Synthesis and transdermal delivery of dual functional phenothiazine ionic liquids

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Abstract

Many pharmaceuticals presently available on the market have disadvantages associated with the solid state (i.e., multiple crystalline states, decreased bioavailability/aqueous solubility, etc.). Prior research has proven that conversion of active pharmaceutical ingredients (APIs) in the solid state to a liquid form (i.e., ionic liquid or IL) is highly advantageous, in that the drug has increased solubility in water or simulated body fluids, improved bioavailability/dissolution, and increased delivery through a skin-mimicking membrane. These liquid state APIs (API-ILs) can also be dual functional, where both drugs forming the IL retain their functionality as well as have synergistic effects. Phenothiazine drugs (PHZ) are good candidates for liquid conversion as they 1.) have disadvantages associated with the solid form, and 2.) have no analgesic effect. Conversion to a liquid form and combination with an NSAID can rectify both of these issues. Here, we synthesized API-ILs of various combinations, with PHZs acting as cations and NSAIDs as anions. Each new API-IL was then purified and analyzed with NMR and IR spectroscopic methods. A select cation and anion were then tested against their respective API-IL combinations *via* transdermal delivery experiments in order to determine if conversion to a liquid form improved upon the drugs' delivery through a skin-mimicking membrane.

Introduction

Phenothiazine drugs have no known analgesic effect, and are typically administered in combination with analgesics for the desired effect. (1) Current administration methods for phenothiazine drugs include oral, parenteral, and rectal delivery. Transdermal delivery offers many advantages to these methods, such as pain minimization, potential for sustained drug release and extended activity, and side effect reduction. (2)

APIs in SOLID FORM

IONIC LIQUID strategy

APIs in LIQUID FORM (API-ILs)

DISADVANTAGES:

- Polymorphic conversion
- Tendency to spontaneously crystallize
- Difficulty in handling or manufacture
- Low bioavailability

ADVANTAGES (1) :

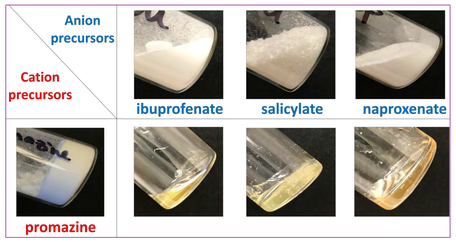
- Increased solubility in simulated body fluids and/or water,
- A more effective delivery of the API through a skin-mimicking membrane
- Improved bioavailability,
- Increased therapeutic efficacy,
- Dual-functionality

Research Questions

A. Will new dual active API-ILs be synthesized by pairing non-steroidal anti-inflammatory drugs (NSAIDs) in their anionic form with phenothiazine drugs in their cationic form?
B. Will the new dual active API-ILs be able to deliver the parent drugs transdermal ?

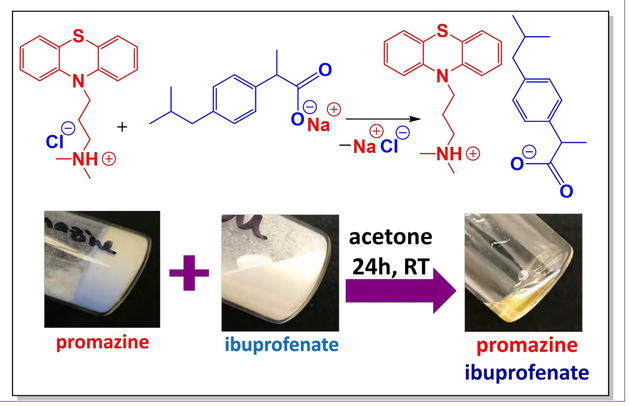
A. Synthesis of new dual functional phenothiazine-NSAID drugs in liquid state

- New dual functional phenothiazine ILs were synthesized by pairing promazine cation with 3 different NSAIDs in anionic form (ibuprofenate, salicylate, naproxenate). Solid state promazine hydrochloride, sodium ibuprofenate, sodium salicylate, and sodium naproxenate were used as cation and anion precursors.



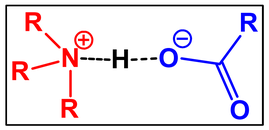
Synthetic methods

- The synthetic procedure used was as follows: a solution of a 1:1 molar ratio of the anion/ cation sources in acetone was stirred at RT for 24 h. The by-product formed (NaCl) was filtered and the solvent from the filtrate was removed by using a Rotovap leading to the formation of the product as a viscous mass. The obtained compounds were characterized using IR and NMR Spectroscopy

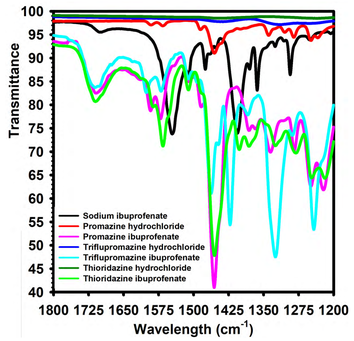


Spectroscopic characterization for Promazine ILs

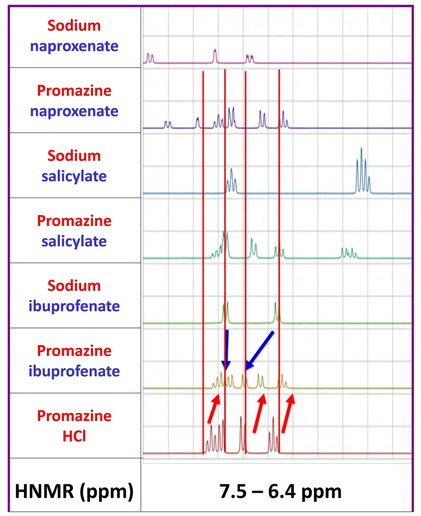
The resulting spectra exhibit a phenomena known as "confused ionic liquids", where the hydrogen is shared between the nitrogen of the PHZ and oxygen of the NSAID. This creates a free acid ibuprofen peak in IR spectra, as well as a change in the NMR peak shifts (move slightly upfield). This shift confirms the formation of the 'confused ionic liquids'.



IR Characterization

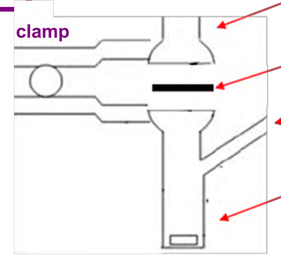


1H-NMR Characterization



B. Will the new dual active API-ILs be able to deliver the parent drugs transdermally ?

- The membrane transport experiments were conducted by following the literature protocols (3), by using a silicone membrane and a Franz diffusion cell.



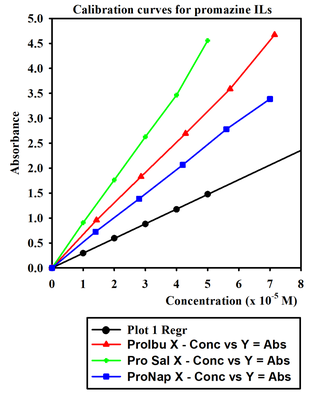
donor chamber
(contains the dual functional IL as an ethanol solution)

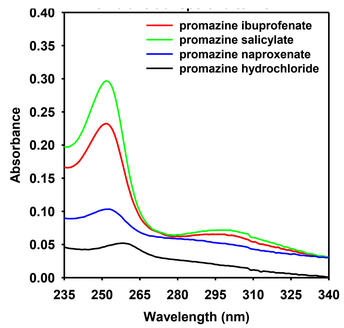
silicone membrane
(membrane that mimics skin with a thicknesses of 0.01")

side arm
(allows for samples to be taken at pre-determined times, after 15 min, 30 minutes, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 9 h, and 24 h)

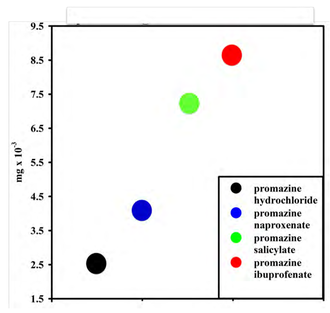
receiver chamber
w/ degassed phosphate buffered saline (PBS, pH = 7.4; buffer solution that mimics body fluid) as the receiver solution

Results





UV-Vis spectra for samples taken after 15 min



Amounts (in mg) of promazine ILs passed through after 15 min

Conclusion

- NMR and IR characterization and physical aspects show the formation of dual active ILs.
- Membrane transport data shows transdermal delivery as a viable treatment option, and a more effective delivery of promazine when converted to a liquid form.
- Future work: TGA,DSC data will be collected and the membrane transport method will be improved upon.

References

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