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New API-ILs derived from Indomethacin and Mebendazole†

Verónica Fernandez-Stefanuto and Emilia Tojo*

Faculty of Chemistry, University of Vigo, Marcosende, As Lagoas, 36210-Vigo, Spain;
* Correspondence: etojo@uvigo.es; Tel.: +34-986-81-2290

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Abstract: The transformation of two solid Active Pharmaceutical Ingredients (APIs) into new ILs that incorporate APIs (API-ILs) is reported. The structures of the APIs (indomethacin and mebendazole) were selected by their susceptibility of being transform into API-ILs (either to form the cation or the anion) and their limited bioavailability due to its low solubility in water. The counterions were carefully chosen aiming for high biocompatibility, low toxicity and high water solubility such as those derived from DMEA, TMG, DBU, TED, *p*-toluensulfonic acid, glycolic acid, methanesulfonic acid and saccharin. The synthesis was carried out by direct treatment of the API with the corresponding selected acid or base. Finally, the solubility in water of all the salts synthesized was determined.

Keywords: ionic liquid; active pharmaceutical ingredients; water solubility.

1. Introduction

The efficiency of a drug or Active Pharmaceutical Ingredient (API) largely depends on its bioavailability [1]. This property is directly related to the permeability of the API and its solubility. Because the accessibility of a drug to its pharmacological target in the body involves its solution in body fluids and the passage through membranes (absorption and distribution), a low solubility leads to a low dissolution rate and absorption, and consequently a higher dose to achieve the therapeutic effect [1]. A low solubility in water is one of the main challenges to deal with during the development of active principles for oral administration, one of the most common routes of drugs administration. The API used in the formulations of medicines are commonly found in their crystalline form to maximize their purity, thermal stability and bioavailability. However, these solid forms have a number of limitations, such as low solubility in water, polymorphism, or difficulty to cross the lipid bilayers due to its insufficient lipophilicity [2].

Considering the unique properties of ionic liquids (ILs), it is not surprising that in recent years they have aroused great interest in biomedical research, not only as catalytic means for drugs synthesis, but also as potential components for the formulations of drugs. In order to solve the disadvantages that drugs have in solid state, new ILs incorporate pharmacological active ingredients into their structures, forming what is known as API-ILs (Active Pharmaceutical Ingredients-ILs), an alternative to the common crystalline salts [3].

In this work, two APIs that are susceptible of being transform into ILs, were selected to improve their solubility in water. The different counterions to form the new API-ILs were chosen aiming for high biocompatibility, low toxicity and high water solubility.

2. Materials and Methods

Chemical reactants and solvents were purchased to Sigma Aldrich and Acros-organics. All solvents were distilled prior to use. The glass material employed in the synthetic reactions was dried in an oven at 60 ºC during 24 h before its use. The evolution of the reactions was monitored by thin layer chromatography (t.l.c.) employing silica-gel sheets (Merck, TLC Silica gel 60 F_{254}). A solution of Hex/AcOEt (2:1) was employed as eluent.

Spectroscopic data were provided by the Center of Scientific-Technological Support to Research (CACTI) of the University of Vigo. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER ARX 4CO spectrometer at 400.1621 (^{1}H) and 100.6314 (^{13}C) MHz, respectively. $CDCl_3$ (ACROS Organics, 99.6+ atom % D) and DMSO (ACROS Organics, 99.5+ atom % D) were employed as deuterated solvents as received from the supplier.

3. Results and Discussion

3.1 Synthesis

The synthesis of the eight novel salts was carried out through direct treatment of the API with the corresponding acid or base [4]. Due to their low solubility in water, their pharmacological properties and their capacity to be transformed into ILs, the selected APIs were indomethacin (water solubility 0.0009 mg/mL, anti-inflammatory) and mebendazole (water solubility 0.09 mg/mL, antihelmintic and antitumor properties). The general synthetic procedures are shown in **Figure 1**.

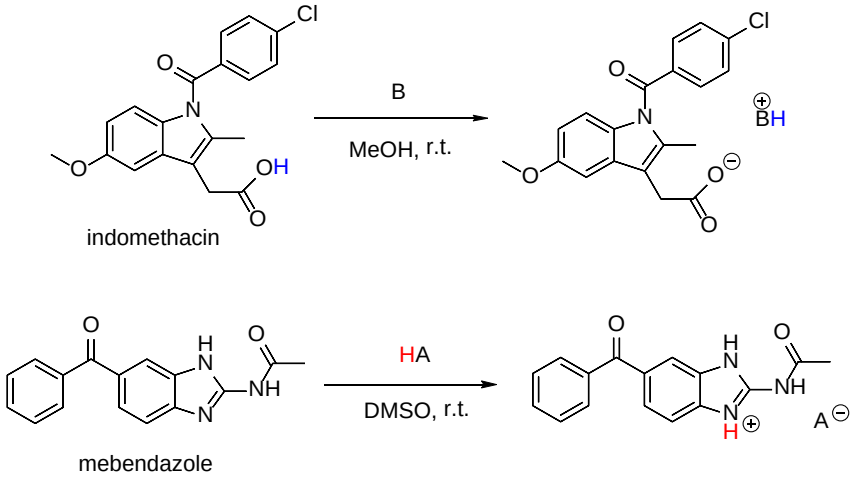

Figure 1. General synthesis of indomethacin and mebendazole based new salts.

The counterions of the ionized APIs were carefully chosen aiming for high biocompatibility, low toxicity and high water solubility. Thus, the bases selected to react with indomethacin, were tetramethylguanidine (TMG), 2-dimethylaminoethanol (DMEA), 1,8-diazabicyclo[5.4.0]undec-7-ene

(DBU) and 1,4-diazabicyclo[2.2.2]octane (TED); while the acids selected to react with mebendazole were *p*-toluensulfonic acid, glycolic acid, methanesulfonic acid and saccharin (**Figures 2 and 3**):

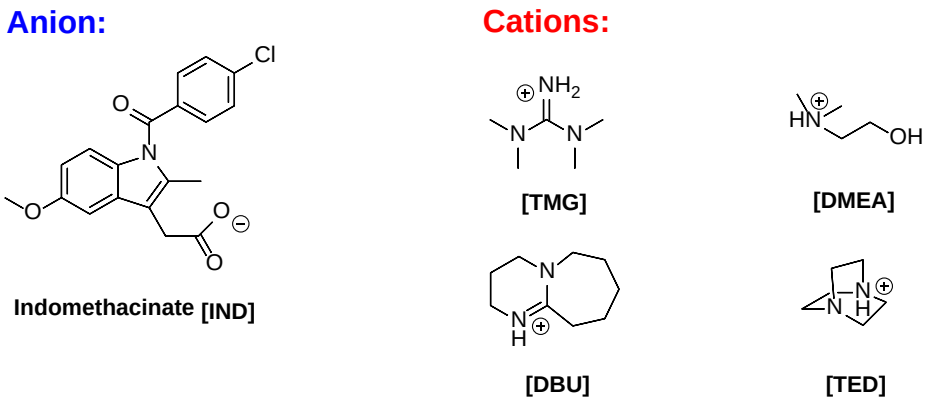

Figure 2. Structures of the synthesized indomethacin based API-ILs.

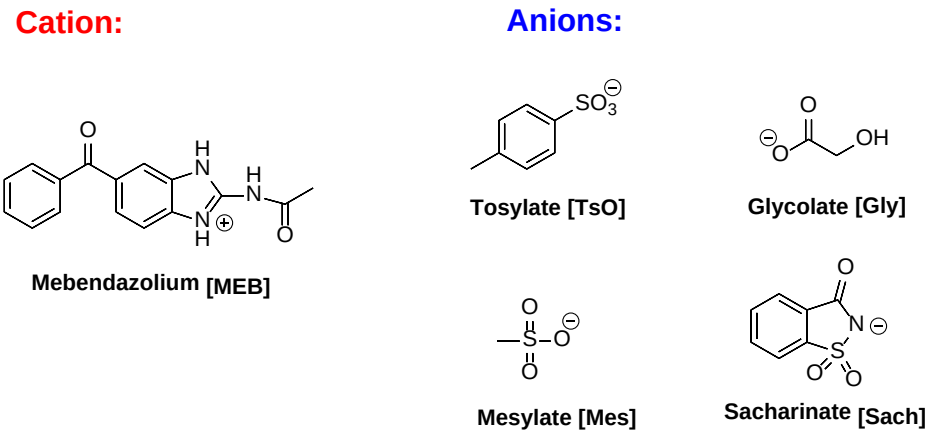

Figure 3. Structures of the synthesized mebendazole based new salts.

Indomethacin based API-ILs were found to be liquids at room temperature while those derived from mebendazole were all solid salts.

The structures of all the new synthesized salts were confirmed by ^{1}H and ^{13}C NMR spectroscopy as well as low and/or high MS spectrometry.

3.2 Solubility tests

A solubility test in water was carried out with all the salts synthesized. To a known quantity of each salt, water was added drop by drop (50 μL each) until completely dissolved. The concentrations (mg/mL) were then calculated to give the results shown in **Tables 1 and 2**. As it can be seen, a significant increase of the solubility of the two selected commercial APIs, indomethacin and mebendazole, was obtained.

Table 1. Solubility (mg/mL) in water of indomethacin based API-ILs.

API-IL	State at r.t.	API-IL solubility	Indomethacin solubility
[TMG][IND]	Liquid	630	
[DMEA][IND]	Liquid	620	0.0009
[DBU][IND]	Liquid	500	
[TED][IND]	Liquid	710	

Table 2. Solubility (mg/mL) in water of mebendazole based new salts.

API-IL	State at r.t. (m.p. ºC)	API-IL solubility	Mebendazole solubility
[MEB][TsO]	Solid (180)	4	
[MEB][Gly]	Solid (175)	25	0.09
[MEB][Mes]	Solid (165)	36	
[MEB][Sac]	Solid (193)	13	

4. Conclusion

With the aim of improving their solubility in water, two solid APIs (indomethacin and mebendazole) were selected to be transformed into new API-ILs. The counterions were carefully chosen looking for high biocompatibility, low toxicity and high water solubility such as those derived from DMEA, TMG, DBU, TED, *p*-toluensulfonic acid, glycolic acid, methanesulfonic acid and saccharin. Indomethacin based API-ILs were found to be liquids at room temperature while the new salts derived from mebendazole were all solids with melting points higher than 100 ºC.

The structures of all the eight new synthesized salts were confirmed by ^{1}H and ^{13}C NMR spectroscopy as well as low and/or high MS spectrometry.

The solubility tests showed a significant increase of the solubility in water for all the salts synthesized, especially for the API-ILs derived from indomethacin.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Jain, S.; Patel, N; Lin, S.; Solubility and dissolution enhacement strategies: current understanding and recent trends. *Drug Dev. Ind. Pharm.* **2015**, *41*, 875–887, DOI: //doi.org/10.3109/03639045.2014.971027
2. Hauss, D.J.; Oral lipid-based formulations. *Adv. Drug Deliv. Rev.* **2007**, *59*, 667-676, DOI://doi.org/10.1016/j.addr.2007.05.006
3. Shamshina, J. L; Berton, P.; Wan, H; Zhou, X; Gurau, G; Rogers, R.D., Green Techniques for Organic Synthesis and Medicinal Chemistry, 2nd Edition, Wei Zhang, Berkeley W. Cue; John Wiley & Sons, **2018**. DOI:10.1002/9781119288152
4. Park, H.J.; Prausnitz, M. R.; Lidocaine-ibuprofen ionic liquid for dermal anesthesia. *AIChE J.* **2015**, *61*, 2732–2738. DOI://doi.org/10.1002/aic.14941