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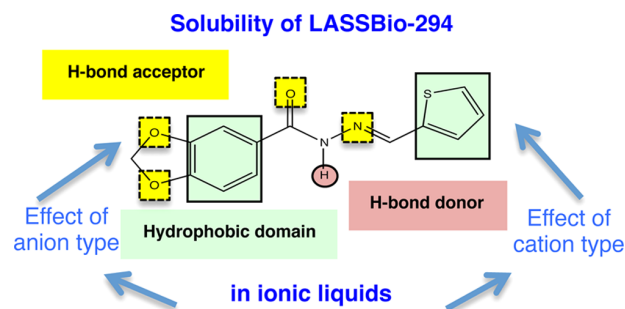
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Solubility of a New Cardioactive Prototype Drug in Ionic Liquids

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ABSTRACT: Solubility in different solvents is an intrinsic material characteristic for a defined molecule. The solubility of a new cardioactive prototype drug, 3,4-methylenedioxybenzoyl-2-thienylhydrazone (LASSBio-294), was determined in seven different imidazolium based ionic liquids (ILs). The ionic liquids selected were 1-ethyl-3-methylimidazolium methyl phosphonate; 1-ethyl-3-methylimidazolium ethyl phosphonate; 1-ethyl-3-methylimidazolium acetate; 1,3-dimethylimidazolium methyl phosphonate; 1-butyl-3-methylimidazolium acetate; 1-butyl-3-methylimidazolium tetrafluoroborate; and 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide. In addition, solubility data of LASSBio-294 in water and in mixtures of water and ILs were also measured. For all solvents, the concentration of drug in saturated solutions was determined by high performance liquid chromatography (HPLC). Solid–liquid equilibrium measurements were performed in a range of temperatures from 288.15 K to 308.15 K, at atmospheric pressure. From the solubility data it can be concluded that the drug showed sufficient solubility in five of the tested ILs so that these compounds can be suitable for further crystallization studies. The aim of this work is also to discuss and understand the solubility of LASSBio-294 in these alternative solvents. The results indicate that the solubility of the drug is dependent on IL structural variations (cation–anion combinations).



INTRODUCTION

3,4-Methylenedioxybenzoyl-2-thienylhydrazone, LASSBio-294, a new bioactive of *N*-acylhydrazone class, was synthesized in an attempt to develop new therapies which simplify the treatment of cardiovascular diseases.^{1,2} Biological studies have characterized the LASSBio-294 as a molecule able to increase the contraction of the muscles of the heart and promote vasodilation through a mechanism different from that displayed by cardiac glycosides and β -adrenergic agonist.^{3–5} These promising therapeutic effects strongly indicate that LASSBio-294 is a novel drug candidate, effective and safer for the treatment of cardiac failure³ and for prevention of myocardial infarction induced by cardiac dysfunction.^{6,7} However, as a poorly water-soluble drug, it exhibits a low solubility and dissolution rate in the gastrointestinal tract, which limits its effective absorption and bioavailability after oral administration.

Drug properties such as crystal morphology, crystallinity, particle size distribution, and dissolution kinetics can be modified in different ways including recrystallization. Among the recrystallization techniques, antisolvent crystallization has been successfully used to improve dissolution kinetics, as shown by a number of reports in the literature.^{8–11} Antisolvent crystallization represents a class of process, which is characterized by the mixing between a solution and an antisolvent to produce solid particles. This mixing generates high supersaturation that subsequently induces nucleation, simultaneous growth, and possibly agglomeration of crystals.

Recrystallization works only when the proper solvent is used. The purpose of this work is to identify alternative solvents for the

antisolvent crystallization of LASSBio-294 in the presence of water as antisolvent. The alternative solvents investigated here are the ionic liquids (ILs).

Unlike conventional solvents, ILs are entirely composed of ions. ILs are organic salts, usually liquid at room temperature, which are composed of a relatively large asymmetric organic cation (e.g., alkylpyridinium, dialkyl imidazolium ions) and an inorganic or organic anion (e.g., halide, hexafluorophosphate, tetrafluoroborate, and ions based on fluorinated amides). These materials are commercially available, and the number of reported ionic liquids continues to increase. They are emerging as novel replacements for volatile organic compounds traditionally used as industrial solvents, owing to their negligible vapor pressures that reduce the risk of air pollution.¹² Furthermore, ILs present the prospective of “designer solvents” since their physicochemical properties can be finely tuned by an appropriate choice of the cation and/or the anion, and there is an enormous range of potential combinations of cation and anion that could be synthesized to produce an IL.¹³ As a result, these solvents can be designed for a particular application or to present a particular set of intrinsic properties such as acidity, basicity, hydrophilicity/hydrophobicity and water miscibility,¹⁴ as well as toxicity.¹⁵ The combination of these excellent properties thus allows for designing green processes based on ILs.^{16,17}

The possibility of engineering the properties of ILs by manipulating the anion–cation combination, in association with their solvent properties and in some cases water-miscibility, makes them promising as potential pharmaceutical solvents in different situations. For instance, these combinations can be used in liquid–liquid extraction,¹⁸ and to influence crystallization habits such as demonstrated in the case of pyrazine-2-carboxamide,^{12,19} isoniazid^{19,20} and paracetamol,¹³ as well as to dissolve poorly water-soluble drugs. Researches in this latter field have been focused on the ability of ILs to solubilize class II BCS compounds such as ibuprofen,¹³ albendazole, and danazol.²¹ Furthermore, our group has reported promising results for the antisolvent crystallization of rifampicin using an imidazolium ionic liquid as solvent and phosphate buffer as antisolvent.¹¹ The ultrafine particles obtained were amorphous with enhanced solubility and faster dissolution rate.

To understand and control such antisolvent crystallization processes, solubility data of the solute in the IL–water mixtures are essential. In the present work a systematic study on the solubility of LASSBio-294 in imidazolium ionic liquids at different temperatures (288.15 K to 308.15 K) is reported. In particular, seven ILs were used: 1-ethyl-3-methylimidazolium methyl phosphonate; 1-ethyl-3-methylimidazolium ethyl phosphonate; 1-ethyl-3-methylimidazolium acetate; 1,3-dimethylimidazolium methyl phosphonate; 1-butyl-3-methylimidazolium acetate; 1-butyl-3-methylimidazolium tetrafluoroborate; and 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide. The solubility data were also analyzed in terms of possible solute–solvent interactions in the solvation process.

As with all solvents, solubility needs to be evaluated for LASSBio-294 in the ILs and in the antisolvent/IL mixtures chosen for recrystallization. The solubility of LASSBio-294 was then measured in water (antisolvent) and in mixtures of water and ILs at different temperatures (288.15 K to 308.15 K) to set up optimal operating conditions in the crystallization process.

EXPERIMENTAL SECTION

Materials. The LASSBio-294, C₁₃H₁₀N₂O₃S, was obtained from Cristália Ltd.a (Itapira, SP, Brazil). Its structural formula is shown in Figure 1. It is in the form of a yellowish solid with a molecular weight of 274.3 g·mol⁻¹ and 99.96 % purity.

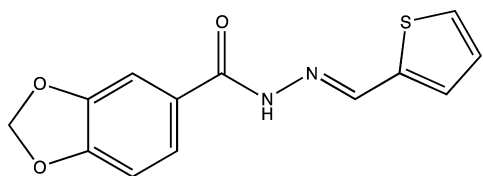


Figure 1. Structural formula of LASSBio-294.

All ionic liquids were purchased from Solvionic (Toulouse, France) and their full names, abbreviations, chemical structures, and purity are given in Table 1. Acetonitrile (HPLC grade) was purchased from Scharlau SL (Spain). Water was distilled and purified using Milli-Q Water Purification System (Purelab Classic DI MK2, Elga, UK). All other chemicals were of an analytical grade.

Solubility Measurement Procedure. The solubility of LASSBio-294 in different ILs, in water, and in mixtures of water and ILs at different temperatures (288.15 K, 298.15 K and 308.15 K) was determined by the following procedure: stirred solutions containing an excess of solid were kept in a bath at a controlled

temperature (measured using a calibrated thermocouple with an accuracy of 0.5 K) and atmospheric pressure for 72 h. In fact, from preliminary experiments, saturation was found to be reached after 24 h, and consequently all samples could be left for at least 24 h to ensure that the saturation solubility was reached (left for 72 h in this work). The suspensions were then centrifuged for 15 min at 4000 rpm. An aliquot of the supernatant was adequately diluted in a mixture of 60 % acetonitrile and 40 % water (w/w). The solutions were filtered (Acrodisc GHP, pore size 0.2 μm, Milipore, Bedford, MA, UK) and analyzed by high performance liquid chromatographic (HPLC) to assess the amounts of solute dissolved. The system consisted of an Agilent chromatograph (model 1100 series) equipped with a UV–vis detector. A Xterra RP18 column 5 μm (150 mm by 3.9 mm) was maintained at room temperature and equilibrated with the analytical mobile phase before injection. The mobile phase consisted of 50 % acetonitrile and 50 % water. The flow rate was 0.8 μm³·min⁻¹, the elution was monitored at 318 nm, and the injection volume was 0.02 cm³.

RESULTS AND DISCUSSION

This study concerns the solubility of a new molecule, LASSBio-294 in ILs as alternative solvents. As solubility depends on the structure and solid-state properties of the molecule, some properties of the original solid sample of LASSBio-294 were initially determined: the melting point (T_m) and the enthalpy of fusion (ΔH_m) by differential scanning calorimetry (DSC), the identification of the solid state by X-ray diffraction (XRD), and its morphology by scanning electron microscopy (SEM). The methodology used and the experimental data obtained are given in the Supporting Information. The original LASSBio-294 has a crystalline solid structure characterized by a T_m of 479.06 K and a $\Delta H_m = 122.9$ kJ·kg⁻¹. This value of T_m is close to that previously given in the literature for LASSBio-294 (478.15 K).²² The same crystalline form (Supporting Information, Figure S2) was identified in previous works.^{23,24} The original crystals present an elongated shape (Supporting Information, Figure S3).

LASSBio-294 Solubility in Ionic Liquids. The solubility of LASSBio-294 (mass fraction) in the chosen ILs at 298.15 ± 0.5 K and at atmospheric pressure is shown in Table 2. Data represent averages from two or three independent experiments. The uncertainties were calculated by the experimental standard deviation of the means. Depending on the molecular structure of the drug substance, one could expect the solubility to change with the nature of the solvent. In fact, Table 2 shows that five imidazolium-based family cation ILs tested in this study have been found capable of dissolving LASSBio-294.

The success of the dissolution of a drug depends on the ability of the solvent to interact with the drug to form interactions more stable than interactions solute–solute and solvent–solvent. The properties of ILs are based on the anion–cation combination. Although imidazolium-based ILs are commonly used, their microscopic nature is not well understood.¹⁶ However, it is known that they can act both as hydrogen-bond acceptors (anion) and hydrogen-bond donors (cation):

- The electronic structure of imidazolium cation contains delocalized 3-center-4-electron configuration across the N₁–C₂–N₃ moiety, a double bond between C₄ and C₅ on the opposite side of the ring, and a weak delocalization in the central region.
- The hydrogen atoms C₂–H, C₄–H, and C₅–H carry almost the same charge, but carbon C₂ is positively

Table 1. ILs Used in This Study

Name	Abbreviation [cation][anion]	Chemical Structure	Purity* (%)
1-ethyl-3- methylimidazolium methyl phosphonate (lot L09012001)	[emim][CH ₃ O(H)PO ₂]		>98
1-ethyl-3-methylimidazolium ethyl phosphonate (lot L11032201)	[emim][CH ₃ CH ₂ O(H)PO ₂]		>98
1-ethyl-3-methylimidazolium acetate (lot L11120102)	[emim][CH ₃ OO]		98
1,3-dimethylimidazolium methyl phosphonate (lot L09011902)	[dmim][CH ₃ O(H)PO ₂]		>98
1-butyl-3-methylimidazolium acetate (lot L08102002)	[bmim][CH ₃ OO]		>98
1-butyl-3-methylimidazolium tetrafluoroborate (lot L09092901)	[bmim][BF ₄]		99
1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (lot L06100201)	[bmim][NTf ₂]		>98

*The purity is provided by the supplier (determined from Karl Fisher titration, IR spectra, and Ionic Chromatography).

Table 2. Solubility of LASSBio-294 in Various ILs at 298.15 ± 0.5 K and 0.1 MPa

ionic liquids	solubility ^a (mass fraction·10 ³)
[emim][CH ₃ O(H)PO ₂]	254 ± 2 ^b
[emim][CH ₃ CH ₂ O(H)PO ₂]	474 ± 3
[emim][CH ₃ OO]	457 ± 5 ^b
[dmim][CH ₃ O(H)PO ₂]	367 ± 2 ^b
[bmim][CH ₃ OO]	473 ± 6 ^b
[bmim][NTf ₂]	insoluble
[bmim][BF ₄]	insoluble

^aThese values correspond to the mean solubility of two independent experiments. The uncertainty given in the table represents the standard deviation of the mean. ^bThree independent experiments. The reported repeatabilities are assumed to be equal the standard uncertainty for the measured solubilities. Standard uncertainties u is $u(T) = 0.5$ K.

charged owing to the electron deficit in the C=N bond, whereas C₄ and C₅ are practically neutral.²⁵

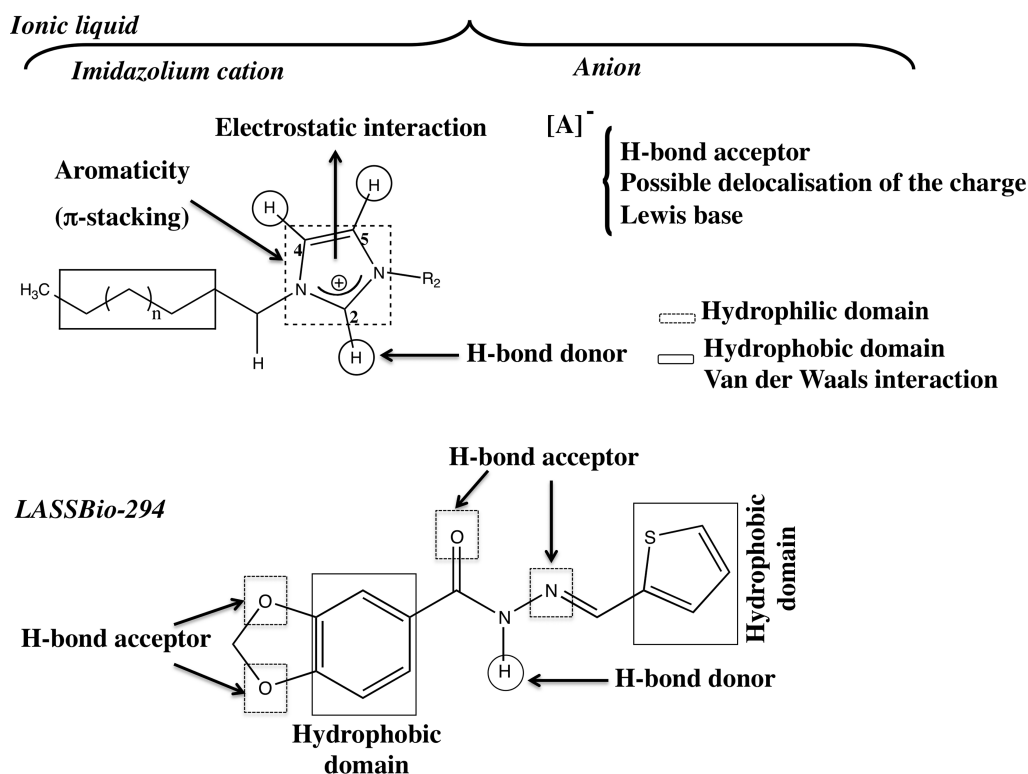
- The aromatic structure of imidazolium cation, hydrophilic domain, offers the possibilities of formation of electrostatic interaction and π -stacking with drugs.

- The hydrogen atom of C₂ can serve as a site for formation of a hydrogen bond. The hydrophobic domain, alkyl chain, allows the formation of van der Waals interactions. In addition, the anion can have the ability to delocalize its charge and act as an acceptor of hydrogen bond and/or Lewis base (Scheme 1).^{25,26}

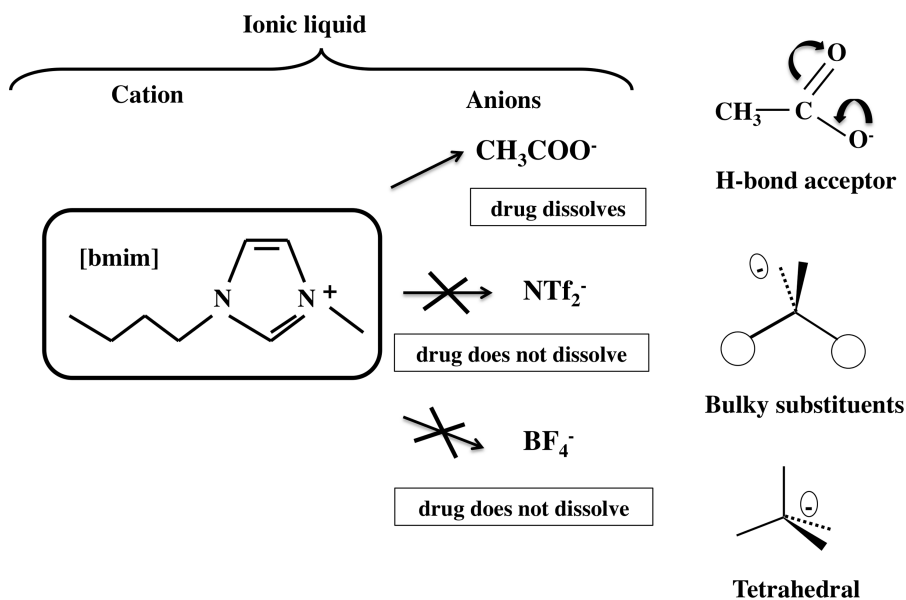
The levels of solubility observed for LASSBio-294 in [emim][CH₃O(H)PO₂], [emim][CH₃CH₂O(H)PO₂], [emim][CH₃OO], and [dmim][CH₃O(H)PO₂] could be due to solute-solvent interactions. Interactions such as hydrogen bonds, van der Waals forces, and π - π interactions between solute-solvent have been suggested as responsible for the solubilization of hydrophobic drugs in ILs.^{12,13,19,21,27} On the basis of the analysis of the LASSBio-294 structure (Scheme 1), it is hypothesized here that the same types of interactions may exist between the LASSBio-294 and the imidazolium-based ILs tested in this study.

Differences in the LASSBio-294 solubility in the seven ILs tested have been observed. To explain these findings, a more detailed analysis of each IL structure is performed, considering favorable and unfavorable interactions between the drug molecular structure and the anions and cations of ILs.

Scheme 1. Schematic Drawing of Hypothetical Interactions between the Imidazolium-Based Ionic Liquids and LASSBio-294. Scheme adapted with permission from ref 26. Copyright 2010 Elsevier.



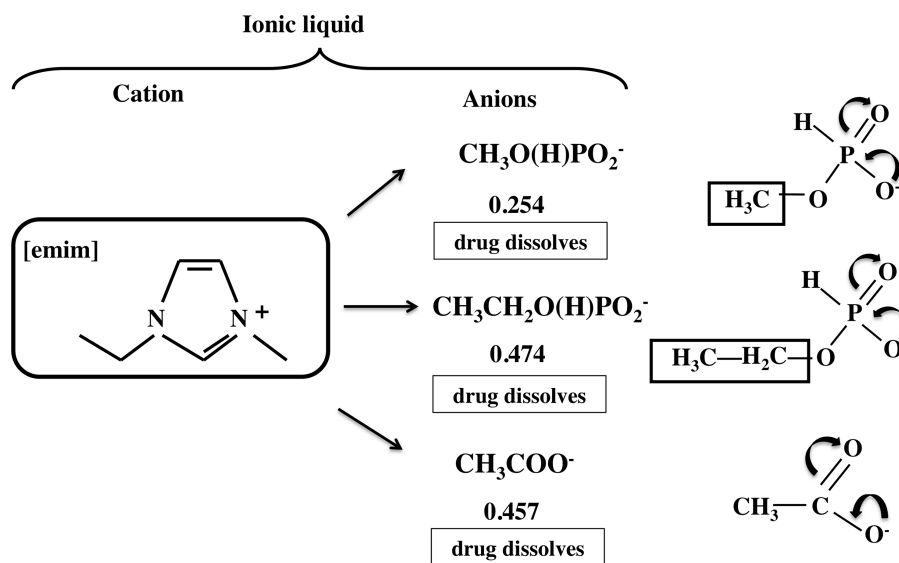
Scheme 2. Hypothetical Relationship between the Anion (CH_3OO^- , NTf_2^- , and BF_4^-) Combined to 1-Butyl-3-methylimidazolium [bmim] and the Solvency Power of the IL toward LASSBio-294



Anion Influence. The contribution of the anion to solubilize the drug is demonstrated by comparing the results obtained with ILs-derived [bmim] and [emim] cations. The combination [bmim] cation- $[CH_3OO^-]$ anion could dissolve the LASSBio-294, contrarily to the combinations [bmim] cation- $[BF_4^-]$ anion and [bmim] cation- $[NTf_2^-]$ anion (Scheme 2).

First, the solubility of the LASSBio-294 in ILs derived with a CH_3OO^- anion can be associated with the good capacity of this anion to form a hydrogen bond and delocalize charges between the oxygen atoms.²⁸ In turn, although the formation of a hydrogen bond between NTf_2^- anion and the drug (N-H group) has been described as the mechanism responsible for the ability of this anion to dissolve drugs such as isoniazid and

Scheme 3. Hypothetical Relationship between the Anion Combined to 1-Ethyl-3-methylimidazolium [emim] and the Solvency Power of the IL toward LASSBio-294. Anions: $\text{CH}_3\text{O}(\text{H})\text{PO}_2^-$, $\text{CH}_3\text{CH}_2\text{O}(\text{H})\text{PO}_2^-$, and CH_3OO^-



pyrazinecarboxamide,^{12,19,20} the presence of the thienyl group of LASSBio-294 probably helps prevent solubilization of this drug. Furthermore, the greater structural complexity of LASSBio-294 in relation to isoniazid and pyrazinecarboxamide as well as the bulky substituents of the NTf_2^- anion probably impedes such interactions with LASSBio-294.²⁸ Finally, the low capability of the BF_4^- anion to dissolve LASSBio-294 may be related to its tetrahedral shape that may hinder interactions with this drug.²⁸

The discussion relating the effect of the anion on the solvency power toward LASSBio-294 of imidazolium-based ILs can be extended to another type of cation, 1-ethyl-3-methylimidazolium [emim], associated with different anions: $\text{CH}_3\text{O}(\text{H})\text{PO}_2^-$, $\text{CH}_3\text{CH}_2\text{O}(\text{H})\text{PO}_2^-$, and CH_3OO^- .

When the [emim] cation is combined with the $\text{CH}_3\text{O}(\text{H})\text{PO}_2^-$ and $\text{CH}_3\text{CH}_2\text{O}(\text{H})\text{PO}_2^-$ anions, the solubility can be linked to the alkyl chain length of the $\text{CH}_3\text{CH}_2\text{O}(\text{H})\text{PO}_2^-$ anion (Scheme 3). The length of this chain (the higher hydrophobicity) induces a greater solubility of the LASSBio-294 in the ILs. A comparison of the solubility data obtained with ILs-derived $\text{CH}_3\text{O}(\text{H})\text{PO}_2^-$, $\text{CH}_3\text{CH}_2\text{O}(\text{H})\text{PO}_2^-$, and CH_3OO^- shows that the differences may be related to the ability to form hydrogen bonds and also to the ability to delocalize the charges between the oxygen atoms (Scheme 3).²⁸

Cation Influence. The effect of the cation is observed when the solubility data obtained with ILs-derived [emim] and [bmim] cations complexed with CH_3OO^- anion and [emim] and [dmim] cations complexed with the $\text{CH}_3\text{O}(\text{H})\text{PO}_2^-$ anion are compared. In the first case, the greater hydrophobicity of the [bmim] cation contributes to interactions with the hydrophobic molecule leading to a higher solubility as described by Muzuuchi and co-workers.²¹

In the second case, the influence of hydrophobicity is not observed. The solubility of LASSBio-294 was higher with [dmim] cation. This suggests that the solubility depends not only on the contribution of each ion separately but also on a combined cation–anion effect. A combined cation–anion effect in a dissolution process has already been described with cellulose,^{29–32} although other scientific works have attributed most of the dissolution ability to the anion.^{33–36}

Effect of Temperature on LASSBio-294 Solubility in Water and in [emim] Cation-Based ILs. The solubility of LASSBio-294 in water was measured as a function of temperature between 288.15 K and 308.15 K. The mass fraction at the equilibrium is lower than $5 \cdot 10^{-6}$ and the accuracy and the precision of the analytical method at this concentration level ($1 \cdot 10^{-6}$) did not permit acquisition of the evolution of the solubility values as a function of temperature.

On the basis of the solubility values of LASSBio-294 in pure ILs at 298.15 ± 0.5 K (Table 2), three ILs were chosen to evaluate the influence of temperature on the drug solubility. They are [emim][$\text{CH}_3\text{O}(\text{H})\text{PO}_2$], [emim][$\text{CH}_3\text{CH}_2\text{O}(\text{H})\text{PO}_2$], and [emim][CH_3OO] ILs.

The LASSBio-294 solubility was determined in the three ILs at temperatures ranging from 288.15 K to 308.15 K. The results are shown in Table 2 and Table 3. It can be noted that the solubility

Table 3. Effect of the Temperature on the Solubility of LASSBio-294 in Different ILs at 0.1 MPa

T/K	solubility ^a (mass fraction · 10 ³)		
	[emim][$\text{CH}_3\text{O}(\text{H})\text{PO}_2$]	[emim][$\text{CH}_3\text{CH}_2\text{O}(\text{H})\text{PO}_2$]	[emim][CH_3OO]
288.15	233 ± 2	475 ± 1 ^b	437 ± 8
308.15	302 ± 1	> 508 ± 8 ^c	> 641 ± 1 ^c

^aThese values correspond to the mean solubility of two independent experiments done at each temperature. The uncertainty given in the table represents the standard deviation of the mean. The reported repeatabilities are assumed to be equal the standard uncertainty for the measured solubilities. Standard uncertainties u is $u(T) = 0.5$ K. ^bThree independent experiments. ^cEquilibrium not reached.

in these pure ILs increased with temperature in the studied range. However, the results for [emim][$\text{CH}_3\text{CH}_2\text{O}(\text{H})\text{PO}_2$] at 288.15 K and 298.15 K show that the solubility is rather constant, which is not the case for the other ILs. This behavior may be due to a problem of the solubility measurement at 288.15 K with this IL. Indeed, this is more viscous (0.14 Pa·s) than the other ones (<0.11 Pa·s), and the separation liquid/solid is more difficult, inducing probably an overestimation of the solubility. At 308.15

K, the equilibrium solubility data in [emim][CH₃CH₂O(H)-PO₂] and [emim][CH₃OO] could not be determined because the drug–IL mixture became a gel.

LASSBio-294 Solubility in Mixtures of Water and ILs Consisting of [emim] Cation Associated with Three Different Anions, [CH₃O(H)PO₂], [CH₃CH₂O(H)PO₂], and [CH₃OO]. The first step to design a drug recrystallization process when using an antisolvent crystallization method is to define the antisolvent/solvent mass proportion to obtain high yields of solid product. In this part of the study, the solubility of LASSBio-294 in mixtures of water/[emim][CH₃O(H)PO₂], water/[emim]-[CH₃CH₂O(H)PO₂], and water/[emim][CH₃OO] was determined at 298.15 ± 0.5 K. The experimental data obtained are shown in Table 4. They revealed that the solubility of LASSBio-294 decreased sharply when water was added to the drug–IL solutions.

Table 4. Solubility of LASSBio-294 in Mixtures of Water and ILs at 298.15 ± 0.5 K and 0.1 MPa

mass ratio water/IL	solubility ^a (mass fraction·10 ³)		
	[emim][CH ₃ O(H)PO ₂]	[emim][CH ₃ CH ₂ O(H)PO ₂]	[emim][CH ₃ OO]
9.00	0.002 ± 0.001	-	-
4.00	0.004 ± 0.001	-	-
2.30	0.012 ± 0.001	-	-
1.50	0.021 ± 0.004	-	-
1.00	0.211 ± 0.004	0.243 ± 0.011	0.254 ± 0.014
0.67	0.307 ± 0.031	0.553 ± 0.001	-
0.43	1.240 ± 0.004	1.323 ± 0.012	-
0.25	5.664 ± 0.054	8.661 ± 0.348	-
0.18	10.701 ± 0.241	-	-
0.11	33 ± 7	105 ± 1	-
0.05	85 ± 1 ^b	315 ± 5	258 ± 6
0.02	160 ± 7	-	-

^aThese values correspond to the mean solubility of two independent experiments done at each mass ratio. The uncertainty given in the table represents the standard deviation of the mean. The reported repeatabilities are assumed to be equal to the standard uncertainty for the measured solubilities. Standard uncertainties *u* is *u*(*T*) = 0.5 K. (-) Not measured. ^bThree independent experiments.

These data indicate that the antisolvent crystallization method is an interesting way to recrystallize the LASSBio-294. The knowledge of the solid–liquid equilibrium in these systems will be used for determining the operating conditions for a crystallization procedure leading to a good solid performance.

Effect of the Temperature on the Solubility of LASSBio-294 in Mixtures of Water and ILs Consisting of [emim] Cation Associated with Three Different Anions, CH₃O(H)PO₂⁻, CH₃CH₂O(H)PO₂⁻, and CH₃OO⁻. The solubility of LASSBio-294 (mass fraction) in mixtures of water/[emim]-[CH₃O(H)PO₂], water/[emim][CH₃CH₂O(H)PO₂], and water/[emim][CH₃OO] for water/IL mass ratios of 0.05 and 1.0 at different temperatures is shown in Table 5. The results confirm that the solubility of LASSBio-294 in mixtures of water with ILs generally increases with temperature. In the mixture water/[emim][CH₃CH₂O(H)PO₂], the solubility change does not follow the same trend as the other mixtures: the solubility does not increase as a function of temperature for the water/IL mass ratio of 1.0 by contrast with the ratio of 0.05. This unexpected result may be due to experimental uncertainties, as already found for pure [emim][CH₃CH₂O(H)PO₂].

CONCLUSIONS

This research is focused on ILs and their application as alternative solvents for LASSBio-294, a new cardioactive prototype and poorly water-soluble drug. The use of ILs as alternative solvents for this type of drug can open new possibilities for LASSBio-294 reprocessing because not only ILs essentially do not evaporate, and so they cannot lead to fugitive emissions, but also several of them acted as good solvents for this drug as shown in this study.

The dissolution properties of ILs depend on both the cation and the anion. Systematic studies about the cation and the anion influence on solubility are currently very scarce and are needed. Overall the results presented here suggest that a design strategy to solubilize a poorly water-soluble drug such as LASSBio-294 can be used for the selection of a specific IL, based on a proper knowledge of the drug molecule structure and of the IL chemistry. The structure of an IL could thus be tuned to maximize its interaction with a targeted drug, and then to favor the drug solubility.

Finally, the sufficient solubility of LASSBio-294 in ILs as alternative solvents obtained in this work can open new perspectives in pharmaceutical processing through recrystallization (antisolvent crystallization process). The residual content of ionic liquid in a solid after crystallization can for instance be removed by washing with water.

ASSOCIATED CONTENT

Supporting Information

Experimental section describing the determination of *T_m* and ΔH_m , XRD diffractogram, and SEM images of the original solid

Table 5. Solubility of LASSBio-294 in Mixtures of Water and ILs at Different Temperatures and 0.1 MPa

<i>T</i> /K	mass ratio water/IL	solubility ^a (mass fraction·10 ³)		
		[emim][CH ₃ O(H)PO ₂]	[emim][CH ₃ CH ₂ O(H)PO ₂]	[emim][CH ₃ OO]
288.15	1.00	0.172 ± 0.040	0.280 ± 0.080	0.226 ± 0.010
	0.05	62 ± 1	264 ± 1 ^b	217 ± 3
298.15	1.00	0.211 ± 0.004	0.243 ± 0.011	0.254 ± 0.014
	0.05	85 ± 1 ^b	314 ± 5	258 ± 6
308.15	1.00	0.253 ± 0.030 ^b	0.377 ± 0.050	0.256 ± 0.010
	0.05	122 ± 1	318 ± 3	312 ± 1

^aThese values correspond to the mean solubility of two independent experiments done at each mass ratio and temperature. The uncertainty given in the table represents the standard deviation of the mean. The reported repeatabilities are assumed to be equal to the standard uncertainty for the measured solubilities. Standard uncertainties *u* is *u*(*T*) = 0.5 K. ^bThree independent experiments.

sample of LASSBio-294, whose solubility in different ILs was the subject of this work. The experimental results are given in Figures S1, S2, and S3. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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