Application, structure, salts and complexes of lidocaine: a review. Part II. Lidocaine in the composition of deep-eutectic solvents, microemulsions and coordination compounds

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Abstract.
The review focuses on lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide), one of the most popular and widely used painkillers. In the first part, the use of lidocaine in various branches of medicine was considered, and the structure of lidocaine, as well as of its salts such as hydrochloride monohydrate, hydrohexafluoroarsenate, bis-p-nitrophenylphosphate, barbiturate and indomethacin-lidocaine complex was discussed. The present paper reports on the use of lidocaine in the composition of deep-eutectic solvents (DESs) with acrylic acids, with such hydrogen bond donors as ibuprofen, 1,8-octanediol, tetracaine, prilocaine and vanillin, with such nonsteroidal anti-inflammatory drugs as ketoprofen, flurbiprofen, acetylsalicylic acid, and meloxicam. The use of lidocaine in DES-microemulsions (MEs) is also considered: lidocaine-prilocaine and lidocaine-ibuprofen prepared and served as the oil phase in ME, and lidocaine-lauric acid as an amphiphilic DES utilized as surfactant in ME. Consideration of lidocaine in the composition of coordination compounds has begun: the results of studying the structure of complexes of lidocaine with chlorides of zinc, copper, cobalt, platinum and iron, as well as with copper bromide, have been discussed.

Keywords:
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Lidocaine in the composition of deep-eutectic solvents and microemulsions

As noted in the first part, the short duration of action (<2 hours) of marketed dosage forms of lidocaine limits their ability to meet clinical needs, and work is underway to develop new forms with prolonged action.

Scientists from Polymer & Biopolymer Research Group, Centro de Investigación y de Estudios Avanzados, Querétaro, Mexico, and Department of Chemistry, Louisiana State University, Baton Rouge, USA, demonstrated that lidocaine hydrochloride – as the ammonium salt – is able to form deep-eutectic solvents (DESs) with acrylic acid and methacrylic acid [1].

Figure 1
DES of lidocaine hydrochloride with acrylic (R=H) and methacrylic (R=CH₃) acid

DESs are systems formed from a eutectic mixture of Lewis or Brønsted acids and bases described by the general formula Cat⁺X⁻zY, where Cat⁺ is in principle any ammonium, phosphonium, or sulfonium cation, and X is a Lewis base, generally a halide anion; the complex anionic species are formed between X⁻ and either a Lewis or Brønsted acid Y, z refers to the number of Y molecules that interact with the anion [2]; LidH⁺Cl⁻n[OHC(O)C(CH₂)R] in the case considered in work [1].

According to Sánchez-Leija and co-authors, the properties of DESs allow frontal polymerization in the bulk with full conversion achieved in a one-pot synthesis, yielding monoliths of polymers loaded with a high concentration of drug. It was shown that in in vitro experiments, the sustained release of the drug occurs in a controlled manner triggered by the pH, ionic strength and solubility of the drug [1].

Later, scientists from the University of Burgos, Spain,
and Texas A&M University, USA and Qatar, conducted a theoretical study on the solubility of lidocaine in DESs [3]. The structure, composition and properties of the lidocaine solvation shells were analyzed together with the possible lidocaine clustering, as well as the changes in the solvent structures upon lidocaine solution were studied. Published results show that the efficient solvation of lidocaine in deep eutectics is due to strong intermolecular interactions between solute and solvent, accompanied by a slight increase in volume and insignificant structural changes in the solvent.

Scientists from the Iowa State University, USA, who examined the solvation characteristics of DESs, consisting of active pharmaceutical ingredients (APIs) as a hydrogen bond donor (HBD) and/or acceptor (HBA), showed that lidocaine can be used as the HBA for the construction of therapeutic DESs (THEDES) [4]. It was found that lidocaine form THEDES characterized by improved solubility of API with such HBDs as ibuprofen (in weight ratio 1:1), 1,8-octanediol (1:1, 1:2, 1:4), tetracaine (1:2), prilocaine (1:3) and vanillin (3:2) shown in Figure 2.

Figure 2
HBDs forming THEDES with lidocaine [4]

It was found that among the API DESs composed 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.
Scientists from the University of Tanta, Egypt, considered lidocaine as eutectic forming agent for enhanced transdermal delivery of such nonsteroidal anti-inflammatory drugs (NSAIDs) as ketoprofen, flurbiprofen, aceclofenac, tenoxicam and meloxicam [5], see Figure 3.

Each NSAID was co-ground with lidocaine at increasing molar ratios, the products were characterized by thermal analysis and FTIR spectra suggested eutectic system formation. Saturated aqueous solutions containing excess of optimum NSAID/lidocaine were evaluated for transdermal delivery with reference to the corresponding saturated aqueous solution of each drug. It was found that drugs with lower melting points formed eutectic with smaller proportion of lidocaine; ketoprofen, flurbiprofen and aceclofenac separated as oily liquid from the saturated aqueous solution of their mixtures with lidocaine, while eutectic mixtures of lidocaine with tenoxicam and meloxicam melted above 50 °C and separated from saturated aqueous solution as solid system.

Lidocaine is used as a component of microemulsions (MEs),

![Figure 3](image-url)
usually consisting of an aqueous phase, an oil phase, a surfactant, and a co-surfactant. It is believed, that ME is an excellent transdermal drug delivery system (TDDS) due to its unique properties, which include low surface tension, small droplet size, and high skin affinity [6]. In 2016, scientists from the Panjab University, Chandigarh, India, developed a phospholipid microemulsion-based hydrogel for enhanced topical delivery of lidocaine and prilocaine [7], shown in Figure 4.

A year later, Chinese scientists from Chandong prepared and studied lidocaine- and prilocaine-loaded solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) [8]. It was found that SLN systems have better ex vivo skin permeation ability than NLCs, but NLC systems revealed a stronger in vivo anesthesia analgesic effect than SLN systems, and it was concluded that both carriers are promising dual drug delivery systems for topical anesthetic analgesic therapy.

Scientists from the Innovation Academy for Green Manufacture, Chinese Academy of Sciences, and from the Sino-Danish College, University of Chinese Academy of Sciences, used microemulsion based on imidazolium ionic liquid and lidocaine-ibuprofen DES for enhancement of transdermal delivery of artemisinin [9], a drug used in the treatment of malaria due to Plasmodium falciparum. The optimal microemulsion carrier was composed of 45 wt. % of water phase, 45 wt. % surfactant phase (Tween-80, Span-20, and ethanol (co-surfactant) with the weight ratio of 1:1:1), and 10 wt. % lidocaine-ibuprofen DES as the oil phase with artemisinin loading of 1.0 wt. %; in-vitro transdermal assay showed a remarkable enhancement of artemisinin transport through the
skin, with the permeation flux being 3-fold of the value for isopropyl myristate system in 6 h.

According to scientists from the East China University of Science and Technology, Shanghai, a new type of therapeutic DES based on lidocaine and lauric acid was obtained [10]. It was shown that the DES displayed good surface activity in constructing a nonaqueous microemulsion with 1,2-propanediol (propylene glycol, PG) and isopropyl myristate being the polar phase and nonpolar phase, respectively (see Figure 5).

![Figure 5](image)

**Figure 5**

Components of microemulsion obtained in [10]

The obtained nonaqueous microemulsion displayed a structural transition from W/O type to O/W type via a bicontinuous structure with an increase of the PG content. The authors of the work [10] also note that the DES developed by them can act as a “gelator” to form a gel in a certain water content range; the rheological measurements suggested the presence of a strong colloidal force.

The review [6] noted the different use of lidocaine in DES-ME: lidocaine-prilocaine (1:1) [7] and lidocaine-ibuprofen (1:1) [9] were prepared and served as the oil phase in ME, respectively; in contrast, lidocaine-lauric acid (1:1, 4:6) was an amphiphilic DES that can be utilized as surfactants/co-surfactants in ME [10].
In 2020, scientists from the Maliba Pharmacy College, Uka Tarsadia University, Surat, India, in order to prolong the local anesthesia, prepared and studied a lidocaine-tripotassium phosphate (tPP, K₃PO₄)-complex loaded ME [11]. The ex vivo diffusion study showed sustained release up to 12 h with ME batches, in comparison to lidocaine hydrochloride (4 h) and ointment base (7 h).

**Lidocaine in the composition of coordination compounds**

The use of complexes of lidocaine with metals such as zinc, copper and cobalt was first reported in 1978-79 by scientists from the Department of Biogenic Amines, Polish Academy of Sciences, Łódź, Poland [12, 13], but their publications did not contain information on the chemical composition and structure of these complexes.

Establishment of the structure of complexes involving lidocaine was started by Polish scientist Główka and Gałdecki, who studied the complex formed by the interaction of zinc chloride (ZnCl₂) with lidocaine hydrochloride (LidHCl) [14]. It was found that in this case, bislidocaine tetrachlorozincate, (LidH)₂[ZnCl₄], is formed in a water-alcohol solution; (LidH)₂[ZnCl₄] crystallizes in monoclinic space group P2₁/c with \( a = 9.137 \) Å, \( b = 19.213 \) Å, \( c = 19.707 \) Å, \( \beta = 95.82° \), \( Z=4 \) (see Figure 6).

![Figure 6](Image)

*Figure 6*

Unit cell of bislidocaine tetrachlorozincate (LidH)₂[ZnCl₄] (edited from [14])
It was noted that the lidocaine molecules are protonated at the diethylamino group (the angle $C_{13}-N_{14}-C_{15(17)}$ is $111^\circ$), the structures of both lidocaine molecules are similar except the conformation “about the N - N bond”: the torsion angles $\theta(O_{12}, C_{12}, C_{13}, N_{14})$ are 12.4 and 38.8$^\circ$, respectively. The specified torsion angle determines the relative position of the oxygen $O_{12}$ and nitrogen $N_{14}$ atoms and the probability of the formation of a hydrogen bond between them (see Figure 7).

![Newman projection of lidocaine with proximal $C_{12}$ and distal $C_{13}$](image)

In the first case, oxygen and nitrogen atoms are in synperiplanar (C) conformation and enter into an intramolecular hydrogen bond N-H-O; in the second case, the torsion angle exceeds the limit set for the C ($\pm30^\circ$) conformation, and the probability of hydrogen bond formation decreases. As for the anion, the [ZnCl$_4$]$^{2-}$ is slightly distorted, the Zn-Cl interatomic distances vary within 2.24–2.29 Å, the Cl-Zn-Cl angles are within 106–113$^\circ$.

Główka and Gałdecki published their work in 1981 and noted that the structure was refined to an R value of 0.114, and the interatomic distances and angles are “not highly accurate”. Twelve years later, the crystal structure of “lignocaine hydrochloride - zinc chloride complex” with strange brutto-formula ZnCl$_4$C$_{28}$N$_4$O$_2$H$_{44}$ was reported by a group of scientists from the University of Mysore, India [15], but the protonation of the amino nitrogen atom was not taken into account and led to conflicting conclusions, so that the study of the structure of bis(lidocaine) tetrachloridozincate(II)
became one of our studies [16] and sections of this review.

In the early 1990s, a group of scientists from the University of Mysore, India, including S.B.Bellad, A.Indira, M.A.Sridhar J.Shashindara Prasad and others, published a number of studies on the structure of complex compounds that included lidocaine, in particular lidocaine tetrachlorocuprate and tetrachlorocobaltate.

It was found that the coordination compound of lidocaine and copper “synthesized with commercially available ligand” with the formula \((\text{C}_{14}\text{H}_{22}\text{ON}_{2})_2(\text{CuCl}_4)\) crystallizes in the monoclinic space group \(P2_1/c\) with \(a = 10.3919(2) \text{ Å}, b = 24.4547(3) \text{ Å}, c = 13.6649(2) \text{ Å}, \beta = 98.075(2)^\circ, Z=4\) [17]; along with the parameters used for the X-ray data collection and the table of final atomic coordinates, the publication contains a projection of the molecule on the best plane edited here (see Figure 8), and in conclusion it is said that “the structure resembles to the structure of the chlorocobaltate, but does not show layering as found in the platinum complex”.

Figure 8

*Projection of lidocaine tetrachlorocuprate molecule on the best plane according to Sridhar et al., 1992 [17]*

Crystal structure of the complex of lidocaine with cobalt chloride was first studied at room temperature [18]. It has been shown that the compound with the formula
(C_{14}H_{22}ON_{2})_{2}(CoCl_{4}) crystallizes in the monoclinic space group P2_{1}/c with a = 9.1059(2) Å, b = 19.2269(3) Å, c = 19.6994(2) Å, β = 96.754(2), Z=4. Projection of the molecule on the best plane was shown (see Figure 9), and again it was pointed out that “the structure resembles to the structure of the chlorocuprate [17], but does not show layering as found in the platinum complex” studied by the same group of Indian scientists [19].

![Figure 9](attachment:projection_of_lidocaine_tetrachlorocobaltate_molecule_on_the_best_plane_according_to_Indira_et_al._1992.png)

Later additional research on the lidocaine tetrachlorocobaltate was carried out [20] (Sridhar et al., 1997a) “at low temperatures” (although the authors indicate 297 K), and it turned out that “the same compound shows the formation of a super-lattice. This can be seen by the fact that the cell volume has doubled due to the twofold increase of one of the cell axes”. According to new data, the compound with the formula (C_{14}H_{22}ON_{2})_{4}(CoCl_{4})_{2} crystallizes in the same monoclinic space group P2_{1}/c with a = 18.053(4) Å, b = 19.093(4) Å, c = 19.695(4) Å, β = 96.24(3)°, Z=4; the authors conclude that “the asymmetric unit has four ligand molecules and two metal groups”, and “the molecules are stacked and the metal and ligands do not form independent layers”; projection of molecule on the best plane (see Figure 10, in the original, the numbering of atoms does not
correspond to the generally accepted) and packing of molecules down crystallographic axis $a$ (see Figure 11) are shown.

**Figure 10**
Projection of lidocaine tetrachlorocobaltate molecules on the best plane according to Sridhar et al., 1997 [20]

**Figure 11**
Packing of lidocaine tetrachlorocobaltate molecules down $a$ according to Sridhar et al., 1997 [20]
No information about hydrogen bonds is given either for lidocaine tetrachlorocobaltate or for lidocaine tetrachlorocuprate. However, according to the coordinates given in [17, 18, 20], the distance between the nitrogen atom N\(_{11}\) and one of the chlorine atoms is ~3.5 Å, which is acceptable, as will be shown below, for the formation of a N–H–Cl hydrogen bond.

When studying lidocaine hydrochloride – platinum complex [19], it was found that the compound with the formula PtC\(_{28}\)N\(_4\)O\(_2\)H\(_4\)Cl\(_6\) crystallizes in the monoclinic space group C\(_{2v}\)/c with \(a = 25.484(2)\) Å, \(b = 11.137(3)\) Å, \(c = 26.701(2)\) Å, \(\beta = 106.66(2)°\), having eight molecules per unit cell, “projection of the molecule on the best plane” shows two lidocaine molecules and two [PtCl\(_6\)]\(^{2–}\) anions (see Figure 12).

![Projection of lidocaine hexachlorocobaltate molecule on the best plane according to Bellad et al., 1992 [19]](image)

The authors indicated that “the bond lengths and bond angles are in good agreement with standard values, the atoms Pt(1), Pt(2), Cl(3) and Cl(4) are occupying special positions, the six chlorine atoms are octahedrally bonded with the
platinum atom, and each octahedral set binds two ligands”, but the conformation of lidocaine and hydrogen bonds were not considered. According to the authors, “the ligands and the octahedral groups form alternating stacks as in the majority of the complexes. The complex is similar to $K_2PtCl_6$ where $K$ has been replaced by two ligands”. However, the analogue of $(K')_2(PtCl_6)^{2-}$ will be bis(lidocaine) hexachloridoplatinate (II), $(LidH)_2[PtCl_6]$, but this does not correspond to the above formula of the compound, in which lidocaine is shown in non-protonated form.

Finally, the authors conclude that “the ligands of the complex are neither covalently bonded with other atoms nor form a part of the molecule”, but the meaning of the latter conclusion is not entirely clear. The article contains a figure showing a unit cell along the crystallographic axis $b$ (see Figure 13 or [010]).

As can be seen from this figure, the lidocaine cations form endless chains lying in the $ac$ plane along the long...
diagonal of the unit cell, the anions are located between these chains, and there is every reason to believe that, along with the Coulomb attraction forces, other interactions take place between cations and anions, hydrogen bonds and CH/π interactions help to stabilize the crystal structure, but these questions have not been addressed by researchers. 

Two pages of the publication of the results of the study of the structure of bis(lidocaine) tetrabromo cuprate(II) [21] are mainly occupied by table of coordinates, it is only indicated that the studied compound was “synthesized with commercially available ligand”, has the formula \((C_{14}H_{22}ON_2)_2CuBr_4\) and crystallizes in the monoclinic space group \(P2_1/c\) with \(a = 14.030(2)\ \text{Å}\), \(b = 25.261(2)\ \text{Å}\), \(c = 10.350(2)\ \text{Å}\), \(β = 98.60(1)°\), \(Z=4\); the only conclusions indicated is that “the copper to bromine distances are comparable to that found in similar complexes of lignocaine”, and “the compound exhibits positional disorder in few atoms of the ligand”, and this can be seen in the figure given in the article – the carbon atom C4 “bifurcates” in both aromatic rings (see Figure 14).

Figure 14
Projection of bis(lidocaine) tetrabromo cuprate(II) molecule on the best plane according to Qayyas et al., 1994 [21]

Brown crystals of lidocaine tetrachloroferrate(III)
complex “were obtained from ethanol with a meager amount of water by slow evaporation” [22], they belong to triclinic space group $P1$ with unit cell parameters $a = 8.7151(2)$ Å, $b = 10.147(2)$ Å, $c = 12.215(3)$ Å, $\alpha = 107.19(2)$°, $\beta = 106.29(2)$°, $\gamma = 92.69(2)$°, $Z=2$.

According to the authors, the bond length and bond angles are in good agreement with the standard values, the complex has the chemical composition $\text{FeCl}_4\text{H}_2\text{N}_2\text{OC}_{14}$, and “the stoichiometry of this complex is 1:1 which is different from the other complexes reported earlier” [17, 18] (see Figure 15), but this is not surprising, since the cited works dealt with complexes with doubly charged anions $[\text{CuCl}_4]^{-2}$ and $[\text{CoCl}_4]^{-2}$, while in this work, the complex of a singly charged $sp^3$-hybridised tetrahedral $[\text{FeCl}_4]$ $^-$ anion was investigated.

![Figure 15](Projection of lidocaine tetrachloroferrate(III) molecule on the best plane according to Babu et al., 1993 [22])

The authors point out that “the packing of the molecules shows a layered arrangement in the three directions in contrast to the packing of the complex of copper” [17], and that “the metal atoms (Fe) are all lying in the (101) plane” (see Figure 16).
In the following articles, other lidocaine complexes with biologically active metals, including those studied by the authors of this review, will be considered.

References:


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dimethylphenyl)acetamide%5D%20tetrahlorozinc%20(lidocaine%20hydrochloride%20zinc%20chloride).&f=false.


