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Ionic liquid pharmaceuticals face similar problems to nanotechnology.

Develop ionic liquid drugs

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.

A new realm of potential drugs is hiding in plain sight. Pharmaceutical research, manufacture and regulation focuses on solid active ingredients, delivered as powders or tablets. Liquid forms are neglected and viewed as an intermediate step, rather than an endpoint.

Yet many promising solid drug candidates are too insoluble for the body to absorb. Of the compounds entering development, 40–70% fail because they cannot be modified simply to allow effective release into the bloodstream[1].

Meanwhile, ionic liquids, an exciting class of chemical that could bypass these delivery problems, are being ignored[2]. Half of all drugs sold are salts[3] that are held together by ionic bonds, among other forces. Salts that are liquid at room or body temperature can have dramatically better solubility, absorbability and stability than do solid forms[4]. Ionic liquids can also be configured to deliver two or more active ingredients at once.

For example, combining active ions from the pain reliever procaine and the non-steroidal anti-inflammatory drug (NSAID) salicylic acid generates a liquid salt, procainium salicylate. It could deliver the medical benefits of both compounds more efficiently and cheaply while opening up new treatment options.

With the drug-discovery pipeline clogged, it is time to try alternatives. We call on chemists and the pharmaceutical industry to develop liquid salt forms of drugs. Chemists will need to learn more about the spectrum of interactions in ionic liquids, how to engineer ionic bonds, and how the choice of ions changes the chemical, physical and biological properties of ionic compounds. Regulations must be updated to consider active ingredients in liquid as well as solid states.

OLD HABITS

Why are ionic liquids being ignored? First, most academic and industrial chemists lack understanding and experience of working with them. Chemistry courses and textbooks teach that new molecules are made by manipulating covalent bonds (where electrons are shared between atoms) rather than ionic ones.

Second, pharmaceutical companies are conservative. Ionic liquids are unfamiliar, unregulated and felt to be too risky to develop commercially.

And there is a perception problem. Over the past 20 years many researchers (including us) have demonstrated the value of ionic liquids as solvents, electrolytes and compressor fluids that are reusable, non-volatile and safe. Yet many researchers and journalists still associate the term with the first such chemicals widely studied: for example, dialkylimidazolium, quaternary ammonium and phosphonium salts, which were explored in the 1990s as potential 'green' solvents and electrolytes. With each new study, the class as a whole became pigeonholed — as expensive, cheap, green, toxic, biodegradable, non-biodegradable, non-flammable, flammable, volatile or non-volatile. In reality, ionic liquids have an infinite range of characteristics.

The effect of an ionic liquid on a living organism (such as toxicity) should be exploited rather than being seen as a problem, especially given that liquid salts can be more soluble in the body than are solids. The rate at which a drug is taken up depends on many factors, including its solubility, permeability, dissolution rate and the metabolic pathways involved.

The solubility of a solid depends so much on its form — for example, the size of the particles and whether it is crystalline or amorphous — that the same dose could be ineffective or toxic in different forms. That form depends unpredictably on the conditions under which the drug is manufactured and stored — temperatures, heating and cooling rates and solvents used[5]. In the late 1990s, for example, production of the antiretroviral ritonavir was halted temporarily when it emerged that an undiscovered, less soluble crystal structure formed from the manufactured drug capsules, making the medication ineffective. Laborious screening of solid forms is now part of the gauntlet of development stages for drugs — steps that would not be necessary for liquid pharmaceuticals.

Ionic liquids will not of course be problem-free. They may absorb contaminants, leach out of carriers, or be prone to subtle differences in biological activity that we do not yet know about. But, in our view, their huge potential for improving drug development, delivery and efficacy is ripe for exploration.

SCIENTIFIC UNDERSTANDING

There is still much to learn. Academic researchers are starting to study the subtleties of ionic bonding in the liquid state. Swapping ions can render a salt soluble in or immiscible with a given solvent, stable or reactive, non-volatile or distillable, and permeable or not. There are many unknowns: how can we predict whether a given ion can be made liquid? How will we purify active ingredients that never crystallize?

Fine distinctions in ionic bonds may be controlled. Chemists are investigating how proton transfer (the moving of a hydrogen (H^+) ion between an acid and a base) and hydrogen bonding (an electrostatic attraction between a hydrogen atom bound in a molecule and another nearby atom) influence the melting points of salts, how easily ions are transported across cell membranes, and the creation of different types of acid–base complexes[6,7].

Industry is starting to take notice. A patch for treating lower back pain based on an ionic liquid combination of the NSAID etodolac and the pain-reliever lidocaine has finished phase III clinical trials (see go.nature.com/urzlks); the next step is to bring it to market. Tests of more ionic liquids and drug combinations are needed, with a wider variety of forms. For instance, an ionic liquid drug loaded on a powder could be taken orally, with the drug's dissolution rate tuned by changing the properties of the powder carrier.

Laboratory studies show how drug properties influence their flow around the body. We have shown, for example, that a liquid combination of lidocaine (a base) and ibuprofen (an acid) forms strong hydrogen bonds between the two components that allow both to pass together through a cell membrane[7]. Likewise, the penetration of other drugs might be enhanced. Whether or not hydrogen-bonded complexes stay together or break apart in the bloodstream is already a topic of debate in the design of solid pharmaceutical co-crystals (crystalline blends of compounds)[8].

REGULATORY GAPS

For industry, the most important question is how ionic liquid pharmaceuticals will be defined and regulated. The US Food and Drug Administration (FDA) guidelines for active pharmaceutical ingredients (see go.nature.com/ivpakv) focus on pure compounds and their stability, and solids are easier to classify and study. The latest guidelines, from April 2013, distinguish crystalline hydrogen-bonded co-crystals and ionized salts — which may differ only in their bonding — even though there is no recognized difference in their biological effects[8].

The FDA considers a co-crystal a blend of a known active pharmaceutical ingredient and inert filler, which does not require stringent tests. It classes salts, on the other hand, as new compounds that require full-length investigation. Physically, such a distinction could correspond to as little as a 0.1-ångström shift of a hydrogen atom position in a crystal.

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Ionic liquids do not fit these regulatory boxes. Different solid forms can be distinguished through measurements (such as X-ray diffraction or melting points). Such methods cannot detect the subtle difference in a liquid between an ionized salt and a hydrogen-bonded moiety. Protons move around in a liquid and may be in any state relative to a nearby ion[9]. Whether liquid compounds are ionized, neutral or hydrogen bonded also depends on temperature and the ingredients involved. Whereas solids retain their identity when they are mixed, blends of free ions in a liquid interact in myriad ways.

NEXT STEPS

Rather than abandon the field as too boulder-strewn, as some chemists have suggested, researchers should define and understand ionic liquids so that regulation can keep pace with the discovery of new therapeutics.

Chemists in academia and industry need to find techniques for proving the structure and purity of ionic liquids. Methods must be developed for identifying certain complexes, free ions or dissociated acids and bases. Classification systems that encompass the varying degrees of ionic bonding should be defined, and methods for assessing the purity of ionic liquids need to be developed. For clinical translation, delivery mechanisms and steps such as demonstration of shelf life will be needed.

Regulators should focus less on the form of a material and more on its clinical properties. Developing a scientific classification system for ionic liquids based on how they perform as drugs will enable regulatory agencies to make legal distinctions in a medical context. Distinctions will need to be made, for instance, between salts that dissociate in solution (and essentially behave like their solid counterparts in the bloodstream) and those that remain associated.

Many of the problems facing ionic liquid pharmaceuticals are shared with nanotechnology: toxicity, relative expense and a need for new terminology. For nanotechnology, investment made those tractable; the pharmaceutical industry should likewise invest.

Designing ionic liquids based on pharmaceuticals already approved by the FDA is a good place to start. Familiarity and success will encourage further investment. There is nothing magic in the design and study of a liquid, it is simply a matter of spending time and money to gain the understanding needed to overcome perceived chemical, biological, manufacturing and regulatory difficulties.

Given its importance to society, the pharmaceutical industry must open its mind to new approaches. ■

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