525 Solutions, Inc. Publications Related to Pharmaceuticals

1. Are myths and preconceptions preventing us from applying ionic liquid forms of antiviral medicines to the current health crisis?

By Shamshina, Julia L.; Rogers, Robin D.

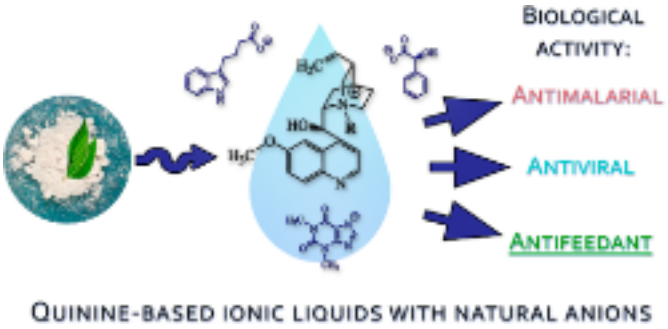
From International Journal of Molecular Sciences (2020), 21(17), 6002. , DOI:10.3390/ijms21176002

A review. At the moment, there are no U.S. Food and Drug Administration (U.S. FDA)-approved drugs for the treatment of COVID-19, although several antiviral drugs are available for repurposing. Many of these drugs suffer from polymorphic transformations with changes in the drug's safety and efficacy; many are poorly sol., poorly bioavailable drugs. Current tools to reformulate antiviral APIs into safer and more bioavailable forms include pharmaceutical salts and cocrystals, even though it is difficult to classify solid forms into these regulatory-wise mutually exclusive categories. Pure liq. salt forms of APIs, ionic liqs. that incorporate APIs into their structures (API-ILs) present all the advantages that salt forms provide from a pharmaceutical standpoint, without being subject to solid-state matter problems. In this perspective article, the myths and the most voiced concerns holding back implementation of API-ILs are examd., and two case studies of API-ILs antivirals (the amphoteric acyclovir and GSK2838232) are presented in detail, with a focus on drug property improvement. The authors advocate that the industry should consider the advantages of API-ILs which could be the genesis of disruptive innovation and believe that in order for the industry to grow and develop, the industry should be comfortable with a certain element of risk because progress often only comes from trying something different.

2. Conversion of Quinine Derivatives into Biologically Active Ionic Liquids: Advantages, Multifunctionality, and Perspectives

By Pernak, Juliusz; Rzemieniecki, Tomasz; Klejdysz, Tomasz; Qu, Fengrui; Rogers, Robin D.

From ACS Sustainable Chemistry & Engineering (2020), 8(25), 9263-9267. , DOI:10.1021/acssuschemeng.0c03501



In this study, we demonstrate that quinine with confirmed antiviral and antifeedant activity can be derivatized and formulated as multifunctional ionic liqs. which allow one to tune their biol., chem., and phys. properties. Following the optimization of quinine alkylation, pure 1-alkylquinine bromides with alkyl chain length ranging from Et to dodecyl were synthesized and extensively characterized. In the next step, these derivs. were combined with counterions of natural origin, which resulted in the formation of naturally derived ionic liqs. Our results indicate that the transformation of quinine into ionic liqs. may improve antifeedant properties by 265% compared to the activity of quinine-free base. Moreover, unlike the majority of known cases, the redn. of the alkyl chain length results in a significant increase in this type of biol. activity. We demonstrate that quinine with proven antimalarial, antiviral, and antifeedant activity can be derivatized and formulated as ionic liqs. allowing one to tune their biol., chem., and phys. properties.

525 Solutions, Inc. Publications Related to Pharmaceuticals

3. Advances in Processing Chitin as a Promising Biomaterial from Ionic Liquids

By Shamshina, Julia L.; Zavgorodnya, Oleksandra; Rogers, Robin D.

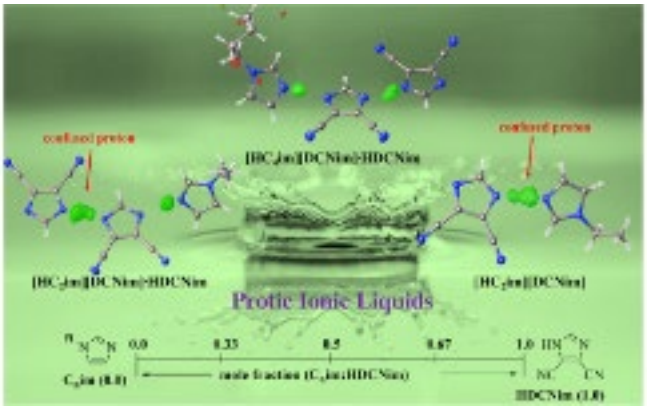
From Advances in Biochemical Engineering/Biotechnology (2019), 168(Application of Ionic Liquids in Biotechnology), 177-198. , DOI:10.1007/10_2018_63

A review. Chitin isolated through microwave-assisted dissoln. using ionic liqs. is a high mol. wt. (MW) polymer that can be manufd. into materials of different architectures (e.g., fibers, films, microspheres, nanostructured materials) to be used as wound care dressings, drug delivery devices, scaffolds, etc. However, because of differences from traditional isolation methods and, thus, differences in polymer length and degree of deacetylation, it could exhibit bio-related properties that differ from those of traditionally 'pulped' chitin. Here we present the initial assessments of bio-related chitin properties in order to provide a useful scientific basis for clin. applications: biocompatibility, cytotoxicity (intracutaneous reactivity), wound healing efficacy, histol. evaluation of the wounds treated with chitin dressing, and antibacterial activity. We also provide the studies that outline potential applications of chitin as a raw polymer for prepn. of biomaterials.Graphical Abstr.

4. Controlling the Interface between Salts, Solvates, Co-crystals, and Ionic Liquids with Non-stoichiometric Protic Azolium Azolates

By Easton, Max E.; Li, Kai; Titi, Hatem M.; Kelley, Steven P.; Rogers, Robin D.

From Crystal Growth & Design (2020), 20(4), 2608-2616. , DOI:10.1021/acs.cgd.9b01733



A non-stoichiometric approach to control the solid-state behavior of protic ionic liqs. (PILs) was demonstrated by direct mixing of 4,5-dicyanoimidazole (HDCNim) with either 1-ethylimidazole (C_2i.m.) or 1-butylimidazole (C_4i.m.) in different mole fractions. Isolation and characterization of three cryst. materials (all having m.ps. < 100°C, thus fitting the PIL definition) revealed three different but closely related systems. The structure of [HC_2i.m.][DCNim] consists of a confused proton system, which is so named for the fast proton exchange between basic and acidic fragments and the formation of hydrogen-bonded anionic oligomers. The compd. [HC_2i.m.][DCNim]·HDCNim consists of an oligomeric delocalized anion (a confused proton located between two azole fragments, in which one acts as a neutral moiety while the other as an ionic fragment, DCNim-H-DCNim) and [HC_4i.m.][DCNim]·HDCNim can be classified as a salt co-crystal. We believe that these observations will allow a deeper understanding of the behavior of "confused protons" and provide addnl. strategies for controlling the properties of important classes of materials such as active pharmaceutical ingredients. A nonstoichiometric PIL approach for the system comprising 1-alkylimidazole (C_ni.m., n = 2, 4), 4,5-dicyanoimidazole, and the protonated/deprotonated compds. illustrating a position of confused protons.

5. Printing of biopolymers from ionic liquid

By Rogers, Robin D.; Zavgorodnya, Oleksandra; Shamshina, Julia L.; Gurau, Gabriela

From PCT Int. Appl. (2019), WO 2019173689 A1 20190912.

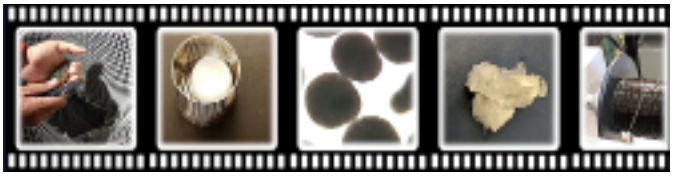
FIG. 1B

The invention relates to a method of printing a three-dimensional (3D) article, comprising: extruding a printing compn. from a deposition nozzle moving relative to a substrate, the printing compn. comprising a biopolymer dissolved in an ionic liq. solvent; depositing one or more layers comprising the printing compn. in a predetd. pattern on the substrate; and treating the one or more layers to form the 3D article. A 3D printed article derived from a method of the invention is also claimed. The invention also relates to a printing compn., consisting essentially of: a biopolymer present in an amt. of 0.1 - 50 wt%, preferably 0.1 - 25 wt%, based on the wt. of the printing compn.; a synthetic polymer, wherein the biopolymer and the synthetic polymer are in a wt. ratio of 1:0.1 - 1:20, preferably 1:1 - 1:20, more preferably 1:1 - 1:10; an ionic liq. solvent for dissolving the biopolymer and synthetic polymer; and a 3D printing additive, preferably selected from a biol. active compd., a plasticizer, a pigment, a fire retardant, a catalyst, a cross-linker, a heat or light stabilizer, an org. or inorg. filler such as a nano-filler, a fiber reinforcement, or a combination thereof.

6. Advances in Functional Chitin Materials: A Review

By Shamshina, Julia L.; Berton, Paula; Rogers, Robin D.

From ACS Sustainable Chemistry & Engineering (2019), 7(7), 6444-6457. , DOI:10.1021/acssuschemeng.8b06372



A review. Chitin is a promising natural polymer to produce functional materials due to the attractive combination of abundance, price, favorable biol. properties, and biodegradability. However, multiple literature examples often confuse processing of chitosan, the deacetylated version of chitin, due to chitosan's much higher soly. in traditional solvents. Nonetheless, despite current challenges to solubilize natural chitin, there is still a large body of literature demonstrating multiple ways to manipulate this polymer into materials of desired forms and properties. Here we review one such area where chitin promises both technol. superiority and potential for com. success, the use of chitin in biomedical research. We discuss techniques which have been utilized to process chitin and to prep. chitin-based functional materials, particularly in the prodn. of fibers, films, beads, and hydrogels. Emphasis is given to the most recent methods and a compilation of a compelling

collection of examples based on current research and existing products. These examples demonstrate the suitability of chitin for prodn. of surgical sutures, wound care materials, tissue engineering biomaterials, and other various biomedical applications.

7. Ionic Liquids in Pharmaceutical Industry

By Shamshina, Julia L.; Berton, Paula; Wang, Hui; Zhou, Xiaosi; Gurau, Gabriela; Rogers, Robin D.

Edited By:Zhang, Wei; Cue, Berkeley W

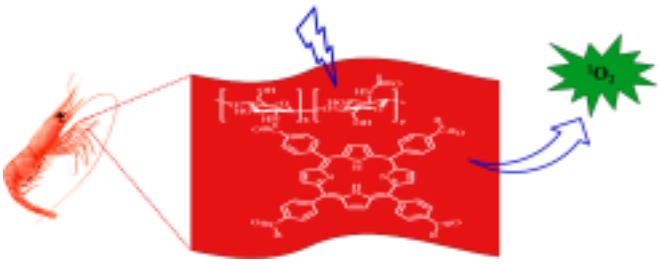
From Green Techniques for Organic Synthesis and Medicinal Chemistry (2nd Edition) (2018), 539-577. , DOI:10.1002/9781119288152.ch20

This chapter reviews the roles of ionic liqs. (ILs) in pharmaceutical manufg. processes, including the use of ILs as solvents in the synthesis of drugs or isolation of drug intermediates, the use of ILs in pharmaceutical crystn., in pharmaceutical sepn., for the extn. of drugs from natural products, to deliver drugs, to detect drugs, and even as active pharmaceutical ingredients (APIs). ILs have also been considered as alternatives to org. solvents in the pharmaceutical industry. A large vol. of volatile org. solvents (VOCs) is used in the process of drug extn. from natural products, resulting in serious environmental problems and replacement of conventional solvents by ILs might prevent the emission of VOCs. While ILs have been shown to be efficient vehicles in transdermal drug delivery, until recently they were not studied as transdermal drugs themselves because ionized salts normally diffuse poorly through lipid membranes.

8. Singlet Oxygen Production and Tunable Optical Properties of Deacetylated Chitin-Porphyrin Crosslinked Films

By Li, Kai; Berton, Paula; Kelley, Steven P.; Rogers, Robin D.

From Biomacromolecules (2018), Ahead of Print. , DOI:10.1021/acs.biomac.8b00605



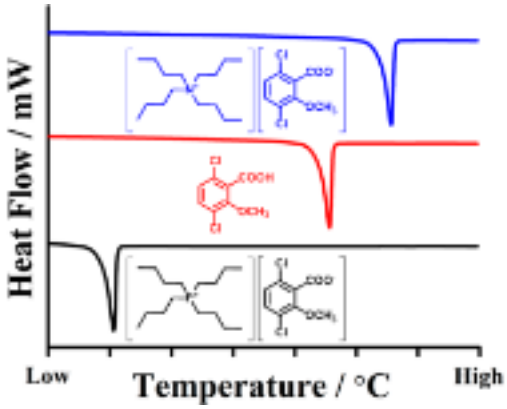
The increasing need for biocompatible materials as supports to immobilize photosensitizer mols. for photodynamic therapy (PDT), led us to investigate the use of chitin as a support for 4,4',4",4"'-(porphine-5,10,15,20-tetrayl)tetrakis(benzoic acid) (mTCPP) for singlet oxygen prodn. Chitin was first extd. from shrimp shells using the ionic liq. 1-ethyl-3-methyl-imidazolium acetate ([C_2mim][OAc]), coagulated as a floc into water, and then deacetylated to varying degrees of deacetylation using 4 M NaOH. The deacetylated chitin (DA-chitin) was dissolved in [C_2mim][OAc] and mTCPP was covalently attached by reaction between the amino groups of DA-chitin and the carboxyl groups of mTCPP using N-(3-(dimethylamino)propyl)-N'-ethylcarbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) as activators. The resulting composite polymers were cast as a film and coagulated with water to remove IL and excess reagents, resulting in homogeneous DA-chitin/mTCPP films. Attempts to prep. films by coagulation from a soln. contg. chitin and mTCPP to phys. entrap the porphyrin, resulted in aggregation of mTCPP in the film. The DA-chitin/mTCPP films had strong optical

absorbance and their absorbance intensity could be tuned by changing the mTCPP content and degrees of deacetylation of DA-chitin in a predictive manner. In addn., metal ions (Cu^{2+}, Zn^{2+}, Gd^{3+}, and Fe^{3+}) could be easily chelated into the DA-chitin/mTCPP films through mixing metal salt solns. with the films and heating. After chelating metal ions, optical properties, such as absorption region and intensities, of the films changed, suggesting chelating metal ions could tune their optical properties. Moreover, the DA-chitin/mTCPP films could generate singlet oxygen under light irradn. and, hence, might serve as a photosensitizer in PDT. The methodol. used in this study is also applicable for developing other functional biomaterial devices.

9. Can Melting Point Trends Help Us Develop New Tools To Control the Crystal Packing of Weakly Interacting Ions?

By Mishra, Manish Kumar; Kelley, Steven P.; Shamshina, Julia L.; Choudhary, Hemant; Rogers, Robin D.

From Crystal Growth & Design (2018), 18(2), 597-601. , DOI:10.1021/acs.cgd.7b01680



Ionic liq. forms of biol. active mols. (e.g., active pharmaceutical ingredients or herbicides) are often designed by using weakly interacting, conformationally flexible ions. Cryst. forms of these mols. involve strong interactions and efficient packing. The salts of biol. active mols. may completely lack the directional supramol. synthons typically used in crystal engineering, and thus new tools must be developed to control the crystal packing without strong directional interactions and predict their structure-property relations in advance. The crystal structures of Bu_4N and phosphonium salts of 2 structurally related, biol. active ions, salicylate and dicamba, show systematic differences from their free acids and metal salts, which are dominated by strong directional interactions. Mol. conformation and the structure of oligomeric ions of acids and their conjugate bases are conserved across multiple structures. The use of flexible, weakly coordinating cations to make salts of high melting biol. active acids can dramatically change m.ps. based on the size and shape complementarity of the ions and the ability of the cations to enhance anion-anion repulsion.

10. Separate mechanisms of ion oligomerization tune the physicochemical properties of n-butylammonium acetate: cation-base clusters vs. anion-acid dimers

By Berton, Paula; Kelley, Steven P.; Wang, Hui; Myerson, Allan S.; Rogers, Robin D.

From Physical Chemistry Chemical Physics (2017), 19(37), 25544-25554. , DOI:10.1039/C7CP04078D

We investigated the ability of the ions comprising protic ionic liqs. to strongly interact with their neutral acid and base forms through the characterization of n-butylammonium acetate ($[C_4NH_3][OAc]$) in the presence of excess n-butylamine (C_4NH_2) or

excess acetic acid (HOAc). The conjugate and parent acid or base form new nonstoichiometric, noncovalently bound species (i.e., oligomeric ions) which change the phys. and chem. properties of the resulting liqs., thus offering tunability. The effects of adding C_4NH_2 or HOAc to $[C_4NH_3][OAc]$ on the resulting thermal and spectroscopic properties differ and suggest that C_4NH_2 interacts primarily with $[C_4NH_3]^+$ to form 3-dimensional polymeric networks likely similar to those in $H_2O/[H_3O]^+$, while HOAc interacts primarily with $[OAc]^-$ to form oligomeric ions (e.g., $[H(OAc)_2]^-$). The densities of the systems increased with the increase of acid content and reached a max. when the acid molar fraction was 0.90, but decreased with increasing amine concn. The viscosities decreased significantly with increasing acid or base concn. The solvent properties of the mixts. were assessed by measuring the solubilities of benzene, Et acetate, di-Et ether, heptane, ibuprofen free acid, and lidocaine free base. The solubilities of the org. solutes and active pharmaceutical ingredients can be tuned with the concn. of acid or amine in the mixts. In addn., crystn. of the active pharmaceutical ingredients can be induced with the modification of the compn. of the mixts. These observations support the usage of these mixts. for the synthesis and purifn. of acid or basic active pharmaceutical ingredients in the pharmaceutical industry.

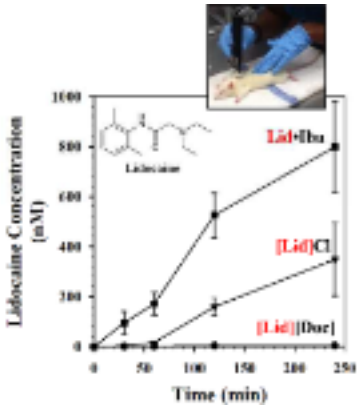
11. Ionic liquids for consumer products: Dissolution, characterization, and controlled release of fragrance compositions
By Berton, Paula; Bica, Katharina; Rogers, Robin D.
From Fluid Phase Equilibria (2017), 450, 51-56. , DOI:10.1016/j.fluid.2017.07.011

Ionic liqs. composed entirely of pharmaceutically-approved ions were used for the dissoln. and storage of volatile fragrance components with improved thermal stability and prolonged release. The presence of the cation of the ionic liq. in the head space was also obsd., highlighting the need for careful selection of the components of the ionic liq. for consumer products.

12. Formation of ionic co-crystals of amphoteric azoles directed by the ionic liquid co-former 1-ethyl-3-methylimidazolium acetate
By Titi, Hatem M.; Kelley, Steven P.; Easton, Max E.; Emerson, Stephen D.; Rogers, Robin D.
From Chemical Communications (Cambridge, United Kingdom) (2017), 53(61), 8569-8572. , DOI:10.1039/C7CC04429A

The ionic liq. (IL) 1-ethyl-3-methylimidazolium acetate was utilized as a liq.-state crystn. agent to form ionic co-crystals using amphoteric azoles selected as model compds. for active pharmaceutical ingredients. Weakly acidic azoles crystallize the IL relatively quickly, while stronger acidic azoles undergo slower ion exchange with the IL to form salts.

13. Transdermal Bioavailability in Rats of Lidocaine in the Forms of Ionic Liquids, Salts, and Deep Eutectic
By Berton, Paula; Di Bona, Kristin R.; Yancey, Denise; Rizvi, Syed A. A.; Gray, Marquita; Gurau, Gabriela; Shamshina, Julia L.; Rasco, Jane F.; Rogers, Robin D.
From ACS Medicinal Chemistry Letters (2017), 8(5), 498-503. , DOI:10.1021/acsmedchemlett.6b00504



Tuning the bioavailability of lidocaine was explored by its incorporation into the ionic liq. lidocainium docusate ([Lid][Doc]) and the deep eutectic Lidocaine·Ibuprofen (Lid·Ibu) and comparing the transdermal absorption of these with the cryst. salt lidocainium chloride ([Lid]Cl). Each form of lidocaine was dissolved in a vehicle cream and topically applied to Sprague-Dawley rats. The concns. of the active pharmaceutical ingredients (APIs) in blood plasma were monitored over time as an indication of systemic absorption.

The concn. of lidocaine in plasma varied between applied API-based creams, with faster and higher systemic absorption of the hydrogen bonded deep eutectic Lid·Ibu than the absorption of the salts [Lid]Cl or [Lid][Doc]. Interestingly, a differential transdermal absorption was obsd. between lidocaine and ibuprofen when Lid·Ibu was applied, possibly indicating different interactions with the tissue components.

14. The A Priori Design and Selection of Ionic Liquids as Solvents for Active Pharmaceutical Ingredients

By Kunov-Kruse, Andreas J.; Weber, Cameron C.; Rogers, Robin D.; Myerson, Allan S.

From Chemistry - A European Journal (2017), 23(23), 5498-5508. , DOI:10.1002/chem.201605704

In this paper we derive a straightforward computational approach to predict the optimal ionic liq. (IL) solvent for a given compd., based on COSMO-RS calcns. These calcns. were performed on 18 different active pharmaceutical ingredients (APIs) using a matrix of 210 hypothetical ILs. These results indicated that the 18 APIs could be classified into three distinct categories based on their relative hydrogen bond donating or accepting ability, with similar optimal IL solvent predictions within each class. Informed by these results, a family of strongly hydrogen bond donating ILs based on the N-alkylguanidinium cation were prepd. and characterized. The soly. of the APIs in each of these classes was found to be qual. consistent with the predictions of the COSMO-RS model. The suitability of these novel guanidinium salts as crystn. solvents was demonstrated by the use of N-butylguanidinium bis(trifluoromethanesulfonyl)imide for the purifn. of crude fenofibrate using dimethylsulfoxide as an antisolvent, which resulted in good yields and excellent purities. Finally, a simple descriptor based model is proposed to suggest the best IL solvent for arbitrary APIs.

15. Polyethylene glycol derivatization of the non-active ion in active pharmaceutical ingredient ionic liquids enhances transdermal delivery

By Zavgorodnya, Oleksandra; Shamshina, Julia L.; Mittenthal, Max; McCrary, Parker D.; Rachiero, Giovanni P.; Titi, Hatem M.; Rogers, Robin D.

From New Journal of Chemistry (2017), 41(4), 1499-1508. , DOI:10.1039/C6NJ03709G

We report the synthesis of four salts composed of the salicylate anion ($[Sal]^-$) paired with tributylammonium ($[HN_{444}]^+$), choline ($[Cho]^+$), 1-methylpyrrolidinium ($[HMPyrr]^+$), and triethylene glycol monomethyl ether tributylammonium ($[mPEG_3N_{444}]^+$) cations. Three of the synthesized salts (room temp. liqs. $[mPEG_3N_{444}][Sal]$ and $[Cho][Sal]$, and a supercooled liq. $[HN_{444}][Sal]$) belong to the category of ionic liqs. (ILs), and one salt (solid $[HMPyrr][Sal]$) was a cryst. solid. ILs in their neat form were studied for membrane transport through a silicon membrane, and exhibited higher transport compared to a control expt. with sodium salicylate dissolved in $mPEG_3OH$ as solvent, but lower membrane transport compared to salicylic acid dissolved in $mPEG_3OH$. The 'PEGylated' IL, $[mPEG_3N_{444}][Sal]$, crossed the membrane with an ca. ~2.5-fold faster rate than that of any of the non-PEGylated ILs. This work demonstrates not only that API-ILs can eliminate the use of a solvent vehicle during application and notably transport through a membrane as opposed to a higher melting cryst. salt, but also that the membrane transport can be further enhanced by PEGylation of the counter ions.

16. Biologically active compounds supported on solid carrier such as silica for controlled release and improved thermal stability

By Riisager, Anders; Fehrmann, Rasmus; Rodriguez, Hector; Bica, Katharina; Rogers, Robin D.; Daly, Daniel T.; Gurau, Gabriela

From U.S. Pat. Appl. Publ. (2013), US 20130203602 A1 20130808.

The present invention relates to biol. active compds., particularly liq. compds., which are immobilized on a solid carrier material, particularly on mesoporous silica. The compds. are non-covalently supported on the solid carrier material thereby forming stable, easily handled solids which have the further advantage that the adsorbed biol. active compds. have improved thermal stability compared with the non-adsorbed compds., and that they are released rapidly and completely from the carrier material when placed in an aq. environment. The present invention relates to biol. active compds., particularly liq. compds., which are immobilized on a solid carrier material, particularly on mesoporous silica. The compds. are non-covalently supported on the solid carrier material thereby forming stable, easily handled solids which have the further advantage that the adsorbed biol. active compds. have improved thermal stability compared with the non-adsorbed compds., and that they are released rapidly and completely from the carrier material when placed in an aq. environment. Thus, tetrabutylphosphonium ibuprofenate (TBPI) was prepd. by reaction of ibuprofenic acid with tetrabutylphosphonium hydroxide. Controlled release of silica-supported TBPI in simulated gastric fluid or simulated intestinal fluid was demonstrated. Thermal stability of TBPI was measured by detg. the inflection point by heating from 25° to 800° with a heating rate of 5°/min under air. The inflection points for non-supported TBPI and silica-supported TBPI loaded at 10% and 20% were 236°, 386° and 263°, resp.

17. Coagulation of biopolymers from ionic liquid solutions using co2

By Rogers, Robin D.; Barber, Patrick S.; Griggs, Chris S.; Gurau, Gabriela; Lu, Xingmei; Zhang, Suojiang

From U.S. Pat. Appl. Publ. (2015), US 20150368371 A1 20151224.

Disclosed herein are processes for providing a biopolymer from a biomass or source of chitin using ionic liqs. The processes involve contacting a biomass or source of chitin with an ionic liq. to produce a biopolymer comprising soln. and pptg. the biopolymer from the soln. with supercrit. CO_2, gaseous CO_2, or combinations thereof.

18. Herbicidal compositions and methods of use

By Pernak, Juliusz; Shamshina, Julia; Tadeusz, Praczyk; Syguda, Anna; Janiszewska, Dominika; Smiglak, Marcin; Gurau, Gabriela; Daly, Daniel T.; Rogers, Robin D.

From U.S. Pat. Appl. Publ. (2013), US 20130109572 A1 20130502.

Disclosed are compns. and methods of prepg. compns. of active herbicidal ingredients. Also disclosed are methods of using the compns. described herein to improve herbicide delivery and efficacy, enhance herbicidal penetration, reduce herbicide volatility and drift, diminish environmental damage from herbicides, decrease water soly. and volatility of herbicides, and introduce addnl. biol. function to herbicides.

19. A platform for more sustainable chitin films from an ionic liquid process

By King, Catherine; Shamshina, Julia L.; Gurau, Gabriela; Berton, Paula; Khan, Nur Farahnadiah Abdul Faruk; Rogers, Robin D.

From Green Chemistry (2017), 19(1), 117-126. , DOI:10.1039/C6GC02201D

A versatile platform for the prepn. of chitin films with tunable strength, morphol., and efficacy of application has been designed from an ionic liq. process for the prodn. of more sustainable high value materials. Films were prepd. by a simple casting method from a soln. of chitin in the ionic liq. 1-ethyl-3-methylimidazolium acetate ([C_2mim][OAc]). The chitin source, the loading in ionic liq., and the drying methods defined film properties such as strength, porosity, and water absorbency. Only chitin directly

extd. from shrimp shells using the ionic liq. (rather than com. available chitin) could be used to cast films strong enough to be handled and dried. The optimal loading of chitin in the ionic liq. was detd. to be 2.5 wt% and different drying methods led to different film properties (e.g., hard and rigid vs. soft and porous). As an exemplary application, loading and release of a model drug (caffeine) was investigated. Interestingly, a burst release of the majority of the caffeine was obsd. in the first 20 min, followed by slow release of the remainder. Although more investigations are needed, the chitin film platform can be thought of as an attr(M. Rinaudo, Prog. Polym. Sci., 2006, 31, 603-632) made from one of Nature's most abundant polymers.active new tool in the development of packaging materials, biomedical devices, and absorbent materials (M. Rinaudo, Prog. Polym. Sci., 2006, 31, 603-632) made from one of Nature's most abundant polymers.

20. Chemistry: Develop ionic liquid drugs
By Shamshina, Julia L.; Kelley, Steven P.; Gurau, Gabriela; Rogers, Robin D.
From Nature (London, United Kingdom) (2015), 528(7581), 188-189. , DOI:10.1038/528188a

Update regulation to spur research into drugs that the body absorbs more easily and that could reach market more quickly, urge Julia L. Shamshina and colleagues. Ionic liq. drugs and formulations, with ionic bonds, offer good potential as better pharmaceuticals with high absorption potential.

21. Hydrogels based on cellulose and chitin: fabrication, properties, and applications
By Shen, Xiaoping; Shamshina, Julia L.; Berton, Paula; Gurau, Gabriela; Rogers, Robin D.
From Green Chemistry (2016), 18(1), 53-75. , DOI:10.1039/C5GC02396C

A review. This review is focused on the fabrication, properties, and applications of hydrogels prepd. from two of the most abundant biopolymers on earth, cellulose and chitin. The review emphasizes the latest developments in hydrogel prepn. (including solvent systems, crosslinker types, and prepn. methods, which det. the "greenness" of the process) using these biocompatible and biodegradable biopolymers. The prepn. of both phys. (without covalent crosslinks) and chem. (with covalent crosslinks) hydrogels via dissoln./gelation is discussed. Addnl., formation of injectable thermoset and/or pH sensitive hydrogels from aq. solns. of derivs. (chitosan, Me cellulose, and hydroxypropylmethyl cellulose) with or without a crosslinker are discussed. This review also compares the design parameters for different applications of various pure and composite hydrogels based on cellulose, chitin, or chitosan, including applications as controlled and targeted drug delivery systems, improved tissue engineering scaffolds, wound dressings, water purifn. sorbents, and others.

22. The Use of Cooling Crystallization in an Ionic Liquid System for the Purification of Pharmaceuticals
By Weber, Cameron C.; Kulkarni, Samir A.; Kunov-Kruse, Andreas J.; Rogers, Robin D.; Myerson, Allan S.
From Crystal Growth & Design (2015), 15(10), 4946-4951. , DOI:10.1021/acs.cgd.5b00855

The application of ionic liqs. (ILs) as solvents is frequently discussed in the context of their tunability, with the potential to tailor the solvent system uniquely to the process being investigated. Instead, here we study the potential for a single IL, 1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([C_2C_1Im][NTf_2]), to be used for the cooling crystn. of a wide range of active pharmaceutical ingredients (APIs). [C_2C_1Im][NTf_2] was selected on the basis of its thermal stability, low reactivity, and miscibility with solvents

of moderate polarity, which suggests that it is miscible with liqs. that possess polarities comparable to those of many API mols. The overwhelming majority of APIs tested were sol. at >50 wt % within $[C_2C_1Im][NTf_2]$ at elevated temps. despite their relatively poor soly. at room temp. This dramatic effect was ascribed to the miscibility of most of the molten APIs with the IL. The soly. curves for nine APIs were measured, which established the potential use of this IL as a crystn. solvent. Finally, cooling crystns. were conducted using acetaminophen contg. common impurities as models. The cooling crystns. within $[C_2C_1Im][NTf_2]$ were found to produce acetaminophen in similar or greater purity with substantially improved yields relative to those of a no. of control cooling and antisolvent crystns.

23. Ionic Fluids Containing Both Strongly and Weakly Interacting Ions of the Same Charge Have Unique Ionic and Chemical Environments as a Function of Ion Concentration

By Wang, Hui; Kelley, Steven P.; Brantley, Jimmy W., III; Chatel, Gregory; Shamshina, Julia; Pereira, Jorge F. B.; Debbeti, Varun; Myerson, Allan S.; Rogers, Robin D.

From ChemPhysChem (2015), 16(5), 993-1002. , DOI:10.1002/cphc.201402894

Liq. multi-ion systems made by combining two or more salts can exhibit charge ordering and interactions not found in the parent salts, leading to new sets of properties. This is studied herein by examg. a liq. comprised of a single cation, 1-ethyl-3-methylimidazolium ($[C_2mim]^+$), and two anions with different properties, acetate ($[OAc]^-$) and bis(trifluoromethylsulfonyl)imide ($[NTf_2]^-$). NMR and IR spectroscopy indicate that the electrostatic interactions are quite different from those in either $[C_2mim][OAc]$ or $[C_2mim][NTf_2]$. This is attributed to the ability of $[OAc]^-$ to form complexes with the $[C_2mim]^+$ ions at >1:1 stoichiometries by drawing $[C_2mim]^+$ ions away from the less basic $[NTf_2]^-$ ions. Soly. studies with mol. solvents (Et acetate, water) and pharmaceuticals (ibuprofen, diphenhydramine) show nonlinear trends as a function of ion content, which suggests that soly. can be tuned through changes in the ionic compns.

24. Double salt ionic liquids with unique chemical environments for separations

By Rogers, Robin D.; Wang, Hui; Kelley, Steven P.

From Abstracts of Papers, 249th ACS National Meeting & Exposition, Denver, CO, United States, March 22-26, 2015 (2015), I+EC-1.

The field of ionic liqs. (ILs) is dominated by binary salts, which are valued for being tunable by changing the ions. However, the tunability of ILs can be further enhanced by combining two ILs or dissolving a solid salt in an IL to give a homogeneous ionic fluid with three or more ions. We have adopted the term Double Salt Ionic Liq. (DSIL) to describe these systems, which are molten analogs of cryst. double salts (salts with three or more ions in a single crystal lattice). While combining molten ILs tends to resemble ideal mixing in some ways, ILs also have a microstructure not commonly found in mol. compds. which would be expected to change upon combination with another ionic compd. Here we present a study of the phys. and spectroscopic properties of DSILs composed of 1-ethyl-3-methylimidazolium ($[C_2mim]^+$) cation and two anions, the hydrophilic acetate ($[OAc]^-$) and the hydrophobic bis(trifluoromethane)sulfonimide ($[NTf_2]^-$). The high basicity of $[OAc]^-$ allows it to draw $[C_2mim]^+$ cations away from the $[NTf_2]^-$ anions, creating ionic clusters which are not possible in either of the parent ILs. The soly. of solvent mols. (Et acetate and water) and active pharmaceutical ingredients with different acidities (ibuprofen and diphenhydramine) were found to be finely tunable by varying the ratio of $[OAc]^-$ to $[C_2mim]^+$. This study points the possibility that DSILs can provide systems

with tunable and unique solubilities which might find use in many new sepn. processes.

25. Pharmaceutically active supported ionic liquids

By Cojocaru, O. Andreea; Siriwardana, Amal; Gurau, Gabriela; Rogers, Robin D.

Edited By:Fehrmann, Rasmus; Riisager, Anders; Haumann, Marco

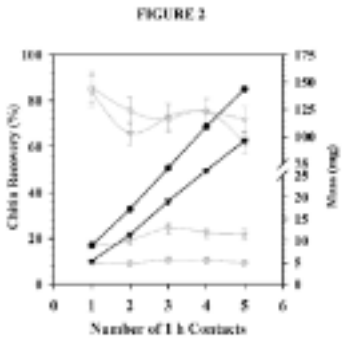
From Supported Ionic Liquids (2014), 387-405.

A review. This article describes the application of ionic liqs. as solvents in synthesis as well as in crystn. and sepn. of the active pharmaceutical ingredients. The liq. property o f the API-ILs seems to be one soln. to overcome the disadvantages of lim ited soly., low bioavailability, variable polymorphs, and limited membrane transport, but in the same time may also present challenges related to their prepn., handling, and the need for special devices for delivery.

26. Coagulation of biopolymers from ionic liquid solutions using CO2

By Rogers, Robin D.; Barber, Patrick S.; Griggs, Chris S.; Gurau, Gabriela; Lu, Xingmei; Zhang, Suojiang

From PCT Int. Appl. (2014), WO 2014125438 A1 20140821.



Disclosed herein are processes for providing a biopolymer from a biomass or source of chitin using ionic liqs. The processes involve contacting a biomass or source of chitin with an ionic liq. to produce a biopolymer comprising soln. and pptg. the biopolymer from the soln. with supercrit. CO_2, gaseous CO_2, or combinations thereof. An ionic liq. contg. 3-ethyl-1-methyl-1H-imidazol-3-ium acetate was used to prep. chitin with the help of a microwave oven.

27. Overcoming the problems of solid state drug formulations with ionic liquids

By Shamshina, Julia L.; Rogers, Robin D.

From Therapeutic Delivery (2014), 5(5), 489-491. , DOI:10.4155/tde.14.28

28. Simultaneous membrane transport of two active pharmaceutical ingredients by charge assisted hydrogen bond complex formation

By Wang, Hui; Gurau, Gabriela; Shamshina, Julia; Cojocaru, O. Andreea; Janikowski, Judith; MacFarlane, Douglas R.; Davis, James H., Jr.; Rogers, Robin D.

From Chemical Science (2014), 5(9), 3449-3456. , DOI:10.1039/C4SC01036A

Using permeation through a model membrane in a Franz diffusion cell, we have demonstrated that acidic and basic active pharmaceutical ingredients (APIs) in deep eutectic 'liq. co-crystal' form can be held tightly together, even in soln., via strong hydrogen bonds or partially ionized interactions, providing simultaneous transport at rates much higher than solns. of their corresponding, com. available cryst. salts, albeit at rates that are lower than the neutral forms of the individual mols. It was also shown that the deep eutectic APIs do not have to be premade, but hydrogen-bonded complexes can be formed in situ by mixing the corresponding API-solvent solns. To understand the behavior, we have extensively studied a range of nonstoichiometric mixts. of lidocaine and ibuprofen spectroscopically and via membrane transport. The data demonstrates the nature of the interactions between the acid and base and provides a route to tune the rate of membrane transport.

29. Ionic liquids in drug delivery

By Shamshina, Julia L.; Barber, Patrick S.; Rogers, Robin D.

From Expert Opinion on Drug Delivery (2013), 10(10), 1367-1381. , DOI:10.1517/17425247.2013.808185

A review. Introduction: To overcome potential problems with solid-state APIs, such as polymorphism, soly. and bioavailability, pure liq. salt (ionic liq.) forms of active pharmaceutical ingredients (API-ILs) are considered here as a design strategy. Areas covered: After a crit. review of the current literature, the recent development of the API-ILs strategy is presented, with a particular focus on the liquefaction of drugs. A variety of IL tools for control over the liq. salt state of matter are discussed including choice of counterion to produce an IL from a given API; the concept of oligomeric ions that enables liquefaction of solid ILs by changing the stoichiometry or complexity of the ions; formation of liq. co-crystals' where hydrogen bonding is the driving force in the liquefaction of a neutral acid-base complex; combining an IL strategy with the prodrug strategy to improve the delivery of solid APIs; using ILs as delivery agents via trapping a drug in a micelle and finally ILs designed with tunable hydrophilic-lipophilic balance that matches the structural requirements needed to solubilize poorly water-sol. APIs. Expert opinion: The authors believe that API-IL approaches may save failed lead candidates, extend the patent life of current APIs, lead to new delivery options or even new pharmaceutical action. They encourage the pharmaceutical industry to invest more research into the API-IL platform as it could lead to fast-tracked approval based on similarities to the APIs already approved.

30. Ionic liquid forms of active pharmaceutical ingredients in drug delivery

By Cojocaru, O. Andreea; Rogers, Robin D.

From Abstracts of Papers, 246th ACS National Meeting & Exposition, Indianapolis, IN, United States, September 8-12, 2013 (2013), AEI-66.

Ionic liqs. (ILs, salts that melt under 100°C) are a unique class of compds. whose chemo-phys. properties can be easily varied and controlled. A wide variety of anions and cations can be used to tune the ILs for specifically targeted properties. This can be seen in the evolution of ILs from solvents (1st generation of ILs) to energetic materials (2nd generation of ILs) and further more to biol. compds. (3rd generation of ILs). This presentation focuses on the application of the IL approach to active pharmaceutical ingredients (APIs) and the advantages offered for improving several properties of currently used solid APIs. Currently, the pharmaceutical industry is facing several problems (e.g., polymorphism, low water soly., and low bioavailability) mainly related to the solid state of the APIs. One soln. to these problems is the liquefaction of solid APIs into IL-APIs which we have shown to exhibit superior properties when compared to the parent API. Combining the IL strategy with several other strategies, such as the prodrug and supported ionic liq. phase (SILP) strategies, can lead to new potential drug delivery systems. These concepts have been supported through release studies of the parent API and of the IL-API from the solid support, resp., into simulated body fluids.

31. Procainium Acetate Versus Procainium Acetate Dihydrate: Irreversible Crystallization of a Room-Temperature Active Pharmaceutical-Ingredient Ionic Liquid upon Hydration

By Cojocaru, O. Andreea; Kelley, Steven P.; Gurau, Gabriela; Rogers, Robin D.

From Crystal Growth & Design (2013), 13(8), 3290-3293. , DOI:10.1021/cg400686e

Anhyd. procainium acetate is a room temp. ionic liq. (T_g = -25 °C); however, in the presence of water, this salt forms a cryst. dihydrate (T_m = 52 °C) that cannot be dehydrated without decompn. Unintended crystn. of any active pharmaceutical ingredient can dramatically alter its soly. and bioavailability, making it essential that ionic liq. APIs be carefully studied for their crystn. behavior.

32. Drug specific, tuning of an ionic liquid's hydrophilic-lipophilic balance to improve water solubility of poorly soluble active pharmaceutical ingredients

By McCrary, Parker D.; Beasley, Preston A.; Gurau, Gabriela; Narita, Asako; Barber, Patrick S.; Cojocaru, O. Andreea; Rogers, Robin D.

From New Journal of Chemistry (2013), 37(7), 2196-2202. , DOI:10.1039/c3nj00454f

Amphotericin B and itraconazole were used to demonstrate that ionic liqs. can be designed or chosen to provide tunable hydrophilicity in one ion and lipophilicity in the other allowing one to match the structural requirements needed to solubilize poorly water sol. active pharmaceutical ingredients. These liq., amphiphilic excipients could be used as both drug delivery systems and solubilization agents to improve the aq. soly. of many drugs. The soly. in deionized water, simulated gastric fluid, simulated intestinal fluid, and phosphate buffer soln. was greatly improved over current methods for drug delivery by utilizing designed ionic liqs. as excipients.

33. Hydrophobic vs. hydrophilic ionic liquid separations strategies in support of continuous pharmaceutical manufacturing

By Wang, Hui; Gurau, Gabriela; Kelley, Steven P.; Myerson, Allan S.; Rogers, Robin D.

From RSC Advances (2013), 3(25), 10019-10026. , DOI:10.1039/c3ra41082j

Taking advantage of the dramatically different solvent properties of hydrophilic ionic liqs. (ILs) when dry vs. when wet allows unique sepns. strategies compared to the use of hydrophobic ionic liqs. This is demonstrated here by comparing the sepn. of a water insol. amide intermediate for aliskiren from its reactants, a water insol. lactone, water sol. 3-amino-2,2-dimethylpropanamide, and the water sol. promoter 2-ethylhexanoic acid, using the hydrophobic ionic liq. 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([C_2mim][NTf_2]) and the hydrophilic ionic liq. 1-ethyl-3-methylimidazolium acetate ([C_2mim][OAc]). Both the water sol. [C_2mim][OAc], when dry, and water insol. [C_2mim][NTf_2] can dissolve the highly hydrophobic and hydrophilic compds. simultaneously, but the two ILs require different strategies to sep. the mixts. of these compds. Using the hydrophobic [C_2mim][NTf_2], the hydrophobic compds. can be sepd. from the hydrophilic reactants by extn. and pptn. with water, however, the hydrophobic IL is more difficult to completely remove after the sepns. In [C_2mim][OAc], the most hydrophobic starting material can be extd. from the IL phase into Et acetate, and then water can be added to ppt. the hydrophobic amide product while at the same time removing the IL from the pharmaceuticals.

34. Prodrug ionic liquids: functionalizing neutral active pharmaceutical ingredients to take advantage of the ionic liquid form

By Cojocaru, O. Andreea; Bica, Katharina; Gurau, Gabriela; Narita, Asako; McCrary, Parker D.; Shamshina, Julia L.; Barber, Patrick S.; Rogers, Robin D.

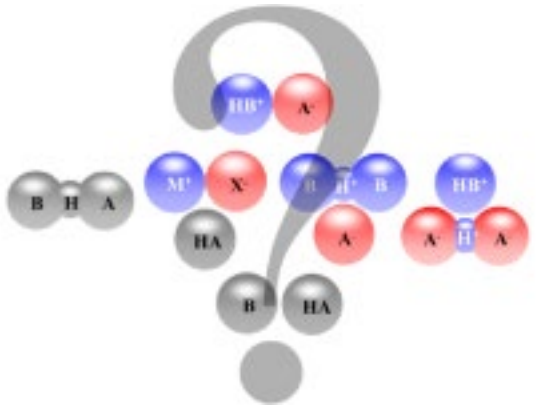
From MedChemComm (2013), 4(3), 559-563. , DOI:10.1039/c3md20359j

Neutral, non- or not easily-ionizable active pharmaceutical ingredients can take advantage of the unique property sets of ionic liqs. by functionalization with hydrolyzable, charged (or ionizable) groups in the prepn. of ionic liq. prodrugs as demonstrated here with the synthesis, characterization, and hydrolysis of cationic acetaminophen prodrugs paired with the docusate anion.

35. Understanding the Effects of Ionicity in Salts, Solvates, Co-Crystals, Ionic Co-Crystals, and Ionic Liquids, Rather than Nomenclature, Is Critical to Understanding Their Behavior

By Kelley, Steven P.; Narita, Asako; Holbrey, John D.; Green, Keith D.; Reichert, W. Matthew; Rogers, Robin D.

From Crystal Growth & Design (2013), 13(3), 965-975. , DOI:10.1021/cg4000439



A review. The incorporation of active pharmaceutical ingredients (APIs) into multicomponent solid forms (such as salts and co-crystals) or liq. forms (such as ionic liqs. (ILs) or deep eutectic mixts.) is important in optimizing the efficacy and delivery of APIs. However, there is a current debate regarding the classification of these multicomponent systems based on their ionicity which could interfere with their consideration in important applications. Multicomponent systems of intermediate ionicity can show a combination of properties, leading to behavior that is neither strictly typical of either purely ionic or purely neutral compds., nor easily described as intermediate between the two. In this perspective, we attempt to illustrate the problems in classifying multicomponent APIs based on one of two categories by discussing selected literature regarding solid and liq. multicomponent APIs and presenting the crystal structures of some relevant systems as case studies. It is clear that a focus on restrictive nomenclature carries with it the risk that a thorough examn. of the physicochem. properties of the compds. will be overlooked.

36. The role of ionic liquids in the pharmaceutical manufacturing processes

By Wang, Hui; Zhou, Xiaosi; Gurau, Gabriela; Rogers, Robin D.

Edited By:Zhang, Wei; Cue, Berkeley W., Jr

From Green Techniques for Organic Synthesis and Medicinal Chemistry (2012), 469-496. , DOI:10.1002/9780470711828.ch17

A review. This article describes about the roles of ionic liqs. in pharmaceutical manufg. processes and products, the synthesis of drugs or drug intermediates, the use of ILs in pharmaceutical crystn., in pharmaceutical sepn., for the extn. of drugs from natural products, to deliver drugs, to detect drugs, and even as APIs.

37. Cellulosic biocomposites as molecular scaffolds for nano-architectures

By Daly, Daniel T.; Spear, Scott K.; Turner, Megan B.; Hough, Whitney Lauren; Rogers, Robin D.

From U.S. Pat. Appl. Publ. (2012), US 20120122691 A1 20120517.

Disclosed are composites that comprise regenerated cellulose, a first active substance, a second active substance, and a linker. Methods for prepg. the composites that involve the use of ionic liqs. are also disclosed. Articles prepd. from the disclosed

composites and methods of using them are further disclosed. For example, regenerated cellulose film was obtained by treating original cellulose with 1-butyl-3-methylimidazolium chloride, and the regenerated cellulose film was treated with poly-lysine hydrobromide to give a functionalized cellulose film. The film was further reacted with glutaraldehyde and laccase to give to give a functionalized composite film, which was used for transestification of Et butyrate to Bu butyrate.

38. Pharmaceutically active ionic liquids with solids handling, enhanced thermal stability, and fast release

By Bica, Katharina; Rodriguez, Hector; Gurau, Gabriela; Andreea Cojocaru, O.; Riisager, Anders; Fehrmann, Rasmus; Rogers, Robin D.

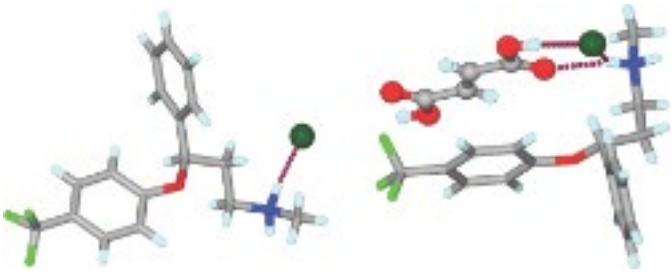
From Chemical Communications (Cambridge, United Kingdom) (2012), 48(44), 5422-5424. , DOI:10.1039/c2cc30959a

Pharmaceutically active compds. in ionic liq. form immobilized onto mesoporous silica are stable, easily handled solids, with fast and complete release from the carrier material when placed into an aq. environment. Depending on specific ion-surface interactions, they may also exhibit improved thermal stability when compared to the non-adsorbed compds.

39. Polymorphs, Salts, and Cocrystals: What's in a Name?

By Aitipamula, Srinivasulu; Banerjee, Rahul; Bansal, Arvind K.; Biradha, Kumar; Cheney, Miranda L.; Choudhury, Angshuman Roy; Desiraju, Gautam R.; Dikundwar, Amol G.; Dubey, Ritesh; Duggirala, Nagakiran; et al

From Crystal Growth & Design (2012), 12(5), 2147-2152. , DOI:10.1021/cg3002948



The Dec. 2011 release of a draft United States Food and Drug Administration (FDA) guidance concerning regulatory classification of pharmaceutical cocrystals of active pharmaceutical ingredients (APIs) addressed two matters of topical interest to the crystal engineering and pharmaceutical science communities: (1) a proposed definition of cocrystals; (2) a proposed classification of pharmaceutical cocrystals as dissociable "API-excipient" mol. complexes. The Indo-U.S. Bilateral Meeting sponsored by the Indo-U.S. Science and Technol. Forum titled The Evolving Role of Solid State Chem. in Pharmaceutical Science was held in Manesar near Delhi, India, from Feb. 2-4, 2012. A session of the meeting was devoted to discussion of the FDA guidance draft. The debate generated strong consensus on the need to define cocrystals more broadly and to classify them like salts. It was also concluded that the diversity of API crystal forms makes it difficult to classify solid forms into three categories that are mutually exclusive. This perspective summarizes the discussion in the Indo-U.S. Bilateral Meeting and includes contributions from researchers who were not participants in the meeting.

40. Membrane transport of active pharmaceutical ingredient-based ionic liquids

By Wang, Hui; Gurau, Gabriela; Rogers, Robin D.

From Abstracts of Papers, 243rd ACS National Meeting & Exposition, San Diego, CA, United States, March 25-29, 2012 (2012), IEC-292.

Currently, the pharmaceutical industry mainly depends on cryst. active pharmaceutical ingredients (APIs). Unfortunately, many of such drugs fail to pass testing due to issues with delivery mechanisms such as dissoln., transport, bioavailability, and poor control over polymorphism. Some years ago, we proposed strategies based on ionic liqs. (ILs) as APIs to impart new or enhanced properties into existing APIs. The API-ILs synthesized from pharmaceutical ingredient salts not only retain pharmaceutical activity but also have the added benefits of existing in a liq. form. Herein, we will discuss the transport ability of some API-ILs through artificial silicon membrane and compare it with that of the starting materials used for the synthesis of API-ILs.

41. Ionic liquids: A platform for innovation

By Daly, Dan T.; Frazier, Rachel M.; Qin, Ying; Spear, Scott K.; Hough, Whitney L.; Rogers, Robin D.

From Abstracts of Papers, 243rd ACS National Meeting & Exposition, San Diego, CA, United States, March 25-29, 2012 (2012), IEC-261.

Ionic liqs. (ILs) have numerous applications, making them ideal materials for platform technologies. A key challenge to any new material is advancing from the lab. to the marketplace, thereby bridging the gap from proof-of-concept to prototype. ILs are no exception to this process, thus we explore the developmental part Alabama Innovation and Mentoring of Entrepreneurs (AIME) plays in transitioning ILs from invention to innovation. Specific technologies have been identified as having significant potential for success and AIME has assisted in developing the technol. beyond proof-of-concept. A sample of technologies to be discussed include: a tunable approach for IL-biomass prodn. and recovery, IL-processed drug delivery devices, exfoliation of graphite in ILs to produce graphene, and new ILs as active layers in photovoltaics. Emphasis will be placed on the distinct advantages of ILs and how this offers a unique advantage in creating a portfolio of complementary technologies.

42. Ionic liquid-active pharmaceutical ingredients loaded on silica: Solids handling for liquid pharmaceutical forms

By Rogers, Robin D.; Cojocaru, O. A.; Siriwardana, Amal; Kolding, Helene; Bica, Katharina; Rodriguez, Hector; Gurau, Gabriela; Riisager, Anders; Fehrmann, Rasmus

From Abstracts of Papers, 243rd ACS National Meeting & Exposition, San Diego, CA, United States, March 25-29, 2012 (2012), IEC-93.

Ionic Liqs. (ILs, salts that melt below 100 °C) loaded on silica have been studied for gas phase reactions, but they have not been used in soln. due to the leaching properties of the ILs and the deactivation of the catalyst. One area where the "Supported Ionic Liq. Phase" (SILP) strategy would be a tremendous advantage would be in the loading of ILs that are intended and necessarily leached in order to carry out their functions, as is the case of ILs of Active Pharmaceutical Ingredients (APIs). We have found that IL-APIs are readily loaded and leached from silica, giving to the material a few advantages including the ability to deliver these liq. salt drugs in solid form as free flowing powders. This presentation will discuss the loading, leaching, and favorable phys. and chem. properties exhibited by these IL-APIs in solid form.

43. Ionic Liquid (IL) based drugs for the $1.2B pain management sector: New disruptive directions in pain management

By Gurau, Gabriela; Daly, Daniel T.; Rogers, Robin D.

From Abstracts of Papers, 243rd ACS National Meeting & Exposition, San Diego, CA, United States, March 25-29, 2012 (2012), COMSCI-8.

As the global market is forecasted to increase at a Compd. Annual Growth Rate of 3.1% over the next few years, and with nearly 18.6m individuals expected to suffer from post-operative pain only, the pharmaceutical sector faces a real challenge: to develop products that induces local anesthesia rapidly in a cost effective manner. The problem with existing pain management medications is short durations of effective treatment leading to multiple doses and potentially dangerous side effects.

525 Solutions, Inc. Publications Related to Pharmaceuticals

525PainManagement (525PM) , has leveraged its knowledge of ionic liqs. (ILs; quite literally liq. salts) to develop pain management drugs, by selectively combining two com. proven- active pharmaceutical ingredients in one IL form, that has been obsd. to produce longer lasting controlled pain treatment. The IL technol. can be most effectively applied to not only give a better control of drug performance and effectiveness, but also help the IL-formed drug to shorten the FDA approval timeline.

44. Physicochemical properties of maize cob cellulose powders reconstituted from ionic liquid solution

By Azubuike, Chukwuemeka P.; Rodriguez, Hector; Okhamafe, Augustine O.; Rogers, Robin D.

From Cellulose (Dordrecht, Netherlands) (2012), 19(2), 425-433. , DOI:10.1007/s10570-011-9631-y

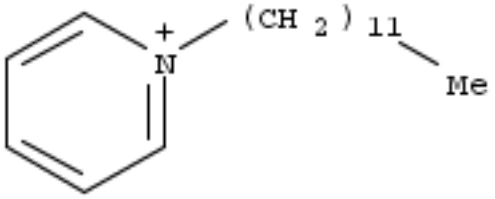
Suitable α-cellulose and cellulose II powders for use in the pharmaceutical industry can be derived from maize cob. α-Cellulose was extd. from an agricultural residue (maize cobs) using a non-dissolving method based on inorg. substances. Modification of this α-cellulose was carried out by its dissoln. in the ionic liq. 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl), and subsequent regeneration by addn. of either water or acetone at room temp., or of boiling water. X-ray diffraction and IR spectroscopy results showed that the regenerated celluloses had lower crystallinity, and proved that the treatment with [C_4mim]Cl led to the conversion of the cryst. structure of α-cellulose from cellulose I to cellulose II. Thermogravimetric anal. and differential scanning calorimetry data showed quite similar thermal behavior for all cellulose samples, although with somewhat lower stability for the regenerated celluloses, as expected. The comparison of physicochem. properties of the regenerated celluloses and the native cellulose mainly suggests that the regenerated ones might have better flow properties. For some of the characterizations carried out, it was generally obsd. that the sample regenerated with boiling water had more similar characteristics to the α-cellulose sample, evidencing an influence of the regeneration strategy on the resulting powder after the ionic liq. treatment.

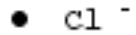
45. Herbicidal ionic liquid compositions and methods of use

By Pernak, Juliusz; Shamshina, Julia; Tadeusz, Praczyk; Syguda, Anna; Janiszewska, Dominika; Smiglak, Marcin; Gurau, Gabriela; Daly, Daniel T.; Rogers, Robin D.

From PCT Int. Appl. (2012), WO 2012006313 A2 20120112.

Disclosed are compns. and methods of prepg. compns. of active herbicidal ingredients. Also disclosed are methods of using the compns. described herein to improve herbicide delivery and efficacy, enhance herbicidal penetration, reduce herbicide volatility and drift, diminish environmental damage from herbicides, decrease water soly. and volatility of herbicides, and introduce addnl. biol. function to herbicides. Exemplary herbicidal ionic liqs. according to the invention are prepd. using mecoprop-P, dicamba and glyphosate with various cationic agents and tested for weed control in comparison to com. prepns. of these herbicides with comparative results.



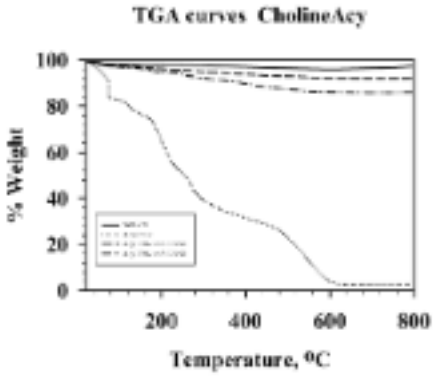


525 Solutions, Inc. Publications Related to Pharmaceuticals

46. Biologically active compounds supported on solid carrier such as silica for controlled release and improved thermal stability

By Riisager, Anders; Fehrmann, Rasmus; Rodriguez, Hector; Bica, Katarina; Rogers, Robin D.; Daly, Daniel T.; Gurau, Gabriela

From PCT Int. Appl. (2011), WO 2011110662 A1 20110915.



The present invention relates to biol. active compds., particularly liq. compds., which are immobilized on a solid carrier material, particularly on mesoporous silica. The compds. are non-covalently supported on the solid carrier material thereby forming stable, easily handled solids which have the further advantage that the adsorbed biol. active compds. have improved thermal stability compared with the non-adsorbed compds., and that they are released rapidly and completely from the carrier material when placed in an aq. environment. Thus, tetrabutylphosphonium ibuprofenate (TBPI) was prepd. by reaction of ibuprofenic acid with tetrabutylphosphonium hydroxide. Controlled release of silica-supported TBPI in simulated gastric fluid or simulated intestinal fluid was demonstrated. Thermal stability of TBPI was measured by detg. the inflection point by heating from 25° to 800° with a heating rate of 5°/min under air. The inflection points for non-supported TBPI and silica-supported TBPI loaded at 10% and 20% were 236°, 386° and 263°, resp.

47. Award Address (ACS Award in Separations Science and Technology sponsored by Waters Corporation). Ionic liquids from there to here

By Rogers, Robin D.

From Abstracts of Papers, 241st ACS National Meeting & Exposition, Anaheim, CA, United States, March 27-31, 2011 (2011), I+EC-148.

Over the last fifteen years, one aspect of the Rogers' Group research has focused on ionic liqs. (ILs), investigating both the application, and fundamental understanding, of how ILs can be used as sepns. media. This research has included advances in their prepn. and studies on toxicity through applications in reaction and sepns. processes for org. mols., radionuclides, metal cations and complexes and biomols., to the development of IL energetic materials and active pharmaceutical agents. However, the story of this work would not be complete without discussion of its roots in undergraduate and graduate research projects on liq. clathrates with Jerry Atwood at The University of Alabama, its manifestation into liq. sepns. in faculty sabbatical research in radiochem. and sepns. with Phil Horwitz at Argonne National Lab., its re-emergence with the IL phenomenon developed in collaboration with Ken Seddon of Queen's University of Belfast, and the many students and collaborators.

48. Ionic liquids as active pharmaceutical ingredients (IL-APIs): The challenges of commercialization

By Gurau, Gabriela; Rogers, Robin D.

From Abstracts of Papers, 241st ACS National Meeting & Exposition, Anaheim, CA, United States, March 27-31, 2011 (2011), I+EC-119.

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Even after two decades of intensive research, ionic liqs. (ILs, broadly defined as salts that melt below 100 °C) are still underutilized to their full potential. Nowadays, the roles of ILs include quite diverse areas such as solvents, electrolytes, lubricants, thermal fluids, photovoltaics, etc. We have recently added another: IL forms of active pharmaceutical ingredients (APIs), where the true potential of pure liq. vs. Solid forms of the APIs is not yet recognized. A crucial aspect in advancing our research to commercialization is recognizing those areas where direct collaboration with established industry is needed vs. Those areas which lend themselves to entrepreneurial start-up companies. This presentation will discuss advances in the IL-API area from scientific, as well as business perspectives.

49. Release of ionic liquid-active pharmaceutical ingredients from biopolymeric beads

By McCrary, Parker D.; Smiglak, Marcin; Spear, Scott K.; Bates, Nicolas S.; Daly, Daniel T.; Rogers, Robin D.

From Abstracts of Papers, 241st ACS National Meeting & Exposition, Anaheim, CA, United States, March 27-31, 2011 (2011), I+EC-106.

This presentation will discuss delivery of pharmaceuticals in the form of ionic liqs. (ILs) by encapsulation into biopolymeric beads to increase their bioavailability. Here the strategy will be illustrated by the synthesis of an IL of the active pharmaceutical ingredient (API) ibuprofen in its anionic form (a common model pharmaceutical) paired with cations of several other APIs. The talk will review the incorporation of the new IL-APIs into natural biopolymer beads via dissoln. and spray drying and discuss the measured release rates of the ILs when the beads are placed in buffer solns. Current challenges and opportunities in the selection of biopolymer platforms for the release of IL-APIs will be discussed.

50. Temperature controlled release of nicotine from its metal complexes

By Sharma, C. V. Krishnamohan; Hines, C. Corey; Rogers, Robin D.

From Abstracts of Papers, 241st ACS National Meeting & Exposition, Anaheim, CA, United States, March 27-31, 2011 (2011), I+EC-28.

Generation of pure nicotine aerosols for inhalation drug delivery provides a novel means for delivering nicotine for smoking cessation purposes. However, the delivery of nicotine aerosols without any additives is a challenging task given its high vapor pressures, the need for dosing accuracy, safety, and cost related issues. In this presentation, we demonstrate that the concepts of crystal engineering and sepn. science could be applied to drug delivery applications - where the thermally reversible coordination complexes of nicotine-metal halides release therapeutically relevant doses of pure nicotine aerosols upon rapid heating.

51. Liquid forms of pharmaceutical co-crystals: exploring the boundaries of salt formation

By Bica, Katharina; Shamshina, Julia; Hough, Whitney L.; MacFarlane, Douglas R.; Rogers, Robin D.

From Chemical Communications (Cambridge, United Kingdom) (2011), 47(8), 2267-2269. , DOI:10.1039/C0CC04485G

The study presented evidence of hydrogen bond formation, not salt formation, as the driving force in the liquefaction of a solid pharmaceutical in the form of a neutral acid-base complex, as exemplified by the liq. formed from a mixt. of the local anesthetic lidocaine with fatty acids; these complexes exist at the boundary between simple eutectics and partially ionized ionic liqs.

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52. Open innovation and the faculty entrepreneur: Opportunities and perils

By Rogers, Robin D.; Daly, Daniel T.; Gurau, Gabriela

From Abstracts of Papers, 240th ACS National Meeting, Boston, MA, United States, August 22-26, 2010 (2010), BMGT-37.

Industry and universities have had a growing relationship in the development of new technol. from the times of industry cutbacks in research labs and capabilities. This relationship has led to a growth in technol. transfer activities at many universities and the assocd. growing pains related to the inherent conflicts in the industry and academic research models. Today, we are seeing an increase in the no. of faculty entrepreneurs that wish to capitalize on the development of new technol. by founding start-up companies. The extension of the open innovation model to these start-ups must consider the unique conflicts and opportunities which exist when a faculty member must answer to both their home university and to their growing business. This presentation will discuss open innovation in light of our efforts to commercialize new ionic liq. technologies in the agrochem. and pharmaceutical sectors via a faculty start-up company, 525Solns.

53. Compounds comprising two or more biologically functional ions and method of treating Parkinson's disease

By Rogers, Robin D.; Rijksen, Christian; Daly, Daniel T.; Caldwell, Kim; Caldwell, Guy; Hough-Troutman, Whitney L.; Bica, Katharina

From PCT Int. Appl. (2010), WO 2010078258 A1 20100708.

Disclosed are compds. and methods of prepg. ionic liq. compns. of active pharmaceutical, biol., nutritional, and energetic ingredients. Also disclosed are methods of using the compns. described herein to overcome polymorphism, overcome soly. and delivery problems, to control release rates, add functionality, enhance efficacy (synergy), and improve ease of use and manuf.

54. Dual functioning ionic liquids and salts comprising active pharmaceutical, biological, and nutritional compounds

By Rogers, Robin D.; Daly, Daniel T.; Gurau, Gabriela; MacFarlane, Douglas; Turanjanin, Jelena; Dean, Pamela M.; Scott, Janet L.; Bica, Katharina; Seddon, Kenneth R.

From PCT Int. Appl. (2010), WO 2010078300 A1 20100708.

Disclosed herein are ionic liq. compns. comprising active pharmaceutical, biol., and nutritional compds., and methods of use. Further disclosed are compns. of matter including liq. ion pairs alone or in soln. and their use; compns. of ionic liqs. that are 'solvated,' for example, 'hydrated' and their uses. The method for prepg. a bioactive ionic liq. compn., comprises (a) providing one or more of the following: (i) one or more cations and one or more anions, wherein either the cations, anions, or both can have a bioactive property; or (ii) one or more cation precursors and one or more anion precursors, wherein either the cation precursors, anion precursors, or both have a bioactive property when the precursor has a net charge; and (b) combining the cations and anions or the cation precursors and anion precursors, thereby producing a co-ionic liq. $[B^1HB^2]A$ or $B[A^1HA^2]$ that is liq. at a temp. at or below about 150°, wherein B, B^1, and B^2 represent cations, and A, A^1, and A^2 represent anions.

55. In search of pure liquid salt forms of aspirin: ionic liquid approaches with acetylsalicylic acid and salicylic acid

By Bica, Katharina; Rijksen, Christiaan; Nieuwenhuyzen, Mark; Rogers, Robin D.

From Physical Chemistry Chemical Physics (2010), 12(8), 2011-2017. , DOI:10.1039/b923855g

It is presented an ionic liq. (IL) approach towards a dual functional liq. salt form of aspirin using different pharmaceutically active cations composed of antibacterials, analgesics, local anesthetics, and antiarrhythmic drugs in combination with acetylsalicylic acid or its metabolite salicylic acid and discuss stability of these ILs in comparison to solid salts. Several low-melting or liq. salts of

salicylic acid with dual functionality and promising properties were isolated and characterized; however, although such ILs with aspirin could be prepd., they suffer from limited stability and slowly decomp. into the corresponding salicylate ILs when exposed to moisture.

56. Confused ionic liquid ions - a "liquification" and dosage strategy for pharmaceutically active salts
By Bica, Katharina; Rogers, Robin D.
From Chemical Communications (Cambridge, United Kingdom) (2010), 46(8), 1215-1217. , DOI:10.1039/b925147b

We present a strategy to expand the liq. and compositional ranges of ionic liqs., specifically pharmaceutically active ionic liqs., by simple mixing with a solid acid or base to form oligomeric ions.

57. Crystalline vs. Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper
By Stoimenovski, Jelena; MacFarlane, Douglas R.; Bica, Katharina; Rogers, Robin D.
From Pharmaceutical Research (2010), 27(4), 521-526. , DOI:10.1007/s11095-009-0030-0

A review. Why not consider liq. salt forms of active pharmaceutical ingredients (APIs) as an alternative versatile tool in the pharmaceutical industry. Recent developments have shown that known APIs can be readily converted into ionic liqs. and that these novel phases often possess different properties (e.g., improved solubilities and dissoln. rates), which may have a direct impact on the pharmacokinetics and pharmacodynamics of the drug. They may also offer the potential of novel and more efficient delivery modes, as well as patent protection for each of the new forms of the drug. Since these pharmaceutically active ionic liqs. represent a thermodynamically stable phase, they avoid the troublesome issues surrounding polymorphism and "polymorphic transformation." In some cases, an active cation and an active anion can be combined to produce a liq. possessing dual functionality. Here we examine and challenge the current industry reliance on cryst. APIs by discussing the breadth and potential impact of liq. salts as a possible approach to phase control.

58. "Drug" ionic liquids: A new phase for the pharmaceutical world
By MacFarlane, Douglas R.; Scott, Janet L.; Rogers, Robin D.
From Abstracts of Papers, 236th ACS National Meeting, Philadelphia, PA, United States, August 17-21, 2008 (2008), ORGN-302.

Many pharmaceutically active compds. are salts of an active ion in combination with a relatively simple and inert counterion. Replacement of that counterion by an alternative ion that has the characteristics familiar to the ionic liq. world opens up the possibility of creating new pharmaceutical compds. which are ionic liqs. Such ionic liq. forms of the active ion offer the potential to create tailored properties such as hydophobicity/hydrophilicity and soly. into the compd. by adjustment of the counterion. In the sense that different polymorphs of an active compd. are recognized in the pharmaceutical world as different, these ionic liqs. are certainly distinct from the other known forms of the active ion. In this work a no. of examples of this concept have been prepd. For example, the pyridostigmine cation (3-(dimethylaminocarbonyloxy)-1-methylpyridinium cation) is an acetylcholinesterase inhibitor marketed as the slightly sol. cryst. bromide salt; when the bromide ion is replaced by the saccharinate ion, a non crystallizable ionic liq. is formed. The liq. was found to have glass transition temp. around 4°C. A further example involves lidocaine docusate (LD), a hydrophobic room temp. IL which, when compared to lidocaine hydrochloride, exhibits modified soly., increased thermal stability, and a significant enhancement in the efficacy of topical analgesia.

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59. An anticrystal engineering approach to functional ionic liquids

By Scott, Janet L.; MacFarlane, Douglas R.; Dean, Pamela; Turanjanin, Jelena; Rogers, Robin D.

From Abstracts of Papers, 236th ACS National Meeting, Philadelphia, PA, United States, August 17-21, 2008 (2008), IEC-178.

An "anti-crystal engineering" approach to the design of functional ionic liqs. provides a means for rational choice (if not design) of ionic components likely to yield low melting, or non-cryst. salts. Thus, if "crystal engineering" entails selection of mol. or ionic components bearing specific features, expected to lead to assembly of a cryst. solid via the formation of supramol. synthons, "anti-crystal engineering" is the intentional avoidance of such complementarity of mol. or ionic features with the goal of generating a non-cryst. salt: an ionic liq. The utility (and limitations) of this approach, with respect to the synthesis of ionic liqs. with specific functionality, such as biol. activity or enhanced vapor pressure, will be discussed. New non-cryst. drug phases provide one example of such functional anti-crystal engineered liq. salts.

60. Ionic liquids then and now: from solvents to materials to active pharmaceutical ingredients

By Hough, Whitney L.; Rogers, Robin D.

From Bulletin of the Chemical Society of Japan (2007), 80(12), 2262-2269. , DOI:10.1246/bcsj.80.2262

A review. Ionic liqs. (ILs) have evolved from salts studied primarily for their phys. properties (low melting salts which could be used as solvents) to tunable materials based upon the phys., chem., and now even biol. properties that can be introduced through either ion. In this perspective, the authors follow this interesting evolution with respect to the authors' work in this growing field, and discuss possible future directions, such as the use of ILs as active pharmaceutical ingredients (APIs).

61. The third evolution of ionic liquids: Active pharmaceutical ingredients

By Hough, Whitney L.; Smiglak, Marcin; Rodriguez, Hector; Swatloski, Richard P.; Spear, Scott K.; Daly, Daniel T.; Pernak, Juliusz; Grisel, Judith E.; Carliss, Richard D.; Soutullo, Morgan D.; et al

From New Journal of Chemistry (2007), 31(8), 1429-1436. , DOI:10.1039/b706677p

A modular, ionic liq. (IL)-based strategy allows compartmentalized mol. level design of a wide range of new materials with tunable biol., as well as the well known phys. and chem., properties of ILs, which thus deserve consideration as 'tunable' active pharmaceutical ingredients (APIs) with novel performance enhancement and delivery options. IL strategies can take advantage of the dual nature (discrete ions) of ILs to realize enhancements which may include controlled soly. (e.g., both hydrophilic and hydrophobic ILs are possible), bioavailability or bioactivity, stability, elimination of polymorphism, new delivery options (e.g., slow release or the IL-API as 'solvent'), or even customized pharmaceutical cocktails. Here we exemplify this approach with, among others, lidocaine docusate (LD), a hydrophobic room temp. IL which, when compared to lidocaine hydrochloride, exhibits modified soly., increased thermal stability, and a significant enhancement in the efficacy of topical analgesia in two different models of mouse antinociception. Studies of the suppression of nerve growth factor mediated neuronal differentiation in rat pheochromocytoma (PC12) cells suggests potential differences between LD and lidocaine hydrochloride at the cellular level indicating an entirely different mechanism of action. Taken together these results suggest that the unique physiochem. properties of ILs in general, may confer a novel effect for the bioactivity of an API due to (at least) slow-release properties in addn. to novel delivery mechanisms.

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62. Multi-functional ionic liquid compositions for overcoming polymorphism and imparting improved properties for active ingredients

By Rogers, Robin D.; Daly, Daniel T.; Swatloski, Richard P.; Hough, Whitney L.; Davis, James Hillard; Smiglak, Marcin; Pernak, Juliusz; Spear, Scott K.

From PCT Int. Appl. (2007), WO 2007044693 A2 20070419.

Disclosed are ionic liqs. and methods of prepg. ionic liq. compns. of active pharmaceutical, biol., nutritional, and energetic ingredients. Also disclosed are methods of using the compns. described herein to overcome polymorphism, overcome soly. and delivery problems, to control release rates, add functionality, enhance efficacy (synergy), and improve ease of use and manuf. Hexadecylpyridinium valproic acid was prepd. by the reaction of hexadecylpyridinium chloride with sodium valproate.

63. Theoretical Scales of Hydrogen Bond Acidity and Basicity for Application in QSAR/QSPR Studies and Drug Design. Partitioning of Aliphatic Compounds

By Oliferenko, Alexander A.; Oliferenko, Polina V.; Huddleston, Jonathan G.; Rogers, Robin D.; Palyulin, Vladimir A.; Zefirov, Nikolai S.; Katritzky, Alan R.

From Journal of Chemical Information and Computer Sciences (2004), 44(3), 1042-1055. , DOI:10.1021/ci0342932

Phenomenol. anal. of existing hydrogen bond (HB) donor and acceptor scales and apparent phys. considerations have enabled the establishment of new quant. scales of hydrogen bond basicity and acidity. Chem. structures represented by mol. graphs and the orbital electronegativities of Hinze and Jaffe are utilized as an input data. The scales obtained correlate well with several exptl. solvent polarity scales such as $\sum\beta 2H$ and $\sum\alpha 2H$, pK(HB), and $E_T(30)$. To demonstrate the applicability of the new quantities, we have applied them to seven equil. partitioning data sets: octanol-water, hexadecane-water, chloroform-water, gas-water, gas-octanol, gas-hexadecane, and gas-chloroform partition coeffs. The hydrogen bond descriptors when supplemented by a cavity-forming term and a dipolarity term show high performance in correlations of the partition coeffs. of aliph. compds. These new HB descriptors can be used in studying hydrogen bonding and fluid phase equil. as well as scoring functions in ligand docking and descriptors in ADME evaluations.

64. Development of Ionic Liquids containing environmentally acceptable and sustainable components

By Holbrey, John D.; Reichert, W. Matthew; Turner, Megan B.; Green, Keith; Rogers, Robin D.

From Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), IEC-128.

There are issues with end-of-life disposal and environmental impact of some ionic liq. (IL) components, particularly perfluorinated anions. Although a solvent does not have to be green to be part of a green process, there is an understandable desire to develop green processes that utilize green components. We are actively investigating approaches to the synthesis of ILs with the aims of achieving atom efficiency, elimination of undesirable metathesis steps, and incorporation of application-enhancing functionality in the ionic liq. core. One area of particular interest is in reducing the requirement for anions that are environmentally hazardous, or for which, there are significant disposal issues. The potential to prep. new ionic liqs. using range of pharmaceutically acceptable anions and the utilization of clean syntheses of imidazolium-based ionic liqs. will be presented.

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65. Quantum mechanical models (AMSOL) for the prediction of the distribution of organic molecules in aqueous biphasic systems.

By Rogers, Robin D.; Carruth, Ashley D.; Willauer, Heather D.; Spear, Scott K.; Huddleston, Jonathan G.

From Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26 (1999), IEC-016.

Recently the SM5.4 quantum mech. solvation model (AMSOL) has been extended so that the free energies of solvation of a solute in almost any org. solvent may be calcd. Using a thermodn. cycle and a ref. solute, we have estd. the distribution of a no. of org. solutes in various solvent water systems. Of particular interest is the est. of log P in octanol/water systems which is widely used as a ref. partitioning system in a range of applications from simple comparison of the relative lipophilicity of different solvent systems to sophisticated quant. structure activity relationships in, for example, drug design. We will present our methods and the results obtained on the calcn. of Ko/w of a no. of low mol. wt. org. solutes. These will be compared to distribution values obtained in PEG - salt ABS. The difficulties inherent in extending the methodol. directly to ABS systems will be discussed. This research is supported by the Division of Chem. Sciences, Office of Basic Energy Sciences, Office of Energy Research, U. S. Department of Energy (Grant No. DE-FG02-96ER14673).

66. Modeling partitioning behavior in aqueous biphasic systems

By Willauer, Heather D.; Huddleston, Jonathan G.; Rogers, Robin D.

From Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (1999), I&EC-043.

Aq. biphasic systems (ABS) are suitable for the sepn. of small org. mols. in industrial and environmental applications, thus it is important to predict org. solute partitioning behavior both for small model compds. (benzene, salicylic acid) and large mols. (PCBs, PAHs, dyes, and pharmaceuticals). System parameters independent of polymer mol. wt. and salt type have been developed to describe partitioning in a PEG/salt ABS. These parameters are based on the degree of phase divergence of the system as measured by tie line length or difference in PEG compn. between the phases. This presentation will discuss our efforts to develop both a system parameter and solute parameter that describe partitioning in an ABS independent of solute type, PEG mol. wt., salt type, and salt concn. used to form the system.

67. Are Myths and Preconceptions Preventing us from Applying Ionic Liquid Forms of Antiviral Medicines to the Current Health Crisis?

By Shamshina Julia L; Rogers Robin D

From International journal of molecular sciences (2020), 21(17).

At the moment, there are no U.S. Food and Drug Administration (U.S. FDA)-approved drugs for the treatment of COVID-19, although several antiviral drugs are available for repurposing. Many of these drugs suffer from polymorphic transformations with changes in the drug's safety and efficacy; many are poorly soluble, poorly bioavailable drugs. Current tools to reformulate antiviral APIs into safer and more bioavailable forms include pharmaceutical salts and cocrystals, even though it is difficult to classify solid forms into these regulatory-wise mutually exclusive categories. Pure liquid salt forms of APIs, ionic liquids that incorporate APIs into their structures (API-ILs) present all the advantages that salt forms provide from a pharmaceutical standpoint, without being subject to solid-state matter problems. In this perspective article, the myths and the most voiced concerns holding back implementation of API-ILs are examined, and two case studies of API-ILs antivirals (the amphoteric acyclovir and GSK2838232) are presented in detail, with a focus on drug property improvement. We advocate that the industry should consider the advantages of API-ILs which could be the genesis of disruptive innovation and believe that in order for the industry to grow and develop, the industry should be comfortable with a certain element of risk because progress often only comes from trying something different.

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68. (15)N-, (13)C- and 1H-NMR Spectroscopy Characterization and Growth Inhibitory Potency of a Combi-Molecule Synthesized by Acetylation of an Unstable Monoalkyltriazene

By Senhaji Mouhri Zhor; Goodfellow Elliot; J Jean-Claude Bertrand; Kelley Steven P; Stein Robin S; Rogers Robin D

From Molecules (Basel, Switzerland) (2017), 22(7).

6-(3-Methyltriaz-1-en-1-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione referred to as EG22 (8a), is an open-chain 3-alkyl-1,2,3-triazene termed "combi-molecule" designed to inhibit poly(adenosine diphosphate ribose) polymerase (PARP) and damage DNA. To delay its hydrolysis, acetylation of N3 was required. Being a monoalkyl-1,2,3-triazene, EG22 could assume two tautomers in solution or lose nitrogen during the reaction, thereby leading to several acetylated compounds. Instead, one compound was observed and to unequivocally assign its structure, we introduced isotopically labeled reagents in its preparation, with the purpose of incorporating (15)N at N2 and (13)C in the 3-methyl group. The results showed that the 1,2,3-triazene moiety remained intact, as confirmed by (15)N-NMR, coupling patterns between the (15)N-labeled N2 and the (13)C-labeled methyl group. Furthermore, we undertook heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments that permitted the detection and assignment of all four nitrogens in 6-(3-acetyl-3-methyltriaz-1-en-1-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione, referred to as ZSM02 (9a), whose structure was further confirmed by X-ray crystallography. The structure showed a remarkable coplanarity between the N-acetyltriazene and the naphtalimide moiety. Thus, we unequivocally assigned 9a as the product of the reaction and compared its growth inhibitory activity with that of its precursor, EG22. ZSM02 exhibited identical growth inhibitory profile as EG22, suggesting that it may be a prodrug of EG22.

69. Choline-derivative-based ionic liquids

By Pernak Juliusz; Syguda Anna; Mirska Ilona; Pernak Anna; Nawrot Jan; Pradzynska Aleksandra; Griffin Scott T; Rogers Robin D

From Chemistry (Weinheim an der Bergstrasse, Germany) (2007), 13(24), 6817-27.

A total of sixty-three choline derivative-based ionic liquids in the forms of chlorides, acesulfamates, and bis(trifluoromethylsulfonyl)imides have been prepared and their physical properties (density, viscosity, solubility, and thermal stability) have been determined. Thirteen of these salts are known chlorides: precursors to the 26 water-soluble acesulfamates, 12 acesulfamates only partially miscible with water, and 12 water-insoluble imides. The crystal structures for two of the chloride salts-(2-hydroxyethyl)dimethylundecyloxymethylammonium chloride and cyclododecyloxymethyl(2-hydroxyethyl)dimethylammonium chloride-were determined. The antimicrobial (cocci, rods, and fungi) activities of the new hydrophilic acesulfamate-based ILs were measured and 12 were found to be active. The alkoxymethyl(2-hydroxyethyl)dimethylammonium acesulfamates have been shown to be insect feeding deterrents and thus open up a new generation of synthetic deterrents based on ionic liquids. The alkoxymethyl(2-decanoyloxyethyl)dimethylammonium bis(trifluoromethylsulfonyl)imides have also been shown to act as fixatives for soft tissues and can furthermore be used as substitutes for formalin and also preservatives for blood.