Team 02:

PolyBioScaffold

Project Proposal and Feasibility Study

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Executive Summary

This report details the initial research and design decisions for the detailed design of a chemical plant that can produce medical-grade polycaprolactone (PCL) on a large scale. These include the constraints on the project as well as decisions about reactor type, catalyst system, and separation methods. A batch reactor will be used to carry out the homogeneous catalysis polymerization reaction of the monomer caprolactone to polycaprolactone. Tin (II) octoate will be the catalyst, with butyl alcohol as the initiator in toluene solvent. We will consider multiple separation methods including polymer devolatilization for separating polymer and recycling solvent mixture. An additive like TINEX® will be used to remove excess tin catalyst to render the polymer product nontoxic.

The primary use of the polycaprolactone will be in PCL-bioactive-glass composite, which can be used in medical procedures such as bone or cartilage repair. A stretch goal for the project is a design for the production of the glass composite itself. Engineering considerations, market factors, and design norms all influenced the results of this report. In addition to the project itself, team organization and membership are also explained.

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1. Introduction

The objective of this senior design project is to develop a preliminary chemical plant design that would mass produce polycaprolactone (PCL) to be used in the production of a PCL-bioactive-glass composite. We will produce a detailed plant design that covers the equipment and chemicals used in the process. Additionally, we hope to design the equipment necessary to combine polycaprolactone with bioactive glass to produce the composite. Since the project is theoretical in nature, computer simulations and hand calculations will be used throughout.

1.1 Project Description

Polycaprolactone may be created from ε-caprolactone, a 7-membered cyclic ester and member of the lactone family, when introduced to a catalyst. Figure 1 shows the basic reaction of caprolactone to polycaprolactone (PCL). PCL is depicted by its repeat unit, many of which would link together to form a long chain.

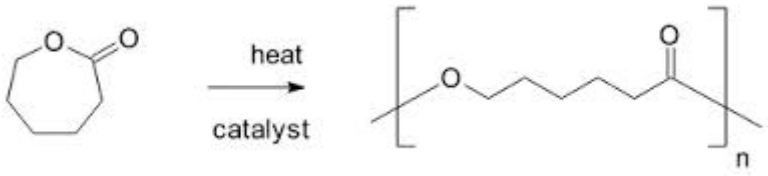

Figure 1: Reaction for manufacturing polycaprolactone [3]

Researchers have found composites containing polycaprolactone and a bioactive glass to possess properties similar to cartilage and the ability to bond to surfaces within the body such as bone [6][10]. The composite may be formed through various processes, including electrospinning, salt-leaching, and thermally induced phase separation [11]. Although the bioactive glass is currently used in bone grafts on some occasions, the composite, with its mechanism for osseointegration and variety potential uses, is still being analyzed [12]. Technological advancements and current needs in human tissue engineering present great potential for the manufacturing of medical-grade PCL for use in this composite, which will be the primary focus of this initiative.

1.1.1 Problem Definition

The current processes for production of medical-grade polycaprolactone are relatively small scale since currently medical applicability is limited. However, the potential for increased medical-grade polycaprolactone demand due to the technological advancements previously presented exposes an

unfulfilled niche in the manufacturing industry. Economies of scale provide a basis for understanding why small-scale manufacturing incurs higher capital and operating costs per unit manufactured. On the other hand, large-scale manufacturing capitalizes on diminishing marginal costs and increased production efficiency. Although the ability to create polycaprolactone of sufficient grade has existed for years, the optimized process for doing so with high capacity has yet to be fully established [1]. The large-scale manufacturing of PCL, and, in turn, the PCL-bioactive-glass composite, will improve the accessibility of cartilage replacement alternatives and decrease the overall expense of these procedures.

1.1.2 Solution

The process consists of two distinct segments: the reaction and the separation. The reaction can be executed using various combinations of solvents, catalysts, and initiators requiring different reaction times and temperatures. Among the most common of catalysts is a tin catalyst - stannous octoate - which is supplemented with an alcohol initiator to perform a ring opening mechanism on the cyclic caprolactone. The opened ring results in a free-radical monomer that proceeds to generate polycaprolactone by free-radical polymerization. This process is shown in Figure 2.

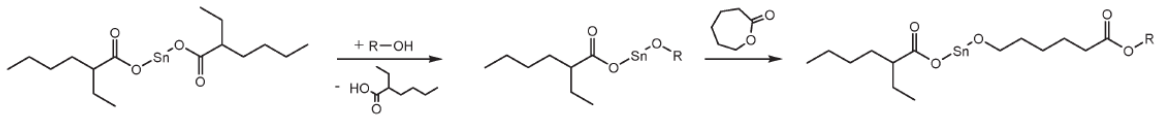

Figure 2: Synthesis of polycaprolactone from caprolactone initiated by alcohol and catalyzed by tin(II) octoate [3]

Various other catalysts were considered for executing the polymerization. However, most potential catalysts were rejected for one of three reasons. They were either complex and therefore too expensive, they reacted to form polymer in low yields or with high polydispersity, or they required a significantly longer reaction time. Past experiments and industrial data indicated that tin (II) octoate was one of the optimal catalysts for the polymerization [2] [12]. Additionally, a journal article had the experimental kinetic data required for analyzing an industrial scale batch reaction [4]. Therefore, tin (II) octoate will be supplemented with a butyl alcohol initiator in toluene solvent to carry out the polymerization of caprolactone [5]

The catalyst system described above had a reaction time of 46 hours in a batch reactor with a conversion of 95% and a polydispersity of 1.28 [3]. Polydispersity is distribution of polymer molecular weights. The reaction produced polymers with an average molecular weight of 73,000 g/mol, which is within the appropriate range for medical uses of a PCL-bioactive-glass compound. The reaction was carried out at

80ºC which is higher than the melting point of PCL, so it is considered liquid in the reactor. Tin (II) octoate is most commonly shipped as a clear to pale yellow viscous liquid, not a solid catalyst. Since the reactor also contains liquid reactants, the reaction is considered homogenous catalysis [4]. This makes the separation of catalyst from products more difficult, but residual tin catalyst can be removed with an additive like TINEX® made by Reaxis [14].

After the reaction is complete, the polymer will be separated from the solvent, initiator, and residual monomer. Following that, the solvent mixture will be further purified for it to be recycled into the next batch, saving raw material costs. Potential polymer separation techniques include melt extrusion, centrifugation, and filtration. Solvent mixture separation would likely be distillation, flash, or liquid-liquid extraction.

1.1.3 Constraints

For the intended use in tissue engineering, the PCL must have the following characteristics: mechanical properties similar to human tissue, biocompatibility, and ease of sterilization. Research has shown that the PCL is biocompatible and, with a molecular weight between 50,000 and 100,000 g/mole, is mechanically similar to human tissue [11] [12]. The method of combining the PCL and the bioactive glass impacts the characteristics of biocompatibility, sterilization, and mechanical-compatibility. Potential combination methods include salt-leaching, electrospinning, polymer impregnation in glass scaffold, infiltration of polymer foams via slurry-dipping, and freeze-drying. Further, biomedical applications demand a high purity polymer due to the various health hazards that arise with tissue repair. These hazardous can include, but are not limited to, introduction of foreign material or remaining tin catalyst in the composite. Any significant amount of leftover impurities could result in sickness, infection, inflammation, or other reactions to the foreign material. Cost analysis and economic feasibility will be conducted to ensure that the required purities can be met at a reasonable expense.

The volume of PCL produced and the economic feasibility of the process will depend on the market for the PCL-glass-composite and its potential uses in tissue engineering. Based on current processes and PCL demand, we predict that a batch reactor will produce a sufficient supply of PCL most efficiently.

1.1.4 Market

The intended market is any clients with specific demands that could require a composite-based cartilage replacement. The composite enables improved cartilage regrowth and a potentially longer lasting lifetime. Polycaprolactone has various other uses outside the medical field, such as hot-melt glue or an additive for

many resins. However, due to the purity and quality of the process and polymer being developed, the use will remain in the medical field for tissue engineering and scaffold implementation. Similar process designs typically involve a patent process, so that companies interested in implementing the design would be required to pay an agreed amount of money to use the patented design. The exact size of the market has not been determined yet since this is emerging technology, so we have set a reasonable estimate of 10,000 kg of composite material needed per year, of the millions of cartilage replacements in the US per year. It was decided that this technology will probably not be suitable for all replacements, so it was estimated that only a fraction of these surgeries would involve implementation of the composite. This will help to better estimate the feasibility of this technology, even considering a relatively small market.

1.1.5 Scope

As previously discussed, the main focus of this project is to develop an optimal process for manufacturing medical-grade polycaprolactone. The methods for development of the PCL-bioactive glass composite will be analyzed following the polymer manufacturing process optimization. The extent and depth to which this portion is analyzed will be dependent on the various obstacles that are presented during the polycaprolactone process. Due to a lack of materials, equipment, and time, experimental data that is typically obtained in the lab will be researched and gathered from others' prior experiments and applied to our circumstances and conditions as appropriate. The potential to look at other applications of polycaprolactone exists, however, to reduce complexity and maintain feasibility of a detailed design, these alternative applications will not be analyzed.

1.1.6 Proposal

The preliminary design for this plant will propose to produce between 5,000 and 8,000 kg per year of polycaprolactone, depending on the optimal ratio of PCL to glass in the composite. This production level of PCL will translate into approximately 10,000 kg per year of the PCL-bioactive glass composite. Caprolactone will be assumed to have a purchase price of $17 per kg [13]. UniSim will be used to create various preliminary plant designs and will aid in modeling key aspects of the proposal such as the reaction and separations processes.

1.1.7 Background

Discovery of the PCL-bioactive-glass composite occurred during research for artificial cartilage-replacement alternatives. Initially, researchers considered bioactive glass as a sole component for cartilage replacement. However, it was soon realized that bioactive glass itself also embodied undesired qualities, such as brittleness and a tendency to fracture when implemented in high stress environments

like knees or hips [1]. These complications stimulated much of the further research that lead to the final PCL-containing composite. After various alternatives were developed and rejected, researchers found a polymer that could be combined with the bioactive glass to better resemble the qualities of actual cartilage. This was polycaprolactone. When combined with bioactive glass, the composite exhibited new characteristics highly desired in cartilage-replacement materials [1]. Not only did the developed composite increase in its rigidity and flexibility, it also was able to bond to surfaces like bone and encouraged cartilage regrowth [1] [11].

1.2 Team Members

1.2.1 Kyle Disselkoen

Kyle was born and raised in Cedar Rapids, Iowa. He is a double major in chemical engineering and chemistry and will attend graduate school for a PhD in inorganic chemistry. He has been a summer research assistant at Calvin College, Vogel Paints, and Michigan State University.

1.2.2 Jenna Sjoerdsma

Jenna Sjoerdsma grew up in the small town of Ayden, North Carolina. She is studying chemical engineering and plans to attend graduate school after Calvin to complete a PhD in Biochemical or Biomedical Engineering. She interned at Vertellus Specialties, Inc. in Zeeland, MI.

1.2.3 Benjamin Tomaszewski

Benjamin Tomaszewski was raised in small, victorian port city, Manistee, MI. He is currently completing his senior year of chemical engineering at Calvin College and desires to work in the pharmaceutical or petroleum industry after graduation in May 2017. He has interned as a chemical engineer for a small startup company called CASEQ Technologies, as well as at Pfizer in Kalamazoo, Michigan.

1.3 Advisors

1.3.1 Faculty Advisor: Jeremy VanAntwerp, PhD

Jeremy VanAntwerp is a chemical engineering professor at Calvin College. He attended Michigan State University for his undergraduate degree and received his doctorate in chemical engineering from University of Illinois, Urbana-Champaign.

1.3.2 Industry Advisor: Phil Brondsema, PhD

Phil Brondsema is a Global Product Steward with Celanese. He holds a doctorate in chemistry and has worked in polymer manufacturing for many years. His contacts and knowledge in the field of polymerization will be invaluable.

1.4 Senior Design

Our team consists of three senior chemical engineering students working on a year-long project that functions as the capstone course for Calvin College. The project occurs in conjunction with a senior design class structured to guide students through the project. Senior design projects incorporate a wide range of classroom learning from technical engineering courses to other STEM courses to humanities courses like Oral Rhetoric. Calvin College is a private Christian liberal arts college with a flourishing engineering program of about 100 graduates per year in four concentrations, i.e. chemical, civil/environmental, computer/electrical, and mechanical engineering.

2. Project Management

2.1 Team Organization

The team will not have one set leader. The team has a “all are leaders” mindset, which provides an advantage through the work ethic and decision-making abilities of each individual. Each individual is able to recommend new ideas, changes, and improvements, which gives everyone equal influence on the tasks throughout this project. However, changes as such must be evaluated by the other members of the team before any modifying action is taken. Tasks are split equally, and major decisions are made as a group. This ensures that the team will be updated to the team’s progress, and the state of each task. Key decisions will be reassessed throughout the lifetime of the project as necessary, such as new advice from an advisor or new research found online. Team meetings have, and will continue, to begin and end with 5-10 minutes of planning and scheduling to ensure that all members are aware and understand the tasks that need to be completed, and their role in each one. A key role for the team is the notes-taker and organizer, Jenna Sjoerdsma, who has the necessary skills to keep organized documentation of the project as it progresses. Each group member possesses a full contact list. This enables each member of the team to contact advisors when it is necessary to do so. The webmaster is Kyle, who will ensure that the project website remains updated and functions as it is intended. As with all important decisions, major aspects of the website will be selected as a team. The project advisor is Ph.D Jeremy VanAntwerp. The team’s mentor/industrial consultant is Phil Brondsema, Ph.D, Global Product Steward at Celanese, who has experience and contacts in polymer manufacturing.

2.2 Managing Schedule

Various resources are used to ensure the team operates in an organized and timely manner. Although the team is currently on schedule to finish the established goals for the end of the semester, it will be necessary to work as far ahead of schedule as possible to allow time for unforeseen problems. The Gantt chart initially created for the class is currently being used as a guide for overall tasks and major deadlines for the project, while Google calendar and weekly meetings are used to schedule quick or short term goals that can be achieved on a steady basis. Jenna is organized and able to keep track of important due dates, so she manages the schedules and ensures things are getting done within the required deadlines. The schedules are modified every Friday after each team meeting, and biweekly schedule changes often occur to adjust for completed tasks or unplanned complications. If issues with meetings or deadlines arise with an individual, the other two members of the design group are able to put in the work to get things done on time. Team members are required to put in work each week and inform the group if there are scheduling

conflicts for the coming week. Typically, each team member is expected to put approximately 6-10 hours in a week, however, this number varies significantly and will likely increase to 12+ hours throughout second semester.

2.3 Managing Budget

Currently, the team has no intention of using any of the money budgeted for the senior design project. Due to the computer-simulation-based nature of the project, no materials will need to be purchased. Optimally, the team would build or utilize an existing small bench-scale or pilot plant version of the design, however, the cost and complexity of doing so is not feasible in this case. The current plan for the simulation is to use UniSim to its full capability by inputting the necessary polymer data, despite the fact that UniSim is not the ideal program for polymer modeling. If a better polymer modeling program (such as Aspen) could be purchased for a price within the set budget, the idea of buying that software may be considered.

2.4 Project Approach

With the developing technology in medical science, there is a significant amount of information about the application of PCL-bioglass composites in the medical field. Articles located through Google Scholar and the Hekman Library have been the main sources for information on the project. General polymer process and design references (such as Schmidt's *The Engineering of Chemical Reactions* and McCabe, Smith, and Harriott's *Unit Operations of Chemical Engineering*) provide information on polymerization reactions and separation processes. Initially, the goal was to simply gather as much information as possible to determine if enough resources about the polymer existed to provide a feasible senior design analysis. As more information was gathered, the research narrowed to specific areas, such as catalysts, reaction rates, and separations techniques. The team takes on large, broad goals by breaking them down into smaller, achievable goals, making consistent small steps.

Communication within the team typically takes place on a Facebook group message or through text messaging, while communication with outside contacts remains on email for a more formal delivery. Team members inform each other of any upcoming meetings, changes in the project, or new information that is found. Jenna is the team organizer, so she informs the team of these upcoming meetings or deadlines as appropriate to ensure that the team remains on a consistent schedule, meeting each deadline on time.

3. Requirements

3.1 Market Requirements

The market for polycaprolactone (PCL) is significantly smaller than similar, more common polymers like polystyrene or polyethylene. Throughout the late 1970s and early 1980s, the market for PCL increased dramatically due its "rheological and viscoelastic properties" [11]. However, newer polymers soon out-competed and replaced PCL, and the market for polycaprolactone subsided. In the past decade, newly developed applications for PCL and similar substances caused the market to expand, and a resurgence of PCL use occurred.

3.2 Biomedical Use

Biomedical applications of any material demands high purity, biocompatibility, and significant testing to prove the feasibility of its application. Biocompatibility is highly important with cartilage and tissue repair, which involves internal surgical binding and long-term service. The composite must be proven to have properties similar to that of actual cartilage to ensure that the cartilage will regrow and the scaffold will remain intact until the cartilage is fully regrown. PCL slowly degrades into biocompatible molecules over three or four years [11], so that the regrowing cartilage may fully repair. The material must also be easily sterilizable. Sterility is key in biomedical applications due to the health hazards that are present when introducing an outside substance into the body. Hazards must not only be recognized but analyzed, and the results of those hazards must be acknowledged and understood. If the product is not able to be sterilized easily, the chance of outside contaminants entering the body increases significantly, which could negatively impact the feasibility of the application.

3.3 Deliverables

The project will include a variety of deliverables, ranging from reports and notebooks to computer simulations and project websites. The preliminary project feasibility study (PPFS) will be the main deliverable for the first semester, although smaller tasks, such as system material balances, the project website, and an overall system process flow diagram (PFD), will be addressed as well. The second semester will demand a final project report, a UniSim (or equivalent polymer modeling program) simulation incorporating key design elements and process flow diagram, excel calculations, design notebooks used throughout the year, and a finished website created by the team. The PFD will include key component designs for the reactor, separations process, auxiliary equipment, and the process layout for optimally executing the manufacturing process of polycaprolactone. This same analysis will be carried out for the PCL-bioactive glass composite, as time allows. The team website contains the documents

submitted throughout the year, a project overview, and details about the team members and Calvin engineering.

4. Task Specifications and Schedule

4.1 Production of PCL

During the fall semester, project planning and feasibility need to be completed. This includes research into the chemistry, product grade requirements, and market size for medical-grade polycaprolactone (PCL). Based on this information, the optimal catalyst, initiator, and solvent could be chosen. The market size for medical-grade PCL and for knee and hip replacement surgeries would inform the yearly production volume and aid in choosing between a batch or flow process. The ultimate goal for the fall semester is the creation of a problem statement that can be followed in the spring semester to complete the project. This problem statement will include a basic process flow diagram (PFD) and a specification of the composition and conditions at the midpoint of the process (the reactor effluent). Many of the stated tasks overlap, but a general schedule may be seen in Table 1. The research is expected to continue throughout the course of the project, so it will not be completed during the fall semester.

Table 1. Task specifications and percent completion for fall semester, in general order of task initiation

Task	Person-hours Estimate	Percent Completed
Research	100	50%
Determination of Catalyst, Initiator, and Solvent	20	75%
Determination of Total Yearly Production Volume	5	50%
Batch or Flow Process Decision	2	100%
Creation of Basic PFD	12	90%
Set Process Midpoint Conditions	8	10%
Problem Statement for Project Continuation	20	10%

The design of the process for producing PCL will be completed in the spring semester. The two main sections of the process are the reactor and the separations. Both sections must be optimized by choosing the optimal equipment and conditions for each. The mid-point set during fall semester will be used to break the two sections apart so that they may be designed simultaneously during the first-round of design. Once the reaction and separations work separately, a recycle stream of solvent and initiator will be added and the entire process will be further optimized. The initial midpoint conditions may be adjusted at any point throughout this design procedure, as needed. An economic analysis shall be used throughout the procedure to aid in design decisions and at the end of the design to determine the feasibility of the process. This analysis will minimize the four main cost areas of capital equipment, materials and chemicals, utilities, and chemical waste processing, while maximizing revenue. Corporate taxes and

capital budgeting principles will also be taken into account. Table 2 shows the task breakdown for the spring semester design of the PCL production process.

Table 2. Task specifications and percent completion for the design of a process for producing PCL during the spring semester

Task	Person-hours Estimate	Percent Completed
Reactor Optimization	18	0%
Reactor Type	2	100%
Feed Conditions	4	0%
Reactor Conditions	10	0%
Auxiliary Equipment	2	0%
Separations Optimization	40	0%
PCL Separation	12	0%
Monomer/Solvent/Initiator Separation	26	0%
Auxiliary Equipment	2	0%
Recycle	5	0%
Economic Analysis	40	0%

4.2 Production of PCL-Bioactive-Glass Composite

As time allows, a process for producing the PCL-bioactive-glass composite will be designed spring semester after the completion of the PCL process design. The optimal ratio of PCL-to-glass and method of combination will be determined through research. A PFD or model of the process will be created. Finally, an economic analysis will be used to critique feasibility of the design.

5. System Architecture

5.1 Process Flow Diagram (PFD)

Much of the process is still be developed. However, the overall system for manufacturing polycaprolactone will consists of two main sections: the batch reactor and the separation processing units. The separations will likely include a batch rectification to separate out most of the lightest components, including the initiator and solvent. TINEX will then be injected in a mixer to contact the polymer slurry and attach to the tin catalyst. The resulting slurry will be passed through a filter to remove the TINEX and catalyst as a filter cake. A melt extruder will be used to further purify the polymer by evaporating off the monomer and remaining light components, which will be recycled. A diagram of this overall system is shown below in Figure 3.

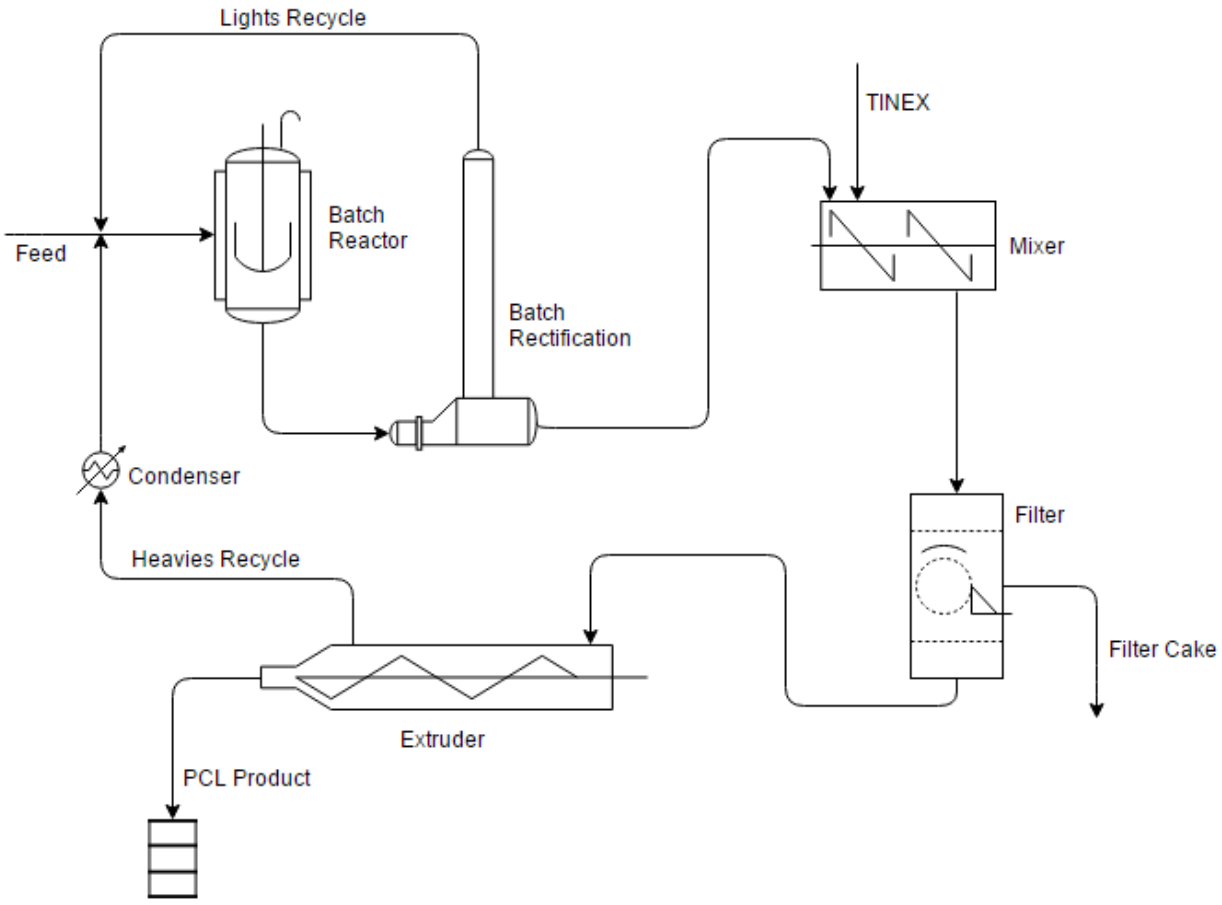

Figure 3. Initial process flow diagram (PFD), including reaction and separation processes

Each of these segments will be economically optimized as a whole, and brought together to develop a feasible process. It is important to note that each of these segments may be divided into multiple

components (multiple reactors, filters, or extruders may be used), although this deeper analysis has not yet been performed. The order of each of these segments will likely remain the same since the separations processes are used to separate the reactor effluent, and a centrifuge or filter will be needed for filtering the polymer prior to distillation.

5.2 Process Flow Decisions

A simple scale-up of feed ratios used in a bench scale experiment resulted in initial approximations of amounts of catalyst, monomer, and initiator to be fed to the reactor ([16], Table 1, Experiment 1). The bench scale used solvent in excess, so a feed amount of solvent was estimated as a starting point. A material balance of the process with stream tables may be found in the appendix.

The TINEX must be well mixed into the polymer slurry in order to contact the tin II octoate catalyst and cause it to precipitate [14]. A filter must then be used to separate the TINEX and precipitated catalyst from the polymer mixture. Dr. Brondsema suggested the use of a melt extruder to purify the polymer. The absolute maximum temperature to which the TINEX should be exposed is 140 °C, but it performs best at or below 90 °C [14]. The normal boiling points of the solvent, initiator, monomer and catalyst are all significantly greater than the optimal maximum temperature of TINEX, as shown in Table 3. Thus the TINEX cannot be added to a melt extrusion process. So the TINEX and catalyst needed to be removed before the mixture entered the melt extruder.

Table 3. Normal boiling points (at 1 atm) of components to be separated from PCL product

Component	Normal Boiling Point
Toluene (solvent)	110.6 °C
n-butanol (initiator)	117.7 °C
ε-caprolactone (monomer)	253 °C
Tin (II) octoate (catalyst)	296 °C

Charring and degradation of a polymer must be considered when exposing it to high temperatures. However, PCL undergoes no degradation until it reaches a temperature of approximately 350 °C [3]. No indication of charring was stated, so the current assumption is that no significant charring will occur below 350 °C. (This assumption will be investigated through further research, including lab research, as needed.) A melt extruder may thus feasibly be used to separate the monomer from the polymer at a temperature of around 300°C.

The decision to use batch rectification to remove most of the initiator and solvent from the polymer mixture prior to adding the TINEX was made due to concerns about filtering out the TINEX and precipitated catalyst from a mixture including these components. This decision will be revisited as the different separation methods and their capabilities are further explored.

6. Design Criteria

6.1 Economics

One of the primary concerns of this project is to determine whether the proposed design will be economically feasible. This will depend on how efficiently the polymer and composite can be manufactured, as well as on how much of the composite the market will sustain. The market for medical-grade PCL is rather small, making competitiveness in this market difficult. Currently, no market exists for the composite, as it has only been produced at bench-scale. Thus, if the composite can be produced at large scale, it will be competing only with traditional methods of cartilage replacement. Much of the economic feasibility analysis will be performed based on current cartilage replacement procedures and evaluations of the benefits that patients would experience with composite-scaffold regrowth of cartilage. These benefits may include, but are not limited to, no need for painful bone grafts and increased cartilage structuring and regeneration.

6.2 Product Grade

Due to the biomedical applications of the PCL, the polymer product must be of medical grade (or quality). Medical grade polymers typically must have very low impurities, (i.e. < 1%), including residual monomer, initiator, and solvent. In order to achieve this quality of material, industry utilizes good manufacturing practices (GMPs), sometimes called current GMPs or cGMPs. In the United States, the FDA's Center for Drug Evaluation and Research (CDER) sets GMPs [8].

The product grade particularly drives the separations used in this process. The high purity required means that rigorous separation techniques and likely multiple solid separations must be used.

6.3 Polydispersity Index and Molecular Weight

We calculated polydispersity values for ideal addition polymerization. Equations 1 and 2 were used to calculate the distribution and the number average polymer length [9]. The instantaneous concentration of the monomer is related to the initial concentration $[M]_0$ (mol/L), the time constant τ (min), a rate constant k (L/mol·min), and the initial concentration of the initiator $[A]_0$ (mol/L). The concentration of the growing polymer $[AM]_j$ (mol/L) is also a function of the number of monomer units j.

$$[M](\tau) = \frac{[M]_0}{1 + k\tau[A]_0}$$ Equation 1

$$[AM_j](\tau) = \frac{[A]_0(k\tau[M])^j}{(1 + k\tau[M])^{j+1}}$$ Equation 2

A kinetics graph of the natural log of the concentration ratio of monomer versus time is shown below [4]. The initial concentration of monomer and initiator was also provided. This allowed us to calculate a rate constant k in [L/mol·min] from the slope of the graph (Fig. 4, below) of line #1.

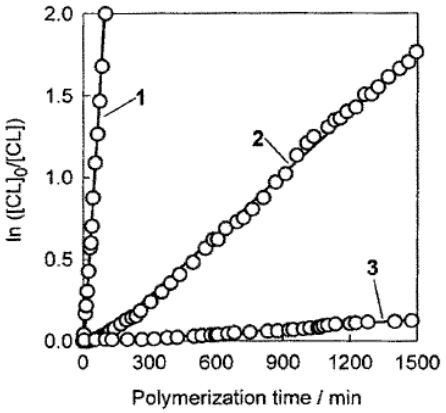

Fig. 4. Kinetics of polymerization of ε-caprolactone (CL) initiated with tin octoate ($Sn(Oct)_2$) followed dilatometrically. Conditions: $[CL]_0 = 2.0\ mol \cdot L^{-1}$, $[(Sn(Oct)_2)]_0 = 0.05\ mol \cdot L^{-1}$, THF solvent, 80 °C; (1) added butyl alcohol (BuOH), $[BuOH]_0 = 0.10\ mol \cdot L^{-1}$, (2) no additive, (3) added 2-ethylhexanoic acid (OctH), $[OctH]_0 = 6.5 \cdot 10^{-3}\ mol \cdot L^{-1}$

First, Equation 1 was used to determine the concentration of monomer as a function of time. Then Equation 2 was used to plot the concentration of the growing polymer chain at various lengths, as shown in Figure 4.

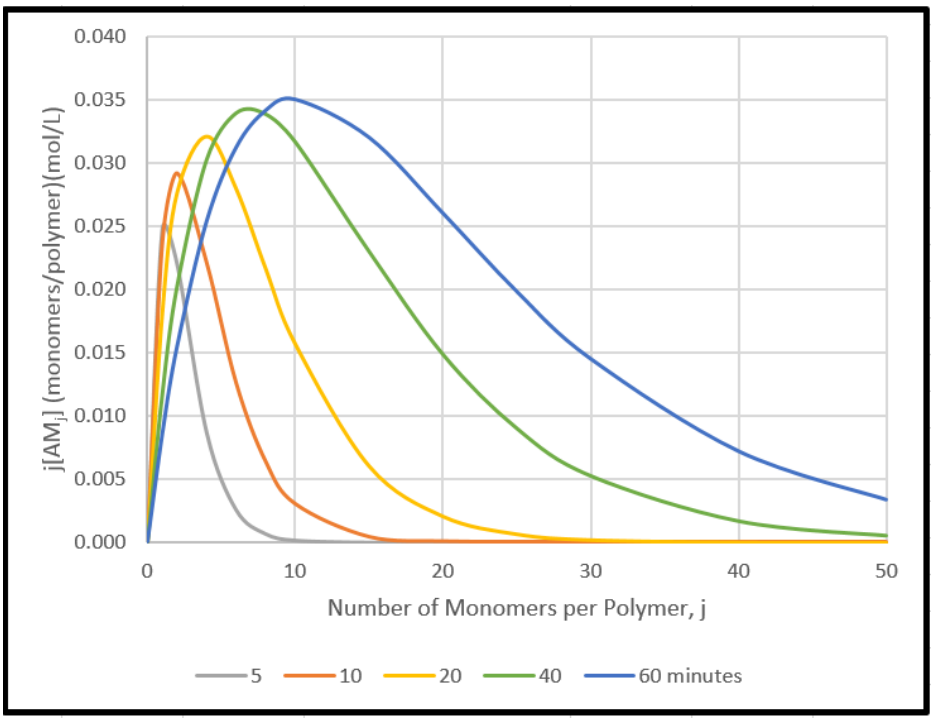

Figure 4. Weight distribution ($j[AM_j]$) as a function of the number of monomers per polymer (j), with time of reaction as a parameter

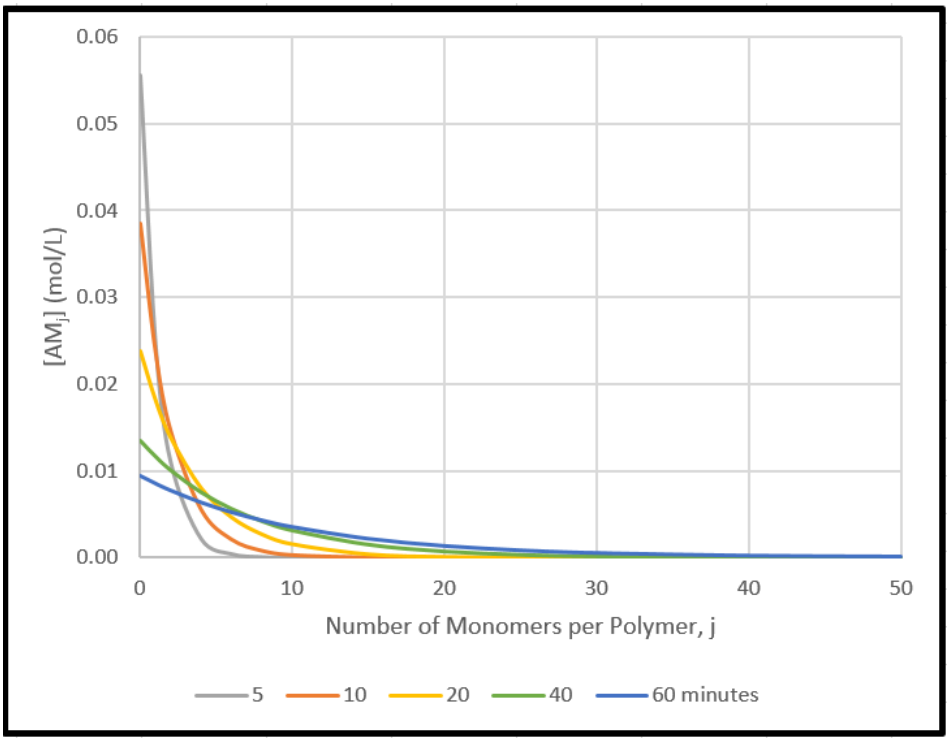

Figure 5. Concentration of polymer of length j ($[AM_j]$) as a function of the number of monomers per polymer (j), with time of reaction as a parameter

6.4 Environmental Impact

According to BASF, caprolactone is a skin, eye, and lung irritant and a potential carcinogen [18]. Caprolactone should not be released to the environment without proper authorization. With large-scale manufacturing, it is likely that purged material will have to be sent to a processing facility due to the environmental hazards of purging large amounts of the reagents.

Butanol is being used as an initiator in the reaction process, which presents the possibility of release to the atmosphere. It is highly mobile in soil, however, it is unlikely for n-butanol to concentrate in the food chain and nearly harmless to marine animals and aquatic microorganisms [17]. However, as a team that strives to be stewards of God's creation, butanol will be recycled as much as possible in the process, and purged initiator will likely be sent for processing as well, which often comes at a significant cost. Toluene is also rather non-harmful to the environment due to its biodegradability and volatility, however, large releases of any chemical, such as toluene, can have negative impacts to the atmosphere. Toluene will likely be processed in a solvent recovery process and reused in the system whenever possible.

Tin (II) octoate, as a catalyst, will be used in relatively small proportions. According to Dow Chemical, the catalyst is "readily biodegradable" and does not typically accumulate in the food chain [17]. Catalyst can typically be reused multiple times. Processing of catalyst emitted from the system should not be required since TINEX, an amorphous silicic acid compound, will be used to reduce tin concentrations as necessary [14].

Most of the materials used in this process are relatively low hazards to the environment in small quantities. Recycling the materials as much as possible decreases the amount of processing that is required for purged material. Outside processing should be minimal since material will only be purged if accumulation begins to occur; most of the feed materials can be reused.

6.5 Marketability

The market for PCL is not as extensive as more common polymers such as PCV or PCP, and with a rather low demand for the substance, the process would likely not draw much interest. However, the end composite is upcoming innovation that does not have widespread competition. Creating a process and supplier that can make medical grade PCL, and then use that product to manufacture cartilage replacement composites would allow the company to operate in their own market. Rather than buying more expensive medical grade polymer, they could manufacture their own from cheaper starting materials. Using that product in creating a cartilage replacement composite, rather than selling the

polymer to an intermediate manufacturer would then allow them to maximize profit since they would be selling the composite material themselves. Running both manufacturing processes themselves would increase upfront and operation costs, but this would be balanced by selling the composite material themselves, rather than just selling the polymer to a composite manufacturer. The market for a cartilage-replacement composite like this also a sole or primary supplier, so being the primary supplier for this composite would make it difficult for competitors to grow. The main competition for this composite, then, would be prostheses. However, prostheses typically only last about 10 years before surgery is necessary again. If the composite can increase this replacement time, or be a one-time surgery, just that development alone would give people an incentive towards the product.

6.6 Design Norms

The design norms of stewardship, integrity, and caring serve as further design criteria for this project [15]. Due to the call to stewardship of the earth and its resource, the design must limit use of hazardous chemicals and reduce waste by recycling where possible. The norms of integrity and caring call for a design that will produce an end product safe for biomedical use and that is capable of performing as claimed.

As engineers and stewards of the earth, we are responsible to all current and future inhabitants of the environment. Engineering involves projects at a scale such that a single decision can have a measurable impact on the environment in ways that daily habits do not. We need to ensure that the environmental impact of our project is considered directly alongside the minimization of costs and the maximization of revenue.

Our product will have integrity if it meets or exceeds expectations given by the medical grade designation and functions reliably despite adverse circumstances. A knee or hip replacement should not cause undue pain to the recipient and should allow them to fruitfully interact with society in ways that were not possible before the surgery.

The impetus for our project was a focus on caring for those in need of a hip or knee replacement. Given the millions of surgeries occurring per year in the United States, it is clear that an improvement in surgical technique would have a significant impact on the health and well-being of the population of the US. A PCL-bioactive-glass composite has the potential to improve surgeries substantially.

7. Design Alternatives and Decisions

7.1 Catalysts, Solvents, and Initiators

Supplementary tables from a review of the various methods of producing PCL detail over 100 catalysts that can successfully polymerize caprolactone to polycaprolactone [3]. Project constraints were applied to the list to eliminate most of the possible catalysts. Overly complex catalysts would be too expensive for large scale production of PCL. Catalysts that did not have high yields would require additional expensive separation processes to separate unreacted monomer from the polymer product. Many catalysts did not produce a polymer product with a molecular weight or polydispersity index within the project constraints. Lastly, availability of the catalyst on a large scale was considered. Some aluminum alkyl catalysts gave similar bench scale results to tin (II) octoate but were not readily available in bulk.

Most polycaprolactone polymerization reactions are either run in THF, toluene, or no solvent. For the tin (II) octoate catalyst, no literature data could be found for the case of no solvent, so the alternatives were limited to THF and toluene. Toluene is a more commonly used solvent, less expensive, and less hazardous than THF. Bench scale data did not indicate significant differences in yield, molecular weight, or polydispersity between the two solvents, so we assume that solvent effects are small.

Butyl alcohol is used as the initiator for the catalysis reaction in [4] that provides kinetic data. Other initiators considered were organic compounds with alkyl groups and alcohol or amide functional groups. Since butyl alcohol is readily available and not challenging to work with, it was a logical choice for an initiator.

7.2 Reactors

Broadly, reactors can be categorized by how material is processed, either in batches (batch reactor) or in a continuous flow (CSTR or PFR). Batch reactors tend to be used for smaller quantities of material or for slow reactions with viscous products. Flow reactors often have better mixing and can accommodate high reactant concentrations. Dr. Brondsema recommended using a batch reactor for the polycaprolactone polymerization process given the benefits above. The designed process is for a relatively small quantity of polycaprolactone and the molten polymer is very viscous so it would be difficult to keep the product flowing in a continuous flow reactor.

7.3 Separation Methods

7.3.1 Solid Separation

In order to purify the PCL to medical-grade requirements, the polymer will need to be separated from the remaining monomer, initiator, catalyst, and solvent in the reactor effluent. Three general processes for solid separations will be examined, namely extrusion, centrifugation, and filtration. Due to the high purity requirements, multiple solid separations methods or iterations may be necessary.

7.3.2 Pre-Recycle Separation

In order to reduce waste and save money, the solvent and initiator remaining in the effluent stream exiting the reactor will be recycled. Due to the possibility of impurity build up in the reactor, we will explore the need for further separations of the solvent-initiator-monomer mixture leaving the solid separations. This further separation could take the form of a batch rectification. It is also possible that a small purge fraction will solve the build-up issue. If a purge will work, a distillation column will not be used since distillation requires huge amounts of energy and thus does not fit with the design norm of stewardship.

7.4 PCL-Glass Combination Methods

Over a dozen documented methods of combining polymers with a bioactive glass exist [6]. The two methods that specifically use PCL are electrospinning [7] and salt-leaching [6]. Other methods may be explored as necessary, but at a minimum the electrospinning and salt-leaching techniques will be evaluated to choose an optimum combination method. The criteria for choosing a combination method will include the porosity of the composite, the maintenance of both PCL and glass properties, ease of purification, and scalability of the process from bench to industrial scale.

8. Conclusion

This report details the initial research and design decisions for the detailed design of a chemical plant that can produce medical-grade polycaprolactone (PCL) on a large scale. These include the constraints on the project as well as decisions about reactor type, catalyst system, and separation methods. Additionally, we hope to design the equipment necessary to combine polycaprolactone with silica to produce the bioglass compound. Engineering considerations, market factors, and design norms all influenced the results of this report. The primary use of the polycaprolactone will be in PCL-bioactive-glass composite, which can be used in medical procedures such as bone or cartilage repair. Ideally we will further design the process to combine PCL with the silica glass to produce the composite material.

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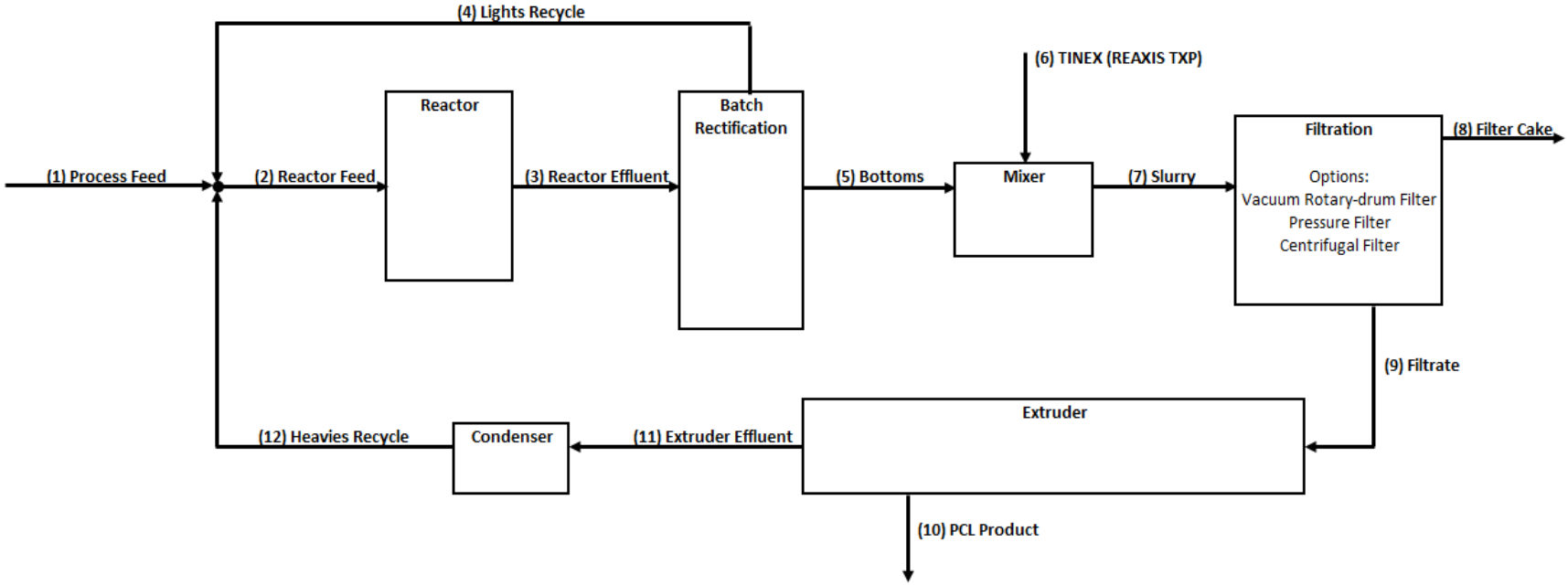
11. Appendix

11.1 PCL Process Block Diagram



Block diagram of PCL production process, including stream numbers and labels

11.2 PCL Process Material Balance Stream Tables

Stream 1: Process Feed (liquid, 30°C)	
Component	**Amount (kg)**
Monomer	2673
Catalyst	1.71
Initiator	100.7
Solvent	33
Polymer	0

Stream 2: Reactor Feed (liquid)	
Component	**Amount (kg)**
Monomer	3463
Catalyst	1.71
Initiator	132.5
Solvent	6586
Polymer	0

Stream 3: Reactor Effluent (viscous liquid, 80°C)	
Component	**Amount (kg)**
Monomer	834
Catalyst	1.71
Initiator	31.9
Solvent	6586
Polymer	2629

Stream 4: Distillate Recycle (liquid)	
Component	**Amount (kg)**
Monomer	0
Catalyst	0
Initiator	28.7
Solvent	5928
Polymer	0

Stream 5: Bottoms (viscous liquid)	
Component	**Amount (kg)**
Monomer	834
Catalyst	1.71
Initiator	3.2
Solvent	659
Polymer	2629

Stream 6: TINEX (liquid)	
Component	**Amount**
TINEX (Reaxis TXP)	0.26 wt% 10.9 kg

Stream 7: Slurry (viscous liquid)	
Component	**Amount (kg)**
Monomer	834
Catalyst	1.71
Initiator	3.2
Solvent	659
Polymer	2629
TINEX	10.9

Stream 8: Filter Cake (solid)	
Component	**Amount (kg)**
Monomer	42
Catalyst	1.70
Initiator	0.2
Solvent	33
Polymer	131
TINEX	10.9

Stream 9: Filtrate (viscous liquid)	
Component	**Amount (kg)**
Monomer	792
Catalyst	0.01
Initiator	3.0
Solvent	626
Polymer	2498
TINEX	0

Stream 10: PCL Product (viscous liquid, 300°C)			
Component	**Amount (kg)**	**Weight Percent (wt%)**	**Parts per Million (ppm)**
Monomer	2	0.0951	951
Catalyst	0.01	0.0005	5.2
Initiator	0	0	0
Solvent	0	0	0
Polymer	2498	99.90	N/A

Stream 11: Extruder Effluent (vapor, 300°C)	
Component	**Amount (kg)**
Monomer	790
Catalyst	0
Initiator	3.0
Solvent	626
Polymer	0

Stream 12: Heavies Recycle (liquid, < 100°C)	
Component	**Amount (kg)**
Monomer	790
Catalyst	0
Initiator	3.0
Solvent	626
Polymer	0

11.3 Polydispersity Index (PDI) Calculations

Variables

	slope	0.015385	min-1
	k	0.153846	L/mol-min
	t	60	min
	$[M_0]$	2	mol/L
	$[Cat_0]$	0.05	mol/L
	$[A_0]$	0.1	mol/L
	[M]	1.04	mol/L
	j	100	(#monomer units)
BATCH:	Number Avg Polymer Length		
	Mn = n	12.05	monomers/polym
CSTR:	$M_n = n$	9.6	monomers/polym
	$[AM_j]$	4.69E-07	mol/L

	kt=	0.769	kt=	1.54	kt=	3.08	kt=	6.15	kt=	9.23
	t (min)=	5	t (min)=	10	t (min)=	20	t (min)=	40	t (min)=	60
j	$[AM_j]$	$j[AM_j]$	$[AM_j]$	$j[AM_j]$	$[AM_j]$	$j[AM_j]$	$[AM_j]$	$j[AM_j]$	$[AM_j]$	$j[AM_j]$
0	0.0556	0.0000	0.0385	0.0000	0.0238	0.0000	0.0135	0.0000	0.0094	0.0000
1	0.0247	0.0247	0.0237	0.0237	0.0181	0.0181	0.0117	0.0117	0.0085	0.0085
2	0.0110	0.0219	0.0146	0.0291	0.0138	0.0276	0.0101	0.0202	0.0077	0.0155
4	0.0022	0.0087	0.0055	0.0221	0.0080	0.0321	0.0076	0.0302	0.0063	0.0254
6	0.0004	0.0026	0.0021	0.0125	0.0047	0.0279	0.0057	0.0339	0.0052	0.0312
8	0.0001	0.0007	0.0008	0.0063	0.0027	0.0216	0.0042	0.0338	0.0043	0.0342
10	0.0000	0.0002	0.0003	0.0030	0.0016	0.0157	0.0032	0.0316	0.0035	0.0350
15	0.0000	0.0000	0.0000	0.0004	0.0004	0.0060	0.0015	0.0230	0.0021	0.0320
20	0.0000	0.0000	0.0000	0.0000	0.0001	0.0021	0.0007	0.0148	0.0013	0.0260
25	0.0000	0.0000	0.0000	0.0000	0.0000	0.0007	0.0004	0.0090	0.0008	0.0198
30	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0002	0.0052	0.0005	0.0145
40	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0016	0.0002	0.0072
50	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0005	0.0001	0.0033