Ionic Liquids in Drug Delivery

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Ionic liquids (ILs) are molten salts composed of a large organic cation and an organic/inorganic anion. The large dimensions of their ions lead to charge dispersion, which makes difficult the formation of a regular crystalline structure. Due to their unique properties, ILs have been applied in the crystallization of active pharmaceutical ingredients (APIs), as solvents, co-solvents and emulsifiers in drug formulations, as pharmaceuticals (API-ILs) aiming liquid therapeutics, and in the development and/or improvement of drug-delivery-based systems.

Keywords: Active pharmaceutical ingredients ; Drug delivery ; Ionic liquids

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Pharmaceuticals play a major role in medical care, boosting life quality and expectancy, especially when considering chronic diseases [1]. The global prescription of medicines is forecast to grow up to nearly $1.2 trillion by 2022 [2]. Although active pharmaceutical ingredients (APIs) can be commercialized in several dosage forms, crystalline forms have been the preferred option [3][4]. However, 40 to 70% of the drugs under development present low water-solubility, which may compromise the bioavailability and therapeutic efficacy and, thus, fail in the later stages of development [5][6]. The irregular gastrointestinal absorption of solid forms, along with the low therapeutic efficiency and possible toxicity and side-effects of polymorphs, are major concerns to overcome [7]. For instance, large differences in bioavailability among different polymorphs require different drug dosages [8]. On the other hand, the therapeutic dosage of a certain API can correspond to a toxic or potential lethal dose if the wrong polymorph is administered. Polymorphism issues result in significant economic losses in sales and in R&D to enable novel formulations back into the market [9][10].

Beyond the well-known downsides of polymorphism, the APIs' solubility in aqueous solution, dissolution, and bioavailability are also dependent on particle size and properties [11]. Attempting to improve the drugs solubility in water as well as their bioavailability, several strategies have been investigated, especially when the oral route is envisaged [5][6]. Nevertheless, most of these strategies still use large quantities of organic solvents in the manufacturing process of these formulations, particularly to induce the crystallization of a given polymorphic form and particle size, having associated health and environmental concerns [12]. Furthermore, solvent molecules can be incorporated into the crystal structure of the API during the crystallization process [13]. Therefore, when considering the use of organic solvents, they must be removed from the API or their levels must be controlled in order to ensure human consumption safety [12]. Despite the existence of extensive literature describing novel and "greener" solvents to this purpose, there is still some reluctance by the pharmaceutical industry to accept and implement these alternatives [14][15][16].

In the above context, liquid forms of APIs are appealing solutions to avoid both polymorphism and improve low-water solubility constraints, while allowing to reduce organic solvents use. The pharmaceutical industry has relied on eutectic mixtures for this purpose, shortly exploring other options for commercialization [17][18]. In addition to these, ionic liquids (ILs) disclose high potential in the pharmaceutical field, which is mainly due to their high versatility in terms of chemical structure design towards a target application. ILs are molten salts that are composed of a large organic cation and an organic/inorganic anion. The large dimensions of their ions lead to charge dispersion, which makes difficult the formation of a regular crystalline structure [19][20]. ILs display a set of unique features, from which is possible to highlight, if properly designed, their high thermal and chemical stability and a strong solvation ability for a wide variety of compounds [21]. The proper selection of cation-anion combinations in ILs enables the use of drugs as ion components, allowing for the conversion of solid active pharmaceutical ingredients into liquid forms (API-ILs). Thus, this strategy solves the problem of polymorphism and provides improved bioavailability, and ideally boosts therapeutic properties [3][22].

Because of the unique properties of ILs, their application in the pharmaceutical field has been extended far beyond the development of novel liquid forms (API-ILs), being investigated as well in other stages of drug development and delivery. The number of publications related to the application of ILs in the pharmaceutical field has grown exponentially in the past 20 years, as illustrated in Figure 1. ILs have been applied in the development of purification platforms for pharmaceuticals for which some recent review manuscripts exist [23][24][25]. Other relevant reviews and book chapters recognizing the advances of ILs in different areas of pharmaceuticals development, spanning from their formulation, biological activity, and application on drug delivery are also available [22][26][27][28][29][30][31][32][33][34].

Figure 1. Number of publications per year in a twenty years perspective related to ILs and active pharmaceutical ingredients (APIs) (number of articles, reviews and book chapters according to a ScienceDirect database search using as keywords “ionic liquids”, “active pharmaceutical ingredients”, and “drug delivery”) (**left**). Overview of the ILs’ applications in the pharmaceutical field reported hitherto (**right**).

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