NEW

THERAPEUTIC APPROACHES

BASED ON IONIC LIQUIDS

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Resumo

Os líquidos iónicos (LIs) definem-se, atualmente, como sais (com pelo menos um ião orgânico) estáveis acima do seu ponto de fusão.

Começaram a ser utilizados principalmente como solventes, mas rapidamente chamaram a atenção das Ciências da Vida, na medida em que algumas das características daqueles compostos podem ser relevantes em aplicações terapêuticas.

Os LIs podem mostrar propriedades físico-químicas mais interessantes ao nível de ingredientes farmacêuticos ativos como, por exemplo, hidrossolubilidade, para além do facto de os LIs (líquidos à temperatura ambiente e/ou à temperatura do corpo humano) não apresentarem polimorfismo, um aspeto que frequentemente limita as condições de uso e a eficácia terapêutica de ingredientes farmacêuticos ativos sólidos.

Esta linha de investigação procura através de uma escolha criteriosa dos iões a emparelhar afinar algumas dessas propriedades, e estudar a combinação de duas moléculas bioativas que tenham grupos ionizáveis de carga oposta, formando líquidos iónicos com efeito terapêutico dual.

Abstract

Ionic liquids (ILs) are currently defined as salts (with at least one organic ion) stable above their melting point.

They began to be used mainly as solvents, but quickly drew the attention of the Life Sciences, as some of the characteristics of those compounds may be relevant in therapeutic applications.

ILs can show more interesting physicochemical properties at the level of active pharmaceutical ingredients such as water solubility, in addition to the fact that ILs (liquids at room temperature and/or human body temperature) do not present polymorphism, an aspect which often limits the conditions of use and therapeutic efficacy of solid active pharmaceutical ingredients.

This line of research seeks, through a careful choice of the ions, to fine-tune some of these properties, and to study the combination of two bioactive molecules that have ionizable groups of opposite charge, forming ionic liquids with a dual therapeutic effect.

Introduction

Ionic Liquids (ILs) are a class of compounds that developed from traditional high temperature molten salts. Although many different early studies have been taken as the true hallmark of the beginning of the ILs era (Angell et al., 2012; Laus et al., 2005; Welton, 2018), the most consensual one is the work developed in 1914 by Paul Walden (Walden, 1914), who deliberately produced ethylammonium nitrate (Figure 1) as a liquid possessing ionic character.

Figure 1. ethylammonium acetate (1) and 1,3-dialkylimidazolium cations (2).

The introduction of ILs in the biosciences and in the pharmaceutical industry has been slow and subtle (Egorova et al., 2017; Ferraz et al., 2011; Shamshina et al., 2015). The pharmaceutical industry firstly regarded ILs as "greener" surrogates of volatile organic compounds (VOCs) used as solvents in the synthesis of active pharmaceutical ingredients (APIs) (Earle et al., 1999; Earle & Seddon, 2000; Ferraz et al., 2018; Welton, 1999). In this connection, and to assess how "green" ILs really were, their toxicity was evaluated, and soon it was recognized that ILs could be used against pathogenic microorganisms (Pernak et al., 2003; Prudencio et al., 2020). This prompted several groups to study antimicrobial activity of known ILs (Carson et al., 2009; Demberelnyamba et al., 2004; Pernak et al., 2001; Pernak et al., 2007), to prepare and test novel ILs based on APIs (Bica et al., 2010; Ferraz et al., 2012; Ferraz et al., 2016; Hough et al., 2007), or to use ILs as co-adjuvants or carriers in drug formulations (Cojocaru et al., 2013; McCrary et al., 2013; Zavgorodnya et al., 2017).

Nowdays, half of all drugs used in medicine are administered in the form of a salt and the formation and formulation of a suitable salt as a drug candidate is recognized as one of the essential steps in the pre-clinical phase of modern drug development.(Berge et al., 1977; Stahl, 2002) The number of examples of compounds with pharmaceutical activity in cationic or anionic form with a biocompatible or inert counter-ion is growing. (Sekhon, 2011) An example of this is the growing number of publications referring to the use of ILs based on active pharmaceutical ingredients. For example, it is reported in the literature that Ibuprofen-based LI (1-(2-hydroxyethyl)-1-3-methylimidazolium ibuprofenate) is about 100,000 times more soluble than ibuprofen.. (Viciosa et al., 2015) It should be noted that ibuprofen is a practically insoluble molecule in water, (Filippa & Gasull, 2013) which tends to decrease its clinical effectiveness.

Thus, it is reasonable to admit that one of the advantages of IL formation may be the increase in the aqueous solubility of existing drugs, among others. The formation of an ion pair also allows the formation of new APIs with possible activity against more than one disease.

Methods of Preparing Ionic Liquids

ILs are frequently produced from ammonium, phosphonium or sulphonates ions[2]. There are two main methods of preparing ILs: metathesis and acid base neutralization (Figure 2). We could also consider another method, for imidazolium cations that was developed by Earl and Seddon: the reaction of imidazole carbenes as strong bases (Earle, 2005).

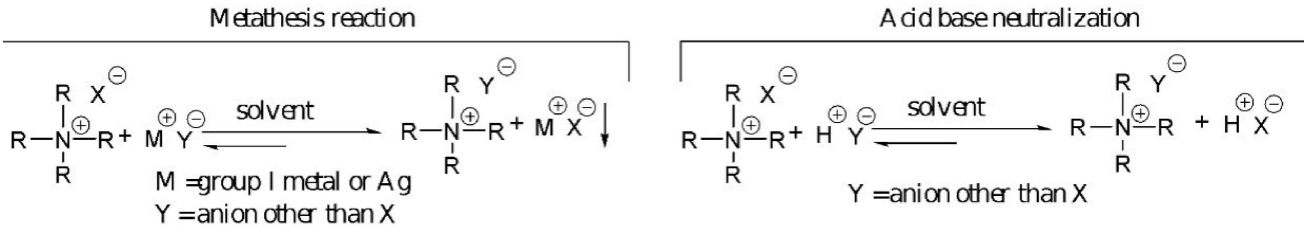

Figure 2. General procedure for the metathesis reaction and acid base neutralization.

There are several alkylammonium halides commercially available and they can be used directly in metathesis reactions [4]. When alkylammonium halides are not availabe, a quaternization reaction is required, when an organic halide salt is formed through the alkylation of a base by a haloalkane [4]. This method can also be used to prepare pyridinium and imidazolium halides (Scheme 2). Currently, the use of non-conventional methods like microwave[5, 6] and ultrasound techniques[5, 7] is being applied in the quaternization reaction with better results[5, 8].

This line of research use the acid-base neutralization method (Ferraz et al., 2020; Silva et al., 2020). This methodology avoids the contamination problem(Ohno & Yoshizawa, 2002). This procedure is also quite simple and through the use of equimolar mixing, it is possible to obtain the salts without the formation of by-products(Ohno & Yoshizawa, 2002). This method results very well with tertiary amines with halide acids or some organic acids.

Perspectives

Our line of work at the moment is developing new Ionic Liquids based on malaria drugs. Basic, because our long experience with these drugs but also because malaria is endemic to poor countries, there is a constant need to fuel the antimalarial drug pipeline with new options, classical antimalarials like primaquine, chloroquine and mepacrine have basic nitrogen-based groups can be easily paired with organic acids.

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