classes of API-DESs is due to the ionic $[Ch^+][Cl^-]$ HBA.

The $[Ch^+][Cl^-]$:API DESs resulted in significant hydrogen bond acidic interactions (*b*-term) and the $[Ch^+][Cl^-]$:Resorcinol DES afforded the highest hydrogen bond acidity (1.02±0.12 at 50 °C). The hydroxyl functional groups present on the resorcinol HBD are capable of undergoing strong interactions with basic probe molecules such as *N*,*N*-DMF and *N*,*N*-DMAC. As shown in Table 4, the retention factors for *N*,*N*-DMF and *N*,*N*-DMAC were observed to be 37.97 and 89.98, respectively, for the $[Ch^+][Cl^-]$:Resorcinol DES compared to retention factors of 9.23 and 15.97 for the $7[N_{8881}^+][Cl^-]$:3Ibuprofen DES, which results in very low to negligible hydrogen bond acidity interactions being measured.

The hydrogen bond basicity (*a*-term) ranged from (3.65±0.15) to (6.51±0.10) at 50 °C in the DESs comprised of ionic HBAs and API-based HBDs. The $7[N_{8881}^+][Cl^-]$:3Ibuprofen DES exhibited the highest hydrogen bond basicity (6.51±0.10 at 50 °C) among the DESs evaluated in this study due to strong hydrogen bonding interactions offered by the chloride anion.[41] The hydrogen bond basicities of the [Ch^+][Cl^-]-based DESs were lower than the DESs comprised of [N_{8881}^+][Cl^-] HBA. For example, the retention factors of cyclopentanol and cyclohexanol were 98.85 and 222.30, respectively, for the 7[N_{8881}^+][Cl^-]:3Ibuprofen DES compared to that of 6.93 and 10.71 for the [Ch^+][Cl^-]:Resorcinol DES, as shown in Table 4.

Dispersive interactions of [Ch^+][Cl^-]-based DESs were relatively lower due to the short alkyl chain substituents of the choline cation and ranged from (0.43±0.02) to (0.60±0.01) at 50 °C. Among these four DESs, dispersive interactions were highest for the [Ch^+][Cl^-]:2Aspirin DES as it contains 2 molar equivalents of the API-HBD compared to one molar equivalent in the other DESs (as shown in Figure 1). The *l*-term for the 7[N_{8881}^+][Cl^-]:3Ibuprofen DES was higher than all of the [Ch^+][Cl^-]-based DESs due to the long alkyl chains substituents within the ammonium halide salt and observed to be (0.80±0.01) at 50 °C. The DESs were further classified into different clusters by plotting their two most dominant interactions, namely, hydrogen bond basicity (*a*-term) and dipolar interactions (*s*-term), as shown in Figure 4. Using k-means clustering (Figure S2), the 20 API-DESs were classified into four clusters. DESs comprised of API-HBAs and carboxylic acid HBDs (**DESs 1-5**, **DES 7**, and **DES 8**) formed cluster A, with exception of the Lid:C_{10}A DES. Cluster B is composed of DESs containing both API-based HBAs and HBDs (**DES 12-15**), DESs containing lidocaine HBA and octane diol HBD in different molar ratios (**DES 9-11**), and Lid:C_{10}A DES. Cluster C is exclusively formed by the 7[N_{8881}^+][Cl^-]:3Ibuprofen DES. All of the [Ch^+][Cl^-]-based DESs fall into cluster D. Figure 4 provides a useful means to differentiate the solvation interactions of different subclasses of the API-DESs and to understand the role played by different excipients. Overall, the ionic HBA-based DESs exhibit higher dipolarity and their basicity can be controlled by varying the anion and/or alkyl chain length of HBA. Among the API-HBA based DESs, the carboxylic acid-based HBDs resulted in lower dipolarity than the octane diol HBD.

Figure S3 shows a plot of hydrogen bond basicity (*a*-term) versus dispersive interactions (*l*-term) of all API-DESs to differentiate the DESs containing ionic components compared to those containing non-ionic components. The DESs can be divided into three clusters based upon k-means clustering, as shown in Figure S4. All of the $[Ch^+][Cl^-]$-based DESs comprise cluster A', the $7[N_{8881}^+][Cl^-]$:3Ibuprofen DES exclusively forms cluster B', and all API-HBA-based and API-API DESs are in close proximity to each other and form cluster C'. It is important to note that all DESs in cluster C' are non-ionic while those within cluster A' and B' contain ionic-HBAs. Furthermore, Figure S3 demonstrates that the dispersive interactions of the $[Ch^+][Cl^-]$-based API-DESs are relatively weaker than other API-DESs and depend significantly upon the chemical structure of API-HBD. The $[N_{8881}^+][Cl^-]$-based DESs afforded stronger hydrogen bond basicity but similar dispersive interactions compared to the API-HBD-based DESs and API:API DESs.

Conclusions

API-based eutectic mixtures have been known long before the formal introduction of DESs. The liquid formulations of APIs overcome challenges such as low water solubility and polymorphism of solid amphiphilic APIs. API-DESs are prepared by mixing an API with another API or an ionic/non-ionic excipient in the appropriate molar ratio. Solvatochromic approaches used for evaluating solvation properties of API-DESs often result in similar solvatochromic parameters for structurally diverse compounds. The inverse gas chromatographic approach employed in this study provides a means to measure simultaneous solute-solvent interactions of the API-DESs.

Among the twenty DESs evaluated in this study, eleven were comprised of API-HBAs and carboxylic acid or octane diol HBDs, four DESs constituted API- HBAs and API-HBDs, and five DESs were prepared by mixing ionic ammonium halide-based HBAs and API-HBDs. API-DESs containing the octane diol HBD offered stronger dipolar, hydrogen bond basicity, and hydrogen bond acidity interactions compared to the carboxylic acid HBDs. Increasing the molar ratio of the carboxylic acid HBD from 1 to 3 resulted in stronger hydrogen bond basicity interactions of the DES while the opposite trend was observed upon increasing the molar ratio of octane diol HBD. API-DESs comprised of the choline chloride-HBA interacted strongly with basic probe molecules and offered strong hydrogen bond acidic interactions. Dispersive interactions of all API-DESs containing non-ionic HBAs and HBDs were stronger than the choline chloride-based API-DESs. DESs were further classified into four clusters based upon their dipolarity/polarizability and hydrogen bond basicity. This study demonstrates that the solvation behavior of API-DESs can be tailored by using a suitable excipient, where the excipient can be employed as the HBA or the HBD and can be ionic or non-ionic. Moreover, the classification of API-DESs into different groups based upon their dominant solvation interactions provides a framework for selecting DESs for particular applications. This study provides fundamental insight into the solvation properties of these unique DESs and can be used to interpret and predict their performance in various applications such as material science, drug delivery, biotechnology, and chemical separations.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

List of all chemicals, reagents, probe molecules and their solute descriptors, water content of the API-DESs, melting point/glass transition temperatures of the API-DESs, multiple linear regression plot of the Lid:Ibuprofen DES, grouping of the API-DESs using *a*-term versus *s*-term and *a*-term versus *l*-term based on *k*-means clustering, and ^{1}H and ^{13}C NMR spectra for the API-DESs evaluated in this work.

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Table 1. System constants for eleven API-DESs comprised of the atropine and lidocaine API-HBA and different carboxylic acid and diol-based HBDs obtained using the solvation parameter model.

No.	DES	Temp. (°C)	System constants								
			c	*e*	*s*	*a*	*b*	*l*	*n* [a]	R^2 [b]	*F* [c]
1	Atr : 2DecA	40	-2.87 (0.04)	-0.17 (0.04)	1.36 (0.05)	3.57 (0.09)	-0.08 (0.07)	0.83 (0.01)	38	0.99	2209
		50	-2.89 (0.04)	-0.14 (0.04)	1.31 (0.05)	3.33 (0.08)	-0.08 (0.06)	0.78 (0.01)	38	0.99	2589
		60	-2.91 (0.04)	-0.13 (0.04)	1.27 (0.05)	3.11 (0.07)	-0.09 (0.06)	0.74 (0.01)	38	0.99	2421
2	Atr : 2DodA	40	-2.84 (0.04)	-0.14 (0.04)	1.21 (0.05)	3.39 (0.09)	-0.07 (0.07)	0.85 (0.01)	39	0.99	2289
		50	-2.85 (0.04)	-0.13 (0.04)	1.17 (0.05)	3.15 (0.08)	-0.08 (0.06)	0.80 (0.01)	39	0.99	2694
		60	-2.85 (0.04)	-0.08 (0.04)	1.09 (0.05)	2.88 (0.07)	0 (0)	0.76 (0.01)	40	0.99	3195
3	Lid : SteA	40 [d]	-3.77 (0.07)	-0.38 (0.08)	1.73 (0.10)	3.76 (0.16)	-0.55 (0.13)	1.01 (0.02)	39	0.99	956
		50	-3.02 (0.04)	-0.28 (0.04)	1.33 (0.05)	3.06 (0.09)	-0.36 (0.07)	0.87 (0.01)	40	0.99	2249
		60	-2.98 (0.04)	-0.23 (0.04)	1.25 (0.05)	2.77 (0.08)	-0.31 (0.06)	0.82 (0.01)	40	0.99	2742
4	Lid : LinA	40	-2.82 (0.04)	-0.27 (0.04)	1.38 (0.05)	3.15 (0.09)	-0.30 (0.07)	0.87 (0.01)	40	0.99	2470
		50	-2.84 (0.04)	-0.24 (0.04)	1.32 (0.05)	2.90 (0.08)	-0.27 (0.06)	0.83 (0.01)	40	0.99	2783
		60	-2.87 (0.03)	-0.22 (0.03)	1.27 (0.04)	2.65 (0.07)	-0.22 (0.06)	0.79 (0.01)	39	0.99	2838
5	Lid : 2DodA	40	-2.96 (0.05)	-0.30 (0.05)	1.36 (0.06)	3.34 (0.10)	-0.17 (0.08)	0.90 (0.01)	39	0.99	1741
		50	-2.92 (0.04)	-0.24 (0.04)	1.26 (0.05)	3.01 (0.09)	-0.12 (0.07)	0.84 (0.01)	39	0.99	2117
		60	-2.96 (0.04)	-0.22 (0.04)	1.22 (0.05)	2.79 (0.08)	-0.10 (0.07)	0.81 (0.01)	40	0.99	2198
6	Lid : DecA	40	-2.97 (0.05)	-0.33 (0.05)	1.59 (0.06)	3.56 (0.10)	-0.40 (0.08)	0.88 (0.01)	39	0.99	1682
		50	-3.02 (0.05)	-0.32 (0.05)	1.55 (0.06)	3.34 (0.10)	-0.37 (0.08)	0.84 (0.01)	39	0.99	1832
		60	-2.98 (0.04)	-0.26 (0.04)	1.45 (0.05)	3.05 (0.08)	-0.36 (0.07)	0.79 (0.01)	39	0.99	2097
7	Lid : 2DecA	40	-2.85 (0.04)	-0.28 (0.04)	1.40 (0.05)	3.35 (0.09)	-0.16 (0.07)	0.86 (0.01)	39	0.99	2088
		50	-2.92	-0.24	1.26	3.01	-0.12	0.84	39	0.99	2118

			(0.04)	(0.04)	(0.05)	(0.09)	(0.07)	(0.01)			
		60	-2.96 (0.04)	-0.22 (0.04)	1.23 (0.05)	2.79 (0.08)	-0.10 (0.07)	0.81 (0.01)	39	0.99	2198
8	Lid : 3DecA	40	-2.80 (0.04)	-0.22 (0.04)	1.19 (0.05)	3.21 (0.08)	-0.09 (0.06)	0.86 (0.01)	38	0.99	2797
		50	-2.92 (0.04)	-0.23 (0.04)	1.20 (0.05)	3.04 (0.08)	-0.10 (0.06)	0.84 (0.01)	38	0.99	2702
		60	-2.93 (0.03)	-0.20 (0.03)	1.15 (0.04)	2.80 (0.07)	-0.09 (0.06)	0.80 (0.01)	38	0.99	3178
9	Lid : OctD	40	-3.01 (0.05)	-0.26 (0.05)	1.68 (0.07)	4.01 (0.11)	-0.13 (0.09)	0.84 (0.01)	40	0.99	2021
		50	-3.01 (0.05)	-0.22 (0.05)	1.65 (0.06)	3.70 (0.10)	-0.12 (0.08)	0.79 (0.01)	40	0.99	2215
		60	-3.09 (0.04)	-0.20 (0.04)	1.56 (0.06)	3.45 (0.09)	-0.10 (0.07)	0.75 (0.01)	40	0.99	2206
10	Lid : 2OctD	40	-3.06 (0.04)	-0.22 (0.04)	1.66 (0.05)	4.11 (0.08)	0.06 (0.06)	0.82 (0.01)	39	0.99	2774
		50	-3.04 (0.04)	-0.18 (0.04)	1.46 (0.05)	3.79 (0.08)	0.12 (0.07)	0.77 (0.01)	40	0.99	2322
		60	-3.02 (0.04)	-0.17 (0.04)	1.52 (0.05)	3.50 (0.08)	0.12 (0.06)	0.72 (0.01)	39	0.99	2456
11	Lid : 3OctD	40	-3.10 (0.05)	-0.19 (0.05)	1.59 (0.06)	4.22 (0.10)	0.24 (0.08)	0.82 (0.01)	40	0.99	1692
		50	-3.11 (0.05)	-0.16 (0.05)	1.53 (0.06)	3.89 (0.10)	0.24 (0.08)	0.77 (0.01)	40	0.99	1749
		60	-3.08 (0.04)	-0.14 (0.04)	1.47 (0.05)	3.59 (0.09)	0.24 (0.07)	0.72 (0.01)	40	0.99	1961

[a] *n*, number of probe analytes subjected to multiple linear regression; [b]R^2, correlation coefficient; [c]*F*, Fisher F-statistic. [d]At 40 °C, the stationary phase becomes a solid resulting in a significant decrease in retention of analytes due to a prevailing gas-solid chromatography mechanism. System constants are observed to deviate from the two other temperatures due to the different separation mechanism. The melting point of Lid:SteA DES is reported to be 43 °C [42]

Table 2. System constants for four API:API DESs comprised of the lidocaine API-HBA and four different API-HBDs obtained using the solvation parameter model.

No.	DES	Temp. (°C)	System constants								
			c	*e*	*s*	*a*	*b*	*l*	*n* [a]	R^2 [b]	*F* [c]
12	Lid : Ibuprofen	40	-2.91 (0.05)	-0.32 (0.05)	1.70 (0.06)	3.43 (0.10)	-0.39 (0.08)	0.84 (0.01)	40	0.99	1621
		50	-2.95 (0.04)	-0.31 (0.05)	1.64 (0.06)	3.20 (0.09)	-0.37 (0.07)	0.80 (0.01)	40	0.99	1879
		60	-2.95 (0.04)	-0.26 (0.04)	1.57 (0.05)	2.93 (0.08)	-0.31 (0.06)	0.75 (0.01)	39	0.99	2173
13	Lid : Tetracaine	40	-3.02 (0.05)	-0.34 (0.04)	1.77 (0.06)	3.44 (0.09)	-0.26 (0.07)	0.86 (0.01)	37	0.99	1595
		50	-2.96 (0.05)	-0.33 (0.05)	1.67 (0.06)	3.18 (0.09)	-0.31 (0.08)	0.82 (0.01)	37	0.99	1666
		60	-3.01 (0.05)	-0.28 (0.04)	1.61 (0.06)	2.91 (0.09)	-0.24 (0.07)	0.79 (0.01)	37	0.99	1788
14	Lid : Prilocaine	40	-2.96 (0.06)	-0.44 (0.06)	1.87 (0.07)	3.55 (0.11)	-0.41 (0.09)	0.87 (0.01)	37	0.99	1449
		50	-2.97 (0.05)	-0.40 (0.05)	1.80 (0.07)	3.27 (0.10)	-0.39 (0.08)	0.82 (0.01)	37	0.99	1539
		60	-2.98 (0.05)	-0.36 (0.05)	1.72 (0.06)	3.00 (0.10)	-0.37 (0.08)	0.78 (0.01)	37	0.99	1523
15	3Lid : 2Vanillin	40	-3.10 (0.05)	-0.29 (0.06)	1.84 (0.07)	3.59 (0.11)	-0.25 (0.09)	0.86 (0.01)	37	0.99	1595
		50	-3.05 (0.05)	-0.23 (0.06)	1.72 (0.07)	3.27 (0.11)	-0.19 (0.09)	0.80 (0.01)	37	0.99	1364
		60	-3.07 (0.05)	-0.23 (0.06)	1.67 (0.07)	3.06 (0.11)	-0.19 (0.09)	0.77 (0.01)	37	0.99	1283

[a] *n*, number of probe analytes subjected to multiple linear regression; [b] R^2, correlation coefficient; [c] *F*, Fisher F-statistic

Table 3. System constants for five API-DESs comprised of ionic excipients and API-HBDs obtained using the solvation parameter model.

No.	DES	Temp. (°C)	System constants c	e	s	a	b	l	n [a]	R^2 [b]	F [c]
16	$7[N_{8881}^{+}][Cl^{-}]$: 3Ibuprofen	40	-3.10 (0.06)	-0.25 (0.06)	1.94 (0.07)	6.89 (0.11)	-0.50 (0.09)	0.85 (0.01)	34	0.99	1643
		50	-3.10 (0.05)	-0.23 (0.05)	1.87 (0.07)	6.51 (0.10)	-0.48 (0.08)	0.80 (0.01)	34	0.99	1820
		60	-3.12 (0.05)	-0.22 (0.05)	1.82 (0.06)	6.19 (0.10)	-0.49 (0.08)	0.77 (0.01)	34	0.99	1812
17	$[Ch^{+}][Cl^{-}]$: 2Aspirin	40	-3.41 (0.05)	-0.13 (0.06)	2.36 (0.07)	4.20 (0.11)	0.45 (0.09)	0.65 (0.01)	39	0.99	1444
		50	-3.36 (0.04)	-0.09 (0.05)	2.27 (0.06)	3.87 (0.10)	0.41 (0.08)	0.60 (0.01)	39	0.99	1740
		60	-3.32 (0.04)	-0.06 (0.04)	2.17 (0.05)	3.63 (0.09)	0.35 (0.07)	0.55 (0.01)	39	0.99	1949
18	$[Ch^{+}][Cl^{-}]$: Resorcinol	40	-3.44 (0.07)	0.33 (0.08)	2.34 (0.09)	3.84 (0.15)	1.10 (0.12)	0.46 (0.02)	37	0.99	822
		50	-3.47 (0.07)	0.32 (0.08)	2.27 (0.09)	3.65 (0.15)	1.02 (0.12)	0.43 (0.02)	36	0.99	774
		60	-3.39 (0.06)	0.33 (0.07)	2.09 (0.09)	3.23 (0.14)	1.08 (0.11)	0.39 (0.02)	35	0.99	844
19	$[Ch^{+}][Cl^{-}]$: Phenyl AA	40	-3.51 (0.06)	0.19 (0.06)	2.39 (0.08)	4.58 (0.12)	0.49 (0.10)	0.56 (0.01)	37	0.99	1338
		50	-3.47 (0.06)	0.22 (0.06)	2.24 (0.08)	4.23 (0.12)	0.51 (0.10)	0.52 (0.01)	37	0.99	1455
		60	-3.51 (0.06)	0.21 (0.06)	2.16 (0.08)	4.06 (0.12)	0.48 (0.10)	0.50 (0.01)	37	0.99	1040
20	$[Ch^{+}][Cl^{-}]$: Acetaminophen	40	-3.49 (0.07)	0.11 (0.08)	2.37 (0.10)	4.56 (0.15)	0.60 (0.12)	0.53 (0.02)	35	0.99	706
		50	-3.40 (0.07)	0.21 (0.08)	2.21 (0.09)	4.14 (0.14)	0.68 (0.12)	0.47 (0.02)	33	0.99	724
		60	-3.28 (0.07)	0.21 (0.08)	2.06 (0.09)	3.80 (0.15)	0.61 (0.13)	0.43 (0.02)	33	0.99	550

[a] n, number of probe analytes subjected to multiple linear regression; [b] R^2, correlation coefficient; [c] F, Fisher F-statistic

Table 4. Retention factors of eighteen probe molecules on ten API-based DESs at 60 °C. The three sub-classes of API-DESs are separated by the bold lines. Note: values of retention factor (k) are determined by: k = ($t_R - t_0 / t_0$) where t_R is the retention time of the probe and t_0 is the dead time of propane, an unretained molecule.

Probe	API-HBA DESs					API:API DES		API-HBD DESs		
	Atr: 2DecA	Lid: 2DecA	Lid: SteA	Lid: 2OctD	Lid: Oct.D	Lid: Ibuprofen	Lid: Prilocaine	7[N_{8881}^+][Cl^-]: 3Ibuprofen	[Ch^+][Cl^-]: 2Aspirin	[Ch^+][Cl^-]: Resorcinol
Methanol	0.40	0.29	0.21	0.68	0.57	0.32	0.34	5.07	0.82	0.76
Ethanol	0.65	0.56	0.37	1.08	0.91	0.51	0.56	5.97	0.93	0.80
1-Propanol	1.82	1.26	1.13	2.50	2.21	1.28	1.60	17.07	1.60	1.53
1-Butanol	4.20	3.67	3.10	6.17	5.67	3.38	4.20	44.01	3.05	1.84
2-Butanol	1.93	1.52	1.23	2.69	2.41	1.35	1.74	14.22	1.24	0.86
1-Pentanol	10.12	10.17	8.45	15.15	14.59	8.84	10.52	102.98	6.28	3.08
Cyclopentanol	12.11	11.00	8.99	18.24	17.05	9.59	11.79	98.85	9.69	6.93
1-Hexanol	23.81	26.76	21.98	34.91	35.82	21.20	26.79	228.86	12.65	5.07
Cyclohexanol	26.62	26.42	21.37	40.86	39.01	22.27	26.99	222.30	18.39	10.71
Cycloheptanol	76.52	81.56	68.90	111.65	110.91	65.80	78.02	- [a]	41.44	21.77
1-Chlorohexane	2.31	3.19	3.21	1.98	2.40	2.63	3.49	2.61	0.44	0.13
1-Chlorooctane	11.28	20.10	20.07	10.24	13.21	15.16	19.59	13.38	2.01	0.92
1-Bromohexane	4.63	6.87	7.05	4.12	5.16	5.63	7.46	2.71	0.88	0.17
1-Bromooctane	24.19	41.57	42.09	20.98	27.96	31.80	41.88	13.47	3.89	1.63
Naphthalene	73.97	97.55	95.60	69.00	90.21	88.47	116.14	111.22	30.40	15.64
Nitrobenzene	53.43	62.63	66.40	65.84	83.71	83.32	110.52	108.15	45.74	18.56
N,N-Dimethylformamide	9.16	13.80	9.39	20.54	18.02	14.31	11.01	9.23	35.51	37.97
N,N-Dimethylacetamide	21.58	38.05	22.70	54.64	45.53	33.44	24.79	15.97	88.81	89.98

[a] The retention factor was not determined due to very high retention of cycloheptanol in the 7[N_{8881}^+][Cl^-]:3Ibuprofen DES column

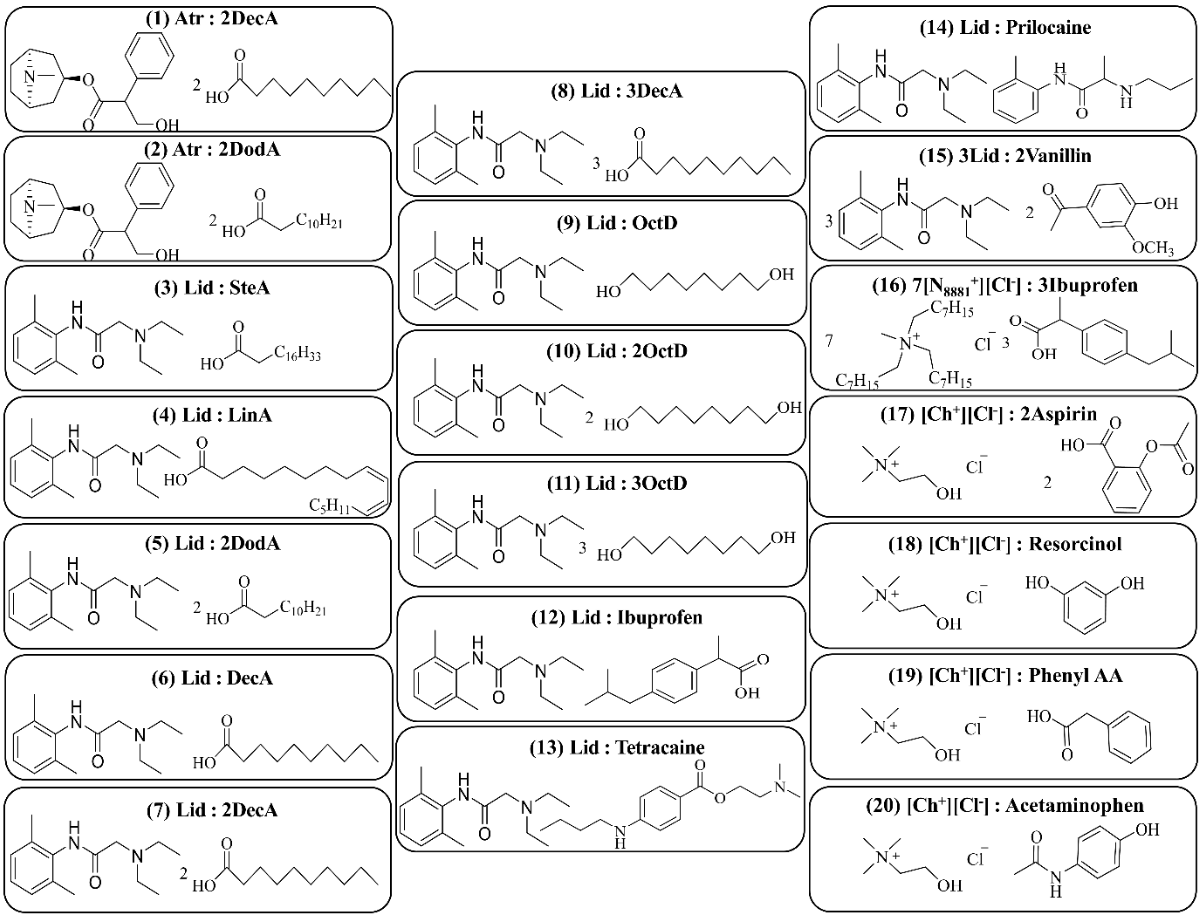

Figure 1. Chemical structures, relative molar ratios of HBA:HBD, abbreviations, and numbering scheme used for the twenty API-based DESs evaluated in this study. Abbreviations: atropine (Atr); lidocaine (Lid); decanoic acid (DecA); dodecanoic acid (DodA); stearic acid (SteA); linoleic acid (LinA); 1,8-octanediol (OctD); choline chloride ($[Ch^+][Cl^-]$); methyltrioctylammonium chloride ($[N_{8881}^+][Cl^-]$); and phenyl acetic acid (Phenyl AA). DESs abbreviations: 1, Atr:2DecA; 2, Atr:2DodA; 3, Lid:SteA; 4, Lid:LinA; 5, Lid:2DodA; 6, Lid:DecA; 7, Lid:2DecA; 8, Lid:3DecA; 9, Lid:OctD; 10, Lid:2OctD; 11, Lid:3OctD; 12, Lid:Ibuprofen; 13, Lid:Tetracaine; 14, Lid:Prilocaine; 15, 3Lid:2Vanillin; 16, 7$[N_{8881}^+][Cl^-]$:3Ibuprofen; 17, $[Ch^+][Cl^-]$:2Aspirin; 18, $[Ch^+][Cl^-]$:Resorcinol; 19, $[Ch^+][Cl^-]$:Phenyl AA; 20, $[Ch^+][Cl^-]$:Acetaminophen.

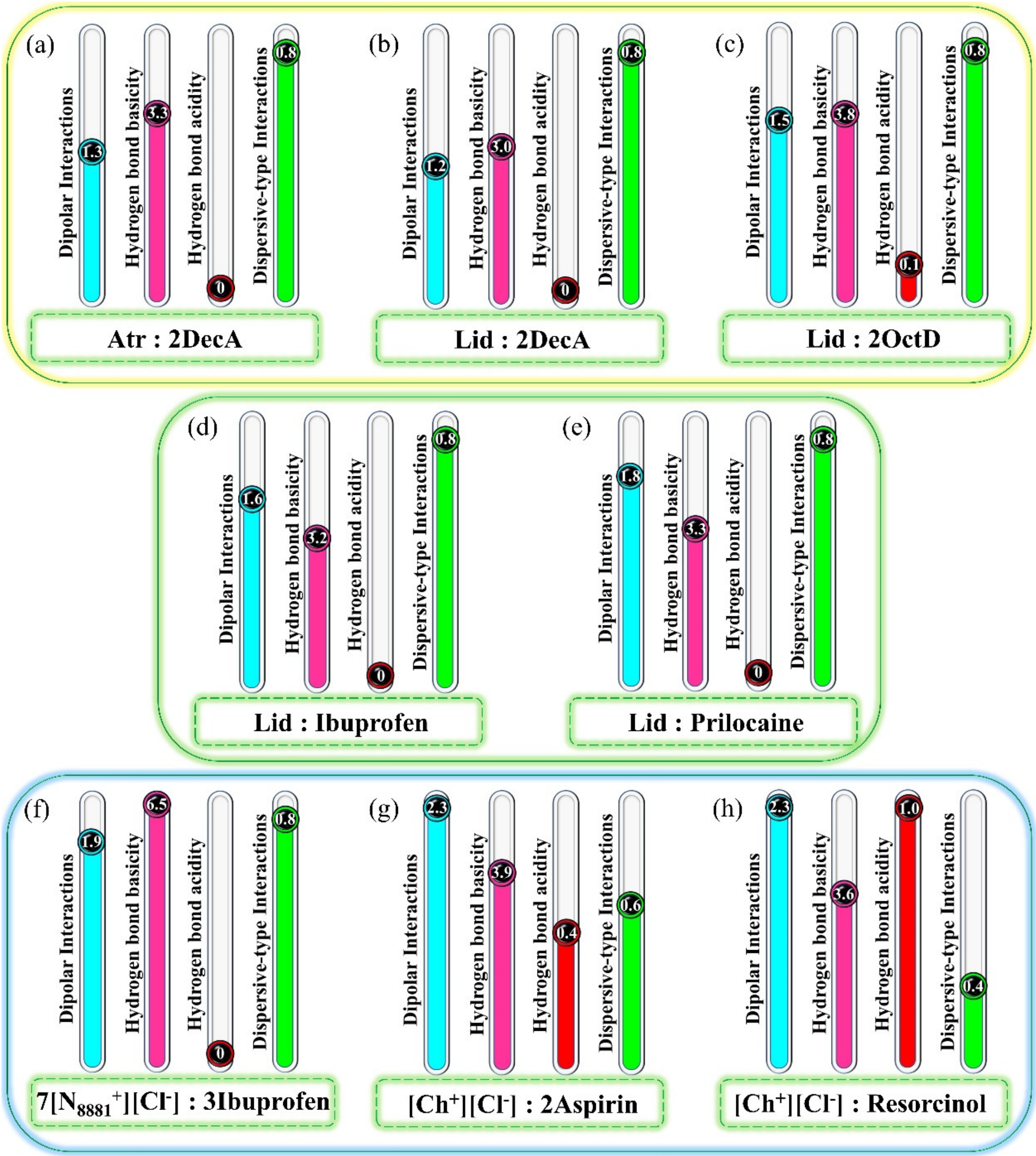

Figure 2. Solvation interactions of API-DESs including dipolar interactions (*s*-term, blue color), hydrogen bond basicity (*a*-term, pink color), hydrogen bond acidity (*b*-term, red color), and dispersive-type interactions (*l*-term, green color) of eight different DES. Where (a) Atr:2DecA; (b) Lid:2DecA; (c) Lid:2OctD; (d) Lid:Ibuprofen; (e) Lid:Prilocaine; (f) 7[N_{8881}^{+}][Cl^{-}]:3Ibuprofen; (g) [Ch^{+}][Cl^{-}]:2Aspirin; (h) [Ch^{+}][Cl^{-}]:Resorcinol.

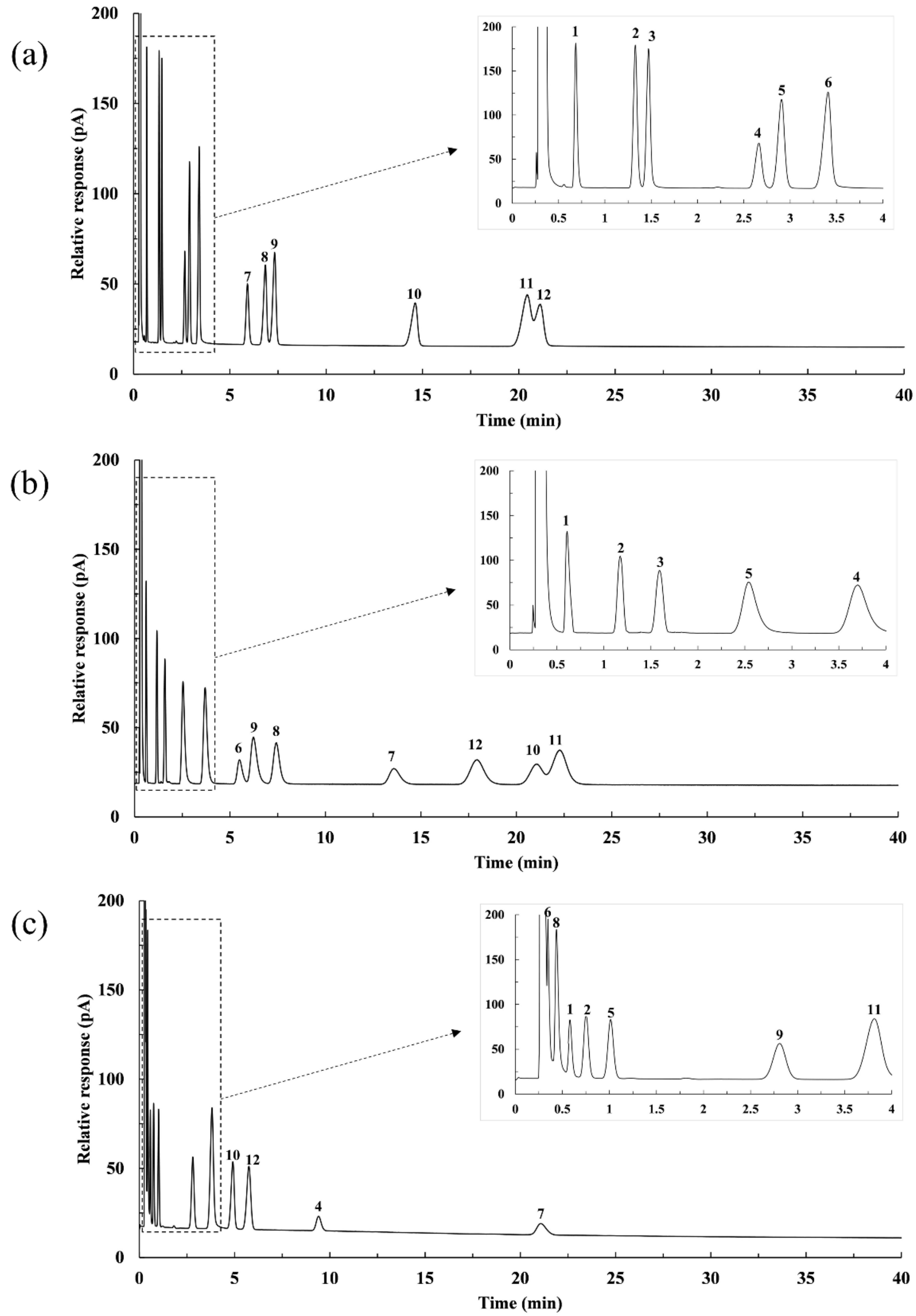

Figure 3. Chromatographic separation of twelve probe molecules on the (a) Atr:2DecA, (b) Lid:Ibuprofen, (c) $[Ch^{+}][Cl^{-}]$:Resorcinol DES stationary phases at 60 °C. The inset within each chromatogram shows the first 4 minutes of the separation so that all chromatographic peaks can be observed. Analytes: 1, 1-propanol; 2, 1-butanol; 3, 1-bromohexane; 4, *N*,*N*-dimethylformamide; 5, 1-pentanol; 6, 1-chlorooctane; 7, *N*,*N*-dimethylacetamide; 8, 1-bromooctane; 9, cyclohexanol; 10, nitrobenzene; 11, naphthalene; 12, cycloheptanol. In the panel (c) of the figure, 1-bromohexane (analyte 3) coelutes with the dichloromethane solvent peak.

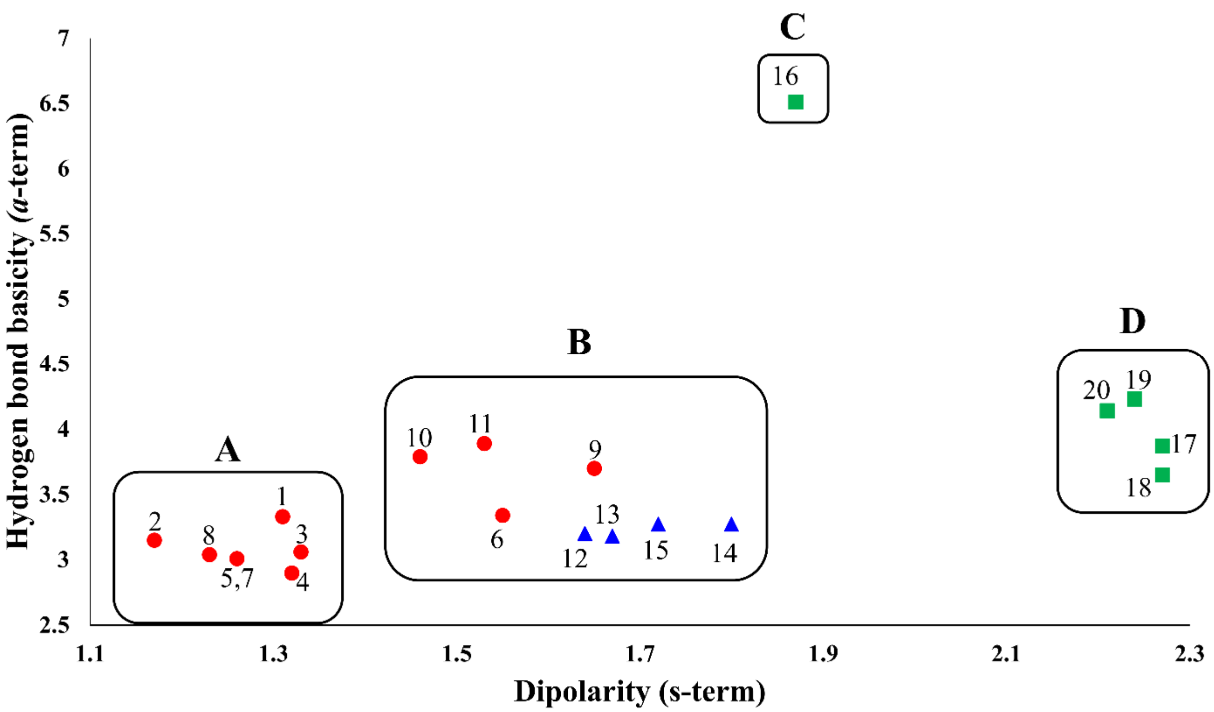

Figure 4. Grouping of 20 DESs into four clusters (A, B, C, and D) based on hydrogen bond basicity and dipolar interactions using k-means clustering. Red circles (●) represent DESs comprised of API-based HBAs, blue triangles (▲) represent DESs comprised of both API-based HBA and HBD, and green squares (■) represent DESs comprised of API-based HBD and ionic HBAs. 1, Atr:2DecA; 2, Atr:2DodA; 3, Lid:SteA; 4, Lid:LinA; 5, Lid:2DodA; 6, Lid:DecA; 7, Lid:2DecA; 8, Lid:3DecA; 9, Lid:OctD; 10, Lid:2OctD; 11, Lid:3OctD; 12, Lid:Ibuprofen; 13, Lid:Tetracaine; 14, Lid:Prilocaine; 15, 3Lid:2Vanillin; 16, 7[N_{8881}^{+}][Cl^{-}]:3Ibuprofen; 17, [Ch^{+}][Cl^{-}]:2Aspirin; 18, [Ch^{+}][Cl^{-}]:Resorcinol; 19, [Ch^{+}][Cl^{-}]:Phenyl AA; 20, [Ch^{+}][Cl^{-}]:Acetaminophen

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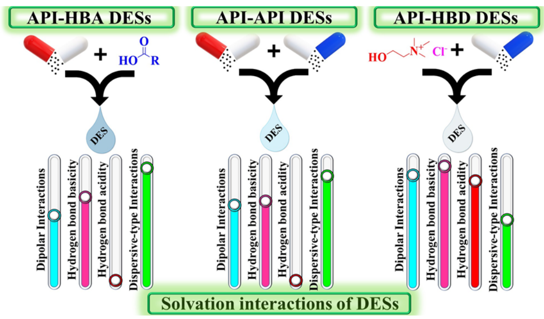

Solvation characteristics of active pharmaceutical ingredient-based deep eutectic solvents are systematically evaluated to interpret their behavior in pharmaceutical chemistry and separation science.