COMMERCIAL SCALE DESIGN FOR DIPHENHYDRAMINE CHLORIDE PRODUCTION USING SOLVENT FREE SYNTHESIS

THE SOCIETAL AND BEHAVIORAL IMPLICATIONS OF BENADRYL'S ACCESSIBILITY: COMPARING OTC AND PRESCRIPTION CONTEXTS EUROPE VS USA

A Thesis Prospectus
In STS 4500
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Bachelor of Science in Chemical Engineering

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: ***Laying Out the General Problem***

"How can the synthesis of Diphenhydramine hydrochloride (DHCl) be optimized to achieve economic and environmental sustainability in pharmaceutical manufacturing?"

The accessibility of over-the-counter (OTC) medications is convenient but begs the question regarding public health and self- medication. In the case of Diphenhydramine hydrochloride (DHCl), widely known by the brand name Benadryl, its availability as an OTC drug in the United States stands as an example of tensions between healthcare companies, public safety, and pharmaceutical regulation. In many European countries Benadryl is prescription-only, due to the risks associated with self-medicating and misuse. However, in the United States, DHCl is an OTC drug, meaning consumers have direct access without the need for prescription or physician supervision. This difference shows to broader regulatory and social questions around medication accessibility, the dangers of self- medication, and the responsibilities of healthcare systems to educate consumers on safe use.

From a technical perspective, the production of DHCl also presents its own set of challenges. DHCl is an essential medication for treating allergic reactions and other symptoms, yet its production process often involves environmentally harmful solvents like toluene and hexane. Improving the sustainability of DHCl synthesis aligns with growing global health and environmental goals, such as reducing hazardous waste and improving production efficiency. The overarching question becomes, first, how can we ensure that OTC medications like Benadryl are both safe and accessible to the public, and second, how can we enhance their production to support environmental sustainability? To answer these questions we must address both the societal implications of OTC accessibility, and the technical innovation required for sustainable pharmaceutical production.

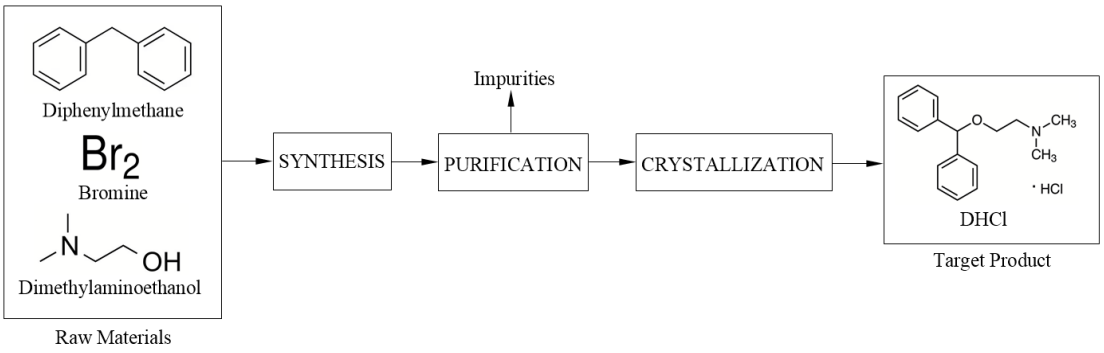
The following sections will explore these questions from both technical and sociotechnical perspectives, beginning with the design of a sustainable DHCl production process and followed by a sociotechnical analysis on the societal impact of Benadryl's OTC status.

Technical Project

Designing a Sustainable Production Process for Diphenhydramine Hydrochloride

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 in which challengers urged viewers to take as many as 12 tablets at a time to supposedly induce hallucinations(*What Is the "Benadryl Challenge?"*, n.d.), this trusted medication has been used for decades to improve people's quality of life. Industry experts predict that the global market for DPH will grow by nearly 50% by volume (*Diphenhydramine Hydrochloride Market Size, Share & Forecast to 2034*, n.d.). This growth may be attributed to expansion into developing regions or an increasing prevalence of allergies caused by urbanization, climate change, and pollution (D'amato et al., 2001). The Diphenhydramine



market is also projected to increase by nearly 50% by volume.

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

This capstone project will focus on 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 reaction between Benzophenone and Sodium borohydride to make benzhydrol. The product then reacts with aqueous hydrogen chloride to form Chloro Diphenylmethane. This product is washed with ethy acetate and is treated with DMAE in solvent free conditions to form diphenhydramine-hydrochloride. This process can be further analyzed in Figure 2.

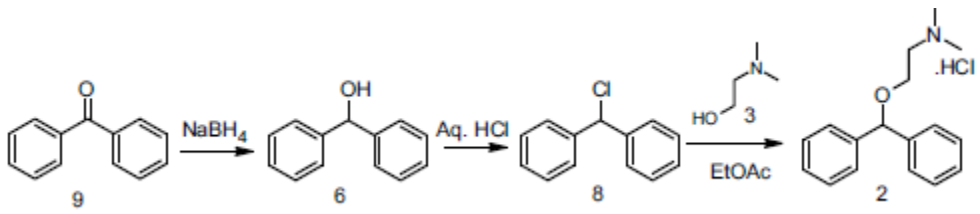


Figure 2. Reaction scheme DHCl synthesis (Sonavane et al., 2017)

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. This method also increases atom efficiency by ~45%, making the process more economical.

By exploring safer alternatives, the project addresses critical public health needs by improving the production of 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.

STS Research Project

"How does consumer behavior differ when accessing Benadryl as an OTC medication versus a prescription medication, and what are the resulting impacts on healthcare practices, public health outcomes, and regulatory responses?"

In the United States, over the counter (OTC) medications like Benadryl (diphenhydramine) are

easy to access. This has both positive and negative effects. On the positive side, OTC medications let people manage allergies, motion sickness, and sleep problems without needing to see a doctor. On the negative side, easy access also creates public health risks. People sometimes misuse these medications, take too much by mistake, or use them in ways they are not supposed to. This is especially common in groups with limited health knowledge. For example, the "Benadryl Challenge," a social media trend where people take large and dangerous amounts of the drug, shows how harmful unregulated access can be, especially for young people (Stevenson and Trawick, 1996; Gabe et al., 2011).

In contrast, countries like Germany and France only allow similar medications to be accessed with a doctor's prescription. These rules focus on safety and healthcare monitoring. While this approach reduces misuse, it also creates barriers for people who can responsibly manage their symptoms. Research shows that such differences in regulations affect how people view medications in terms of risk, convenience, and trust (Morgan et al., 2006; Christiaens et al., 2011). This research will study how these rules shape consumer behavior and what they mean for public health, healthcare systems, and policy decisions. By comparing OTC and prescription systems, this study will evaluate the benefits and challenges of both approaches.

Background and Literature Review

In the U.S., OTC medications like Benadryl allow people to treat their symptoms quickly and cheaply without needing to visit a doctor. This makes healthcare more accessible. However, this convenience has drawbacks. Research shows that unrestricted access increases the chances of people misusing the medication, particularly if they do not fully understand how it works (Stevenson and Trawick, 1996). Studies find that convenience, low cost, and the belief that OTC medications are always safe can lead to poor decisions about dosage and long-term use (Morgan et al, 2006). Research also warns about the risks of OTC medications. For example, using Benadryl incorrectly can cause confusion, drowsiness, or even death. Some people also misuse it for recreation or as a sleep aid (Pitts, 2006).

In countries like Germany and France, medications like Benadryl require a prescription. This allows doctors to monitor how patients use these drugs and reduces misuse. Such rules focus on protecting public safety (Christiaens et al, 2011). However, these regulations also make it harder for responsible users to access the medication they need. Requiring prescriptions adds steps that can discourage even legitimate users (Stevenson and Trawick, 1996).

Although there is not much research specifically on Benadryl, studies about OTC and prescription medications give useful insights. For example, healthcare rules need to balance safety and accessibility. Gabe et al. Additionally, different policies influence how people view the safety and importance of medications. This debate between public safety and personal freedom is central to comparing the approaches in the United States and Europe.

Theoretical Framework

This research uses Actor-Network Theory (ANT) and Behavioral Economics to study how rules

about medication affect consumer behavior. These two ideas help us understand both the big picture and the small details about how systems and individuals interact.

Actor-Network Theory focuses on how people and systems, like consumers, doctors, government agencies, and social media, work together in a network. Rules about medication and product labels also act as parts of this network, influencing consumer behavior and public health. ANT helps explain how these parts work together and how they shape access to medication, safety risks, and healthcare outcomes.

Behavioral Economics looks at why people make the decisions that they do. It studies behaviors such as why people might act impulsively or take risks. For example, people in OTC systems often assume medications are safe simply because they are easy to buy. In contrast, requiring a prescription makes people think more carefully but might also discourage them from seeking treatment. Combining these two ideas lets us look at both the overall system and the individual decisions people make.

Methodology

This research will use multiple methods to compare consumer behavior and systemic impacts under OTC and prescription regulations for Benadryl. A comparative analysis on behavior will involve consumer data on self-medication patterns and risk perception. Document analysis from both U.S. and European populations will provide insights into how the different accessibilities of Diphenhydramine influence behavior, with a specific focus on misuse and assumptions of safety. This research will also examine existing policies and regulations, and review studies regarding public health.

Case studies, including an in-depth analysis of the "Benadryl Challenge" in the U.S. and adherence challenges in European prescription-only contexts, will provide further examples of how regulatory policies shape behavioral outcomes. These case studies will serve as illustrative tools to connect theoretical concepts with real-world phenomena, offering a deeper understanding of the interplay between access, behavior, and public health.

This research will also include interviews with doctors currently practicing in the UK, as well as input from a Pakistani physician via phone, to explore differences outside of the European context.

Conclusion/Expected Results

This study aims to show how different rules about medication access affect behavior, healthcare, and public health. It will look at patterns in how people misuse or properly use medications in OTC and prescription systems. This information can help policymakers create better rules that balance safety and accessibility.

The study will also provide insights into how healthcare systems work. By using Actor-Network Theory and Behavioral Economics, this research will show how different parts of the system interact and how these interactions affect medication access and public health. It will provide useful insights for comparing the approaches in the United States and Europe.

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Comments: I won't go through a full re-grade on this because there's too much work to do on it. I was surprised that you simply entirely replaced your STS section (and without altering the Intro). Unfortunately, the result is clearly genAI created and as a result, doesn't really make sense. The central conflict is still there and nicely set up (though the Background section mirrors the Intro). But the remaining portion will not work.

- The question makes consumer behavior the driver, but why?
- The background mostly repeats what is in the intro and cites no literature.
    - A quick search on Web of Science (limited to the social science and arts & humanities "editions") found little on Benadryl, as you said, but a lot on over the counter medication. Much of it was either from Economics or more Medicine-focused journals, but there was a lot of policy stuff in there, too. It's enough to get you going on exploring at least the policy comparison between the US and Europe. I also found a few other articles that might be helpful. (You'll have to use a proxy link or the libkey nomad tool.)
        - https://doi.org/10.1080/13698575.2011.596189 (seems pretty helpful)
        - https://doi.org/10.3109/14659891.2011.615002
        - https://doi.org/10.1016/j.clinthera.2006.08.007
        - https://doi.org/10.1016/S0277-9536(02)00377-5
        - https://doi.org/10.1016/S0277-9536(96)00257-2 (would have to get via ILL)
- The description of theory doesn't cite anything, mentions ANT only once, and invokes Behavioral Economics, an entirely different (if somewhat related) field.

Further, the theory does not seem to apply to any other part.

- The methods and outcomes are just bullet points. There's no clear connection between the methods and the rest of the paper, no rationale for a particular method, and no real discussion of what applying that methodology would look like. What would you learn from these methods, and how would that knowledge help answer your question?

Try doing this without genAI, starting from the issue that some drugs are available over-the-counter in the US, but not in Europe.