Pharmaceutical Research, Vol. 27, No. 4, April 2010 (© 2009)
DOI: 10.1007/s11095-009-0030-0

Commentary

Crystalline *vs.* Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper

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Received September 30, 2009; accepted December 4, 2009; published online February 9, 2010

Abstract. Why not consider liquid 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 liquids and that these novel phases often possess different properties (e.g., improved solubilities and dissolution 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 liquids 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 liquid possessing dual functionality. Here we examine and challenge the current industry reliance on crystalline APIs by discussing the breadth and potential impact of liquid salts as a possible approach to phase control.

KEY WORDS: active pharmaceutical ingredient; delivery modes; ionic liquid; polymorphism; salt.

INTRODUCTION

More than 50% of drugs on the market today are sold as organic salts (1). Salification (i.e., salt formation) of a drug substance, a crucial step in drug development, can have a huge impact on its properties, including solubility, dissolution rate, hygroscopicity, stability, impurity profile and particle characteristics. The cation that is most commonly used in the salification process in FDA-approved pharmaceutical salts is the sodium ion, while the most encountered anion is chloride (2). The pharmaceutical industry relies predominantly on *solid, primarily crystalline* forms for the delivery of APIs, mainly for reasons of purity, thermal stability, manufacturability, and ease of handling. In contrast, liquid drug formulations are only rarely found and are usually based on eutectic mixtures (3). However, problems associated with the solid form of many drugs exist, including polymorphic conversion, low solubility, and low bioavailability for crystalline solids, and the tendency of amorphous forms to spontaneously crystallize (4). For these reasons, but also for considerable financial interests caused by legal ramifications, a constant screening for new drug forms, including salts, solvates, and co-crystals, is ongoing (5).

Most screening protocols for salt, solvate, co-crystal, or indeed even neutral APIs, discard any results for which an 'oil' is obtained. That is, if the result of the test conditions is not a solid, the material and the result are discarded and typically unreported in the open literature. The protocols are typically designed to produce crystalline forms, despite the fact that if the counterion is carefully chosen, an API can be *designed* to possess a low, or even non-existent, melting point and hence be present as a liquid at room temperature or below (6–9). These liquid salts represent a new phase of any given pharmaceutical active ingredient (API) and therefore offer a potentially new suite of properties for that active, not to mention intellectual property. Equally, these liquid salts offer a versatile solution to phase change issues with known APIs.

The reliance of pharma on the solid state remains, despite the fact that many drugs exhibit multiple crystalline forms (polymorphs, solvates, etc.), which can have a profound effect on the solubility, physical and chemical stability, dissolution rate and, in some cases, bioavailability of the compound (10–12). An interconversion between crystal forms occasionally occurs, which can create differences in the bioavailability of the drug, leading to inconsistencies in its efficacy. The pharmaceutical industry's concern with this phenomenon has intensified as a result of "polymorphic transformations," where one crystal form transforms into another during storage or manufacturing processes, and the legal ramifications of this effect. A number of court cases regarding the polymorphism of salts have proven to be extremely significant and remarkably costly (e.g., GlaxoSmith-Kline *vs.* Apotex–Paxil) (13), leading to the establishment of a legal precedent concerning polymorphism. Thus, different

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phases of a given drug can, in principle, be separately patented (1). It is also now accepted by regulatory bodies in the US that different solid forms of a drug are effectively different drugs, i.e., have different pharmacokinetics and pharmacodynamics; however, European regulators currently view them to be the same.

A *liquid phase* of the given active is therefore considered to be a usefully different form of the active compound as it certainly avoids the issues arising from polymorphism. Other developments have been approaching similar territory where liquid drug formulations were prepared as eutectic mixtures (14); however, this tends to introduce a substantial quantity of inactive ballast in the formulation, diluting the API. In addition, pure liquid phases of APIs would lend themselves to many alternative delivery or treatment options.

Ionic liquids (ILs) are commonly accepted as being salts or mixtures of salts that have melting points below 100°C (15), an extremely broad classification. In the present context of pharmaceutical applications, the liquid phase is preferably present below room temperature. These low melting points are largely induced by packing frustration of the usually asymmetric cations. In addition, a more diffuse charge on one or both of the ions typically yields a lowering of the melting point. For example, 3-ethyl-1-methylimidazolium chloride is a simple organic salt with a melting point of 77–79°C; replacment of the chloride with a dicyanamide anion lowers the melting point below room temperature, and, thus, the salt at room temperature appears as a stable, fluid liquid with a glass transition of −104°C and a melting point of −21°C (16).

The huge interest in ILs has led to an extensive and diverse range of ions known to support IL formation. An equally diverse range of applications has emerged, from electrochemical devices (17–19) to chemical solvents (17,20), biopolymer solvents (21), and protein formulations (22–25) to name a few. While the popularity of ILs in biosciences might have been delayed by the (sometimes heated) debate on the toxicity of some ILs, this very property can be desirable and lead to a variety of pharmaceutical applications (26). For instance, the antimicrobial activity of ILs is subject to an increasing number of publications and can be beneficial for the development of new bioactive materials, for example as antiseptics or as antifouling reagents, or even as potential anticancer therapeutic agents (9,27–32). Carson *et al.* have investigated the antibiofilm activity of 1-alkyl-3-methylimidazolium chloride ILs and reported potent, broad spectrum activity against a variety of clinically significant microbial pathogens, including MRSA (33).

There is certainly no doubt that many pharmaceuticals and other bioactive moieties can be made into an ionic liquid phase. A number of examples have been published recently where APIs have been combined with counterions capable of lowering their melting point below room temperature. One approach taken is to pair an active ion with a counterion which is a known excipient. For example, the IL *propantheline acesulfamate* contains the active cation from the API propantheline bromide (an antimuscurinic used to treat a number of conditions such as excessive sweating, cramps, spasms of the stomach, etc.) with *acesulfamate*, a known artificial sweetener and a pharmaceutical additive (6). The IL formed from these two ions has no observable melting point and passes into a glassy state at −20°C; bulk samples of this material have been stable in the liquid state for more than one year.

One of the most appealing features of ILs for pharmaceutical application is that they are *customisable materials* that can be specially made with pre-selected characteristics by varying the cations and anions of which they are comprised. Combinations of different cations and anions result in various ILs which can provide wide ranges of hydrophobicity/hydrophilicity, acidity/basicity, viscosities, etc. (34). Perhaps most importantly in the context discussed here, combining cations and anions with little opportunity for strong attractive intermolecular (or interionic) hydrogen bonded interactions in an "anti-crystal engineering" approach decreases the likelihood of crystallization and provides an elegant access to pharmaceutically active ILs (6). This approach will inherently lead to different salts (ion combinations) that would otherwise not be explored where crystallization is the prime objective. Indeed, the frequently used term "designer solvents" for ILs might as easily be adapted for IL "designer drugs," since physical, chemical and biological properties of a drug can be tuned by choice of the counterion rather than by covalent modification (Fig. 1).

What new treatment options are we missing when drug discovery or development approaches are exclusively focused on the crystalline state? Let us explore some aspects of ILs that we should start to consider when looking to refill our product portfolio.

ELIMINATION OF POLYMORPHISM

If polymorphism is an issue, one can design an IL form of the API without changing or compromising the molecular integrity or solubility of the API. Ranitidine hydrochloride (Zantac™), an anti-ulcer drug that gained dubious fame for extensive litigations over polymorphic forms and purity (35) was easily reacted with sodium docusate, a common emollient (36), to form the room temperature ionic liquid *ranitidine docusate* with a glass transition temperature of −12°C. Similarly, propantheline bromide is an API that can be present in different polymorphs (37); the *propantheline*

Fig. 1. Designer drugs: tunable properties by design and choice of ions.

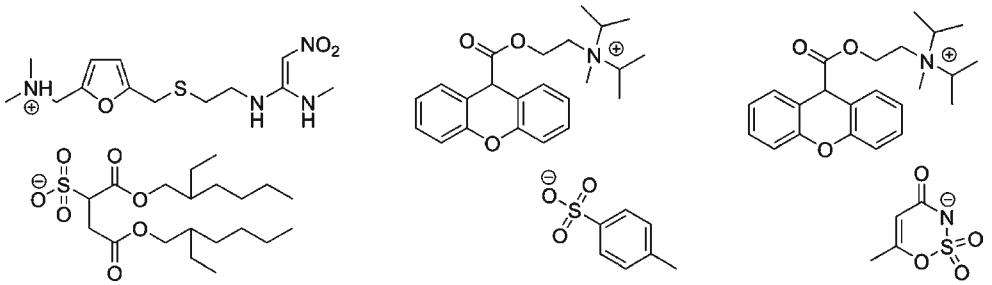


Fig. 2. Ranitidine docusate (*left*), Propantheline toluenesulfonate (*middle*), and Propantheline acesulfamate (*right*).

acesulfamate, and the other *propantheline* ILs described in reference 6, are new compounds of this API that avoid the polymorphism problem (Fig. 2).

CONTROLLED SOLUBILITY

While the elimination of polymorphism in an IL formulation of drug is a logical consequence, it is by far not the only potential advantage arising from use of the liquid state. Many Phase II trials of new active compounds end in failure due to their poor efficacy, often related to limited solubility (38). The design of the IL via the choice of the counterion can dramatically improve or decrease the solubility of the API (39,40). While most current salt approaches aim to increase solubility, ILs also offer the possibility of rendering an active *less* soluble, giving rise to hydrophobic liquid salts and new concentrated liquid delivery modes.

Strongly hydrophilic ionic actives often possess insufficient ability to penetrate biological membranes (1). Combining such an active ion with another of a more lipophilic character may offer a solution to this problem. For example, *lidocaine docusate*, an IL form of the local surface anaesthetic lidocaine, combines the relatively hydrophobic lidocaine cation with a hydrophobic anion, docusate (an emollient), to produce a hydrophobic IL salt, which exhibits *reduced or controlled* water solubility (Fig. 3) and thus should exhibit extended residence time on the skin (41).

A number of delivery modes can be employed to deliver such hydrophobic liquid salts to the site of action more efficiently than dissolved crystalline APIs in a more concentrated and effective manner, including iontophoresis, passive patches, aerosols, etc. Hydrophobic IL phases of an active make it possible to deliver a concentrated drug in a more localised manner, potentially avoiding the toxic impact of the drug and its metabolites on the rest of the body. While such hydrophobic properties can be achieved in crystalline APIs which are then used in a concentrated solution form, one of the advantages of the IL phase in this respect is that the ion combination used to prepare the salt is not required to produce a high melting point to be a useful drug; much wider combinations of ions are applicable.

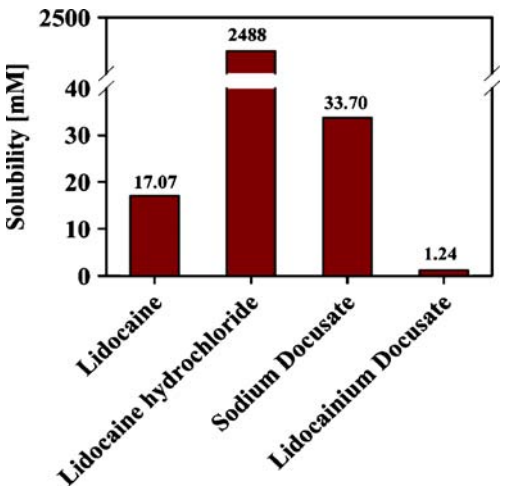


Fig. 3. Improved hydrophobicity and decreased solubility of lidocaine docusate.

ION-PAIR BASED TRANSPORT

Whether the IL ions will stay together in aqueous solution as ion pairs or clusters rather than independent solvated ions remains to be investigated. ILs are designed to be chaotropic, and, thus, the aqueous and solution chemistries are only sparingly explored (42). Recent molecular dynamics simulation studies (43–45), as well as spectroscopic investigation via NMR techniques (46,47), suggest that ILs do not dissolve as independent ions but keep a nanostructured organization in aqueous media. After all, the inherent properties of ILs are not like traditional crystalline salts, and the very properties that make ILs low melting also make them behave differently both in the melt and in solution.

Some pharmaceutically active ILs are highly ion-associated systems displaying high viscosities and low conductivities. This phenomenon has already been encountered and described in the IL field where tetradecyltrihexyl- and tetrabutyl-phosphonium cations are paired with chloride and sulfonylamide anions to yield highly viscous and low conducting compounds (48,49). These liquids are thought of as being an intermediate state between true ionic and true molecular liquids.

In the pharmaceutical world, drugs that are highly ionic have difficulty crossing the membrane in order to reach their site of action. Ion-pair formation enhances the transport of various ionic drugs through the skin and across the absorbing membrane (1). Therefore, highly ion-associated pharmaceuti-

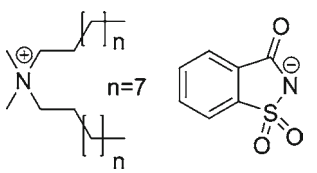


Fig. 4. Dual biological function: Didecyldimethylammonium saccharinate.

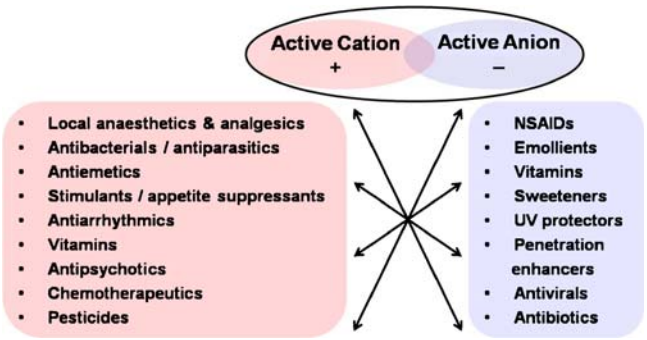


Fig. 5. A number of different combinations possible for dual functional liquids.

cally active ILs would be highly beneficial forms of the original pharmaceutical active salts, as they could cross the membrane more rapidly (50). In fact, measurements show that one of the propantheline salts, *propantheline* p-*toluenesulfonate* (Fig. 2) is one of these highly paired ionic liquids.

EXPLOITING THE FULL POTENTIAL OF SALTS—DUAL FUNCTIONALITY

With (solid) salts frequently used to provide the desired physico-chemical properties of a neutral drug, the chosen counterions are usually of inactive nature. There have been a few examples of 'combination salts' utilizing two actives in a single compound (1) but the overall promise of such an approach seems to be moderated by a) the need to have a crystalline material, and b) the fixed stoichiometry of actives found in such a crystalline salt. So called 'dual functionality' has been a highly explored aspect of the IL field in general, for example in dual acidic or double chiral ILs (51). In the context of APIs it adds new avenues for exploration in pharmaceutical action.

Only recently have examples in the IL literature appeared which report the designed incorporation of two biologically active ions where both the cation and anion were chosen based on the desired physical, chemical, and biological properties (9). Sweet and antimicrobial salts can be prepared from antibacterial quaternary ammonium cations and non-nutritive sweetener anions such as acesulfamate or saccharinate. *Didecyldimethylammonium saccharinate* (Fig. 4) and *didecyldimethylammonium acesulfamate* not only retain their initial antimicrobial properties, but exhibited decreased water solubility, high thermal stability, and good deterrent activity against insects. While these quaternary ammonium cations

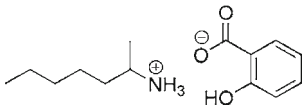


Fig. 7. Partially ionised 1-methylhexylammonium salicylate.

are frequently found as antimicrobials and disinfectants (52), the introduction of sweetness as a second functionality in one formulation can certainly be an additional factor for oral applications, e.g. mouthwashes.

In the context of APIs, a variety of approaches can be contemplated where the two actives can be chosen (Fig. 5), for example on the basis of:

- one counteracting the side effects of the other active ingredient;
- both ions being pharmacologically independent, but either aiding the therapeutic properties of the other or providing treatment for a different symptom; or
- the ions acting in a synergistic manner supplementing the desired effects (1).

It is important to also note that a co-formation of two separate solid actives in a solid dosage form does significantly differ from a dual functional IL formulation (Fig. 6). The ions in an IL will dissolve in the body fluids in exactly the same way—since one ion cannot dissolve without the other; this is not true of separate solid forms administered at the same time since each may dissolve at quite different rates.

PROTIC IONIC LIQUIDS FROM API ACIDS AND BASES: A QUESTION OF IONIZATION AND CONFUSION

A subclass of ILs, protic ILs (PILs), is based on an acid/base exchangeable proton system. As a result of the exchangeable proton, these ILs have been used as solvents in various acid catalysed reactions (53,54) and are suitable as proton conductors (55). Pharmaceutically active acids and bases can be utilised to produce pharmaceutically active protic ILs, and, in fact, an overwhelming majority of all pharmaceutically active salts in use are protonated species. It is thought that $\Delta pKa^{aq} > 10$ is needed for full ionisation to occur (56); $\Delta pKa^{aq} < 10$ implies low degree of ionisation, hence a dynamic mixture of ions and parent acid and base. There may be a significant advantage of drugs with low degree of ionisation over the fully ionised ones due to their ability to

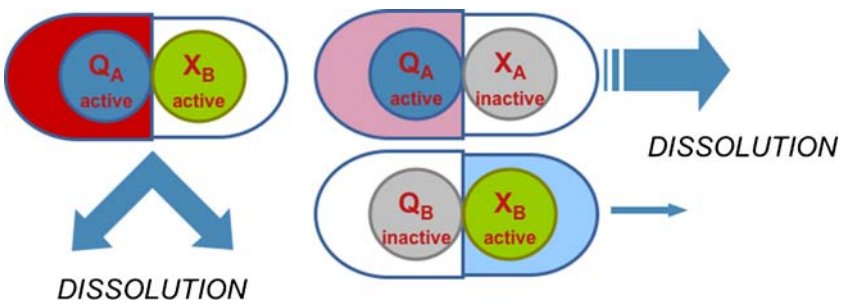
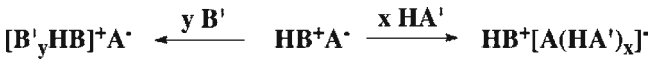


Fig. 6. Schematic illustration demonstrating a potentially different dissolution of dual functional liquid (*left*) *vs*. solid co-formulation of 2 active salts (*right*).



Scheme 1. Altering stoichiometry to produce oligomeric anions or cations.

cross membranes more efficiently. An example of a partially ionized pharmaceutically active IL is *1-methylhexylammonium salicylate* (Fig. 7) (57). Salicylic acid, an analgesic with a p*K*a value of 2.98, was reacted with 1-methylhexylamine, a nasal decongestant with a p*K*a value of 10.5, to produce a liquid at room temperature with a T_g at −40°C and a ΔpK_a^{aq} of 7.52. Walden plot (48) analysis of this compound shows a low degree of ionisation implying incomplete proton transfer from salicylic acid to 1-methylhexylamine. In fact, it is most probable that this compound is a mixture of the parent acid and base and salicylate and 1-methylhexylammonium ions.

Most current research on ILs, and indeed virtually all modeling efforts, deals with salts of definite chemical composition. However, in light of growing understanding of IL behavior, we have begun to question whether modification to the stoichiometry, especially non-integral stoichiometry, is not, in fact, an unrecognized tool to improve IL physical properties. Angell and others studied "proton transfer RTIL systems" using reactions between neat Brønsted acids and bases and found that when one of the components is used in excess, the resulting proton transfer is incomplete, and cations and anions exist in equilibrium with molecular species, resulting in formation of either associated ions or weak proton transfer systems (58–60). With proper knowledge of the chemistry, the properties of the ILs can be modified by addition of excess solid or liquid acid or base in order to form oligomeric anions or cations (Scheme 1) (61).

CONCLUSIONS AND FUTURE DIRECTIONS

We propose here that IL phases offer much promise, incredible flexibility, and an ability to finely tune physical, chemical, and biological properties without covalent manipulation of the active. Certainly there are issues which must be addressed, including manufacturing, scale-up, purification, stability, and delivery, to name a few. Nonetheless, the headlong rush to find new pharmacophores via molecular manipulation and discovery may have obscured the fact that many known actives can be manipulated into more effective treatments by simple salt chemistry—albeit a salt chemistry unlike any other yet attempted by the industry.

While better strategies for prediction and proper design for pharmaceutically active ILs are needed and many unknown aspects of synergies, antagonists, ion pairing, and aggregation are involved, the risk in conducting such research would seem to be outweighed by the potential for dramatically increasing our product portfolios. We therefore suggest that the liquid state *per se* should not be ignored—or worse, discarded—but more considered as an alternative to common solid-state techniques. A plethora of new possibilities, challenges, and thrilling opportunities might be the reward.

ACKNOWLEDGEMENTS

DRM is grateful to the Australian Research Council for his Federation Fellowship.

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