Synthesis of Chlorpromazine Ibuprofenate Ionic Liquid and its Application to Pharmaceutical Use

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Abstract

In pharmacies around the world, solid-state pharmaceuticals sit on shelves changing day by day. These detrimental transformations are coined by the term polymorphism—the event of a substance crystallizing into more than two crystalline forms. This leads to a change in a drug's effectiveness and a decrease in aqueous solubility and limited bioavailability. These disadvantages can be resolved through conversion to a liquid form (ionic liquid- IL) that can have a greater therapeutic effect on users. ILs can be synthesized from two different parent compounds, which combine to create an IL that possesses dual functionality, in that both parent drugs retain their functions in the liquid form. The IL of interest for this project is chlorpromazine ibuprofenate. Spectroscopic methods such as NMR and IR are employed to determine the purity of the ILs. Water and simulated gastric fluid (SGF) are used to administer solubility studies for each substance. This step is completed in preparation for further study of membrane transport to test transdermal application of the ILs. For this compound, the supported ionic liquid phase (SILP) methodology is used. This procedure is favorable for a liquid drug due to the adsorption into silica, consolidating the benefits of an IL with the ease of transfer and handling, which is a convenient quality of solid-state drugs. Following this, leaching studies will be performed in order to test the potential for this drug delivery mechanism. If successful, this holds the possibility to provide a more effective way to ingest medications.

Synthesis of Chlorpromazine Ibuprofenate

- The compound of interest for this project is Chlorpromazine Ibuprofenate (Chl Ibu). Chlorpromazine hydrochloride (Chl – HCl) is the phenothiazine cation precursor while sodium ibuprofenate (Na Ibu, an analgesic) is the anion precursor.

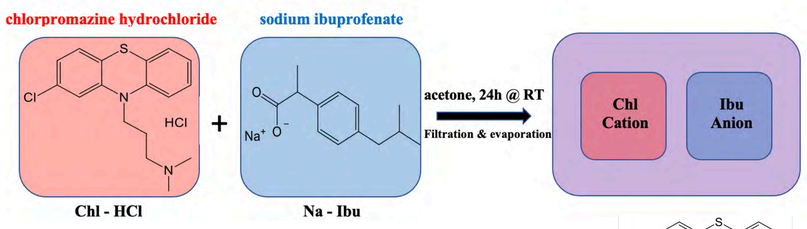


Figure 1: Synthesis of Chl-Ibu

- ***Procedure used** (Figure 1)*: In a 1:1 molar ratio, the cation precursor, Chl-HCl, and the anion precursor, Na-Ibu, were dissolved in acetone. The obtained mixture was stirred at room temperature for approximately 24 hours. The formation of the inorganic solid-state by-product, NaCl, indicated the reaction was taking place. The insoluble NaCl was removed through filtration and the solvent from the obtained solution was evaporated to afford the Chl-Ibu compound as a viscous liquid (Figure 2). After this process was completed, the compound was characterized through Infrared Spectroscopy (IR) and Nuclear Magnetic Resonance Spectroscopy.

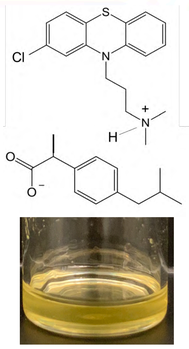


Figure 2: Chl-Ibu Ionic Liquid

Spectroscopic Characterization of Chl-Ibu

To determine compound's purity, Infrared (IR) and Nuclear Magnetic Resonance (NMR) Spectroscopy were utilized. These techniques aided in identifying the different bonds within the formed compound by comparing the obtained characterization data with the data for the starting materials.

- IR Spectroscopy showed a shift in the C=O signal from ~1550 cm^{-1} in Na-Ibu to ~1720 cm^{-1} in Chl-Ibu.
- ^{1}H-NMR Spectroscopy showed the signals corresponding to all the hydrogen atoms from Chl cation and Ibu anion

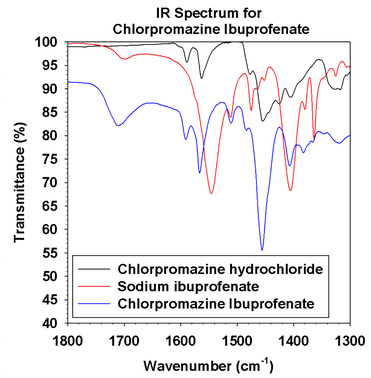


Figure 3: Infrared Spectroscopy

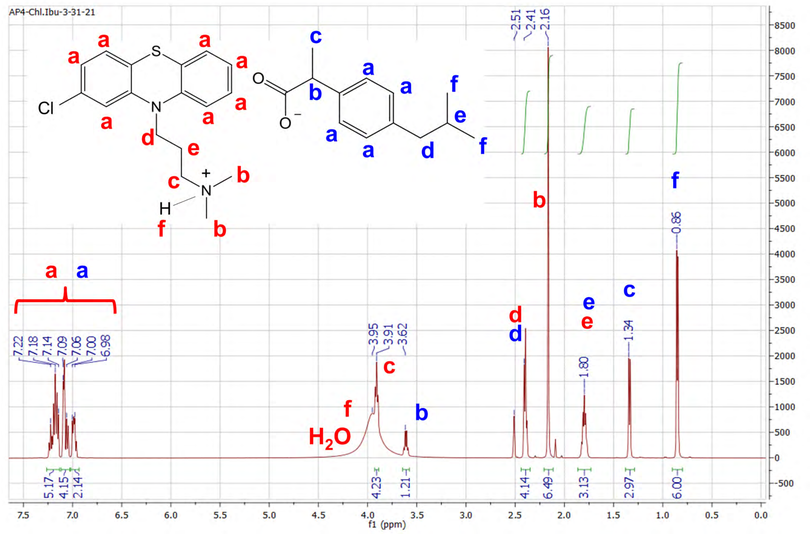


Figure 4: NMR Spectroscopy

Adorption of Chl-Ibu onto silica

- Loading of Chl-Ibu onto silica (Figure 5) was completed using a 9:1 wt:wt ratio between silica and Chl-Ibu compound respectively. The two materials were mixed with ~15 mL of ethanol and stirred at room temperature for approximately 2 hours. After the mixture was stirred, the solvent was completely evaporated using a rotary evaporator. Once this process was completed, the supported ionic liquid phase (SILP) material consisting of 10% adsorbed Chl-Ibu onto silica was obtained.

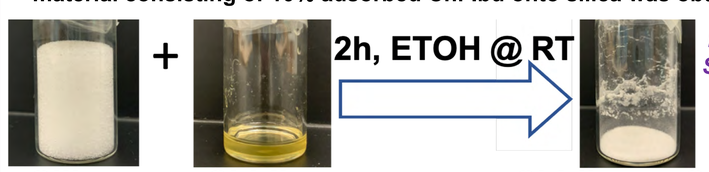


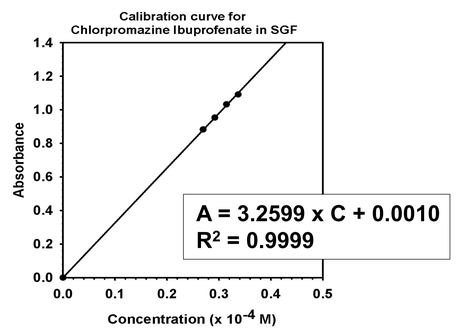
Figure 5: Synthesis of SILP

Leaching studies

The leaching of this compound in Simulated Gastric Fluid (SGF; pH = 1.2) was investigated. First, a calibration curve for Chl Ibu in SGF was constructed.

- Calibration curve (Figure 6):

Using a stock solution comprised of a known mass of Chl-Ibu in 100 mL SGF, 4 dilutions were made and the compound's absorbance at 254 nm was determined using UV-Visible spectroscopy. The absorbances found from each dilution were then plotted using the known concentrations as the A = f(c) function found in Beer's Law. The linear regression obtained was used to determine the a and b coefficients from $A = a \times C + b$ where A = measured absorbances and C = known molar concentrations for the used dilutions.



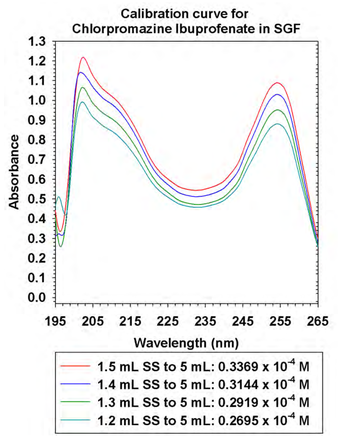


Figure 6: Calibration Curve in SGF

- Leaching Studies

50 mg of SILP material was placed in 50 mL SGF. The resulting mixture was rotated at 150 RPM speed. Four 1 mL aliquots were removed from the flask at varying time intervals, namely at 0.5 h, 1h, 3h, and 21h. The aliquots were diluted to 5 mL with SGF. After dilution, UV-Visible spectroscopy was utilized in order to determine their absorbances at 254 nm. The obtained absorbance values and the a and b coefficients obtained from the calibration curve were used to find the molar concentration of the samples by using the previously obtained linear regression: $A = 3.2599 \times C + 0.0010$.

- Results (Figure 7):

Leaching showed that approximately 97% of the Chl-Ibu was released from the silica within 30 minutes of rotating at 150 RPM. This indicates that silica is a favorable solid support for SILP due to its ability to release a drug when delivered to the human body.

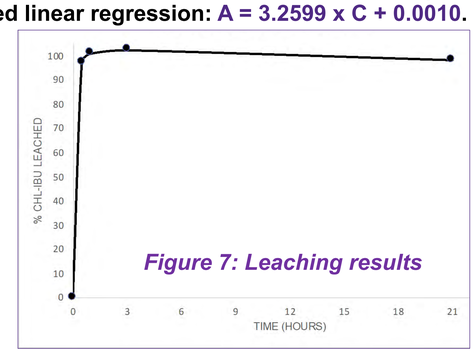


Figure 7: Leaching results

Conclusions and Future Work

- Chl-Ibu is a highly viscous IL that can be released in SGF at a high rate when adsorbed in a 10% wt/wt concentration on silica solid support. These results suggest that SILP is a good strategy for the delivery of highly viscous liquid state drugs into media of various pHs.
- Future work will focus on investigating whether the leaching of Chl-Ibu from silica will be influenced by the amount of Chl-Ibu loaded on silica or by the mesh size of the silica material.

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