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Research Paper

Transformation of acidic poorly water soluble drugs into ionic liquids

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ABSTRACT

Poor water solubility of active pharmaceutical ingredients (API) is a major challenge in drug development impairing bioavailability and therapeutic benefit. This study is addressing the possibility to tailor pharmaceutical and physical properties of APIs by transforming these into tetrabutylphosphonium (TBP) salts, including the generation of ionic liquids (IL). Therefore, poorly water soluble acidic APIs (Diclofenac, Ibuprofen, Ketoprofen, Naproxen, Sulfadiazine, Sulfamethoxazole, and Tolbutamide) were converted into TBP ILs or low melting salts and compared to the corresponding sodium salts. Free acids and TBP salts were characterized by NMR and IR spectroscopy, DSC and XRPD, DVS and dissolution rate measurements, release profiles, and saturation concentration measurements. TBP salts had lower melting points and glass transition temperatures and dissolution rates were improved up to a factor of 1000 as compared to the corresponding free acid. An increase in dissolution rates was at the expense of increased hygroscopicity. In conclusion, the creation of TBP ionic liquids or solid salts from APIs is a valuable concept addressing dissolution and solubility challenges of poorly water soluble acidic compounds. The data suggested that tailor-made counterions may substantially expand the formulation scientist's armamentarium to meet challenges of poorly water soluble drugs.

1. Introduction

Oral dosage forms of active pharmaceutical ingredients (API) are a preferred image for drug administration. Oral delivery typically requires (nearly) complete dissolution of the API at its absorption site and prevention of precipitation during gastrointestinal transit until complete absorption, a process typically lasting about four hours [1]. This poses specific challenges, especially for poorly water soluble drugs with low solubility (with solubility being defined as the molar concentration of API in ionized and unionized form in equilibrium state or not) driving poor bioavailability and often unacceptable pharmacokinetic variability [1]. Pharmaceutical strategies addressing these challenges without modification of the chemical structure of the API include particle size reduction, cocrystal formation, polymorph selection, complexation, salt formation, solubilization or presentation in amorphous form, e.g. as molecular dispersions in polymer carriers thereby reducing the interaction between the API molecules [2]. These dosage forms may result in improved dissolution rates but are typically challenged by solution stability with potential precipitation before the API is adequately absorbed. A simple concept combining salt formation and a reduction of the interaction between the API molecules is the preparation of an ionic liquid (IL). The approach has been demonstrated to stabilize dissolved APIs in supersaturated states for several hours following dissolution from an amorphous, solid state [3].

ILs are defined as organic salts with melting points below 100 °C [4]. Those ILs which are liquid at ambient temperature and pressure are referred to as room temperature ILs (RT-ILs) [5]. During the last years the application of ILs was extended from solvents in ('green') chemistry and catalysts for synthesis to pharmaceutical application with the ultimate goal to improve API dissolution, solubility and bioavailability and to prevent polymorphism [4,6–14].

Tetrabutylphosphonium (TBP) has already been used for the preparation of an IL with Salicylic acid and Ibuprofen [11,13]. However no detailed solubility data were provided. Another study reported a TBP IL of an anti-migraine drug and determined a faster dissolution and supersaturation in solution leading to improved transport kinetics *in vitro* in comparison to the free acid and the API's potassium salt [3].

In this study we detailed the potential of transforming 7 commonly used acidic APIs into TBP salts and compared them to their respective sodium salts. These TBP salts were characterized with ^{1}H nuclear magnetic resonance (NMR) and infrared spectroscopy (IR), X-ray powder diffraction (XRPD) and differential scanning

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calorimetry (DSC). Hygroscopicity was assessed by dynamic vapor sorption (DVS). Dissolution rate, saturation concentrations and 24 h solubility profiles were determined photometrically.

2. Results

2.1. Salt metathesis and physico-chemical characteristics of TBP salts

TBP salts of drugs with one carboxylic acid group, in the case of Diclofenac, Ibuprofen, Ketoprofen, and Naproxen, and with one sulfonamide group, as in Sulfadiazine, Sulfamethoxazole, and Tolbutamide, were prepared from the corresponding free acids (Fig. 1). TPB salts of Ibuprofen, Ketoprofen, Naproxen and Sulfamethoxazole were clear, slightly yellow viscous liquids at room temperature and RT-ILs, whereas TBP salts of Diclofenac, Sulfadiazine and Tolbutamide were slightly yellow solids.

Moisture content of TBP salts was determined by Karl Fischer Coulometer directly following production and found to be 0.5% for Ibuprofen (RT-IL), 0.2% for Ketoprofen (RT-IL) and Naproxen (RT-IL), and less than 0.2% for all other TBP salts (data not shown).

The free acids and their corresponding TBP salts were analyzed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy (Supplementary Fig. 1). Since the salt formation is characterized by a loss of the acidic proton, the corresponding ^{1}H NMR signal at 10–12.5 ppm disappears upon IL formation (all NMR spectra are provided as Supplementary Information 1). The proton signals for TBP were recorded at 0.9–2.3 ppm and included a signal for the 12 protons of its terminal methyl groups at δ = 0.92 ppm (t, ^{3}J = 7.1), 16 protons recorded for its intermediate ethylene groups at δ = 1.55–1.30 ppm and 8 for the methylene groups next to the phosphonium δ = 2.30–2.10 ppm. The integration of these signals for TBP and comparison with the integrals of the signals recorded for the respective APIs confirmed a 1:1 stoichiometry for all ILs tested. Apart from signals from the acid and the counterion no further signals were observed for any of the TBP salts, indicating the good stability of the API during salt formation.

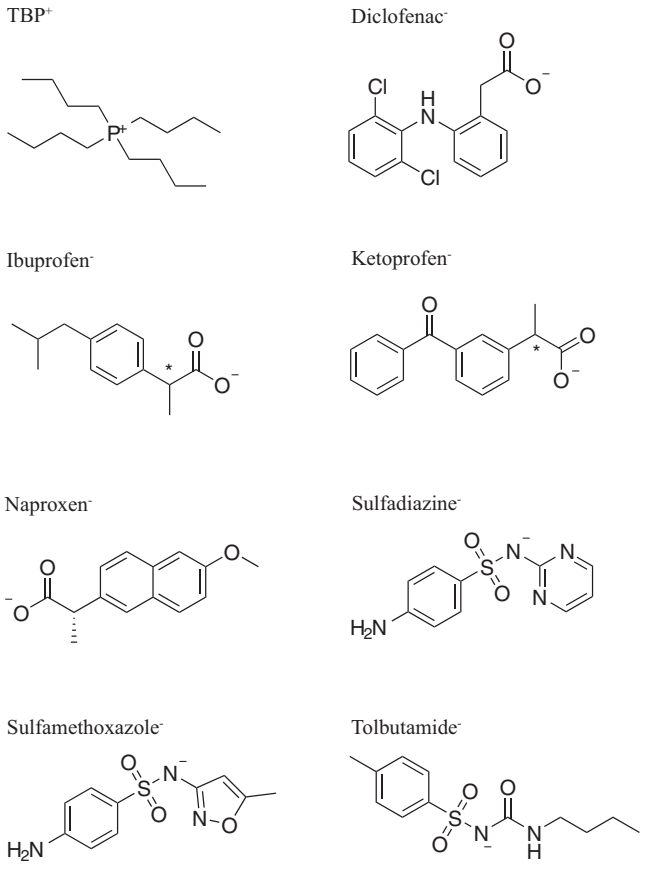

Fig. 1. Structures of the counterion tetrabutylphosphonium (TBP^{+}) and the ionized APIs Diclofenac, Ibuprofen, Ketoprofen, Naproxen, Sulfadiazine, Sulfamethoxazole and Tolbutamide.

Signals for Diclofenac differed slightly from the generally observed pattern recorded for the other APIs: Diclofenac signals at δ = 12.7 ppm and 7.2 ppm represented the proton of the free acid and of the amine proton, respectively (Supplementary Information 1). Whereas the signal of the carboxylic proton disappeared upon TBP salt formation as expected, the amine signal shifted to 10.9 ppm in the TBP salt, suggesting the formation of an intramolecular H-bond between the amine proton and the (deprotonated) carboxyl moiety.

The ionic nature of the TBP salts was further supported by IR spectroscopy (Supplementary Fig. 1). For APIs with a carboxylic function the typical O—H and C=O stretching vibrations were observed at 2885 cm^{-1} and 1690 cm^{-1} (Diclofenac), 2954 cm^{-1} and 1709 cm^{-1} (Ibuprofen), 2938 cm^{-1} and 1694 cm^{-1} (Ketoprofen), and 3162 cm^{-1} and 1726 cm^{-1} (Naproxen) [15]. Following deprotonation, symmetric and anti-symmetric stretching vibration for carboxylic anions were observed at 1575 cm^{-1} and 1346 cm^{-1} (Diclofenac TBP), 1580 cm^{-1} and 1376 cm^{-1} (Ibuprofen TBP), 1592 cm^{-1} and 1372 cm^{-1} (Ketoprofen TBP), and 1588 cm^{-1} and 1369 cm^{-1} (Naproxen TBP) along with missing O—H stretching vibration [15]. The broad bands between 3330 cm^{-1} and 3290 cm^{-1} for Ibuprofen TBP, Naproxen TBP, Ketoprofen TBP were assigned to residual water [15]. For the sulfonamide groups of Sulfadiazine, Sulfamethoxazole and Tolbutamide, deprotonation was detected by a shift of the two typical sulfuric bands from 1324 cm^{-1} and 1149 cm^{-1} to 1235 cm^{-1} and 1122 cm^{-1} (Sulfadiazine), from 1303 cm^{-1} and 1142 cm^{-1} to 1232 cm^{-1} and 1123 cm^{-1} (Sulfamethoxazole) from 1316 cm^{-1} and 1177 cm^{-1} to 1243 cm^{-1} and 1124 cm^{-1}, respectively (Tolbutamide; Supplementary Fig. 1). From NMR and IR data it can be stated that all APIs were ionized and formed TBP salts.

Sodium salts of the APIs were selected for comparison with the TBP salts. Sodium salts of Ketoprofen, Sulfamethoxazole and Tolbutamide were prepared in house and quality of the resulting white crystalline powders was confirmed by elementary analysis. Sodium salts of Diclofenac, Ibuprofen, Naproxen and Sulfadiazine were purchased. For all sodium salts deprotonation was assessed by ^{1}H NMR and IR. Based on the elementary analysis, NMR and IR data sodium salt formation could be confirmed.

Melting points and glass transition temperatures were determined by DSC (Fig. 2). For all TBP salts the melting point and glass transition temperature, respectively, were lower than the melting point of the corresponding free acid and sodium salt. All liquid TBP salts (Ibuprofen RT-IL, Ketoprofen RT-IL, Naproxen RT-IL and Sulfamethoxazole RT-IL) had glass transition temperatures below 0 °C. The melting point of the solid and crystalline (*vide infra*) Tolbutamide TBP salt was 56 °C. TBP salts of Diclofenac and Sulfadiazine TBP salts were crystalline (*vide infra*) with melting points exceeding 100 °C; hence, they did not fulfill the definition of an ionic liquid. All melting points of all sodium salts were exceeding 100 °C and exceeded those of the corresponding free acids, with one exception only: for Tolbutamide the melting points of the free acid and the sodium salt were almost identical (Fig. 2).

The diffraction pattern of the free acids and the solid TBP salts (Diclofenac, Sulfadiazine, Tolbutamide) was collected by XRPD. All solid substances were crystalline. Different diffraction patterns were observed for the TBP salts as compared to the corresponding free acids, reflecting changes in crystal structure as a result of salt formation (Fig. 3).