Undergraduate Thesis Prospectus

Large-scale Production of mRNA and Lipid Nanoparticle Synthesis and Purification for RNA vaccines

(technical research project in Chemical Engineering)

The Cost of Insulin: Who Gets to Decide?

(sociotechnical research project)

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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General Research Problem

How can healthcare be made more accessible in the United States?

According to the Commonwealth Fund, the U.S. ranks as the worst in critical areas of healthcare among 10 developed countries. These areas include preventing deaths, access to quality treatment, and consistent treatment among gender, income, and location (Blumenthal, 2024). Many people in the U.S. are deterred from being insured based on cost, which barricades them from receiving vital treatments. According to Rakshit et. al (2024), 28 percent of people reported delaying healthcare based on cost in 2022. With out-of-pocket prices for drugs also soaring, people are unable to take care of their dire health needs. Policy and technology are at the forefront of improving healthcare accessibility. By involving the government in drug sales and enacting more inclusive policies, crucial drugs can be made accessible for both the insured and uninsured. Efficiency in production of drugs and a movement towards large-scale production can also drastically reduce the costs of choice drugs.

Large-scale production of mRNA and lipid nanoparticle synthesis and purification for RNA vaccines

How may the cost efficiency of mRNA and lipid nanoparticles production be improved?

RNA vaccines have recently emerged as an effective and versatile technology to treat infectious diseases, cancers, immunological diseases, rare diseases, and tissue damage (Zhang, 2023). Challenges such as instability, high raw material costs, and inefficient delivery systems persist, so it is critical to improve upon current delivery mechanisms, specifically lipid nanoparticles (LNPs) (Matarazzo, 2023). LNPs encapsulate mRNA via rapid mixing, protecting it from enzymatic degradation and facilitating its release into the cytoplasm for antigen synthesis (Hou, 2021). The goal of the project is to replicate and optimize the mRNA vaccine production process with a particular focus on the LNP delivery system and rapid mixing technique. Using TB as a case study, we seek to address the complexities of bacterial infections and employ mRNA technology to develop more efficacious vaccines, aligning with recent technological innovations and global public health priorities. My technical advisor is Professor Eric Anderson in the chemical engineering department, and my project collaborators are Elli Brna, Abbie Frost, Ian Sellors, and Jason Wieder.

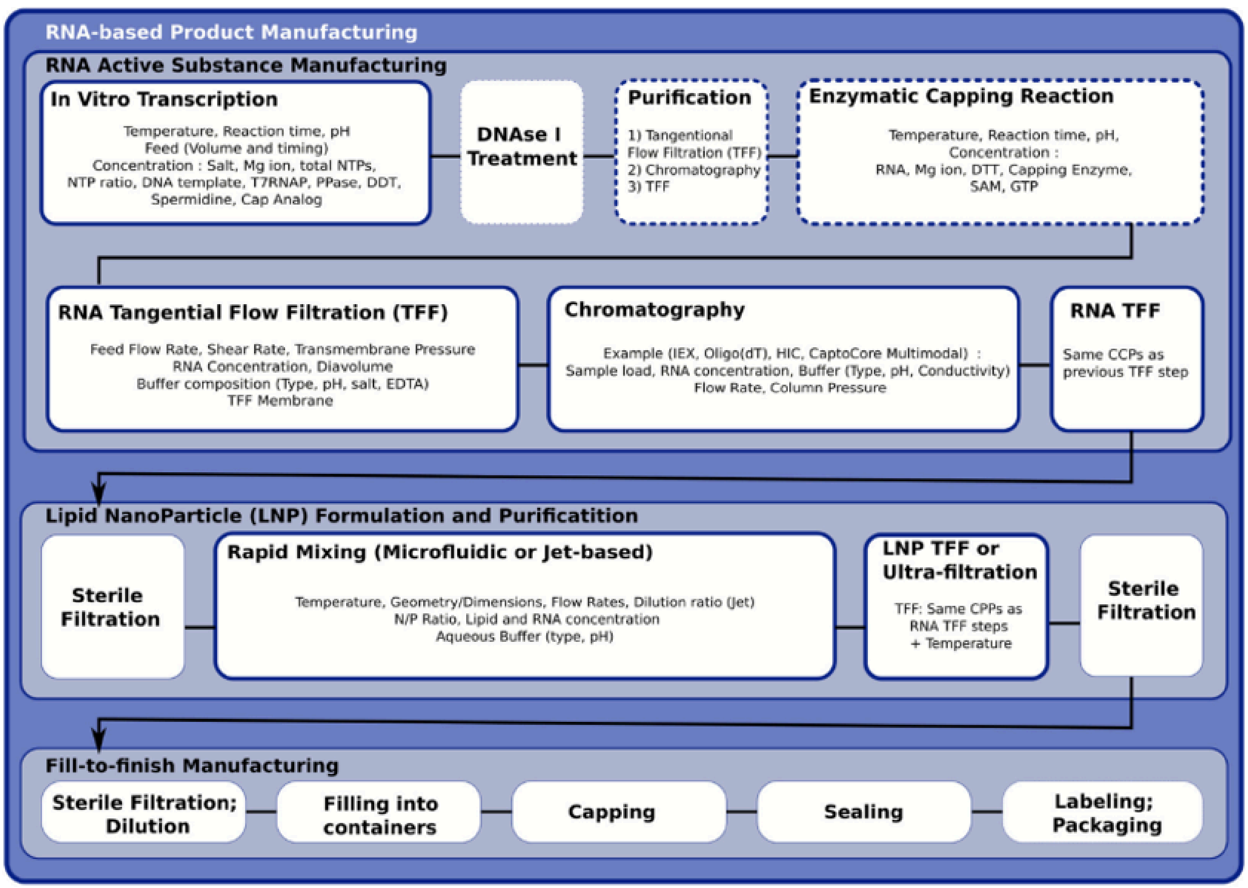

Figure 1. Process Flow Diagram of the mRNA Vaccine Manufacturing Process (Daniel et al, 2023)

Our process will be designed based on the research of Daniel et al. (Figure 1), which reflects the current “state-of-the-art”. The research identifies three main phases of RNA vaccine manufacturing which include the manufacturing of the RNA active substance, formulating and purification of the lipid nanoparticles, and the final fill-to-finish. The design will focus exclusively on the mRNA and lipid nanoparticle synthesis and purification, ending at the sterile filtration step identified in Figure 1. The feeds to our process will include all necessary nucleotides, enzymes, and lipids to synthesize mRNA and lipid nanoparticles at an industrial scale. Our finished product will be a purified and sterilized suspension of lipid nanoparticles formulated with a desired mRNA sequence.

Our mRNA vaccine manufacturing process will involve several unit operations. A batch-fed bioreactor will perform both the in vitro transcription and enzymatic steps (DNA degradation and capping) of the process. For purification, we will employ a combination of chromatography methods, including affinity resin-based, anion-exchange, and hydrophobic interaction chromatography. These methods will purify full-length mRNA from impurities such as DNA fragments, enzymes, unreacted nucleoside triphosphates, unreacted caps, incomplete mRNA sequences, etc. (BioPhorum, 2023).

Tangential-flow filtration (TFF) will be used with chromatography to purify and concentrate mRNA after transcription, enzymatic capping, and lipid nanoparticle (LNP) formation, before fill-to-finish. Sterile filtration will be implemented in three stages: before LNP formation, after LNP formation, and before filling. In all, these processes will ensure that our final mRNA product meets quality standards and is safe for patients.

For encapsulating the mRNA product, we will use either jet-based mixing or microfluidic mixing to form the LNPs. The final choice between these two methods will be determined at a later stage of development.

Our design for developing an mRNA manufacturing process will be carried out over two semesters. By the end of the fall semester, we aim to clearly define the scope and scale of the process. The project will culminate in a final report that includes detailed design calculations and an economic analysis.

Regarding computation tools and software, we will use Aspen Plus to model applicable sections of the process. For more detailed calculations, data analysis and process modeling that cannot be done in Aspen, we will use MATLAB or Python. We may also explore alternative software options, such as COMSOL, for specific simulations involving fluid dynamics and heat transfer.

To gather necessary design data, we will seek to understand current mRNA manufacturing processes and review papers and articles on lab-scale operations. We also plan to consult experts, such as Dr. Mike King, who have industry experience, to gain insights into challenges and opportunities specific to our process. Essential data will include, but are not limited to:

- mRNA synthesis “recipes” – amount of base pairs, enzyme concentrations, etc. based on sequence length
- LNP formulation details – lipid combinations and ratios for achieving desired perticle size and properties
- Dosing and market size information (based on TB) (National Institutes of Health, 2023**)**
- Information on potential solvents and adjuvants, including thermodynamic properties

Our approach will emphasize a balance between individual responsibility and team collaboration. By leveraging a wide range of computation tools and reliable data sources, we aim to develop a safe, feasible mRNA therapeutic manufacturing process. The end goal is to create a process that will undergo clinical trials and serve as the new “state-of-the-art” for vaccine manufacturing.

The Cost of Insulin: Who Gets to Decide?

In the US, how do proponents of lower insulin prices pursue their agenda?

Diabetes affects roughly 38.4 million people of all ages in the United States, accounting for 11.6 percent of the population (CDC, 2021). For diabetic patients, their natural insulin production is disrupted, causing glucose build-up in the bloodstream. They use insulin injections to compensate for the lack of functional hormones in their system. According to the Health Care Cost Institute, there has been a 184% increase in insulin prices in the United States from 2012 to 2021, with a 30-day supply increasing from $271 to $499 (Gordon, 2023). In 2019, the out of pocket price for a month of insulin for people with insurance was $63 per fill (Schwarz, 2023). Cost serves as a barrier for many diabetics. T1International found that one in four diabetics reported intentional underuse and rationing of insulin in order to mitigate the cost of the hormone (T1International, 2018).

Past policies and structural factors are two determinants of high insulin prices. Medicare Part B, effective in 2017, was found to inadvertently contribute to the high costs of insulin. The policy enacted changed the reimbursement process for 30 infused drugs, one being pump-delivered insulin. The reimbursement process was inconsistent, with Medicare overpaying pharmacies for some infused drugs while consistently underpaying for insulin (Brown-Georgi, 2020). Pharmacies then resorted to charging patients more for insulin to compensate for the lack of funds from Medicare. Changing the policy surrounding the competition of prescription drug manufacturers is a possible countermeasure to increased insulin prices. The American College of Physicians outline several policy recommendations to counteract increased drug prices and prevent market manipulation. One of the most emphasized policy recommendations is to promote competition by adding low-cost generics or biosimilar drugs to the marketplace. Current insulin injections are made by three top companies, so broadening the playing field would cause a cascade of lower drug prices (Daniel, 2020). With more competitors, generic drug prices decrease dramatically. In 2019, the FDA found that before generic competition, a single generic competitor price is 39% lower than brand name. In increasing the number of competitors to 2 and 4, the manufacturer price became 54% and 79% lower than brand-name prices, respectively (Conrad, 2019).

Participants in advocating for lower insulin prices include the Biden-Harris administration, Federal Trade Commision, the American Diabetes Association (ADA), and pharmaceutical business managements (PBMs). In 2020 the Inflation Reduction Act introduced an insulin cap of $35 for a 30-day supply (HHS, 2023). The Biden-Harris administration and the Federal Trade Commission (FTC) have kept PBMs accountable for the price of insulin by re-delegating and apprehending those responsible for negotiating the price of insulin. The Inflation Reduction Act gives Medicare the authority to negotiate prescription drug prices (Rome, 2023). According to the Centers for Medicare and Medicaid Services, the Inflation Reduction Act “makes Medicare stronger for current and future enrollees. It makes health care more accessible, equitable, and affordable by lowering what Medicare spends for prescription drugs and limiting increases in prices” (CMS, 2024). On September 20, 2024, the FTC sued three of the largest PBMs– Caremark Rx, Express Scripts, and OptumRx– for engaging in practices that artificially inflated the price of insulin (FTC, 2024). The ADA also claims a stake in decreasing the price of insulin, claiming that they are “fighting to make it more affordable” through “tireless advocacy and powerful partnerships with health organizations and insulin manufacturers” (ADA, 2024). PBMs act as middlemen between manufacturers and patients, receiving a percentage of the payments made for prescription drugs (Nuys, 2022).

Sayed (2023) contends that if the IRA insulin cap had been in effect before 2020, Medicare beneficiaries could have saved $761 million from 2020 to 2023. Rome (2023) estimates that from 2026 to 2028, the IRA will save Medicare $26.5 billion. Because PBMs have tended to pay more for insulin when insulin sales decline, the IRA may be costly to them (Nuys, 2021).

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