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Editorial

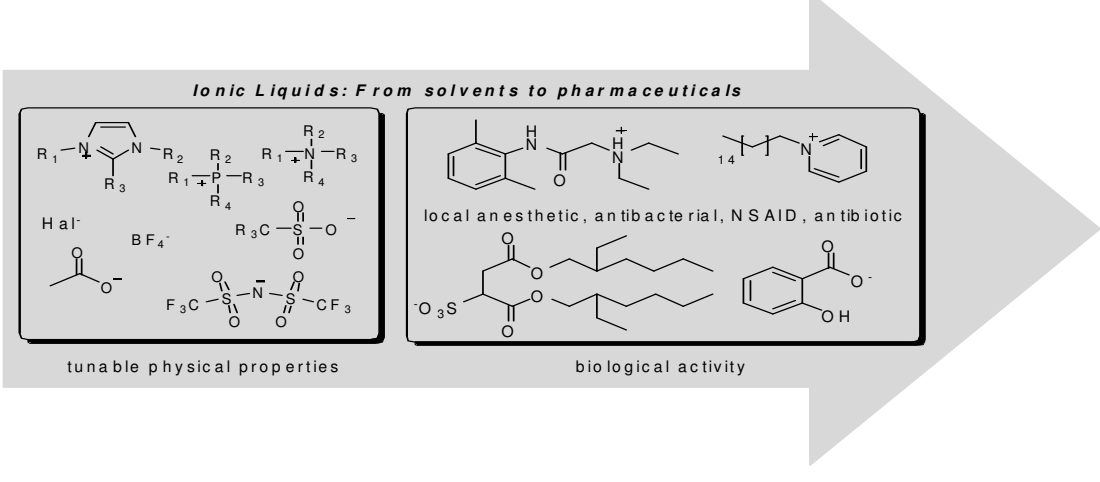
Ionic Liquid Technology: A Potential New Platform for the Pharmaceutical Industry

The pharmaceutical industry is undoubtedly facing a series of challenges. Although many of these challenges are related to the nature of this industry and current business models, there is also an urgent need for new science to bring forward innovative and effective drugs and therapies. The classic strategies currently being followed are reaching a saturation point in which it is getting harder to come up with effective, acceptable new chemical entities.

Less than a tenth of the drugs in clinical trials make it to the market, causing the companies to incur huge losses, and reducing the availability of efficient pharmaceuticals in the market for the people who need them. In a scenario in which the number of new drugs annually approved continues to decay, the novel active compounds now proposed tend to have more and more problems in matching all the desired requirements of solubility, bioavailability, stability, etc.

A well established, widely applied approach to overcome such limitations consists of the development of salts of the targeted active compounds. But still, old problems remain, such as the spontaneous polymorphic transformations of crystalline drug forms, which can be a nightmare for drug designers, and which can change an effective dose into a lethal dose by altering the solubility of the active ingredient. Co-crystals, amorphous forms, and polymer embedded pharmaceuticals may hold part of the answer to overcoming some obstacles, but the arrival of ionic liquids into the pharmaceutical world may offer even more design options.

Ionic liquids are salts of low melting point (usually, the arbitrary mark of 100 ºC is considered), but many of them are liquid at room temperature and below; many with no observable crystallization at all. The low melting points are related to the frustration of



crystalline network formation, basically caused by the geometric characteristics of the constituent ions and their charge diffuse nature.

One of the major strengths of ionic liquids resides in their internal plural nature: since at least one kind of cation and one kind of anion have to be present, the properties of the resulting products can be tuned by judicious choice of cation(s) and anion(s). Any two ionic liquids, even with one ion in common, can range from hydrophilic to hydrophobic, or their melting points can differ by over 100 ^{o}C. The possible combinations of ions which could form an ionic liquid are practically countless, as are the physical, chemical, and biological property sets that can be obtained by "designer salts".

About a decade ago, mainly due to the tunable properties and the extremely low volatility of many ionic liquids, these substances started to catch the attention of the academic and industrial communities as potential alternative solvents (with some use within the field of the pharmaceutical industry). Some years later, a notable interest in materials applications of these liquid salts also arose, thus focusing attention not only on the physical properties of the ionic liquids, but on their chemical properties, as well. But only recently has a major emphasis been placed on ionic liquids as bearers of desired biological activity (even though ions known to be biologically active have been used in ionic liquids for quite some time).

With this primary focus on the biological properties, a door is open to the design of active pharmaceutical ingredients (APIs) in the form of ionic liquids, with the potential to overcome many problems currently encountered by APIs, as well as to offer innovative solutions in new treatment and delivery options. For example, pairing an API with known tendencies to undergo undesired polymorphic transformations, with a counterion with known ability to produce low melting ionic liquids, one can prepare a liquid salt of the API which, as a liquid, will not be susceptible to polymorphism.

One can also envision an approach where the negative side effects of a given active compound can be treated by delivering it as an ionic liquid in which the counterion neutralizes the unwanted side effects, or where two active ions are paired for dual treatment therapies with synergistic rather than additive results. In a recent example, the local anesthetic lidocaine was proven to have enhanced and prolonged effect on rats when applied as an ionic liquid in the form of lidocainium docusate, when compared to the commonly used solid hydrochloride salt.

The examples cited above are simply glimpses of the future of ionic liquids as APIs. It is clear that there will be many challenges and perhaps regulatory hurdles ahead. Nonetheless, with some imagination, one can envision a drug discovery strategy which includes the formation of liquid salts of active cations or anions, as a major strategy in Society's struggle for new pharmaceuticals and new treatment options.

Héctor Rodríguez,[1] Katharina Bica,[1] and Robin D. Rogers[1,2]

[1]The QUILL Research Centre and School of Chemistry and Chemical Engineering, The Queen's University of Belfast, Belfast, Northern Ireland, United Kingdom, BT9 5AG

[2]Center for Green Manufacturing and Department of Chemistry, The University of Alabama, Tuscaloosa, AL 35401

E-mail: r.rogers@qub.ac.uk