

Milrinone Alternative Delivery System

Team Beyond the IV

Preliminary Design Report

October 7th, 2026

Section 310

Client:	Dr. Lenard Markman	lenmarkman@gmail.com
Advisor:	Dr. William Murphy	wlmurphy@wisc.edu
Team:	Sam Glanville (Team Leader)	skglanville@wisc.edu
	Yisi Yang (Communicator)	yang829@wisc.edu
	Steve Lee (BSAC)	cle623@wisc.edu
	Katie Wright (Co-BWIG)	kawright7@wisc.edu
	Noelle Johnston (Co-BWIG)	nejohnston@wisc.edu
	Leo Thayer (BPAG)	lthayer@wisc.edu

Abstract

Stage D congestive heart failure is an advanced chronic condition in which patients often depend on continuous intravenous (IV) infusion of milrinone, a phosphodiesterase-4 inhibitor, to maintain cardiac function. Outpatient IV delivery requires a central venous catheter and a portable infusion pump, which limits mobility, increases the risk of bloodstream infection, and demands ongoing clinical monitoring and device maintenance. Alternative delivery routes, including oral, nasal, transdermal, and nebulized have been explored in patents and early studies, but none has replaced continuous IV therapy, and the PROMISE trial raised safety concerns about oral milrinone. This project aims to develop a noninvasive alternative that maintains plasma concentrations within therapeutic range of 100 to 300 ng/mL without continuous vascular access. Three concepts were evaluated with a weighted design matrix: sublingual pouches, a nasal spray, and an extended release oral capsule. The extended-release oral capsule scored highest (87/100, compared with 73 for the nasal spray and 69 for the pouch) because of its ease of fabrication, ease of use, low cost and twice daily dosing. The proposed design is a size0 vegetable cellulose capsule filled with a surrogate compound that has physiochemical properties similar to milrinone. Release will be tested in simulated gastric and intestinal fluids at 37 °C and quantified by UV-Vis spectrophotometry. These tests will show whether release can be sustained over 12 hours and will guide formulation changes before any testing with milrinone itself.

Table of Contents

Milrinone Alternative Delivery System.....	1
Abstract.....	2
Table of Contents.....	3
Introduction.....	4
Background.....	5
Preliminary Designs.....	5
Design 1: Milrinone Sublingual Pouches.....	6
Design 2: Milrinone Nasal Spray.....	6
Design 3: Milrinone Extended-Release Oral Capsules.....	7
Preliminary Design Evaluation.....	8
Proposed Final Design.....	10
Fabrication.....	10
Testing and Results.....	11
Discussion.....	11
Conclusions.....	12
References.....	12
Appendix.....	13
Appendix A: Product Design Specification.....	13
Appendix B: Team Expense Spreadsheet.....	17

Introduction

Congestive heart failure is a chronic condition where the heart cannot pump blood efficiently enough to meet the body's needs. Advanced heart failure is classified as Stage D and is characterized by severe symptoms that interfere with daily life and are extremely difficult to manage despite medical treatment [1]. Patients with Stage D heart failure typically require continuous administration of intravenous medications to maintain cardiac function, such as milrinone. Milrinone is a phosphodiesterase-3 inhibitor that promotes vasodilation, improving blood circulation and reducing the workload of the heart [2]. Milrinone is often administered through continuous intravenous (IV) infusion in patients who require continuous inotropic support [3].

While continuous IV milrinone effectively supports Stage D heart failure patients, the current delivery method presents several challenges for outpatient treatment. This method requires a central venous catheter connected to a portable infusion pump, which can significantly interfere with daily activities. Long-term catheter use also poses risks of bloodstream infections and other complications associated with vascular access. Additionally, continuous infusion requires clinical monitoring and regular device maintenance and preparation, contributing to the method's limitations for outpatient use. These disadvantages highlight the need for an alternative delivery method that reduces or eliminates continuous vascular access while effectively administering the medication.

Medication delivery methods, including oral, intranasal, transdermal, and nebulized administration, have been investigated as alternative delivery systems for the continued infusion of milrinone. Patent US20190091156A1 describes a controlled-release oral milrinone formulation designed to provide sustained release through a cellulose-derived coated capsule [4]. Another relevant patent, WO2023133460A1, describes a nasal delivery method that identifies milrinone as one of the many potential active compounds that could be delivered through the system [5]. These patents reflect the current alternative delivery methods being explored, but do not establish any clinically proven replacements for the continuous IV milrinone system. Previous research studies have also emphasized significant safety concerns associated with alternative milrinone administration. The 1991 PROMISE trial found an increased mortality rate in patients who received milrinone delivered orally compared to the placebo [6]. This trial highlights the importance of evaluating long-term safety risks in addition to drug delivery effectiveness.

Developing an alternative method of milrinone delivery could reduce the risks and limitations associated with continuous IV therapy, while effectively providing continuous inotropic support. An alternative delivery system must maintain drug stability and accurate dosage delivery while reducing complications from continuous vascular access and improving patient independence in daily activities. The goal of this project is to develop a feasible alternative to continuous IV milrinone delivery that addresses the limitations associated with the current method without compromising treatment effectiveness and patient safety.

Background

Milrine is a medication that is intended for patients with acute heart failure, pulmonary hypertension, or chronic heart failure [2]. Milrine is a phosphodiesterase inhibitor which increases the strength of heart muscles and widens blood vessels, allowing the heart to pump blood more effectively. Furthermore, milrine has a molecular weight of 211.1 and is slightly soluble in methanol, and even less so in chloroform and in water. Through studies it has been found that the therapeutic range of plasma milrine concentrations is 100ng/mL to 300 ng/mL [7], which signifies the range of medication that the device needs to administer in order for the patient to achieve the desired effects of the drug. The formulation of the drug should be consistent and reproducible so as to avoid arrhythmia, hypertension, or thrombocytopenia. Currently, milrine does not have an antidote, meaning the administration of milrine should be discontinued if overdose symptoms arise. As outlined in the Product Design Specification (Appendix A), the product must comply with pharmaceutical and medical device safety regulations, which would likely require FDA review. Additionally, the product should have a shelf life of up to 3 years while sealed and in standard room temperature conditions. It will also not have any light sensitivity, oxygen sensitivity, or strong temperature sensitivity for ease of daily use. On the patient side, the milrine delivery system should be lightweight and portable and not interfere with the patient's mobility and daily activities. The device is intended to administer the drug dosage in a typical indoor or at home environment without any specialized conditions or additional training.

In order to design the prototype of the milrine delivery system, further research needs to be conducted into the previous studies that investigated the alternative methods of milrine administration. This research will provide insight on different methods of delivery and how milrine affects the patients. Understanding the advantages and limitations of different administration methods will help determine a proposed product and assist with designing a prototype. Additionally, research needs to be done on molecules that have similar chemical and physical properties of milrine to help identify compounds that can be used for testing. Testing with a molecule similar to milrine for our prototype can give information on drug absorption and release rate within the patient.

The client of this project is Dr. Lenard Markman, who is a doctor of Osteopathic Medicine and currently works as a family practitioner in Stevens Point, Wisconsin [8]. Markman is interested in improving the ease of milrine delivery, due to observing the daily life of his brother who is receiving milrine intravenously for his congestive heart failure.

Preliminary Designs

Three preliminary designs were considered for alternative milrine delivery: sublingual pouches, nasal spray, and extended-release oral capsules. These concepts aim to simplify medication administration and reduce the equipment required for intravenous delivery. Each design was evaluated based on its anticipated fabrication requirements, ease of use, fabrication cost, administration frequency, environmental impact, choking hazard, and comfort.

Design 1: Milrinone Sublingual Pouches

The pouch consists of a small, plant-based cellulose fiber pouch containing milrinone formulation. The pouch would be placed beneath the tongue, where saliva would wet the contents and allow dissolved medication to pass through the pouch material. The intended delivery mechanism is absorption through the sublingual mucosa.

The proposed pouch would include a permeable outer enclosure, a sealed perimeter to retain the contents, and a hook or anchor to reduce displacement beneath the tongue.

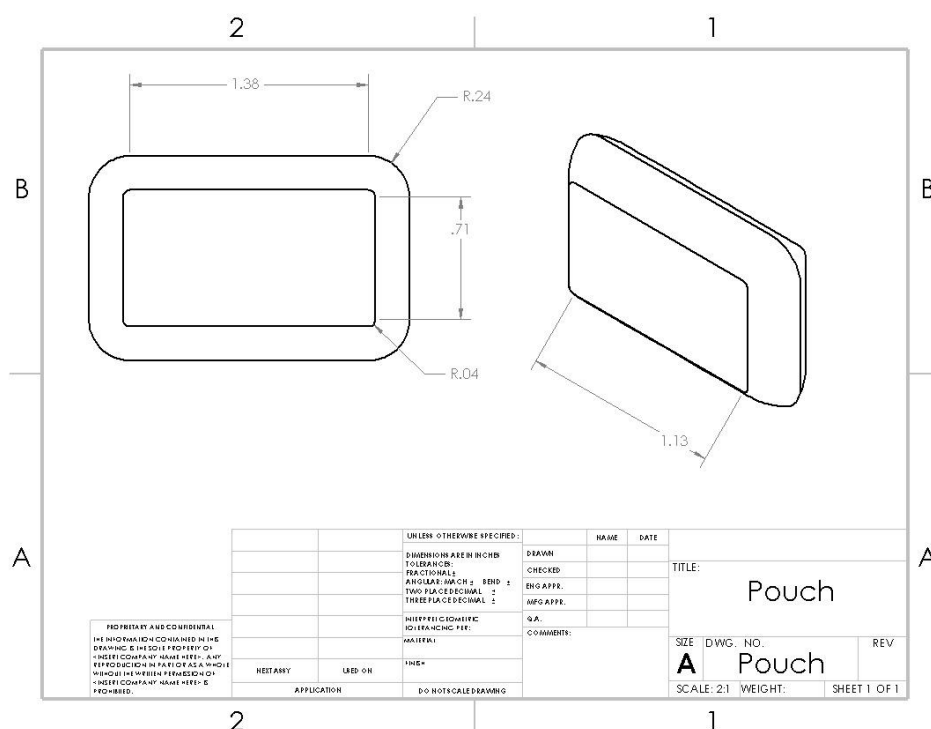


Figure [1]. Milrinone Sublingual Pouches

Design 2: Milrinone Nasal Spray

The nasal spray design consists of a multidose container containing a liquid milrinone formulation and a pump assembly intended to deliver a controlled volume into the nasal cavity. Its principal components would include the container, dip tube, metering pump, actuator, spray nozzle, and protective cap. The formulation would be deposited onto the nasal mucosa, with the intended goal of absorption through the nasal tissue.

Potential advantages include brief administration, avoidance of swallowing a solid dosage form, and multiple administrations from one container. Anticipated limitations include the need to characterize spray performance, formulation compatibility, and nasal comfort.

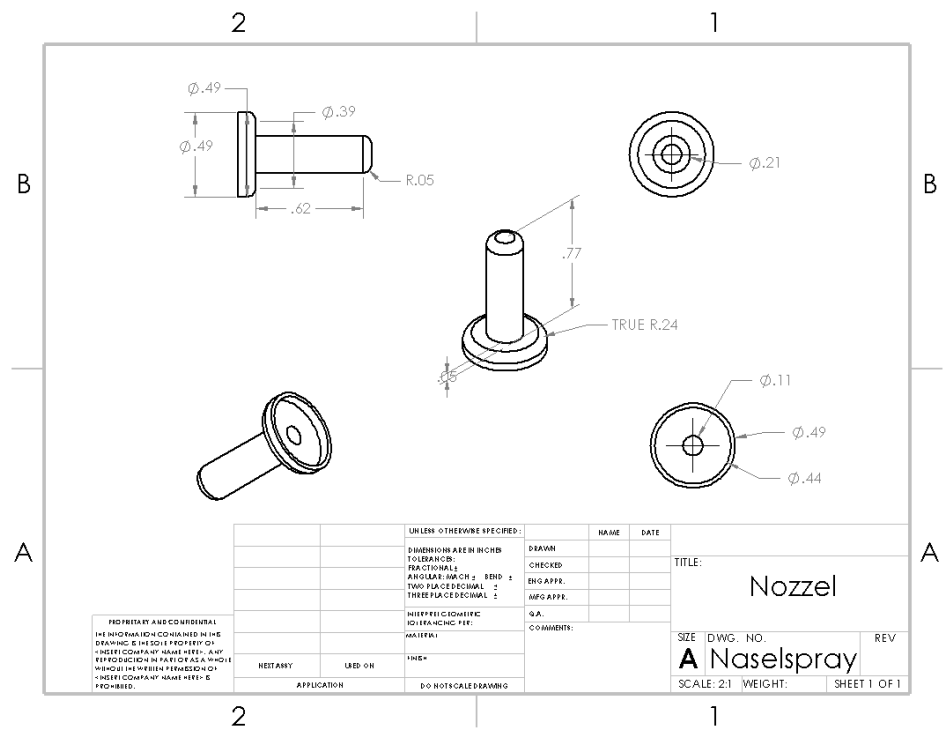
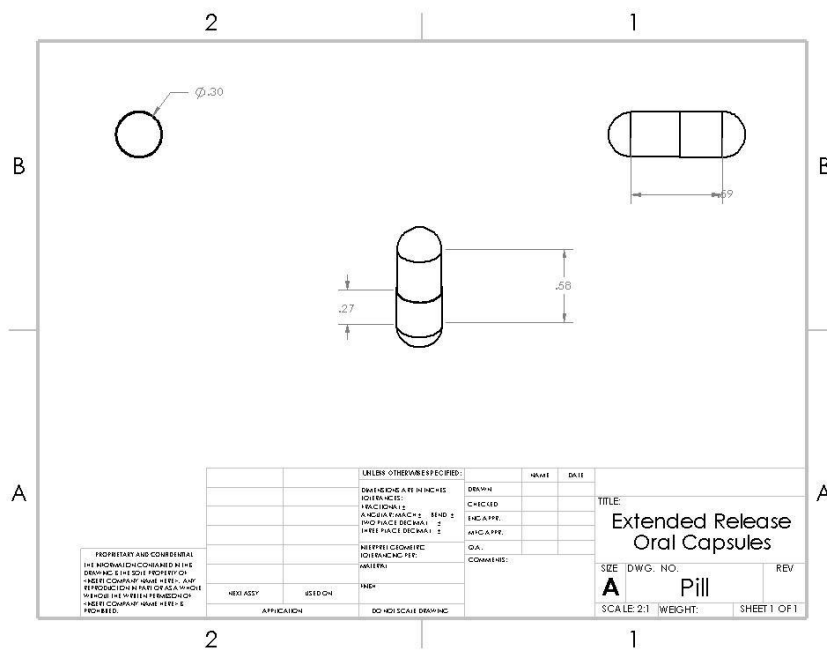


Figure [2]. Milrinone Nasal Spray

Design 3: Milrinone Extended-Release Oral Capsules

The extended-release oral capsule design consists of commercially available gelatin or polymer capsule shells containing a milrinone formulation engineered to control drug release. The capsule would enclose the formulation and provide a convenient unit for administration. The extended-release function would depend on the internal formulation, such as a suitable release-controlling matrix or coated particles, rather than on a standard gelatin shell alone.

The design targets medication release over 12 hours, supporting a proposed twice-daily administration. This interval is development objective and would require verification through release testing and subsequent assessment of drug absorption.



(20)			
Environmental Impact (5)	2	5	2
Choking Hazard (10)	2	5	1
Comfort When Applied (10)	3	5	4
Total (100)	69	73	87

Table [1]. Design Matrix

- Ease of Fabrication (15):

This category is weighted at 15%, it assesses the ease of fabricating the design, including the production and assembly of its components. The extended release oral capsules are rated 5 as the capsule can be purchased online. The sublingual pouches are rated 3 and the nasal spray are rated lower as we will need to design the pouch or the spray from ground up and it does not align with the technical skills of the team. A higher score in this category reflects a design that aligns with our fabrication skills and can be more readily scaled for commercial production.

- Ease of Use (25):

This category is weighted at 25%, it assesses the administration steps, processing time and patients administer the correct dosage of milrinone themselves on a daily basis. Pouches received a 4 because they can easily be applied to the gums; however, this design requires an element that anchors the pouch to the mouth so that they don't become displaced. Nasal spray and oral capsules both received a 5 because the dosage can be taken with ease for the patients.

- Cost of Fabrication (15):

This category is weighted at 15%, it defines the estimated costs of all materials and processes incurred during the fabrication, testing, and presentation of the design. It is weighted at 15% because the strict budget of 100 USD for our project plays a large role in determining the viability of a design solution. The extended-release capsules received a 5 as the anticipated affordability of commercially available gelatin capsule shells. Sublingual pouches received a 4 due to the limited availability of suitable pouch materials. Nasal spray received a 3 due to having the largest number of parts to configure including the bottle and nozzle of the spray.

- Number of Dosages per Day (20):

This category is weighted at 20%, it evaluates the quantitative number of medication administration per patient-day. The extended-release oral capsule received a 5 because it only requires twice administration per patient-day. The sublingual pouch received a score of 4 because it requires at least 3 administrations per patient-day. The nasal spray received a 2 because it is expected to be administered at least 5 times per patient day, which means patients have to wake up during sleep to use the medication. These scores

reflect projected dosing per patient-day.

- Environmental Impact (5):

This category is weighted at 5%, it accounts for waste from repeated treatment. Pouches and capsules each received 2 based on assumed disposable materials and packaging, while nasal spray received 5 because a multidose bottle serves multiple administrations. These environmental scores remain provisional until packaging quantities, device lifespan, and waste over an equivalent treatment period are compared.

- Choking Hazard (10):

This category is weighted at 10%, preventing choking is an important patient safety concern. Sublingual pouches received 2 because they could become displaced while held in the mouth; nasal spray received a 5 because it does not require an oral administration; capsules received 1 because they require swallowing a relatively big dosage.

- Comfort When Applied (10):

This category is weighted at 10%, it assesses the comfort of the design when in use particularly regarding if there would be any bar from use due to short or prolonged discomfort. The nasal spray received a 5 because it is a sleek design that will deliver medication quickly and with minimal discomfort. The extended oral release capsule received a 4 due to an initial discomfort from swallowing. The sublingual pouch received a 3 due to its prolonged use within the mouth leaving patients unable to eat and drink while using a pouch.

Proposed Final Design

Based on the weighted design matrix and team discussion following the preliminary presentation, the extended-release oral capsule was selected as the proposed final design. This concept received the highest overall score of 87/100, compared with 73/100 for nasal spray and 69/100 for the sublingual pouch. The capsule scored highest in ease of fabrication, ease of use, fabrication cost, and number of dosages per day. These categories collectively account for 75% of matrix weight, reflecting the importance of developing an affordable prototype that simplifies daily medication administration.

The proposed design consists of a commercially available gelatin or polymer capsule shell containing a milrinone formulation engineered for extended release. Commercially available shells are expected to simplify prototype assembly and help the team work within the \$100 project budget. A preset quantity of 28-37mg of milrinone per day (which means 14mg to 19 mg of milrinone per capsule) will support a target of twice-daily administration.

Fabrication

The delivery vehicle is an extended release capsule made of vegetable cellulose as shown in figure [3]. This material was chosen because it allows medication to bypass harsh stomach acid and reach the small

intestine where a delayed release is viable. Cellulose-based capsules are also widely available, compatible with a range of different substances and avoid gelatin cross linking giving it a longer shelf life[12]. The intended active compound is milrinone, however, due to milrinone being a prescription drug and the need for clinicians orders testing will be done by means of a surrogate compound. Future work will determine a compound with similar physicochemical properties to milrinone so that its release profile is representative.

Release testing requires simulated gastric fluid (pH 1.2, no enzymes), simulated intestinal fluid (pH 6.8 phosphate buffer), and a UV-Vis spectrophotometer for quantifying the released compound. A complete list of materials and the budget are provided in Appendix B

The surrogate candidates will be compared against milrinone using published values. The criteria are Molecular weight, Aqueous solubility, pKa and charge state, and Lipophilicity. The size of the surrogate must be similar to milrinone at roughly 211 g/mol since this would affect how the compound packs in the capsule and diffuses out[13]. The solubility in a given aqueous solution must be similar as this governs dissolution in the small intestine. The surrogate must also have a similar ionization behavior across the gastric to intestinal range, since solubility release depends on charge. Finally it must be comparable in its interaction with the capsule material and the surrounding fluid.

Size 0 vegetable cellulose capsules are then filled with a measured mass of the surrogate, with the mass varied across capsules to evaluate how payload amount affects release behavior. Fill masses of [20, 50, 75, 100mg] are with three capsules prepared per mass. Each mass is then weighed on an analytical balance using weight paper and the powder transferred into the capsule body with a spatula. Care is to be taken to avoid powder on the capsule rim so the seal would not be compromised. Capsules are closed according to manufacturers instructions. Each capsule is then reweighed after closing to confirm the fill mass. Filled capsules are then separated, labeled and stored in a dry room until testing.

Testing and Results

For testing the deliverable, we will simulate the pH environment of the stomach, small intestine, and large intestine to assess the effects of traveling through the gastrointestinal tract of a patient. For simulating a stomach environment we plan to create a strongly acidic environment ranging from a pH of 1-4. We will be altering this pH throughout the testing to simulate the changes in pH before and after eating food in a real stomach [14]. We will maintain a constant temperature of around 37 degrees celsius and even have a magnetic stir rod to simulate the movement of fluids in a human stomach [15]. We will first observe physical changes such as cracks, swells, matrix changes, or premature release spots on the actual capsules when introduced to the environment. From here we will run multiple tests of removing tablets at certain times to measure mass and hence the release rate of our tablet over set time periods. After this we will move the tablets to a pH environment of around 5.3-5.7 to simulate the large and small intestines [16]. When changing environments we will make sure to measure whether the release rates change or if any drastic changes occur due to the change in environment. From this we can modify our formulation or matrix tablet design to ensure our release rates stay within the therapeutic range for the entirety of the tablets effective use time.

Discussion

The discussion will focus on interpreting the results of the extended-release tablet testing, particularly changes in release rate over time and the implications of these changes for the intended delivery of milrinone. We will look at any physical changes that happen to our capsules during testing and analyze why these changes may have occurred. One limitation of these trials is that the limited availability of materials may restrict the number of independent trials that can be conducted. This could lead to issues of observed swelling, matrix changes, or cracks in the tablet that wouldn't be present if we were able to run more independent tests. Overall, these trials will provide preliminary information about the physical aspects of our tablet design in the gastrointestinal tract before much more thorough testing could begin beyond the scope of our design project.

Conclusions

The primary goal of this project is to develop an alternative delivery system for the drug milrinone that is noninvasive, administers accurate dosages, and promotes patient's quality of life. The design selected is an extended-release oral capsule that will slowly release the milrinone within the patient's system over an extended period of time [17]. This product would allow patients to receive less doses of the medication per day, while still remaining in the therapeutic index that the patient requires. Through research, milrinone extended-release tablets have worked to improve patients' symptoms and quality of life in pilot studies [18], which prompts more examination on why these studies did not continue further. Future work could also involve determining a molecule that is similar in properties to milrinone in order to conduct testing of extended-release capsules. Milrinone is a small molecule that has a solubility of <1 mg/mL [13], which are important distinctions that would be helpful in finding a similar substance. Other future work included conducting more research on the various types of extended-release capsules that are currently on the market and determining which would work best for milrinone and patients with heart failure.

References

- [1] Cleveland Clinic, "Heart failure: Symptoms, causes & treatment," Cleveland Clinic. [Online]. Available: <https://my.clevelandclinic.org/health/diseases/17069-heart-failure-understanding-heart-failure>. [Accessed: Oct. 8, 2026].
- [2] Ayres JK, Maani CV. Milrinone. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: <https://ncbi.nlm.nih.gov/books/NBK532943/>
- [3] "Ambulatory inotrope infusions in advanced heart failure: A systematic review and meta-analysis," JACC: Heart Failure, 2018, doi: 10.1016/j.jchf.2018.03.019.

[4] D. M. Kaye, G. Krippner, and G. T. Mariappan, "Milrinone controlled-release formulation," U.S. Patent Application US20190091156A1, Mar. 28, 2019. [Online]. Available: <https://patents.google.com/patent/US20190091156A1/en>

[5] "Improved nasal administration of pharmaceutical formulations," Patent WO2023133460A1, Jul. 13, 2023. [Online]. Available: <https://patents.google.com/patent/WO2023133460A1/en>

[6] Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med. 1991 Nov 21;325(21):1468-75. doi: 10.1056/NEJM199111213252103. PMID: 1944425.

[7] "Milrinone Lactate Injection," Pharmacological product manual or prescribing information, Oct. 2025. Accessed: Oct. 08, 2026. [Online]. Available: <https://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=7388>

[8] "Speaker Details," Wemsaexpo.com, 2026. <https://www.wemsaexpo.com/wemsa2026/speaker/2110545/lenard-markman-do> (accessed Oct. 08, 2026).

[9] S. Klein, "The Use of Biorelevant Dissolution Media to Forecast the In Vivo Performance of a Drug," The AAPS Journal, vol. 12, no. 3, pp. 397–406, May 2010, doi: 10.1208/s12248-010-9203-3.

[10] "To test pill coatings, try a stomach in a flask | Science News Explores," June 07, 2017. <https://www.snexplores.org/blog/eureka-lab/test-pill-coatings-try-stomach-flask> (accessed Oct. 08, 2026).

[11] Z. Xie, W. He, A. Gobbi, H. C. Bertram, and D. S. Nielsen, "The effect of in vitro simulated colonic pH gradients on microbial activity and metabolite production using common prebiotics as substrates," BMC microbiology, vol. 24, no. 1. England, p. 83, Mar. 11, 2024. doi: 10.1186/s12866-024-03235-2.

[12] B. Bhatt and V. Kumar, "Regenerated Cellulose Capsules for Controlled Drug Delivery: Part III. Developing a Fabrication Method and Evaluating Extemporaneous Utility for Controlled-Release," Eur J Pharm Sci, vol. 91, pp. 40–9, Aug. 2016, doi: 10.1016/j.ejps.2016.05.021.

[13] National Center for Biotechnology Information. "PubChem Compound Summary for CID 4197, Milrinone" PubChem, <https://pubchem.ncbi.nlm.nih.gov/compound/Milrinone>. Accessed 21 September, 2026

[14] S. Klein, "The Use of Biorelevant Dissolution Media to Forecast the In Vivo Performance of a Drug," The AAPS Journal, vol. 12, no. 3, pp. 397–406, May 2010, doi: 10.1208/s12248-010-9203-3.

[15] "To test pill coatings, try a stomach in a flask | Science News Explores," June 07, 2017. <https://www.snexplores.org/blog/eureka-lab/test-pill-coatings-try-stomach-flask> (accessed Oct. 08, 2026).

- [16]Z. Xie, W. He, A. Gobbi, H. C. Bertram, and D. S. Nielsen, “The effect of in vitro simulated colonic pH gradients on microbial activity and metabolite production using common prebiotics as substrates,” *BMC microbiology*, vol. 24, no. 1. England, p. 83, Mar. 11, 2024. doi: 10.1186/s12866-024-03235-2.
- [17] Nezhad Mohseni M, Najafpour Darzi G, Ramezani R, Jahani A. A developed composite hard-gelatin capsules: delayed-release enteric properties. *Heliyon*. 2022 Dec 19;8(12):e12265. doi: 10.1016/j.heliyon.2022.e12265. PMID: 36619422; PMCID: PMC9813726.
- [18] Nanayakkara S, Byrne M, Mak V, Carter K, Dean E, Kaye DM. Extended-Release Oral Milrinone for the Treatment of Heart Failure With Preserved Ejection Fraction. *J Am Heart Assoc*. 2020 Jul 7;9(13):e015026. doi: 10.1161/JAHA.119.015026. Epub 2020 Jun 18. PMID: 32552264; PMCID: PMC7670502.

Appendix

Appendix A: Product Design Specification

Function

The device shall provide a non-invasive alternative delivery system for milrinone therapy in congestive heart failure (CHF) patients, enabling outpatient and long term self management without the need for intravenous administration. The system shall consist of two complementary components: a rapid- onset formulation(e.g., nebulized/inhaled, oral liquid or nasal spray) for fast daytime symptom control, and a longer-acting oral formulation for sustained, steady state dosing overnight. Together these formulations shall deliver Milrinone with pharmacokinetic and pharmacodynamic profiles that are therapeutically equivalent to existing IV administration, while reducing adverse side effects, simplifying the dosing regimen and improving patient adherence and overall quality of life.

Client requirements

- Target population: Address the needs of patients with stage D congestive heart failure who require milrinone pumped IV therapy, including patients who are not eligible for heart transplant.
- Delivery method: Prioritize evaluation of an oral pouch for milrinone delivery if possible, reflecting the client’s report that his brother, who is a patient receiving milrinone through pumped IV, prefers a pouch over a nasal spray. Nasal and other delivery methods remain alternatives pending feasibility assessment.
- Duration of action: Aim to provide sustained delivery that is suitable for overnight use and reduce the need for frequent administration of milrinone. Investigate whether sustained-release pouches or a daytime pouch combined with an extended-release nighttime formulation could meet this need. Required duration and administration frequency will be established with the client and clinical specialists.
- Ease of use and replacement: Design for convenient routine administration by the patient or caregiver, with a clearly defined pouch replacement schedule. Determine whether any delivery-system components can be reused without compromising hygiene.

- Patient comfort and material safety: Select pouch material for contact with the oral lining and evaluate potential irritation effects on teeth, and ingredient-related allergy risks.

Design requirements

1. Physical and Operational Characteristics

a. Performance requirements

- i. The milrinone delivery system product is targeted towards patients with stage D cognitive heart failure that currently require a constant IV infusion of milrinone. However, the alternate milrinone administration system should deliver the medication to the patient in a safe route that allows for patient mobility and activity, eliminates the risk of infection, and be more affordable. The correct milrinone dosage should be administered in short acting formulations during the day and long acting dosage at night. The dosage of milrinone delivered to the patient should work to increase cardiovascular functions and manage heart failure.

b. Safety

- i. The device must comply with pharmaceutical and medical device safety regulations, likely requiring FDA review under an NDA and if paired with delivery hardware such as a nebulizer, inhaler, or nasal applicator regulation as a drug device combination product under 21 CFR Part 4, as well as device quality standards, relevant device specific standards, and biocompatibility requirements for any patient contacting components. Chemically, because Milrinone has a narrow therapeutic index, the formulation must ensure consistent, reproducible dosing to avoid arrhythmia, hypertension, or thrombocytopenia from overdose, with validated stability and preservative safety over shelf life. Mechanically, delivery hardware must minimize choking, breakage, or aspiration risk and require minimal actuation force for elderly or weakened patients; if electrically powered the device must meet electrical safety and EMC standards and battery safety standards, with any heating elements maintaining drug safe, non-injurious temperatures. Finally, clear labeling and warnings must distinguish the fast acting daytime formulation from the long acting nighttime formulation to prevent dosing confusion, specify overdose symptoms and emergency guidance and provide storage, handling and device cleaning instructions.

c. Accuracy and Reliability

- i. The device must deliver Milrinone within a validated dose accuracy range across its full intended dosing range, with repeatability maintained within a similarly tight tolerance across the device's rated number of actuations/uses, given Milrinone's narrow therapeutic index and the risk of arrhythmia or hypotension from over or underdosing.

d. Life in Service

- i. If implementing the capsule version of mirinone, the life in service is one capsule per dosage. The frequency of dosage is currently undetermined however it is expected to be 2-3 capsules per day. The specific frequency will be determined once an effective dosage of milrinone administered has been determined

- ii. If implementing the nasal spray solution, the life in service will be a few dosages per container. The specific dosage and number of dosages per nasal spray container will be determined with the formulation of a nasal spray as well as the chamber design for the nasal spray mechanism. The solution will be sealed, non-refillable, and able to be disposed of by standard means.
- e. **Shelf Life**
 - i. The product will have a shelf life of up to 3 years while sealed and in standard room temperature conditions. After being unsealed or opened, the shelf life will fall to 72 hours. The product will not have any light sensitivity, oxygen sensitivity, or strong temperature sensitivity as long as it stays at or under 25 degree celsius climates. Outside of shelf life, the product must be disposed of.
- f. **Operating Environment**
 - i. The product is intended to be administered to the patient in a typical indoor environment without any specialized environmental conditions or restraints during administration. Normal variations in temperature, humidity, lighting, and patient surroundings are expected during use. The product shall be designed to function as intended under the environmental conditions reasonably anticipated during administration and use.
- g. **Ergonomics**
 - i. The product will be designed to be used by the patient itself. The oral capsule version will be designed so that the patient can easily swallow with minimal discomfort.
 - ii. The nasal version will have two flaps on the side to anchor the nasal spray and a push bottom in the middle for administering the medicine. The product will also be designed to be used for the patient by others in case of emergency, similar to an Epipen but a nasal version.
- h. **Size**
 - i. The oral capsule version will be designed to maximize the effectiveness of the medicine, further research will be required for the exact capsule type.
 - ii. The nasal version will hold 15 mL of medicine in a bottle with a tip for administration. The product should be easy to fit within a pocket or a small medicine pouch allowing ease of transport. The tip should be able to be removed for cleaning.
- i. **Weight**
 - i. The milrinone delivery system should be lightweight and portable. The patient should be able to have easy access to the milrinone dosage throughout the day. Additionally, the overall weight of the product should not interfere with the patient's mobility and daily activities.
- j. **Materials**
 - i. The product would include a safe dosage of milrinone that can be administered to the patient throughout the day.
 - 1. If implementing a capsule version of milrinone, the proposed device would require an extended release tablet that can be made out of either a gelatin or polymer. The specific capsule type would need to be determined based on the

dosage of milrinone that needs to be administered to the patient over a specific period of time.

2. If the proposed device is a nasal spray, the final product would be a liquid dosage form of milrinone. The spray should come in a device that is ergonomic and allows patients to easily administer the drug while on their own.

k. Aesthetics, Appearance, and Finish

- i. The milrinone delivery system should have a simple compact appearance that allows for patient comfort and ease of use. Due to the fact that this device may be used multiple times throughout the day, the product should be portable and allow for the patients to administer the prescribed dosage. Furthermore, the product exterior should be easy to clean and durable, withstanding daily wear and tear.
- ii. If the device consists of a capsule or tablet, it should be a reasonable shape and size and have a smooth finish to allow for ease of swallowing. For a nasal spray product, the device should be user-friendly and allow for a controlled administration of the milrinone.

2. Production Characteristics

a. Quantity

- i. The client called for a short-acting and a long-acting prototype for the project. The team will focus on the short-acting version for this semester with the goal of producing 1 final prototype for demonstration at the end of the semester.

b. Target Product Cost

- i. The product was aimed to cost similarly with an Epipen, which the average cost is around 126.35 per unit [].

3. Miscellaneous

a. Standards and Specifications

The proposed device would deliver milrinone through a new method of administration, so regulatory approval would be required before it could be marketed for clinical use. The following standards and regulatory requirements must be considered depending on the final design pursued:

1. ISO 10993 ~ Biological Evaluation of Medical Devices
2. USP <711> ~ Dissolution
3. USP <905> ~ Uniformity of Dosage Units
4. FDA Nasal Spray Drug Product Guidance
5. USP <601> Inhalation and Nasal Drug Products

The above specifications and regulatory requirements ensure consistent and accurate dosage, dosing frequency, absorption rate, and maintenance of required therapeutic plasma concentration.

b. Customer

The current method of continuous IV delivery of milrinone is uncomfortable, restrictive, and has negative health effects. So the alternative method of delivery must be more comfortable and have fewer health risks for the customer while effectively delivering the drug.

The final design should eliminate long-term vascular access, be suitable for outpatient use, require minimal maintenance, improve customer ability to perform daily activities, be portable, minimize dosage frequency, and consistently administer the correct drug dosage.

c. Patient-related concerns

The device is intended for patients with stage D congestive heart failure who currently require continuous IV milrinone. Therefore, patient safety, dosing accuracy, and ease of use. The delivery device must minimize risk of infection and reliably deliver the therapeutically appropriate dose. The final design should consider the following patient-related concerns:

1. Cleaning and sterilization: reusable parts of the device that come into contact with the patient must be replaceable or be easily sterilized
2. Dose accuracy: the device must prove the accurate dose of the drug consistently
3. Ease of use: patients must be able to administer the drug themselves with minimal physical effort
4. Mucosal safety: repeated administration of intranasal delivery of the drug must not irritate the nasal mucosa
5. Patient variability: Patient differences such as nasal anatomy, technique, gastrointestinal absorption, and others must be considered

d. Competition

The current method of delivery is continuous IV milrinone, which is the method that the final design should be compared against. The benefits of this method include: delivering a constant dosage of the drug. Limitations associated with the continuous IV include: patient mobility, infection, infusion equipment, and long-term vascular access. Other similar methods already exist and are present in literature and patents, including:

- WO2016131051A1 Patient Milrinone composition and method for administering same
 - Nebulized/inhaled milrinone formulations for treating heart failure
 - Formulations containing 10-20mg/mL milrinone and single doses of 6-24mg
 - Administration includes nasal administration
- US20190091156A1 Milrinone Controlled-release Formulation
 - An oral controlled-release formulation for treating heart failure
 - Drug containing core and sustained release coating designed for extended release
- WO2023/133460A1 Improved Nasal Administration of Pharmaceutical Formulations
 - Nasal drug delivery patent
 - Identifies milrinone as a drug that can be used in the system

Appendix B: Team Expense Spreadsheet

Item	Description	Manufacturer	Mft Pt#	Vendor	Vendor Cat#	Date	QT Y	Cost Each	Total	Link
Material Costs										
Size 0 vegetable cellulose capsules	Capsule shells used to contain the extended-release formulation	Capsuline	TBD	Capsuline	TBD	TBD	1	\$23.09	\$23.09	https://capsuline.com/products/colored-size-0-empty-vegetarian-capsules-by-capsuline-sage-green
Extended-release matrix	Polymer matrix used to control and slow the release of milrinone	TBD	TBD	TBD	TBD	TBD	1	\$20.00	\$20.00	TBD
Testing Costs										
Milrinone mimic	Compound that will mimic milrinone for testing purposes	TBD	TBD	TBD	TBD	TBD	1	\$30.00-\$40.00	\$30.00-\$40.00	TBD
Project Budget	\$100							TOTAL:	\$73-83	