Allergy Relief at Scale: Plant Design for Diphenhydramine Hydrochloride

How have chemical and industrial accidents shaped the evolution of safety education in chemical engineering programs?

A Thesis Prospectus
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By
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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Seasonal allergies in the United States affect nearly 1 in 3 adults and over 1 in 4 children, resulting in over 100 million Americans experiencing symptoms annually (Facts and Stats, n.d.). People with allergies produce histamines when the body's immune system interprets something harmless as a threat and invokes an inflammatory response (*Antihistamines*, 2017). Histamine is a natural signaling chemical that detects infections and causes allergic reactions. Diphenhydramine hydrochloride (DHCl), an H1 receptor antihistamine known by its brand name Benadryl®, is a widely used over-the-counter medication that provides relief from symptoms caused by allergies and colds such as red and itchy eyes, sneezing, and runny nose (Diphenhydramine, n.d.). It also helps manage symptoms of motion sickness, insomnia, and Parkinson's disease (What's Hot in PD?, 2015). DHCl works by blocking histamine receptors and drying up bodily secretions by blocking acetylcholine receptors, thus alleviating allergy symptoms (Diphenhydramine Oral, n.d.). This non-addictive and non-toxic product has minimal harmful side effects, which presents a significant advantage over many over-the-counter drugs. Although there is some potential for misuse, such as the Benadryl Challenge, this trusted medication has been used for decades to improve people's quality of life (*What Is the "Benadryl Challenge?"*, n.d.). This capstone project will focus on designing an economically and environmentally sustainable plant to produce DHCl.

When synthesizing chemicals, there are always dangers to be aware of as a safety incident can lead to major consequences. In 1984, a storage tank in Bhopal containing methyl isocyanate (MIC) was exposed to water which led to a runaway reaction. This runaway reaction caused 40 tons of a toxic MIC gas to be released killing approximately 4000 people (Broughton,

2005). A runaway reaction occurs when a reaction reaches a temperature or pressure ideal for that reaction so it accelerates so fast it can be impossible to control. They are responsible for some of the worst process safety incidents in history. Along with runaway reactions, the chemical engineering industry is susceptible to disasters from broken valves, chemical hazards, and explosions. It is important for aspiring chemical engineers to be educated on process safety to reduce the risks associated with this field.

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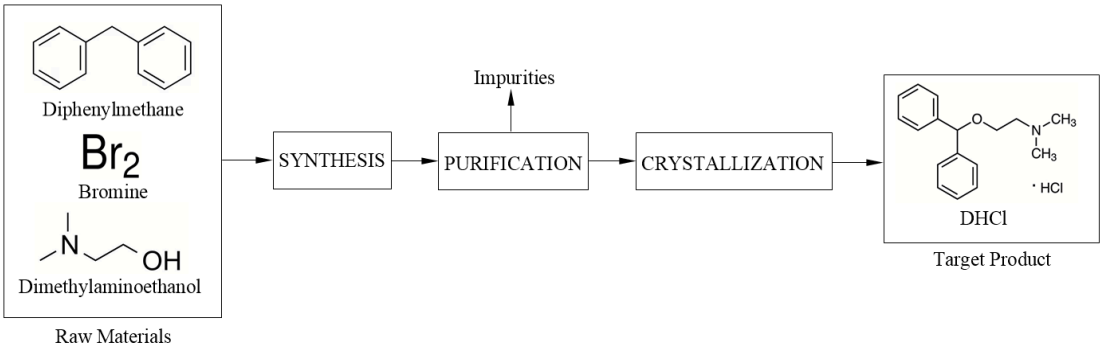

Figure 1. Block Flow Diagram for DHCl Synthesis (Adapted from Snead & Jamison, 2013)

This capstone project will be designing an economically and environmentally sustainable plant to produce DHCl. This process will involve three major stages: synthesis, purification, and crystallization (Figure 1). The process starts with a halogenation reaction between diphenylmethane and bromine to make bromodiphenylmethane. The halogenated product then reacts with *N*,*N*-dimethylaminoethanol to form diphenhydramine hydrobromide, which is then converted into diphenhydramine-hydrochloride. To improve yield, a major byproduct from the first reaction, diphenylmethanol, undergoes further reactions to be converted into the final product (Figure 2).

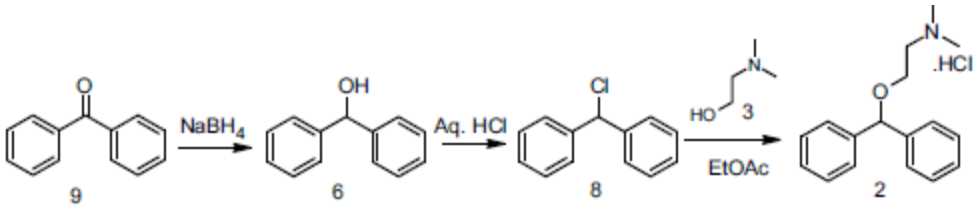

Figure 2. Reaction scheme DHCl synthesis (Sonavane et al., 2017)

Given the recent focus on green chemistry, one of our objectives is to enhance the environmental sustainability of this process. Toxic solvents like toluene and hexane are commonly used in the production of DHCl, and we plan to use alternative synthesis methods that minimize the use of harmful solvents.

By exploring safer alternatives, the project addresses critical public health needs while improving the production of an essential, high-demand medicine. Enhancing the cost-effectiveness of production can increase access to DHCl in low-income countries, which supports global health goals for equitable healthcare access. Overall, this project is well-positioned to contribute positively to society, especially with emerging advancements in green chemistry.

This project is part of our two-semester capstone course (CHE 4474/4476) and will be executed by a five-person team. It is focused on designing a chemical process through extensive research, collaboration, and computation. We will begin by continuing our literature review to gather relevant experimental data and reported findings, utilizing online databases and journals to find specific design data. We will divide the project into key components and delegate responsibilities based on individual strengths and interests.

To visualize the overall process, we will create detailed flow diagrams and sketch designs for each unit operation. Each member will apply chemical engineering principles to design their assigned unit operations, and the team will integrate them into the overall process together. We

will use computational tools like Aspen Plus for modeling and simulating process operations and conducting sensitivity analyses. We will also use MATLAB and Python for data analysis and visualization, spreadsheets for calculations and data management, and MS Project for project management.

Our team will hold weekly meetings where all members will come prepared with completed work to evaluate progress and next steps. We will also schedule optional work sessions for focused collaboration, particularly for complex tasks. To ensure quality, we will establish a peer review system and assign most tasks to a subgroup of two members based on interest and prior experience. By following this structured approach, we aim to successfully complete our capstone project, producing a comprehensive and innovative chemical process design that leverages each team member's expertise.

How have chemical and industrial accidents shaped the evolution of safety education in chemical engineering programs?

This research project will focus on how process safety education has evolved over the years due to chemical incidents in the industry and academic settings. Every accident that has occurred in a laboratory or industrial setting could have been prevented if proper safety measures had been taken. In 2008, at UCLA, a student researcher lost her life due to negligence of lab safety measures. She was doing her normal lab work not wearing a lab coat when she used a syringe to pick up Tert-Butyllithium, which ignites spontaneously in the air. The fire burned more than 40% of her body (Kemsley, 2023). There are plenty of other incidents in both academia and industry where negligence of safety procedures have led to fatal consequences.

That is why this research paper is exploring how process safety education has evolved over time and if the evolution has led to a decrease in accidents.

These types of accidents don't only occur in academia. They also happen at a larger scale in industrial settings. In 2015, in Torrance, California, an explosion occurred at a chemical refinery owned by Exxonmobil. A piece of equipment in the refinery called the "expander" malfunctioned and turned the whole process into standby mode. In standby mode, side valves closed to shut the unit off, however, one of these valves had eroded over the years so it could no longer act as a proper barrier. Due to this, flammable hydrocarbons started leaking into a reactor containing catalysts. This buildup of hydrocarbons caused an explosion which scattered catalyst dust up to a mile away from the refinery. The explosion caused two injuries to workers, serious property damage, and gas prices in California skyrocketed for a whole year following the explosion (Zou, 2022). Experts studying this case believe this should not have happened because the company should have required a more robust safety management system as well as regular maintenance checks on all the valves in the system. Every process safety incident that I have found during my research always appears to have been preventable if safety measures had been followed. Safety can be expensive, but accidents definitely cost a lot more.

At University of Virginia, it is a requirement for chemical engineering undergraduates to take a 1 credit course during their final year dedicated to process safety. This course focuses on the prevention of fires, explosions, and accidental chemical releases. All of which can lead to injuries, fatalities, property damage, and environmental impact. This research paper will study how these process safety requirements came to be and if all universities follow the same safety requirements as UVA. It will also research how process safety education has evolved over time

as more accidents occurred in both academia and industry. Research will be conducted through case studies, academic journals, and university curriculum.

Throughout this research, the STS framework that will be examined is higher education. The research will examine how higher education has changed over the years to implement safety education into their curriculum. It will also analyze how different institutions differ from one another. As a fourth year currently going through the job search process, I have found that companies prioritize students who have taken a process safety course. It made me realize that I am at an advantage over other students because UVA does require process safety education while other universities do not. Four years ago when I was researching colleges, a process safety requirement was not something I ever thought about as it is just a 1 credit course at most schools. Realizing how important it is to go to a school that requires safety education is something I realized this year, and did not even know about last year as a third year. After talking to my peers, they agreed with me that we are grateful we chose this school because if we did not we would be at a disadvantage due to a decision we made at 18. This connects to how universities such as Duke or University of Colorado collected data from students without their consent (Crawford, 2021). Students at those universities also chose to attend these schools at the age of 18 with no idea that their data would soon be taken from them without their consent. It is interesting to see how there are so many factors that go ignored when choosing a university to attend that become important later.

My research is discussing how process safety education was implemented as well as what qualifies as process safety education. Another discipline that has been implemented into engineering education recently is Science, Technology and Society (STS) education. As read in class, Bauer discusses in his paper “Barriers against Interdisciplinarity: Implications for Studies

of Science, Technology, and Society (STS),” all of the insights STS education gives which is why it was implemented into curriculums. Similarly to process safety education, there are distinct reasons why STS education has been implemented as well as research conducted on how it has evolved over the years.

Conclusion

Allergies affect millions of people every day. I am someone that is personally affected by them as I suffer through them every time I go home and see my pets, as well as every spring due to pollen. Diphenhydramine is a medicine that I take every time I suffer an allergy flareup, so I am looking forward to exploring the synthesizing process and hopefully making it more environmentally friendly. The synthesis of diphenhydramine will have risks since it is using chemical reactions, so a risk assessment will need to be done by my capstone group in the spring. The risk assessment portion of the technical component is what inspired the sts research project. Process safety education at UVA is taken seriously so I want to learn about its evolution throughout time. I also want to research how the failures in industry have happened, who cleans them up, and how do companies move forward from an incident.

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