Isolation and Characterization of Degradation Products of Amiodarone HCl Associated with Microcrystalline Cellulose

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BACKGROUND

- Amiodarone HCl is a common anti-arrhythmic drug dating to the 1960's.
- Dosage forms for amiodarone are not readily available for pediatrics.
- Challenges come from stability of drugs when compounding, directly related to excipients.
- Previous study evaluated 3 common excipients: mannitol, lactose, and microcrystalline cellulose.
- They identified an unknown degradation of amiodarone when paired with cellulose.

OBJECTIVE

- Isolate and characterize the unknown degradation product from the reaction of amiodarone and cellulose.

METHODS

- A forced degradation study (labeled t=120) was prepared using amiodarone HCl with each of the following excipients: microcrystalline cellulose, mannitol USP powder, and lactose monohydrate.
- These powder mixtures were allowed to incubate in an oven for several months to determine if degradation would occur.
- High performance liquid chromatography with mass spectroscopy (LCMS) was used to identify presence of degradation product and to aid characterization.
- Control samples (t_0) were compared to forced degradation samples.
- To analyze the chemical structure, nuclear magnetic resonance (NMR) proton (^1H) and carbon (^{13}C) was used.
- A pH evaluation was also conducted of the excipients and amiodarone.

RESULTS

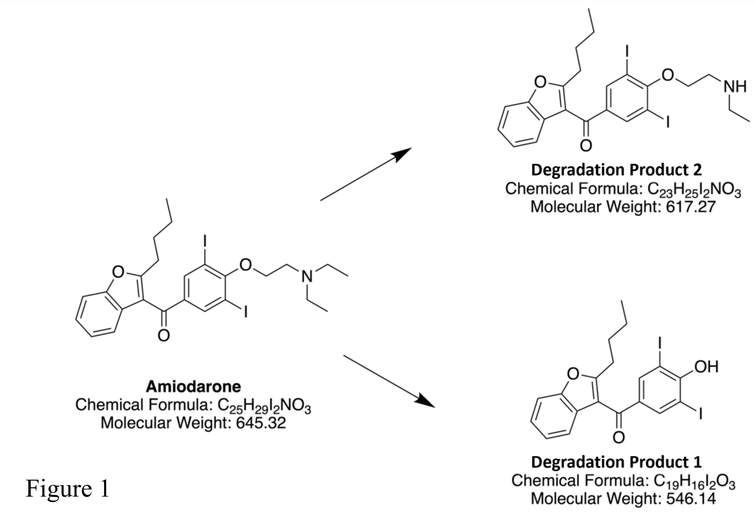

Figure 1

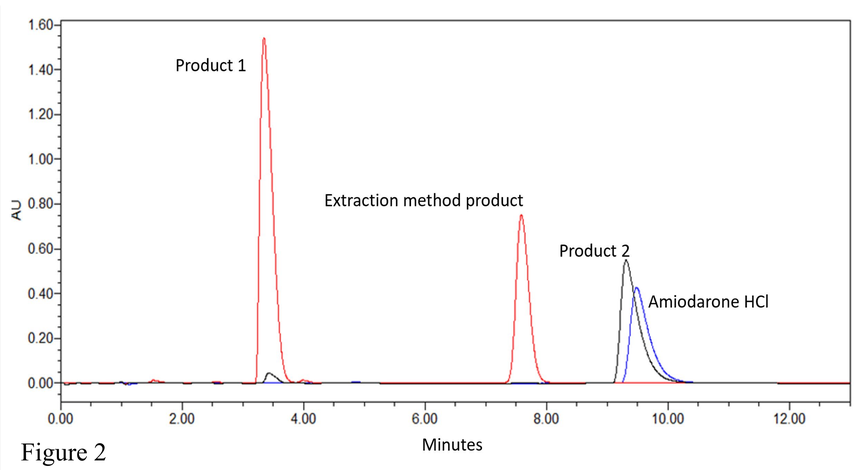

Figure 2

Results (Chromatography and NMR):

- Two degradation products were found with amiodarone and microcrystalline cellulose with LCMS.
- Molecular weights were used to identify the two products
  - Named Product 1 and Product 2.
- NMR analysis showed consistency with molecular formulas (see Figure 1).
- Product 1 is the predominant degradation product and is a O-dealkylation of the ether group.
- Product 2 is an N-dealkylation of one of the ethyl groups which was not isolated in pure form and is currently working to purify to finalize the characterization.
- The peaks of the products can be seen in Figure 2.

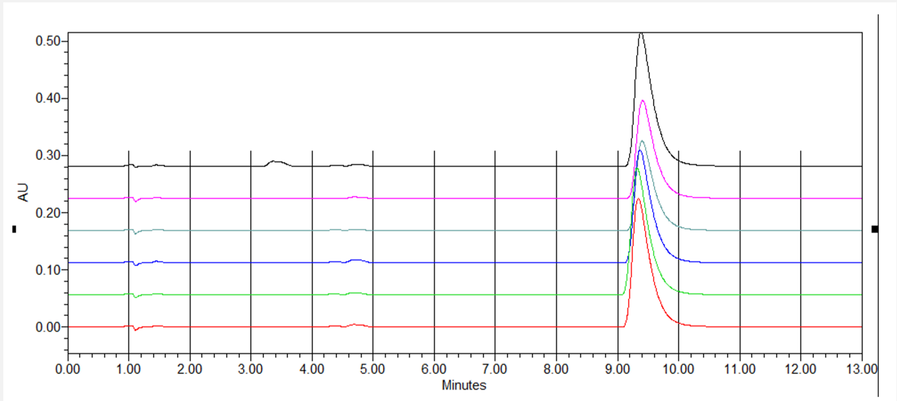

Figure 3: *Control (t) vs t=120; from descending order: black line – t=120 amiodarone + cellulose; pink line – t amiodarone + mannitol; grey line – t amiodarone + lactose; blue line – t amiodarone + cellulose; green line – t=120 amiodarone + mannitol; Red line – t=120 amiodarone + lactose*

Results (Amounts Detected and pH evaluation)

- Forced degradation (t=120) study vs control (t_0) showed:
  - Only amiodarone + microcrystalline cellulose had Product 1 in large amounts (Figure 3, peak at 3.5 minute).
  - No t_0 sample contained any degradation.
  - Quantifiable detected degradation differences between t=120 samples is 19.38% form microcrystalline cellulose, 0.33% and -3.93% (lactose and mannitol respectively).
- pH of the samples acidified over time in thermal conditions.
  - The pH of the samples did not contribute to formation of any degradation product.

CONCLUSION

- Amiodarone HCl coupled with microcrystalline cellulose showed a predominant degradation of Product 1, an O-dealkylation of the ether group.
- Further evaluation of amiodarone compounded formulations should be explored.
- Product 2 needs further work up to fully characterized.

References

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2. Brun D, Curti C, Lamy E, et al. Beyond-Use Dates Assignment for Pharmaceutical Preparations: Example of Low-Dose Amiodarone Capsules. *J Pharm Technol*. 2021;37(4):178-185. doi:10.1177/87551225211015566