High Speed Blood and Transfusion Equipment

Final Report

Prepared by:

University of Nevada School of Medicine
Trauma Institute
Department of Surgery
2040 W. Charleston Blvd #302
Las Vegas, NV 89102
&
Rocky Research
1598 Foothill Drive
Boulder City, NV. 89005

for

Office of Naval Research, Code ONR 342
875 N. Randolph Street
One Liberty Center
Arlington, VA. 22203-1995

Award No. N00014-10-1-0869
Program Officer
Dr. Michael B. Given, Ph.D.

CONTENTS

High Speed Blood and Transfusion Equipment

Final Technical Report

INTRODUCTION

The Rocky Research Portable Fluid Infusion Warmer is an entirely portable device capable of heating blood and other intravenous fluids utilizing proprietary thermal energy storage (TES) system referred to as a thermal battery. This novel thermal battery technology, developed by engineers at Rocky Research, is based on a sorption process that can be charged intermittently and used completely independent of electric power, or operated indefinitely while connected to external power. The proof-of-concept prototype was developed to test the capability of this unique technology as an energy source for a Portable Fluid Infusion Warmer. The medical device allows for the infused fluid, be it blood or supplementary fluid, to be warmed to a body temperature of 37 °C for critically injured trauma patients. The most unique characteristics of the device are (1) it stores energy for heating fluid when not attached to an external power source, (2) it accommodates infusion rates from 2 mL/min up to 200 mL/min on thermal battery power, and (3) it is portable.

After consultations with military and civilian University Nevada School of Medicine (UNSOM) affiliated trauma surgeons, a need was identified for the Portable Fluid Infusion Warmer to administer routine maintenance intravenous (IV) fluids (2 mL/min) in addition to rapid infusion (> 200 mL/min) during critical care transport where electrical power is not available. This characteristic of accommodating low flow rates has been added to the initial proposal as an improvement in treatment capabilities by preventing hypothermia among injured soldiers who require both rapid/large-volume resuscitation and routine IV fluid administration during critical care transport. The objectives of the project are threefold. First, provide a portable medical device capable of heating 1000 mL of blood from 4°C to 37°C at infusion rates from 2 mL/min up to 200 mL/min for corresponding time frames of 5 min to 8 hours utilizing the TES system. Second, demonstrate the thermal battery proof-of-concept by examining the device's capabilities through a series of bench performance tests. Third, prepare as much documentation as possible for future Food and Drug Administration (FDA) 510(k) approval of the device.

PROTOTYPE OVERVIEW

The fluid infusion warmer is capable of operating independently from external electrical power. Such a design inherently lends the device for portable applications. Specifically, military applications where weight management, durability, and portability are essential to overall system design and functionality. Utilizing Rocky Research's complex compound technology, the device is capable of storing energy that can be harnessed to heat fluid remotely from electrical power, creating a thermal battery or thermal energy storage (TES) system. The thermal battery, or absorber, is completely rechargeable by reversing a chemical reaction. Additionally, the ability to entirely recharge the system when external electrical power is available is a distinguishing advantage conducive to military requirements.

The heat of absorption delivered by means of a chemical reaction is the exploited mechanism for storing energy in the fluid infusion warmer. The process consists of a working fluid, ammonia, covalently bonded to an inorganic salt, CC260-1260, to produce an exothermic reaction. The bonding reaction forms a coordination complex compound, releasing a large amount of energy in the form of heat, as the refrigerant (ligand) is absorbed onto the salt (absorbent). The absorbent salt complexes the ammonia vapor directly from the gas phase, releasing energy in the form of heat. This reaction is known as absorption, where discharging of the thermal battery occurs. The extremely high energy density harnessed through the complex compound reaction is a distinguishing advantage over comparable appliances for similar applications. It makes the device portable so that it can be utilized on the battle field when electrical power is unavailable or during a power surge, common scenarios in combat situations.

The absorption process is entirely reversible. By heating the absorber the ammonia refrigerant is removed from the salt in the vapor phase. The endothermic reaction, known as desorption, is in essence the recharging process of the thermal battery. The rate of desorption for the current rapid infusion warmer prototype has been optimized to ensure full capacity during a recharge while limiting the interruption of functioning ability for the device. Such methodology provides an optimal balance between regained system capacity and the downtime required to recharge the appliance.

The vapor pressure is independent of the absorbed ligand concentration, known as a monovariance characteristic. The advantage to the thermal storage system pertains to the driving force of the reaction kinetics. The monovariant capability allows for constant suction and discharge pressures. An increase in vapor pressure during absorption preludes to difficulties in quantifying and controlling ligand vapor mass flow rate. The ability to effectively control the rate of absorption by modulating refrigerant flow with a solenoid valve is difficult to accomplish without the monovariant quality. As available ligand quantity decreased, the heating capacity would also consistently diminish. However, with the monovariant attribute a single pulse of the solenoid valve corresponds to a consistently quantifiable volume of ammonia absorbed under the same operating conditions. By controlling the reaction kinetics, the heat flux produced can be precisely modulated to regulate heat input into the targeted infused fluid. Resultantly, the outlet temperature of a fluid traversing the heat exchanger cartridge of the device can be accurately controlled.

The fluid infusion warmer is capable of operating via AC power when an external electrical source is available. The heatable volume when operating on external power is unlimited. The thermodynamic limit, implying perfect heat transfer with no heat losses, can accommodate a volumetric flow rate of blood up to approximately 360 cc/min. When operating utilizing the thermal battery, the sorber has been sized to heat 1000 mL of blood 33°C, from 4°C to 37°C. At the minimum required flow rate the specification accommodates a blood infusion for duration of 500 min, while at the maximum infusion rate a target of 5 min is obtainable. The total heatable system capacity when operating utilizing the thermal battery pertains strictly to the volume of fluid being heated and is therefore independent of fluid flow rate. Heatable fluid volume is also reliant on the heat capacity of the infused fluid.

Originally, the device was developed to permit high infusion flow rates up to 500 mL/min. However, after close interactions with medical personnel experienced in trauma combat situations, it was deemed

more prevalent to enhance the portability of the device over accommodating fast infusion rates. Consequently, the current fluid infusion warmer is capable of maintaining heat input for a water volumetric flow rate of 200 mL/min utilizing the thermal battery and 330 mL/min utilizing an external power source.

The large refrigerant holding capacity of the fluid infusion warmer provides a thermodynamic advantage, allowing for an optimal balance between the heating capability and size and weight of the appliance. The end result is a small, compact, lightweight appliance, in comparison to similar devices, capable of controllably heating a relatively large quantity of fluid. The following schematics are representative of the ammonia flow path during absorption and desorption cycles respectively. The absorption cycle results in a heat flux output while the desorption recharge process requires an input of heat. Presented in figure 1 is a system flow schematic for the absorption fluid infusion cycle, while in figure 2 the desorption system recharging flow schematic is depicted.

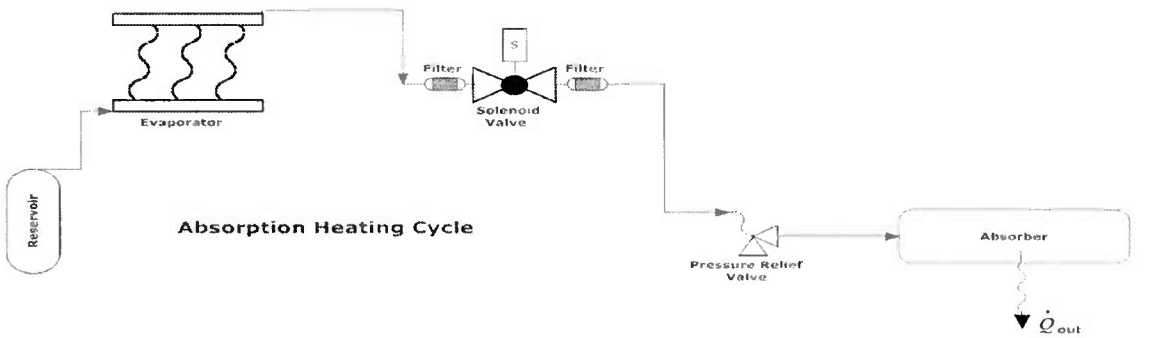


Figure 1. Absorption cycle flow schematic

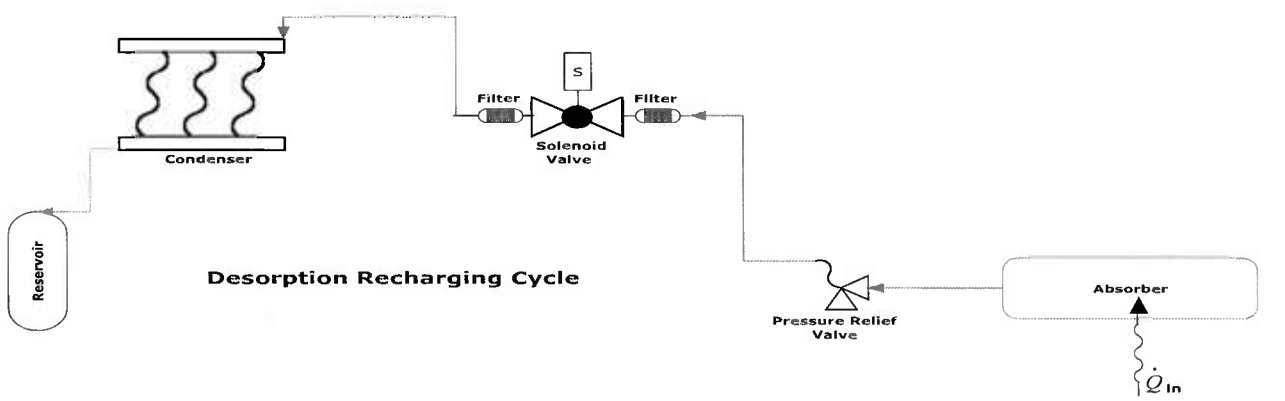


Figure 2. Desorption cycle flow schematic

CONCISE ACCOMPLISHMENTS

Rocky Research

- Completely redesigned and revamped Portable Fluid Infusion Warmer prototype.
- Improvements to nearly all critical system components have been designed implemented and evaluated for quality of performance.
- The Single Patient Cartridge (SPC) heat exchanger has been redesigned to mitigate concerns of stagnant residual blood not being flushed from the cartridge. Single helical flow channel cartridge has replaced the existing multi-channel cartridge and optimized for an ideal balance between heat transfer and pressure drop.
- Sorber fabrication has been redesigned to accommodate the new SPC, as well as reduce stored energy in the vessel, resulting in high temperatures gradients that preludes blood hemolysis if fluid flow stops.
- The solenoid valve has been replaced with a valve of a more suitable maximum operating pressure differential (MOPD) for the application at hand along with a smaller pulsating orifice for improved control of refrigerant flow. The new solenoid valve allows for better control of the ammonia flow rate during absorption and subsequently improved regulation of fluid outlet temperature during infusion.
- The aircoil utilized on previous prototypes has been replaced with a custom coil that can be obtained reliably from a reputable source.
- The mounting structure and orientation of the sorber within the appliance has been completely redesigned.
- Thermistors of higher accuracy for monitoring cartridge fluid temperature have been acquired and assimilated into the fabrication of the SPCs.
- The control board has been completely redesigned in the latest fluid infusion warmer prototype, improving system capability, reliability, appliance robustness, and safety.
- A pressure relieve valve has been incorporated into the ammonia containing subassembly in order to alleviate the possibility of dangerous system failures.
- The case, display, and keypad of the appliance have all been improved, tested, fabricated, and conformed into the appliance design.

UNSOM

- Quality systems established to support future FDA 510(k) submission.
- Preliminary FDA 510(k) Review packet prepared for showing Substantial Equivalence to a predicate device in future 510(k) submission.
- User Needs, Hardware Product Specifications, and Biocompatibility Plan working documents prepared for future FDA 510(k) submission.
- Biosafety protocol developed and approved by University's Institutional Biosafety Committee (IBC).
- Test methods were optimized for SPC feasibility studies.

- Multi-channel and single helical channel SPC feasibility studies were performed using human packed red blood cells (pRBCs).
- Bench performance testing was performed on three prototypes to determine similarities in heating capabilities by thermal battery and AC power.
- Bench performance test was conducted on SPCs to determine similarities in heat transfer and flow rate.
- Bench performance testing was performed on Rocky Research Portable Fluid Infusion Warmer prototype and compared to four commercial fluid warmers.
- Thermal battery proof-of-concept was demonstrated by examining the device's warming capabilities under several test conditions.

EXPANDED ACCOMPLISHMENTS

UNSOM and Rocky Research

1. *Implemented Proof-of-Concept Prototype Refinement Plan.*
   A report was delivered to Rocky Research engineers from UNSOM affiliated trauma surgeons on operational experience gained from application testing of the prototype by UNSOM staff during previous contract. The engineers and trauma surgeons had several meetings during the first year of project to discuss recommendations in improving prototype. Most of the recommended changes related to controls and user interface, such as safety features, error codes clarification, and programming the device to recognized low flow rates. Hardware features improvements included verification of proper contact between SPC to sorber, addition of a small air blower to reduce cooling time following battery recharge, 4 lb weight reduction of device, and new design package to allow support on an IV pole or sit on a flat surface. UNSOM previous testing of the device was only with crystalloid fluids. Further feasibility testing of the SPC was required with packed red blood cells (pRBCs) to determine the safety and efficacy of cartridge.

2. *SPC Redesign*
   A feasibility study was performed on multi-channel SPC using pRBCs to test efficacy. Both pre and post cartridge blood samples were evaluated to determine if any damage may have occurred to blood cells. The following tests were run by UNSOM: potassium leakage, percent hemolysis, osmotic fragility, Adenosine Triphosphate (ATP), and phosphatidylserine (PS). There were no statistical differences between the pre and post samples. However, Rocky Research engineers and UNSOM surgeons were concerned of the possibility of stagnant areas or deficiencies, which may cause damage to blood cells and restrict fluid flow. Rocky Research carried out more testing of their own on the cartridge and did find stagnant areas. The tests performed by Rocky Research are explained in more detail under their section of "Expanded Accomplishments" (See pg 13 – 18). Due to Rocky Research findings, a new single helical channel design was implemented for the SPC.

Rocky Research

The fundamental heat engine of the rapid fluid infusion warmer consists of an ammonia containing subassembly comprised of an absorber, air coil, solenoid valve, filters, liquid-vapor reservoir, charge port,

and associated plumbing. A comprehensive depiction of essential system components is presented, along with enhancements from previous fluid infusion warmer implementations. A SPC is the heat exchanger utilized as the interface between the device and the infused fluid. The cartridge has been optimized for an adequate balance between pressure drop and heat transfer. Additional device components consist of structural sheet metal, a pressure relief valve, insulation, a glass filled nylon casing, and electronic peripherals such as a control board, battery pack, power supply, keypad, and fans. A detailed description of all primary components is presented, along with how they have been evolved and modified to come to fruition. Individual component overview is intended to elaborate on how system components are integrated to form a fully functional appliance along with how they have been enhanced over the current reporting period. A comprehensive overview of essential system components is presented.

Device Design

Absorber

The sorber is comprised of complex compound disks, fins, heaters and a refrigerant flow channel. The sorber internals include disks of fiberglass that have been impregnated with complex-compound forming a metal inorganic salt. Aluminum fins separate the absorbent disks. Fins fit tightly inside the sorber to provide good thermal contact with the shell. A target total of 133 sorbent disks and fins are used in the sorber core. They are stacked at 11 fins per inch, to give a sorber core length of 12".
A thermocouple encompassed in a thermowell is also contained within the sorber for controlling AC heating, recharging, and monitoring stored energy resulting in temperature gradients within the device.

In addition to fins and sorbent disks, the sorber core contains a porous sleeve to transport ammonia vapor axially inside the sorber, and three aluminum tubes into which heaters are inserted. The refrigerant flow channel is designed to maintain diffusion rates of 600 g/hr of ammonia, enough to accommodate heat of absorption rates for water being infused at a rate of 200 mL/min. Maintainable refrigerant flow rate is conducive to the heat of absorption required for the entire flow regime of the infused fluid, a substantial factor in sorber geometry and design. The heaters used are cartridge heaters of dimensions 1/8" OD x 12" long. Nominal rated heater power is 750 W at 120 VAC, 250 W a piece. The sorber shell is 6061 aluminum with 1.93" inside diameter. The outside of the sorber is tapered. The outside diameter is nominally 2.046" on the small end and 2.178" on the large end.

Significant modifications have been made to the absorber of the current fluid infusion warmer prototype within the last year. The sorber design currently supports a helical cartridge flow channel with an ideal balance between heat transfer and pressure drop characteristics, a redesign from the previous multi-flow channel employment. The prior cartridge design had an open split down the side, allowing for the sorber shell to be wrapped around the core and welded shut. The weld protruded above the sorber shell at the same location as the split down the SPC so there was no contact interference resulting in an obstruction of how the SPC fit on the sorber. The new concentric helical flow channel design does not accommodate such an interposing weld. The initial modification approach was to construct the sorber in a similar manner as originally implemented and grind the weld down so that the SPC would fit appropriately. Grinding the weld down, however, gave rise to problems with the sorber leaking and degradation in component reliability. Resultantly, a new approach was developed. Rather than splitting and compressing the sorber shell around the stacked core, the core was stacked directly into the shell. Such an

approach eliminated the need for a weld down the side of the sorber, making the sorber robust, reliable, and safe. Figure 3 depicts how the sorber core is currently stacked directly into the weld-less sorber shell. The top and bottom end caps of the sorber are still welded to the shell as implemented in previous designs.

Figure 3. Sorber core stacked directly into weld-less shell lengthwise

Another substantial adaptation made to the sorber design pertains to the electrical heaters and fins utilized in stacking the core. Previously, there was a single electrical heater in the center of the core running the length of the sorber. The problem associated with such a design was that a significant amount of energy would get stored in the center of the sorber when utilizing external electrical heating during an infusion. Since hemolysis of blood can occur at 45 °C, just 8 °C above the target infusion temperature, good heat transfer through the sorber and cartridge media is a necessity to ensure low temperature gradients throughout the appliance. With previous design implementations, if fluid flow stopped during an infusion fluid temperatures would spike well above practical operating limits and damage the blood cells. The new design consists of three 1/8'' 250 W heaters distributed as close as practical to the edge of the sorber, with the intent of reducing stored energy and temperature gradients in the appliance. Ideally, the innovative application allows for the stoppage of blood flow without the deterioration of red blood cells. The new fin design was intended to alleviate the concerns associated with large temperature gradients.

A thermowell has been installed and is designed to accommodate a 0.0625'' diameter thermocouple running 2.5'' axially down the sorber, starting from the base. The thermocouple is utilized to monitor sorber core temperatures for heater control regulation during desorption and controlling infusion temperatures when operating the appliance utilizing external electrical power. Previously, the sorber top temperature was being utilized to approximate sorber working temperatures. It was determined that such an approach did not provide an accurate depiction of the sorber operating conditions and hence led to the necessity of adding the internal thermocouple. Figure 4 presents a drawing of the new fin design, with the

3-heater holes distributed towards the edge of the sorber shell. 2.5'' of fins located at the base of the sorber have an additional hole to accommodate the thermowell.

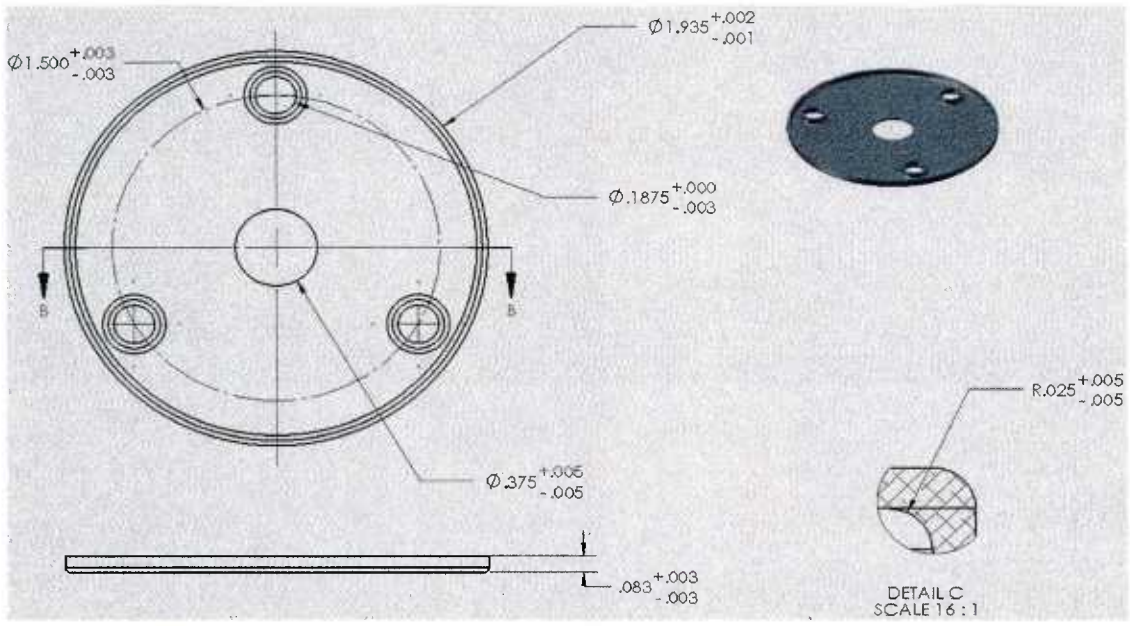


Figure 4. Modified fin for 3-heater sorber

Initially, stored energy levels were still above optimal conditions for stop flow scenarios at high infusion flow rates of 150 cc/min or greater. The culprit was attributed to the harnessable energy losses associated with heating sorber mounting peripherals comprised of aluminum. In order to resolve temperature gradients due to sensible heat losses high temperature Polyether ether ketone (PEEK) was utilized to mount the sorber. Initial testing has demonstrated reduced temperature gradients during high infusion rates, accommodating stop flow conditions. By utilizing better insulated components the required sorber temperatures do not exceed temperatures preluding to the hemolysis of blood if fluid flow is stopped. Along with the control scheme, the thermocouple temperature in the sorber core is utilized to ensure that the sorber does not exceed desired practicable temperatures of the infused fluid under stop flow conditions.

Solenoid Valve

A solenoid valve is utilized to modulate the pulsating of ammonia during absorption, allowing for intimate control over the heat generation rate of the sorber. Previously, the solenoid selected for prototype fabrication was not rated for the proper maximum operating pressure differential (MOPD) of the system and had a relatively large orifice preluding to difficulties in controlling absorption rates within the system. A solenoid rated for the proper MOPD with a smaller pulsating orifice has since been selected, installed, and thoroughly tested. The new solenoid has an orifice size of 1/16'', whereas the previous solenoid orifice was over twice as large at 5/32''. Furthermore, the replacement solenoid is rated for a MOPD of 400 psi, well above the required 350 psi of the system. The previous solenoid had an MOPD of 100 psi, requiring an over-voltage for a short period of time to force the valve open. Such an implementation raises the apprehension of possibly damaging the valve. The new solenoid allows for

better control of ammonia flow rate during absorption, and subsequently improved regulation of fluid outlet temperature during infusion. It also eliminates the concern of damaging or frying the valve. While replacing the solenoid, fittings were installed within the prototype to allow for the interchangeability of components without disassembly of the entire unit. 100 mesh filters were also integrated into the design at the inlet and outlet of the valve to eliminate particulate matter from effecting proper operation of the valve.

Liquid-Vapor Separator

The ammonia reservoir serves as a separator between the liquid and vapor ammonia. The reservoir accommodates the condensing of liquid ammonia during system recharge while supplying ammonia in the vapor phase to the absorber during an infusion. For the current fluid infusion warmer design the reservoir is 3'' in diameter by 7.5'' tall. The reservoir is oriented horizontally to accommodate the geometry and design of the updated fluid infusion warmer implementation. A vertical tube extends from the bottom of the reservoir to allow vapor ammonia to be drawn to the absorber. The bottom of the reservoir is plumbed to the bottom of the aircoil to allow for the condensing of ammonia to fill the reservoir from the bottom. A cross-sectional depiction of the ammonia liquid-vapor separator is presented in the following figure, figure 5.

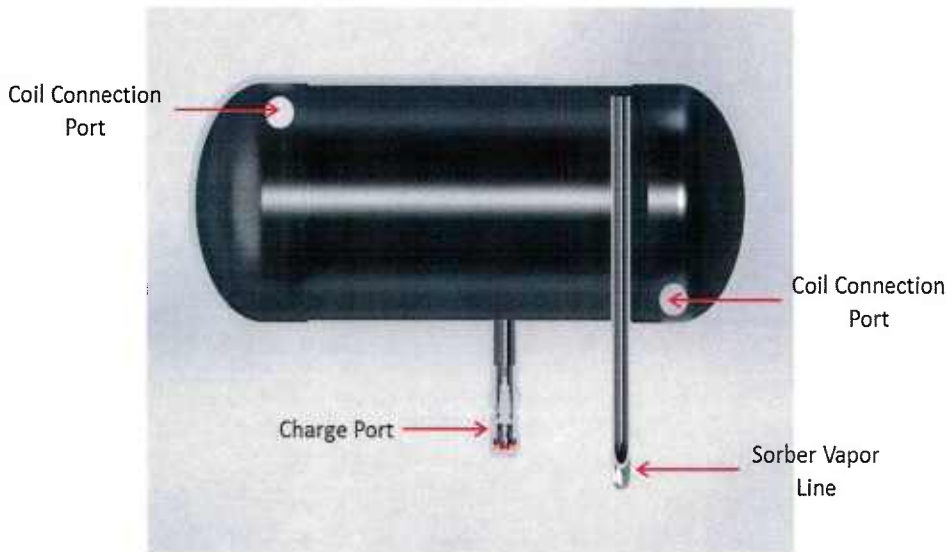


Figure 5. Cross-sectional view of liquid-vapor separator

Air Coil

The air coil utilized in the fluid infusion warmer has been designed and fabricated specifically for the current prototype. Originally, the coil was intended to be harnessed from a CPU cooler; however, the evaporator/condenser coil sized is no longer available. The new coil utilized in the latest available CPU cooler was pressure tested and found not to be feasible for the operating conditions of the fluid infusion warmer. Resultantly, a custom coil had to be designed, which is capable of withstanding 450 psi operating pressures. The evaporator/condenser is a brazed aluminum assembly with parallel micro

channels and aluminum fins. Overall dimensions are 5.4" x 7.2" x 1.9". The evaporating and condensing rate of ammonia in the fluid infusion warmer maximizes at about 500 W. A coil with large capacity is used to permit close temperature approach to ambient air. The coil has been analyzed and tested for proper functionality over a barrage of operating conditions.

Electrical components

The fluid infusion warmer has AC and DC electrical components. Recharge is performed when the unit is connected to 120 VAC power, since the electrical heaters in the sorber operate only on 120 volts. The DC circuit is 24 volts nominal. A polymer Li-Ion battery pack provides DC power when the unit is not connected to external power. The battery pack has 7 Li-Ion cells and nominal working voltage of 25.9 volts. Capacity of the battery is 5.2 Ah, twice that of previous fluid infusion warmer implementations. The battery is used to drive control circuits, power two 24 VDC fans and operate the solenoid valve that controls flow of ammonia vapor. Battery charging is done with a charge controller acquired independent of the battery. Control components and power supply reside on a custom printed circuit board.

Control Board

Vast improvements have been implemented to the multilayer printable circuit board (PCB) utilized to drive the fluid infusion warmer, both in terms of system functionality as well as device reliability and safety. The additional proficiencies improve the ease of operation and enhance the capabilities of the appliance. A complete redesign of the board was implemented to accommodate better documentation and subsequent system reliability. Rocky Research has recently updated the micro-controller design and the associated drawings and bill of materials have been completed. The new PC Board design uses a total of six layers i.e. Top, +5V, Ground, +24Vdc, +3.3V and Bottom. Numerous incremental enhancements of the components listed on the bill of materials, such as the connectors, are standardized. Standardizing components makes board replacement a quick and effortless process. The enhancements are presented as internal and external modifications to the board.

Internal: The previously external timer that controls the charger has been incorporated and placed into the new PCB design. The new design is capable of turning off the control; therefore, the control will not discharge the battery. A more accurate thermocouple reader I.C. has been incorporated into the control, and the number of thermocouple inputs have been doubled. Additionally, a door switch input has been added; a significant enhancement from the previous board. The new design includes in-circuit serial programming (ICSP) capability to allow for quicker and easier updating of the control code. The +5V and +24Vdc supplies are now protected by additional fuses to the solenoid, fan drive, and blower output drive circuitry. The control is capable of automatically selecting between the battery and external +24Vdc. The control can now read the battery voltage directly and determine if a low battery condition exists. Furthermore, a reference was added on the A-D for enhanced accuracy in thermistor readings.
External: A less costly power supply, capable of handling a better temperature range, has been selected. Several PC Boards have been thoroughly analyzed. A cable adaptor has been designed and fabricated to retrofit the existing/older infusion warmer design, allowing for testing of the new board. Higher accuracy thermistors, 1%, with more standard components have also been acquired. Rocky Research has implemented diagnostic software for testing and troubleshooting the fluid infusion warmer control board.

A list of the diagnostic tests evaluated is presented, offering PCB quality assurance before installing in a prototype:

Thermistor Inputs	- Reads Thermistor inputs
Thermocouple Inputs	- Reads Thermocouple Inputs
I/O Expander Inputs	- Reads Digital I/O on Expander
FET Toggle Outputs	- Writes to the FET Outputs
Triac Toggle Output	- Writes to the Triac Output
Display Exerciser	- Writes all Printable Ascii Characters
Aux LED Toggle Output	- Writes to the LED a 1 or 0
Charge rDC Toggle Output	- Connects or Disconnects the Charger
Buzzer Toggle Output	- Turns on or off the Alarm
Battery ON/OFF Toggle	- Connects or Disconnects the Battery
4-LED Cycle Output	- Scans the LED's

As the previous display was obsolete a new display replacement was selected and purchased. It has been incorporated into the current fluid infusion warmer design and tested successfully. The display is readily in stock and available from the vendor. Originally, the backlight of the display was very dim. Consequently, the design of the driving circuit has been modified to accommodate a brighter display. The driving circuit for the heaters is only subjected to a small portion of the total wattage. Even so, the triac was moved to the edge of the PCB, allowing for a heat sink to be utilized off the board. The modification renders the previous design obsolete. An additional diagnostic was developed to display the battery voltage. The top and bottom layers of the board consist of traces. AC is on the ground and 24V layers. The ground layer is intentionally located on an inner plane so that it acts as a shield between power and control circuits. Spacing between the layers varies. Between the top and +5V layer is 0.005''. Between the +5V layer and the ground layer is 0.014''. Between the ground layer and the +24Vdc layer is 0.0135''. Between the +24Vdc layer and the +3.3Vdc layer is a 0.014'' space. Finally, between the +3.3Vdc and bottom layer is a 0.005'' space. The layer spacing modifications eliminate the threat of interspatial plane shorting, a concern with the previous multi-layer board implementations. The adjustment improves the layout considerably and ensures a higher quality board, with more current carrying capability where necessary. The following control functionality has been added: flowmeter input, membrane inputs for the push buttons and LED output driver (6-inputs for pushbuttons and 5-inputs for leds). The flowmeter input is not currently utilized in lieu of the fact that a feasible flowmeter capable of metering the entire flow regime for infusions is nonexistent. The total number of components has been reduced, eliminating useless functions. The current board is shown below in figure 6 without the membrane pigtail connections that interface to the controlled components.

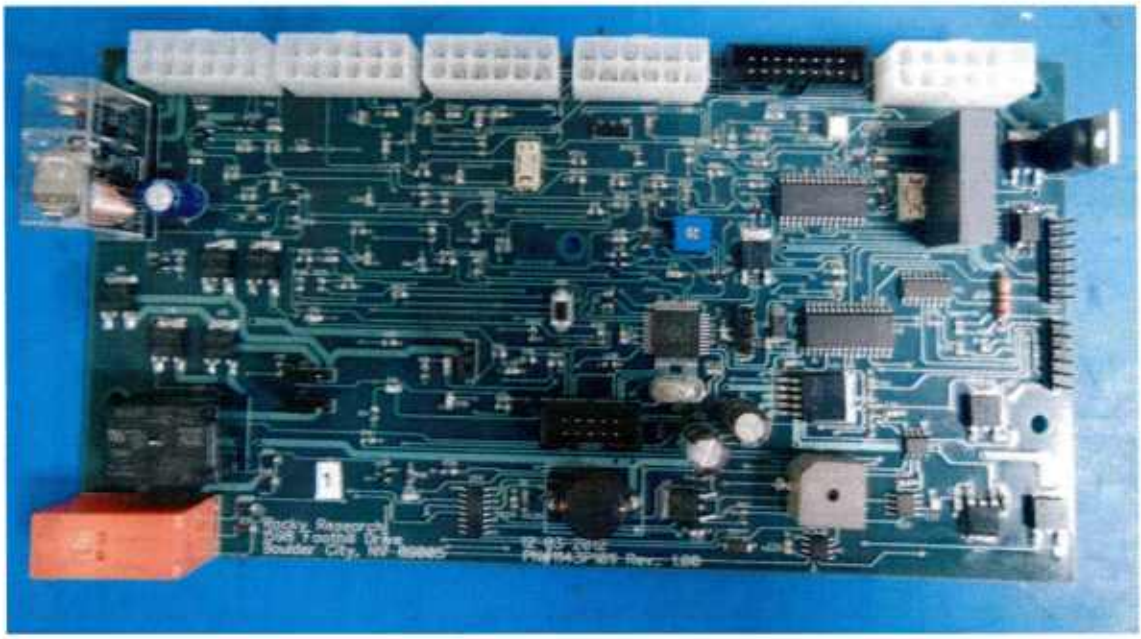


Figure 6. Fluid infusion warmer updated circuit board

Presented are the additional safeties included in the latest software implementation:

1) SPC must be removed before a system recharge is allowed.
2) All three fluid temperatures must be detected before an infusion can be implemented.
3) A recharge is prohibited when operating on +24Vdc power.
4) High temperature audible alarms have been implemented if the infused fluid overheats.

Single Patient Cartridge (SPC)

Extensive testing implemented by medical personnel raised apprehensions pertaining to stagnant areas within the original multi-channel SPC design that resulted in residual blood not being flushed from the system. Stagnant zones can produce hemolyzation of blood as a result of overheating and can also restrict fluid flow. As a solution, a single pass helical flow channel of rectangular dimensions was designed, constructed, and evaluated to mitigate such concerns. Rectangular channels of small dimensions with short fluid traversing lengths provide a good ratio between heat transfer and pressure drop, which was the motivation behind the initial multi-channel design. The new SPC was designed with similar performance characteristics in terms of heat transfer. The enhanced helical channel design has a cross-sectional area of 0.25'' wide by 0.1'' deep. Figure 7 is a drawing depicting the geometry of the newly improved SPC.

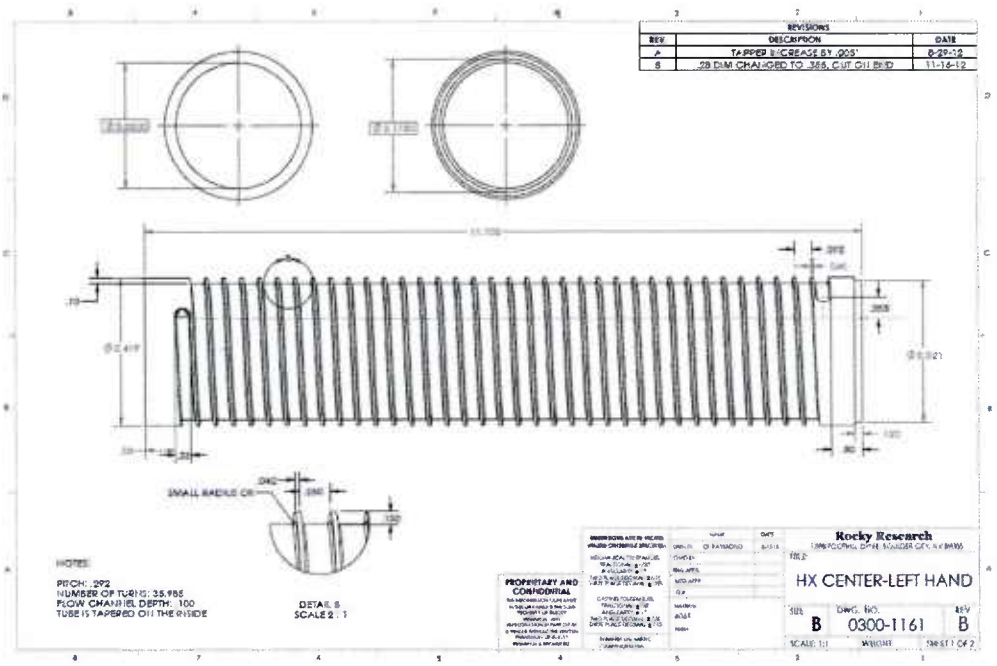


Figure 7. Helical flow channel SPC of cross-sectional area 0.25'' by 0.1''

SolidWorks Flow Simulation computational fluid dynamics (CFD) software was utilized to evaluate the performance of the cartridge design before fabrication; both in terms of flow behavior as well as heat transfer characteristics. Analysis was implemented utilizing the properties of blood with four specified boundary conditions. The fluid inlet velocity was specified at 250 mL/min; 50 mL/min over the targeted maximum volumetric flow rate utilizing the TES. The flow channel outlet static pressure was set to atmospheric pressure at sea level, 101,325 Pa (14.7 psia). The heat generation rate was specified at 550 W on the inside wall of the cartridge in order to simulate heat transfer from the sorber. Lastly, an adiabatic wall (no heat transfer in or out) was specified on the outside shell of the cartridge. Figure 8 presents the pressure distribution for the flow simulation model along with the boundary conditions. The top picture depicts only the fluid profile, while the bottom image portrays the pressure profile along with a translucent representation of the cartridge.

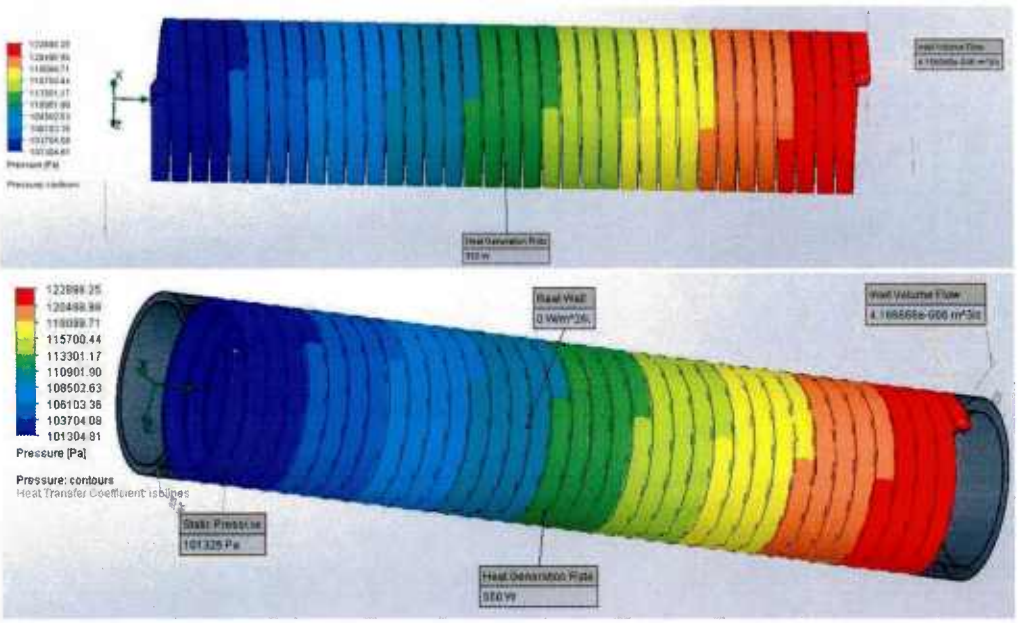


Figure 8. Helical SPC pressure profile

As can be observed from the CFD simulation results, for the specified boundary conditions, there is an approximated pressure drop of 21,593 Pa (3 psia) through the flow channel of the cartridge. Such a pressure drop was deemed appropriate for proceeding forward with prototype fabrication. It is important to recognize that the pressure drop simulated does not include or incorporate the manifolds from which the fluid enters and exits the cartridge or any medical tubing resulting in additional pressure drop. The temperature profile was also analyzed for the blood with the same boundary conditions. The results are presented in Figure 9. Similar to the pressure contour plots, the top image depicts only the fluid profile while the bottom picture also portrays the translucent cartridge as a reference frame.

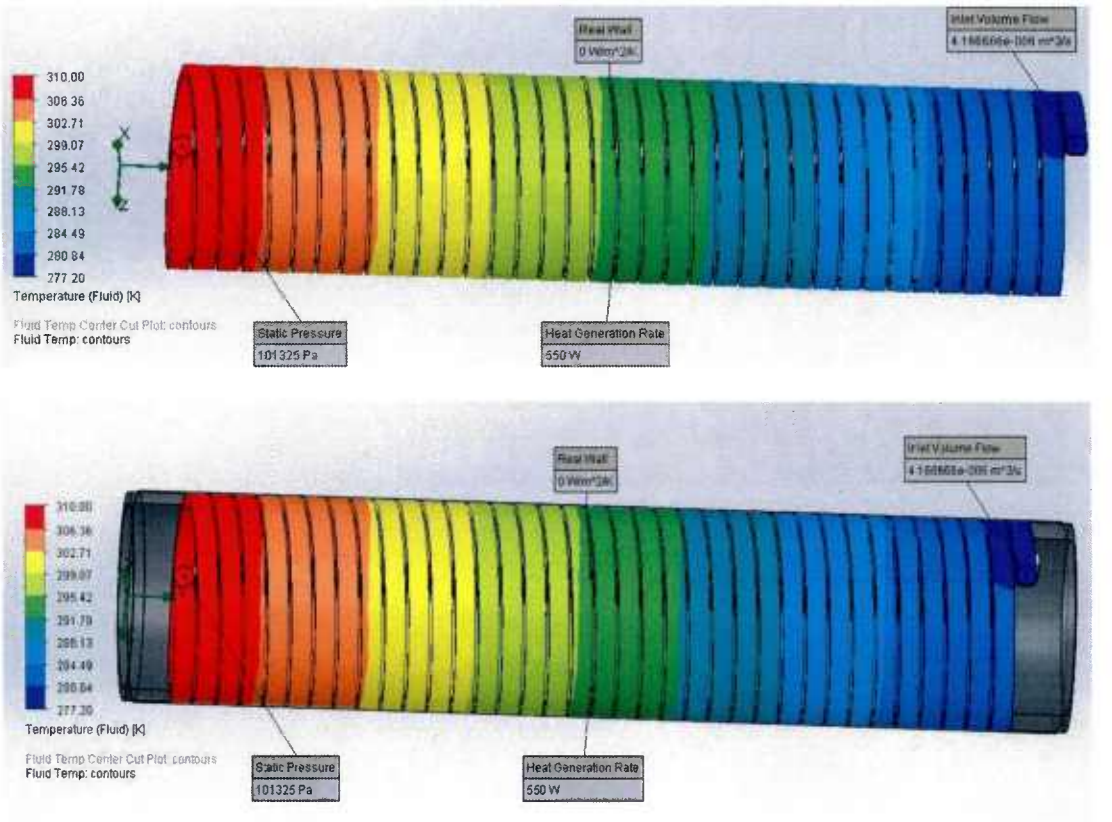


Figure 9. Helical SPC temperature profile

With a heat generation rate of 550 W, a simulated increase in blood temperature of 33 °C was achieved before completely propagating to the outlet of the SPC. Therefore, the CFD analysis implies 550 W is sufficient for meeting the goal of heating fluid from 4 °C to 37 °C at the specified flow rate with the new SPC channel design. Three electrical heaters, 250 W each for a total of 750 W, are utilized when operating the unit off electrical power. Dependent on complex compound loading densities, the thermal battery capacity varies. Sorber complex compound content was sized for the ability to heat blood 33 °C at a flow rate of 200 mL/min for five minutes, for a total capacity of 1 L.

With promising results from the CFD analysis, prototype cartridges were fabricated and evaluated. In order to assess the performance of the new SPC channel design, flow behavior was first visually observed at varying flow rates in an effort to ensure that air was no longer being trapped within the system and that the fluid was propagating through the cartridge as desired. Figure 10 on the left portrays air trapped near the exit of the old multi-channel design resulting in stagnant flow; on the right the new channel implementation is depicted. Both tests were fulfilled at similar infusion pressures, approximately 100 mmHg.

Figure 10. Old SPC vs. new SPC flow visualization

As can be observed, there are no stagnant zones present or air trapped within the cartridge for the helical SPC design tests. Although the new cartridge eliminates stagnant zones entirely, and is more efficient at purging air from the system, a separate gas vent is still critical to overall system application. During an infusion process, heating of the fluid often results in outgassing within the system and subsequently gas generation. Although the new cartridge design does not allow for gas to accumulate within the cartridge, it still must be purged from the line before the fluid is injected into the patient. For that reason, a Smiths Medical F-30 gas vent/filter assembly replacement unit identical to those utilized in Level 1® fluid infusion units was identified to be incorporated into the medical tubing configurations.

Volumetric flow vs. infusion pressure correlations have been established for the helical flow channel heat exchanger of different orientations, the most relevant being the horizontal alignment in which the cartridge is positioned within the infusion warmer. The infusion pumps utilized to drive fluid flow have an occlusion limit of 300 mmHg. Two test runs were performed for each infusion pressure, ranging from 50 mmHg to 300 mmHg in 50 mmHg increments, resulting in a total of ten data measurements for each pressure rating. The pressure correlations vs. volumetric flow are specific to the cartridge and do not include the associated medical tubing, gas vent, or catheter. The correlations do incorporate the inlet and outlet saddles which were not modeled in the CFD analysis. The infusion pressure vs. volumetric flow rate has been plotted out and polynomial curve fit. A sixth order polynomial curve fit is presented with the respective R^2 value and associated trend line. The curve fit can be utilized to approximate pressure drops through the cartridge at various flow rates over the entire pressure range of the medical infusion cuff.

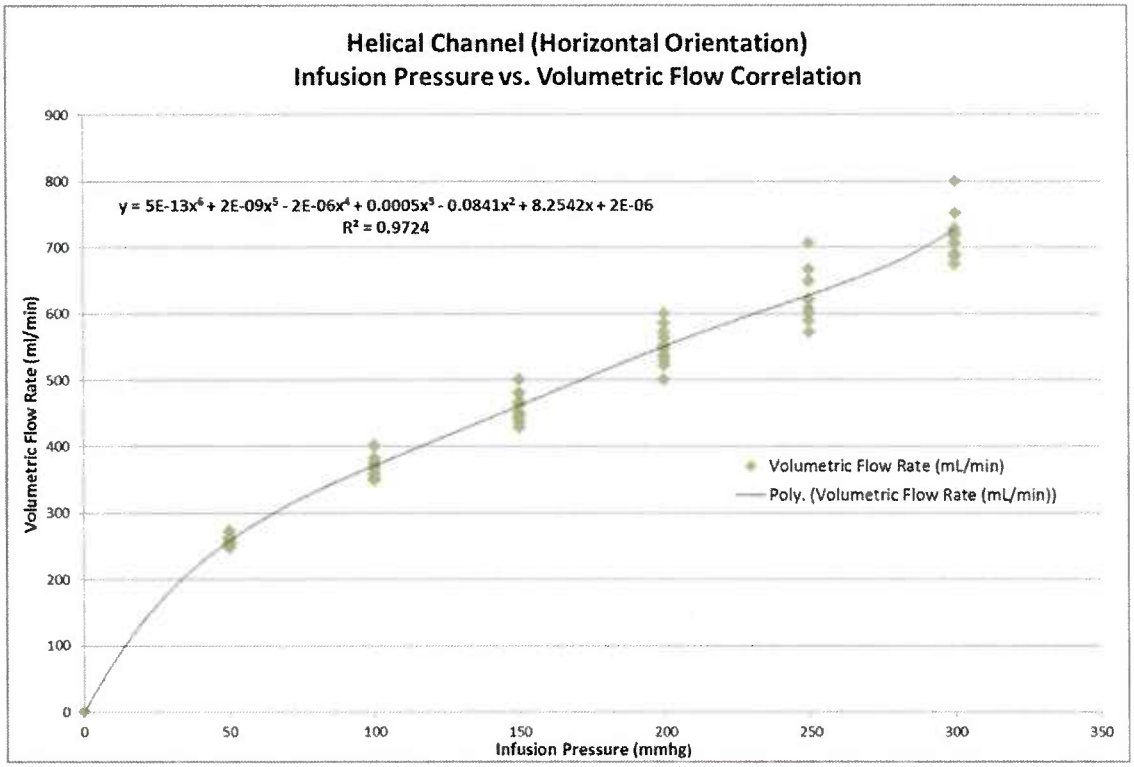


Figure 11. Helical SPC infusion pressure vs. volumetric flow correlation

The presented data confirms that through the SPC alone, the infusion pump is capable of maintaining a maximum volumetric flow rate of water at approximately 700 mL/min, 3.5 times the target maximum flow rate traversing the infusion warmer. Flow rates were also further evaluated with various medical tubing configurations selected by University of Nevada School of Medicine (UNSOM) to ensure that the target volumetric flow rate of 200 mL/min was achievable in the final product implementation, incorporating the total pressure drop from the cartridge, tubing, air vent, catheter, and associated fittings. The first medical tubing configuration analyzed consisted of large grade animal medical tubing with a large 14 gauge catheter intended for fast infusion rates. The setup consisted of 37'' of Level 1 large bore tubing (3/16'' ID) connected to the cartridge, connected to 8'' of large animal tubing (1/4'' ID), connected to the gas vent, connection to 80'' of large animal tubing (1/4'' ID), then connected to the 14 gauge catheter (0.064'' ID). With such a configuration the infusion pump was able to maintain a volumetric flow rate of 390 mL/min of water. With a high flow rate achievable with the large animal tubing, a more practical configuration consisting of a Hospira Y-type filtered blood set was also examined. That setup was configured with 100'' of the Hospira Y-type filtered blood set (0.12'' ID), connected to the cartridge and air vent, connected to a 32'' Hospira extension set (0.1'' ID), and then connected to a 14 gauge catheter (0.064'' ID). With such a configuration a volumetric flow rate of 275 mL/min of water was achieved. The same Hospira tubing configuration with an 18 gauge catheter (0.04'' ID) supported a flow rate of 190 mL/min. The tests demonstrate that the target flow rate of 200 mL/min is easily attainable with the new SPC design. These results are a vast improvement over the previous SPC design, which was not capable of accommodating flow rates of 200 mL/min with any of the medical tubing configurations.

The SPC is the only component in the fluid infusion warmer system that contacts infusion fluid. It is intended that the cartridge may be utilized for an extended period of time and for multiple infusions, but will only be used with one patient. The cartridge has an internal taper that matches a taper on the absorber, and is installed by simply sliding it over the sorber to achieve a good contact fit. The tapered interface between the sorber and cartridge was chosen because this contacting method resulted in easy removal and installation of the cartridge, and results in the lowest thermal contact resistance between the sorber and cartridge of all the designs investigated. The figure below depicts the cartridge and how the cartridge slides onto the tapered sorber.

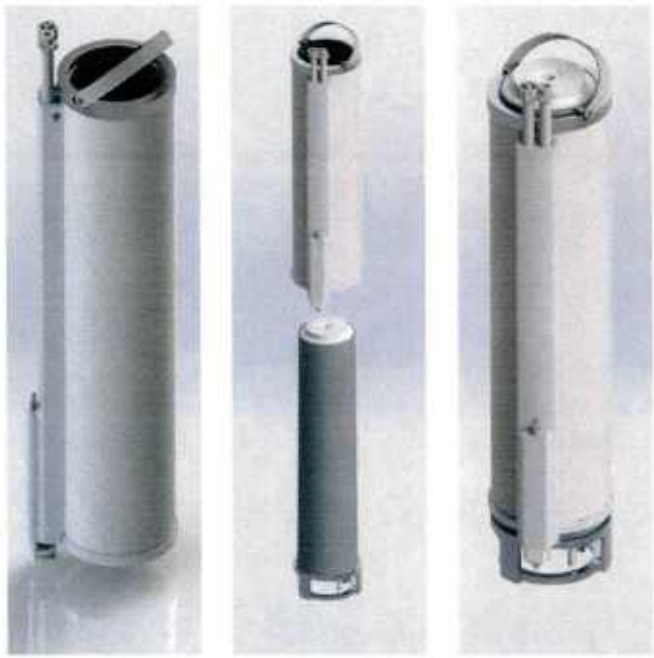


Figure 12. Helical SPC infusion pressure vs. volumetric flow correlation

The cartridge assembly has internal temperature sensors. Electrical contact to the device for the temperature sensors is made as the cartridge is inserted over the sorber. A plastic cover on one side covers fluid tubes and wires connected to temperature sensors. A connector at the bottom of the plastic cover inserts into a matching connector in the device to connect temperature signal wires to the control board. A thin aluminum cover, handle, and saddles for fluid tube connections are adhesive bonded to the machined core to complete the cartridge assembly. Biocompatible epoxy compliant to ISO 10993 standards for use in medical devices were used for assemblage. Once completely assembled, with saddles, medical tubing, and fittings each cartridge were independently pressure checked to 40 psi for leaks. Figure 13 presents a photograph of a completely assembled cartridge.

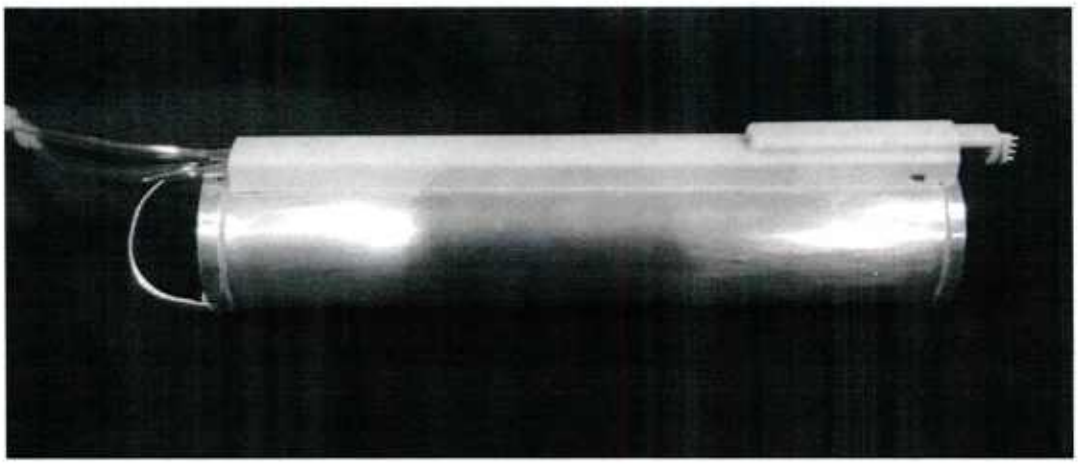


Figure 13. Assembled SPC with current enhancements

Complete Assembly

The ammonia containing subassembly is the fundamental engine of the fluid infusion warmer, consisting of the sorber, evaporator/condenser coil, solenoid valve, and reservoir. Figure 14 is a representation of the ammonia-containing subassembly.

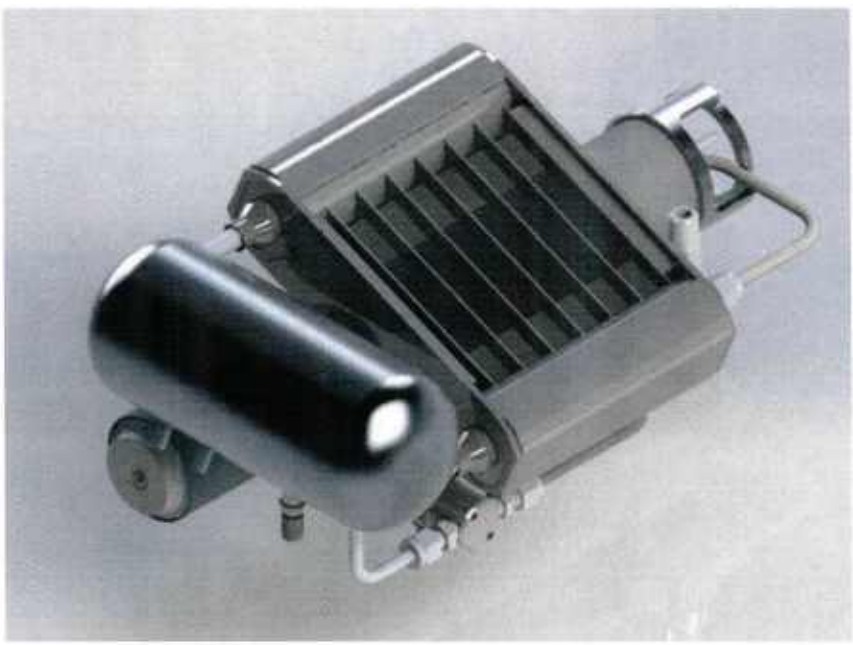


Figure 14. Ammonia containing subassembly

The ammonia-containing subassembly is assimilated into the functioning device along with the other component modifications presented. Figure 15 portrays a picture of the ammonia containing subassembly along with a 3D rendering of the appliance without the cover. System components are individually labeled. The Sorber is contained within a heat shield as a result of the high temperatures required to achieve absorption.

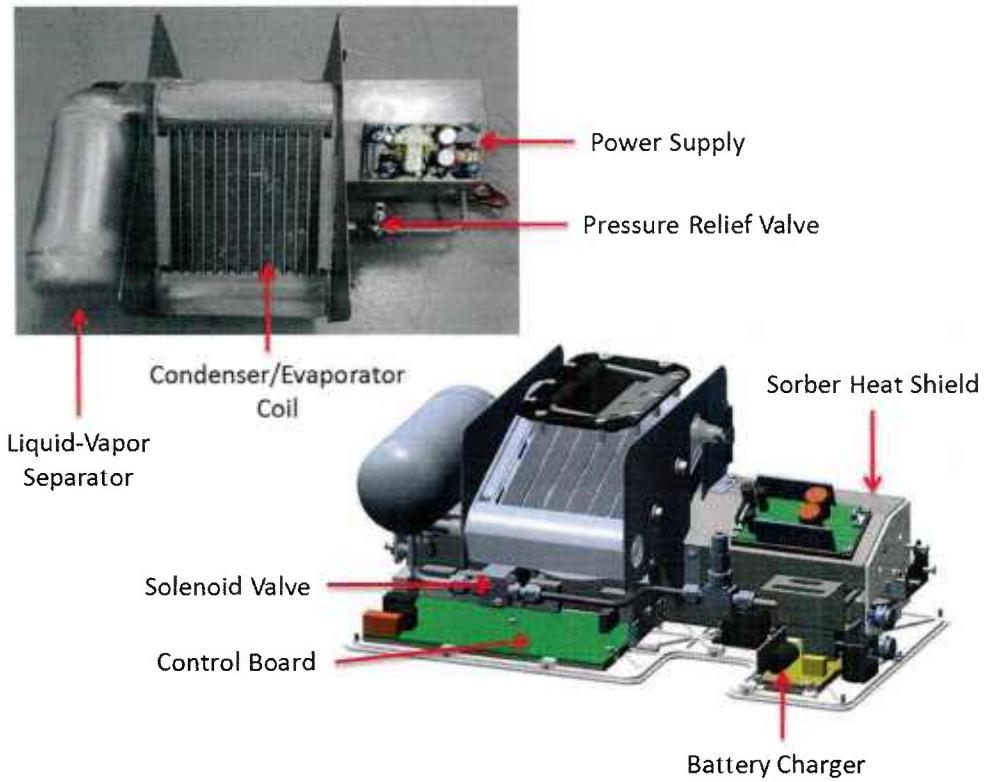


Figure 15. Fluid infusion warmer internal system components

SolidWorks 3D models have been developed and systems fabricated, for the fluid infusion warmer with the modified sorber, SPC, keypad and all other supporting components and hardware. Several changes have been made to the auxiliary enclosure of the heating subassembly in order to accommodate the latest design changes. These changes to the casing and the sheet metal have been implemented and both mechanically and cosmetically evaluated. Furthermore, a new membrane keypad has been functionally integrated into the design. Presented in figure 16 is a model of the latest infusion warmer enclosure, while figure 17 is a comprehensively functional prototype with the new membrane keypad incorporated into the appliance design. The button depiction of the device is intended to be self-explanatory, making the appliance easy for the end user to operate. The top and bottom of the case are both 3D printed from glass filled nylon. The interior faces of the case are then electromagnetic interference (EMI) shielded with a metallic coating system that utilizes a non-oxidizing copper as the conductive agent.

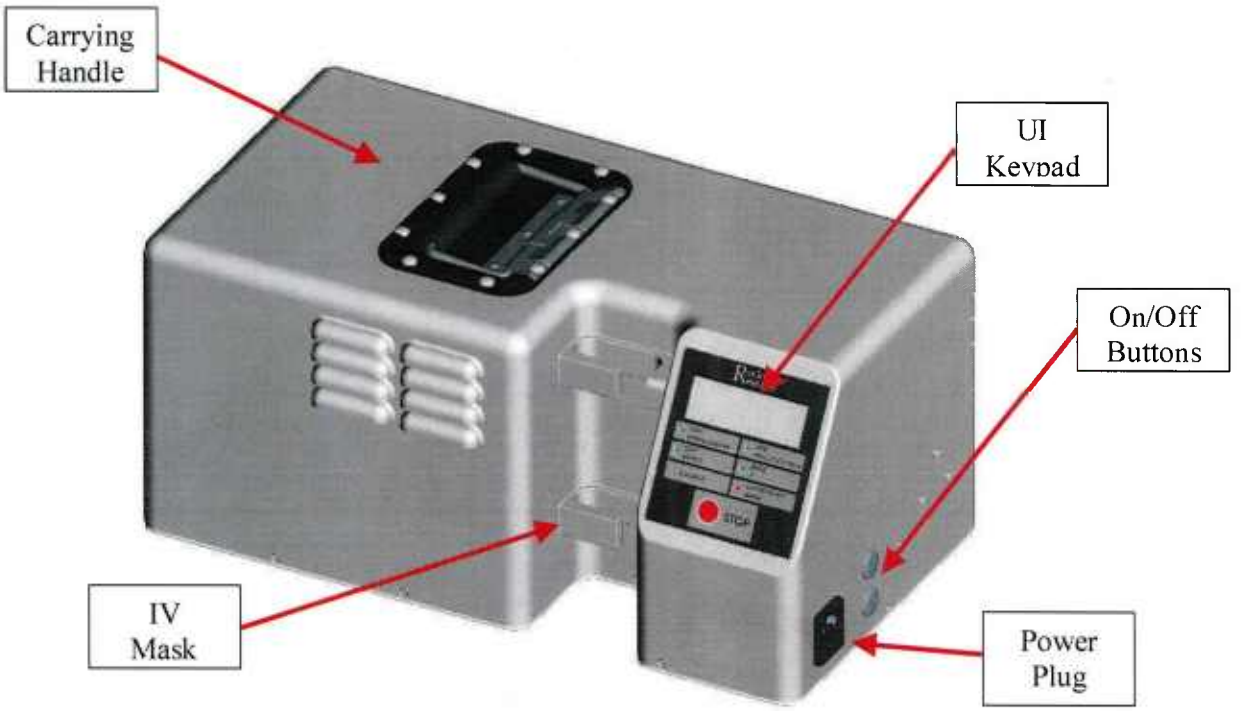


Figure 16. Fluid infusion warmer case with membrane keypad

Figure 17. Fluid infusion warmer fabricated prototype with cartridge

Rocky Research Performance Testing

Once assembled, the new sorber design was tested with the helical channel SPC for performance characteristics. First, the infusion process was tested utilizing the electrical heaters. A water bath was configured to constantly circulate water through the cartridge at controlled flow rates. The heaters were then set to the heat transfer rate required to elevate the fluid temperature 33 °C. Steady state conditioners were achieved while monitoring sorber and fluid temperatures. After maintaining steady state conditions for several minutes fluid flow was stopped while simultaneously turning off the electrical heaters. The fluid was allowed to sit stagnant in the cartridge for 90 seconds, subjected to the stored energy in the sorber core. Fluid flow was then re-initiated and the spike in fluid outlet temperature from the cartridge was monitored. Higher flow rates require a higher heat input from the heaters and consequently larger temperature gradients across the sorber, as well as more energy stored in the sorber core. Resultantly, flow stoppage results in higher elevated temperatures for faster flow rates upon the re-initiation of fluid flow. For that reason the highest flow rate test results are presented in figure 18. Flow was specified at 200 mL/min with a heat input from the heaters of 457 W, and a water entrance temperature to the cartridge at approximately 4 °C. Figure 19 presents the corresponding heater wattage along with the mass flow and heat transfer rate into the fluid. The results are indicative of testing implemented on an isolated and insulated sorber and cartridge.

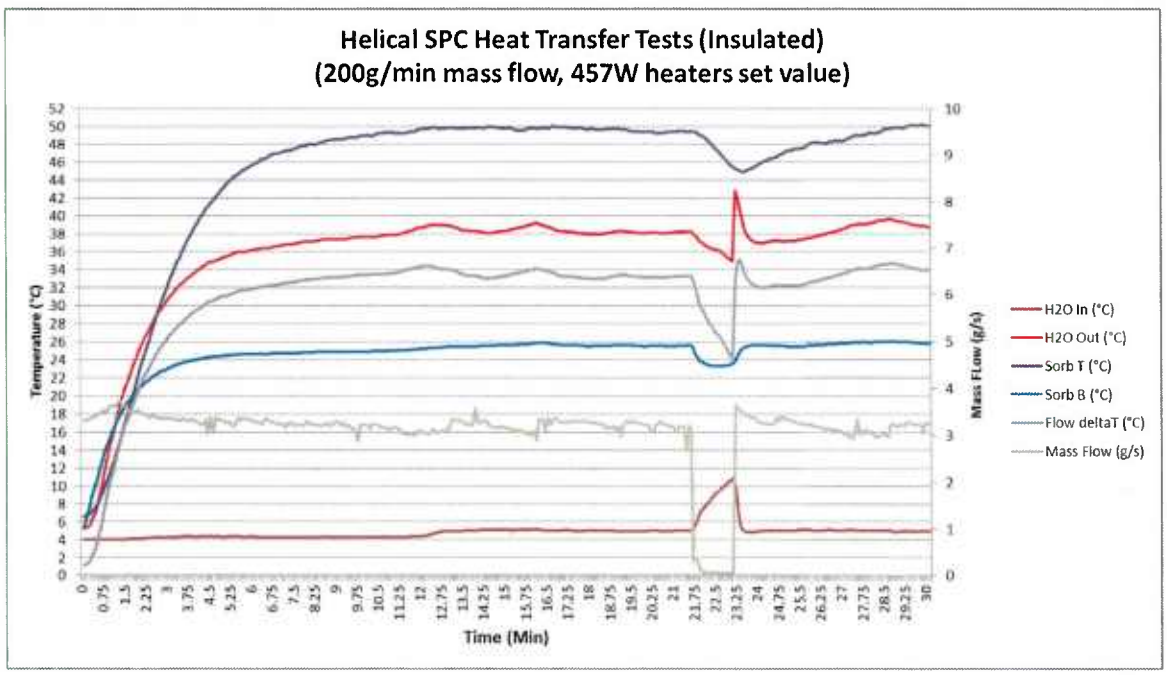


Figure 18. Electrical heater infusion temperature profiles

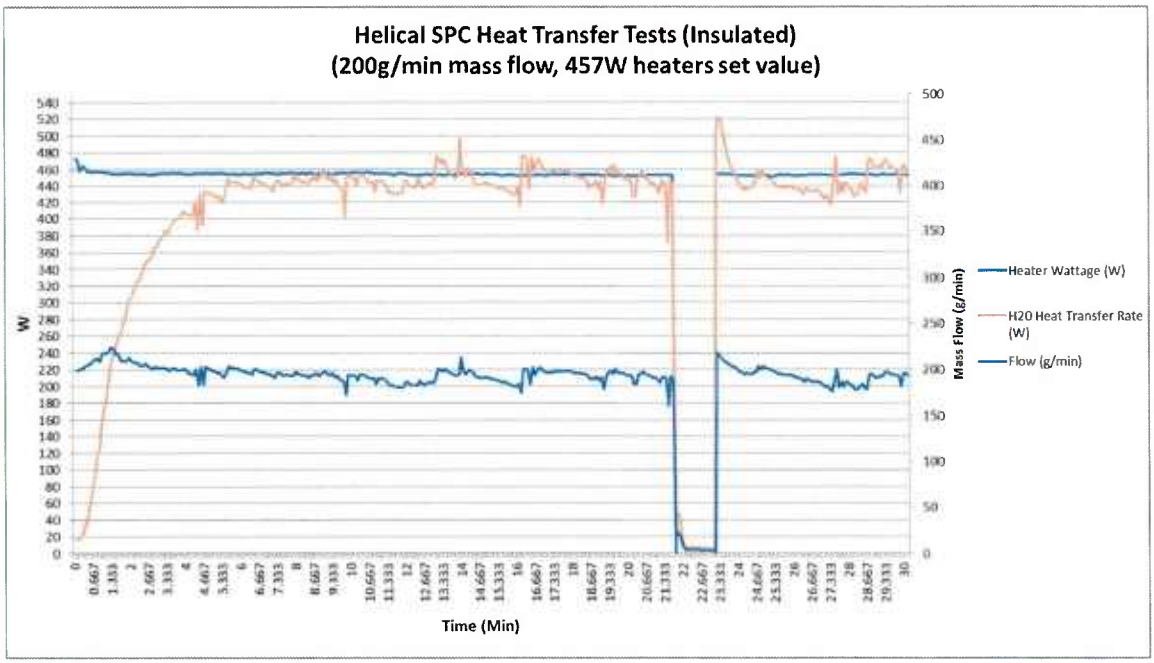


Figure 19. Electrical heater infusion heat transfer profile

Figure 18 demonstrates that once steady state conditions were achieved, 457 W was adequate in maintaining a 33 °C increase in fluid temperature. Figure 19 shows that once the sorber and cartridge have been heated, nearly all of the energy is being transferred into the fluid. At the 21 minute and 45 second mark fluid flow was stopped. At the 23 minute and 15 second mark flow was re-initiated and the spike in fluid outlet temperature reached 43 °C, 2 °C less than the temperature in which the hemolysis of blood occurs at 45 °C. The results demonstrate good heat transfer between the new sorber design and helical flow channel SPC. The results also establish the effectiveness of the new three heater design in reducing stored energy and large thermal gradients in the sorber. Reducing the stored energy in the sorber accommodates the stopping of fluid flow without detrimental deterioration of red blood cells during an infusion.

With efficient heat transfer demonstrated utilizing the electrical heaters, the thermal battery and absorption efficiency was examined. Instead of utilizing electrical heaters, a ligand column was configured to drive and control ammonia flow rates based on the required absorption energy to heat the fluid. Similar to the electrical heater tests, a bath was utilized to regulate water flow through the cartridge at constant flow rates. Figure 20 presents the test set up configuration for analyzing the thermal battery performance.

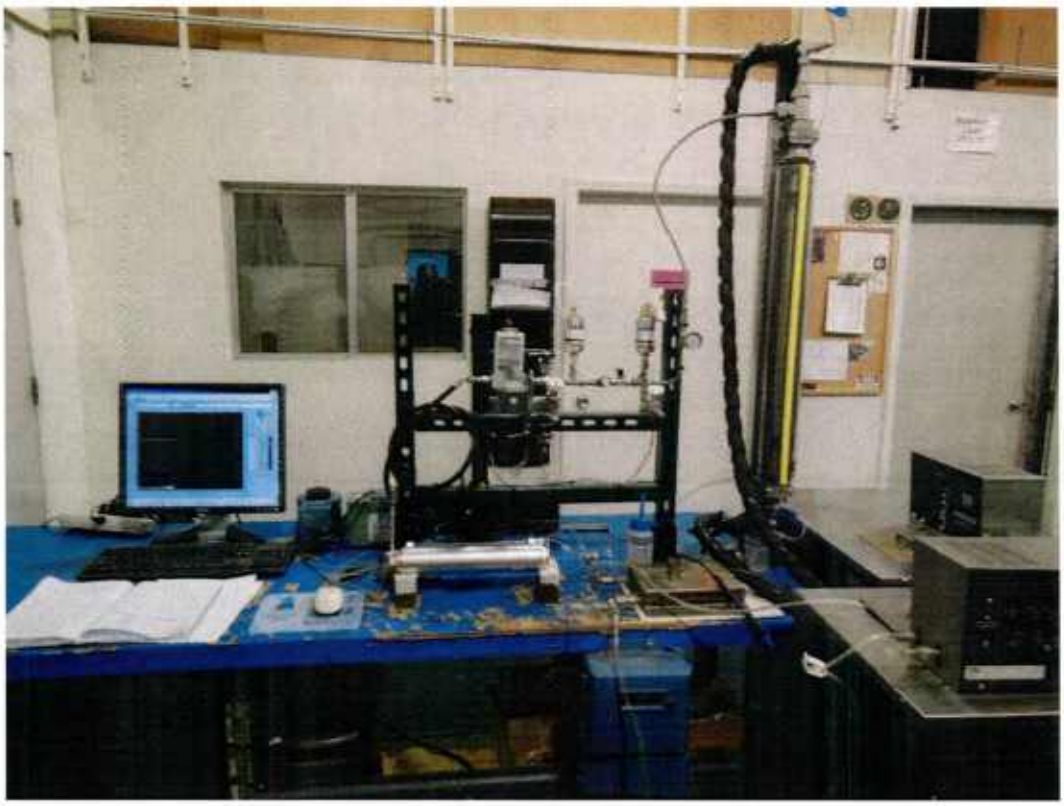


Figure 20. Sorber performance test stand configuration

The most relevant absorption test for the thermal battery was again with a fluid volumetric flow rate of 200 mL/min, due to the higher level of absorption energy required to heat the fluid. A constant ammonia mass flow rate of 600 g/hr was utilized for testing with a water flow rate of 200 mL/min; determined by the available complex compound absorption energy required to heat the fluid 33 °C by generating 460 W of heating. Again, the goal was to be able to heat fluid flowing at 200 mL/min for five minutes for a total heatable volume capacity of 1 L of fluid utilizing the thermal battery. Complex compound loading density was designed for such capacity by also taking into consideration the energy required to preheat the sorber and cartridge from normal ambient conditions. Furthermore, since the specific heat of blood is lower than that of water, less energy is required in elevating the temperature of blood 33 °C. Depending on temperature, the specific heat capacity of water is approximately 1.165 times that of blood. Therefore, if complex compound loading density provides enough absorption energy to heat water 33 °C at a flow rate 200 mL/min for the targeted 5 minutes it has the capacity to heat blood at the same flow rate for about 5 minutes and 30 seconds when considering the difference in density between the two fluids. Presented in figure 21 is the change in fluid temperature from absorption under the specified conditions.

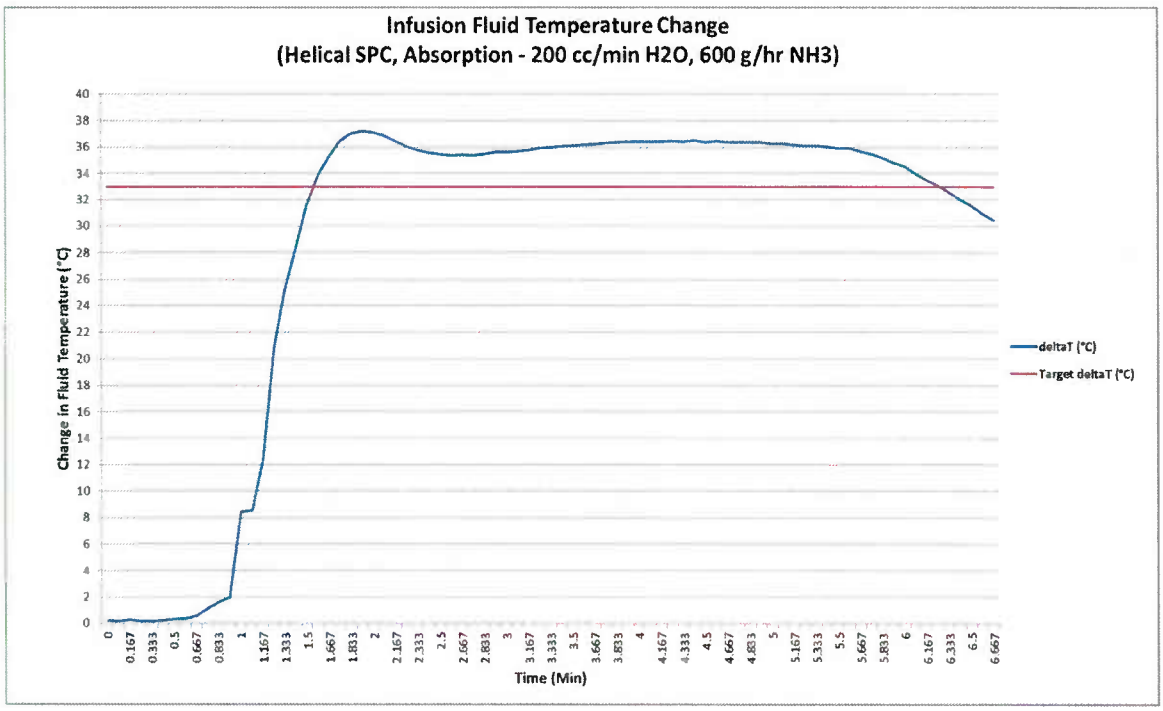


Figure 21. Thermal battery absorption test

In figure 21 the red line portrays the target increase in fluid temperature of 33 °C, while the blue line depicts the actual change in fluid temperature during the absorption. As can be observed, the sorber was capable of heating the water over 33 °C for almost exactly 5 minutes. It is significant to note that there was enough energy available to preheat the sorber and SPC and still heat the total targeted volume of water at the target flow rate. Since the temperature was slightly overshot by manually controlling the ammonia flow rate, the heating length at a temperature increase of exactly 33 °C would be slightly longer than what is presented. Therefore, the designed complex compound loading density and total capacity was sufficient in meeting the heating goals of the sorber during absorption.

Results presented are integral to an isolated sorber and cartridge well insulated to mitigate heat losses. Once incorporated into the actual system design the performance characteristics were slightly different than depicted due to heat losses to the ambient and mounting components of the sorber. Resultantly, the mounting components were modified from stainless steel to PEEK. The inner heat shield was also 3D printed from glass filled nylon, the same material as the case, and then coated with Zyvax for cleaning purposes in case of a spill. The modifications were effective in both reducing thermal gradients stored in the appliance as well as increasing the total system infusion capacity by reducing the sensible heat of peripheral components.

User Interface

Based on discussions with UMC, the user interface and keypad for the fluid infusion warmer has been modified. Primarily, the modifications were implemented to add specific functionality in operating the fluid infusion warmer as requested by medical professionals. Furthermore, the membrane keypad was adapted to be a smooth flush surface for cleaning and sanitary reasons. Presented in figure 22 is a

representation of the new membrane keypad. The membrane keypad is intuitive to the user and easy to comprehend, allowing for easy operation of the appliance during high stress situations. In order to do so, only critical operational functionality is displayed on the keypad. Presented in the following figure is a rendering of the keypad. The functionality of all the buttons available on the keypad is also presented.

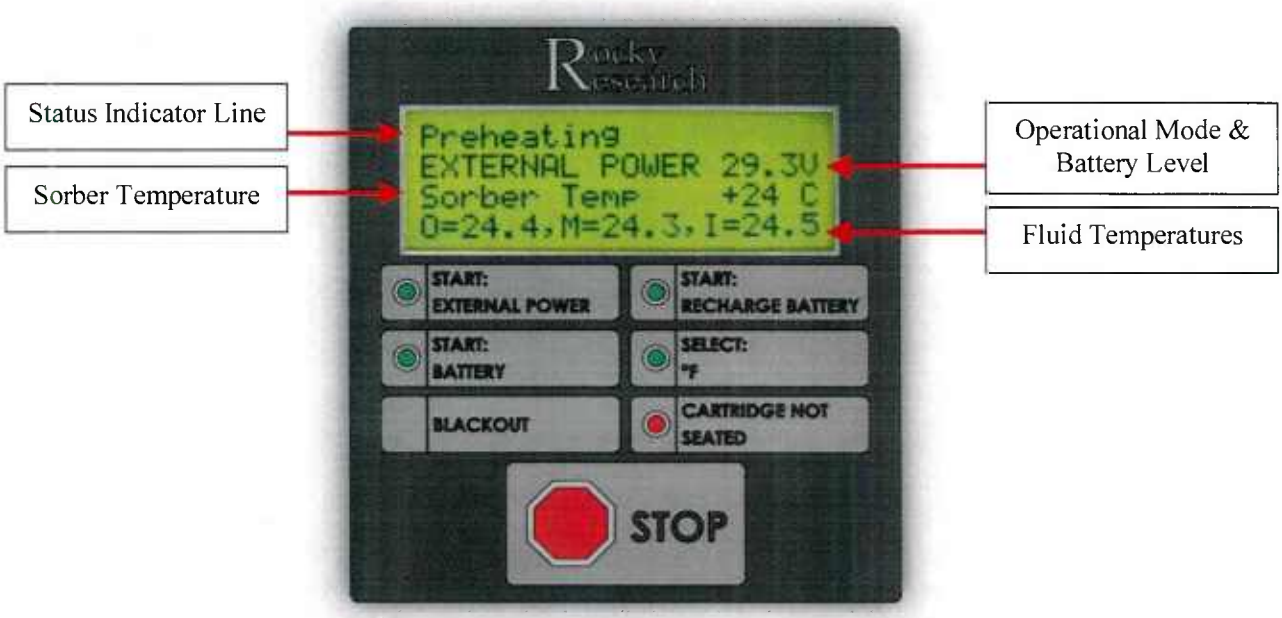


Figure 22. New fluid infusion warmer membrane keypad

Four lines are displayed on the LCD screen. From top to bottom, the first line is a system status indicator. The status indicator is utilized to inform the user the status of the appliance. For example, if the device is preheating the cartridge the status indicator line will portray "Preheating". The second line on the display of the LCD is representative of the operational mode. The operational modes consist of READY, EXTERNAL POWER, BATTERY, and RECHARGING. A detailed explanation in regards to the operational modes of the device is presented.

Operating Modes

1. READY – Ready implies that the appliance is either ready to be recharged or ready to start an infusion utilizing external ac power or the thermal battery. Ready is the idle mode of the appliance whether or not the system is charged. It is not an indicator of the thermal battery available capacity. Ready will be depicted on the LCD display when a cartridge is seated and the unit is capable of implementing an infusion. It will also be displayed if the appliance is in a state for which a thermal battery recharge can take place.

2. EXTERNAL POWER – External power is executed by selecting the "START: EXTERNAL POWER" button. This mode implies that the appliance is heating for an infusion utilizing external ac power. When the fluid being heated within the cartridge is coming to target temperature "Preheating" is displayed on the status line of the display. Once the device reaches the targeted preheat temperature, currently set to 34°C, the appliance will prompt the user to initiate flow by portraying "Start Flow" on the status line. Upon flow initiation, as instigated by

the user, the status line depicts, "Flow Detected", indicating the device is in active control operation based on the user regulated flow rate of the fluid being infused. The operating infusion capacity of the device while functioning off of ac power is limitless as long as a constant power source is provided.

3. BATTERY – Battery mode is implemented by selecting the "START: BATTERY" button. The mode is indicative of heating utilizing the thermal battery. It implies that the system is capable of performing an infusion remotely from external electrical power. Similar to the external power mode, upon selecting the "START: BATTERY" button, the status line informs the user that the cartridge is preheating before an infusion should be initiated. Once the preheat temperature is achieved the user is immediately prompted to "Start Flow" on the status line. "Flow Detected" is portrayed on the status indicator as soon as fluid flow is recognized. Depending on the infusion fluid flow rate, and the starting conditions for preheat, the operation time of the thermal battery can vary drastically. The thermal battery system capacity is targeted for 1000 mL of blood. For the target flow rates of 2 mL/min – 200 mL/min, the capacity accommodates an operation length of 5 min to 500 min respectively, based on a 33°C ΔT heating requirement.

4. RECHARGING – Selecting the "START: RECHARGE BATTERY" button initiates a thermal battery recharge, or desorption. The system status indicator line of the display will specify to the user that the system is "Recharging". Recharging commences once the absorber is above a certain temperature (160°C) and the rate change of sorber temperature surpasses a specific threshold or when the absorber reaches 190°C. Recharging the thermal battery is a finely controlled process, designed to ensure complete restoration of the TES capacity regardless of ambient operating conditions.

5. COOL DOWN – Once the TES has been completely recharged the device will enter a cool down mode and "COOLING DOWN" will be depicted on the display. During cool down, a small fan will force air down the length of the sorber and out the inner heat shield, rejecting heat from the sorber to the ambient via forced convection. When the sorber internal temperature has reached 35°C the appliance will go back to "READY" mode, implying the device is again capable of performing an infusion utilizing either external power or the TES. The cool down temperature was selected in order to eliminate the potential for the hemolysis of blood in the event that a user places a primed cartridge on the device directly after cooling down. In the event of inadvertently terminating a cool down, the appliance can be actively forced into cool down mode. The sequence for actively initiating cool down consists of pressing the blackout button, turning the unit off, powering the unit back on, and then releasing the blackout button. The device must be above the cool down set point of 35°C in order to force active cool down. In the event that the device is under the regulating temperature of 35°C there will be a momentary initiation of cool down and the appliance will transition to a standby state depicting "READY" as the operational mode.

Operation Mode Safeties

Several safeties have been integrated into the controls of the fluid infusion warmer to preserve the integrity of the device and ensure safe operation by the user. If the user attempts to initiate an infusion

without a cartridge seated the device informs the user that the cartridge is not seated via a red LED indicator for the "CARTRIDGE NOT SEATED" warning on the keypad. If the user attempts to instigate a TES recharge with a cartridge seated the device will instruct the user "Remove Cartridge" via the status line of the display. If the user attempts to initiate a TES recharge without an AC connection to the appliance the status line will portray, "Plug into Ext. Power". If the user attempts to initiate transfusion utilizing external power when the device does not have a connection they will be prompted with an error message stating "Plug into Ext. Power" from the status prompt.

Operational Indicators

Upon turning on the device a scroll through all the keypad lights is instigated and the audible alarm beeps twice to alert the user of proper functionality. During an infusion, if the fluid temperature ever reaches 42°C the audible alarm peeps to indicate potentially dangerous infusion temperatures. It is then up to the user of the appliance to gauge whether infusion will be terminated by stopping flow. If the user does not cease infusion there is a potential to overheat the fluid, which may have a detrimental impact on the patient.

Functions of Control System

A typical desorption will have a temperature profile of the sorber similar to that depicted in figure 23. The temperature profile is relatively steep until energy is utilized to move ammonia back to the reservoir. For the current system configuration the phenomena occurs at about the point when the sorber temperature reaches 155°C. At that point the energy, in the form of heat, is utilized to drive the ammonia back to the reservoir. Consequently, there is a decrease in the slope, or rate change, of the sorber temperature profile. Once desorption is complete, and all the ammonia vapor has be released from the sorber back to the reservoir, the slope will again increase.

The control logic utilizes the slope of the temperature gradient in order to determine when a thermal battery recharge is complete. The control logic limits the sorber from exceeding 190°C, and at 195°C, should the sorber ever reach such a temperature, an audible alarm is triggered to aware the user of a critical malfunction. A thermal battery recharge is therefore a seamless process for the user. Simply select the button and when complete the user is made aware the system is again ready to perform an infusion. The desorption algorithm ensures complete recharge of the system while maintaining safe operating temperatures of the sorber. The following figure is indicative of a typical desorption curve temperature profile resulting in a complete system recharge.

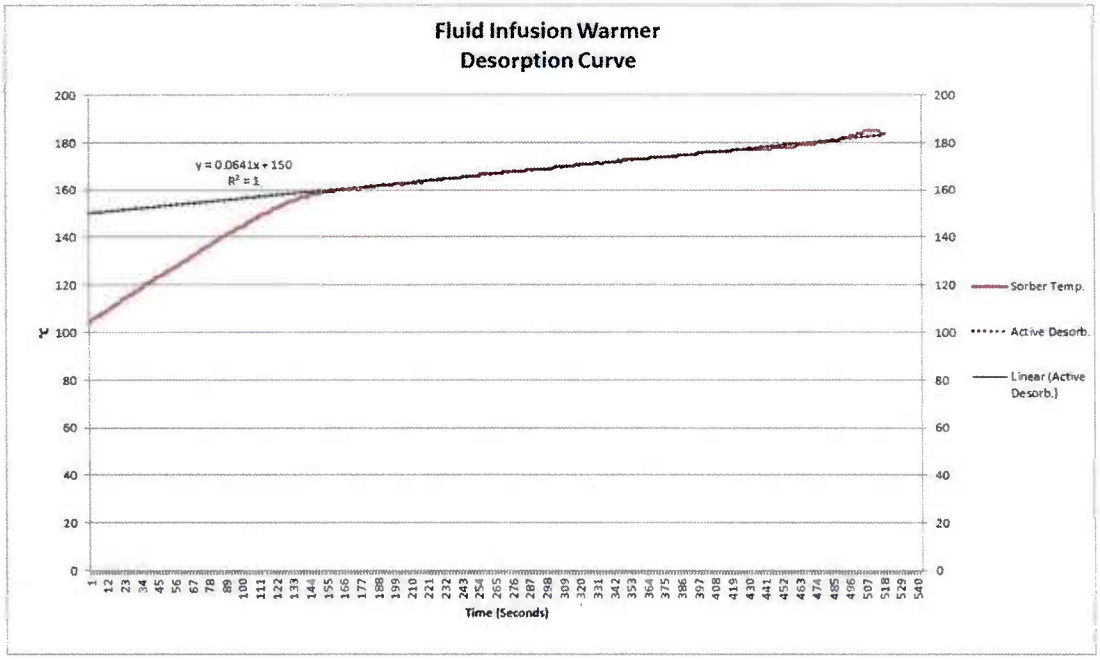


Figure 23. Fluid infusion warmer temperature profile

UNSOM

FDA working documents were created for future 510(k) submission. Feasibility studies were conducted to determine safety and efficacy of the portable fluid warmer prototype in using pRBCs. Bench performance studies were performed on the fluid warmer evaluating flow rate and temperature.

FDA 510(k) Documentation

The following working documents have been prepared for future FDA 510(k) submission of Rocky Research Portable Fluid Infusion Warmer.

1. Quality Systems

UNSOM implemented current Good Manufacturing Practice (cGMP) requirements associated with medical devices as defined by the Code of Federal Regulations (CFR) Title 21 Part 820 – Quality System (QS) Regulation for future submission of FDA 510(k) of portable fluid infusion warmer. The cGMP requirements set forth in the QS regulation are proclaimed under Section 520 of the Federal Food, Drug and Cosmetic (FD&C) Act. The medical device quality system regulation requires an "umbrella" quality system intended to encompass the design, production, and distribution of all medical devices. It specifies general requirements such as the use of trained employees, design reviews, design validation, calibrated equipment process controls, etc. and allow the individual companies to implement systems that demonstrate they are in control.

A consulting firm (Regulatory compliance Initiatives Inc [RCI]; Las Vegas, NV) was hired to assess the quality systems and good manufacturing practice compliance within UNSOM. A gap analysis was conducted at Rocky Research and UNSOM department of surgery research laboratory to determine what quality systems, processes, and basis documents would be required for FDA 510(k) submission.
A gap analysis report was provided to UNSOM by RCI detailing the gaps in the organization QS. The following have been completed or are in working progress:

- UNSOM has established their Quality Policy
- UNSOM continues to establish an organization consistent with cGMP requirements.
- UNSOM has established Quality Assurance (QA).
- UNSOM has established Standard Operating Procedures (SOPs) Format, Form, Numbering, Review and Approval system.
- UNSOM has implemented a document control system which delineates those documents that will be reviewed and approved by QA. The list of controlled documents include SOPs, procedures, protocols, reports, etc.
- UNSOM has established a training SOP and training program.

Signed and Approved UNSOM SOPs and Policies:

- Creation, Format and Review of SOPs SOP
- Quality Policy
- Management Responsibility and Organization Policy
- Validation Policy
- Instrument & Equipment Calibration and Maintenance Policy
- Regulatory Inspection Policy
- Records Retention Policy
- Training SOP
- Corrective and Preventive Actions (CAPA) SOP
- Change Control SOP
- Issuance & Control of Notebooks/Logbooks SOP
- Qualification of Vendors & Contract Facilities SOP
- Internal Audits SOP
- Laboratory Notebook Entry & Review Guide SOP
- Significant Figures and Rounding SOP
- Investigating Out of Specifications (OOS) Test Results SOP
- Personal Hygeine SOP
- Central Documentation SOP
- Equipment Validation Procedure SOP
- Data Integrity SOP
- Chemistry Analyzer Use and Maintenance SOP
- Milli-Q Integral 5 Water System Use and Maintenance SOP
- Hematological Analyzer Use and Maintenance SOP
- Analytical Balance Use and Maintenance SOP

- Multi-Mode Microplate Reader Use and Maintenance SOP
- pH Meter Use and Maintenance SOP

UNSOM Instrument Validation Qualifications completed

- Nova Biomedical Stat Profile Critical Care Xpress chemistry analyzer.
- Abbott Cell-Dyn Emerald Hematological Analyzer
- BioTek Multi-mode Synergy MX Plate Reader
- Mettler Toledo Dual Range Analytical Balance
- BD FACSAria III Cell Sorter
- Milli-Q Integral 5 Water Purification System
- Mettler Toledo SevenCompact pH meter

2. *User Requirements Document*

A User Requirements Document was written with the assistance of a medical device consultant. The purpose of this working document is to provide User Requirements for Rocky Research Portable Fluid Infusion Warmer with SPC. The document includes device description, intended use and user specifications. The user specifications section was broken down into the following categories:

- Environmental Requirements
- Performance/Operational Requirements
- Environmental Protection
- Serviceability
- Physical Specifications
- Cost
- Standards/Regulations
- Biocompatibility & Materials Characterization Requirements
- Packaging/Shelf Life
- Labeling
- Sterilization
- Software
- Electrical
- Suppliers

3. *Product Specifications Document*

A Product Specifications document was written with the guidance of a medical device consultant. The purpose of this document is to provide Product Specifications for Rocky Research Portable Fluid Infusion Warmer with SPC. The document includes device description and intended use, device biological safety evaluation classification, and product specifications. The product specifications section was broken down into similar categories as the user requirements document except for the following additional categories:

- Required operational environments
- Transport
- Reliability

4. *Biocompatibility Plan Document*

UNSOM hired a medical device consultant to write a biocompatibility plan for helical channel SPC. The purpose of the plan is to provide a biocompatibility-testing outline. It identified device biological safety evaluation classification and biocompatibility tests for future biocompatibility testing of a final product prior to FDA 510(k) submission. The Rocky Research Portable Fluid Infusion Warmer was classified according to ISO 10993-1 Table A.1 as a limited contact ($\leq$ 24 hours) device with external communication for circulating blood. The test plan was based on the listed device materials, predicate devices, and device classification.

5. *510(k) Preliminary Review for Rocky Research Portable Fluid Infusion Warmer*

UNSOM hired a medical device consulting company to compile a 510(k) preliminary review packet for Portable Fluid Infusion Warmer. A thirty five-page packet identified detailed areas to work towards in showing Substantial Equivalence (SE) to a predicate device that has been selected to use in future 510(k) submission to the FDA. In the review, Rocky Research Portable Fluid Infusion Warmer was identified under FDA regulatory requirements as a Class II device, regulation number 864.9205, regulation title of "blood and plasma warming device, product code KZL, BSB, and submission type 510(k). The following categories were discussed and filled out in the packet:

- Intended Use Statement
- Indications for Use Statement
- Summary of Regulatory Requirements
- Device Description
- Component Information
- Identified Predicate Device(s)
- Summary of several 510(k) sections which includes the following headings: Truth and Accuracy Statement, Class III Summary and Certification, Financial Disclosure, Declaration of Conformity and Summary Reports, Executive Summary, Device Description, Substantial Equivalence Discussion, Proposed Labeling, Sterilization and Shelf Life, Biocompatibility, Software, Electromagnetic Compatibility and Electrical Safety, and Performance Testing.

Biosafety Protocol

A memorandum of understanding and agreement (MOUA) on use of biological agents was written for SPC feasibility and bench performance studies using packed red blood cells (pRBCs). Personnel involved in the project were identified. Packed red blood cells were identified as the biological agent to be used in the study, how such tissue may be a hazard to humans and classified. Locations of use and storage were identified by a laboratory map. Experimental, decontamination, disposal, emergency, security, facility operation and monitoring procedures were outlined in relation to safety practices. The biosafety protocol was approved by the University's IBC for the use of human blood in UNSOM's department of surgery research laboratory. An Istitutional Review Board (IRB) was not required due to identifiers will not be on present on blood units.

Multi-channel SPC Feasibility Study

A feasibility study was performed to determine if RBCs were damaged by multi-channel SPC. The fluid path through the SPC was the only component of the portable fluid infusion warmer that comes in contact with infused blood or fluid.

1. Study Design and Set up

All units of pRBCs were collected in CPD anticoagulant and purchased from Biological Specialties, Corp. (Colmar, PA). Prior to use, pRBCs units were gently mixed by inverting the bag thirty times. Ten units of pRBCs (stored between 13 – 16 days to simulate older and more fragile RBCs. Expiration date for pRBCs stored in CPD was 21 days) were run through Rocky Research Portable Fluid Infusion Warmer via intravenous (IV) tubing. The fluid warmer was run on AC power. The IV tubing set up consisted of a macrobore 100" Y-type filtered blood set (0.12'' ID, Hospira) spiked into a unit of pRBCs and connected to the inlet port of SPC. Two LifeShield™ TwinSite™ 32" extension sets (Hospira) with Clave™ y-sites were connected together with one end of the extension set connected to the outlet port of the SPC and the other end connected to waste container (See figure 24). The pRBCs were run through the warmer using a hand operated pressure bag. For each unit of blood, two flow rates were achieved by starting with a high flow rate (144 mL/min ± 23) for the first 100 mL of blood (after priming) that passed through the cartridge and then flow was slowed to a low flow rate (approximately 2 mL/min). Pre-infusion samples were collected from the tubing port located directly upstream from the SPC. Post-infusion samples were collected from the tubing port located directly downstream of the SPC.

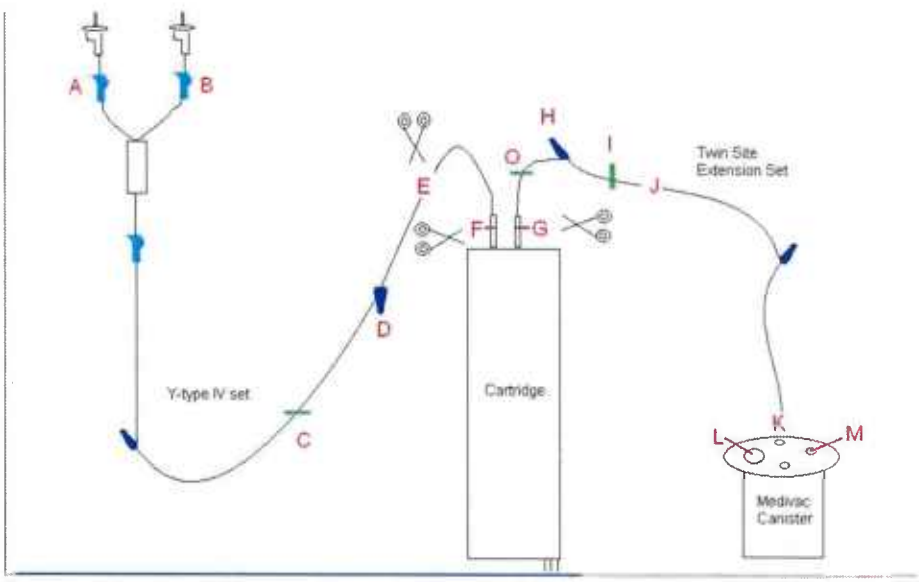


Figure 24: The feasibility study set up allows for seamless flow through intravenous tubing into the SPC through port F, out of the SPC through port G, then into a waste canister for disposal. Pre-cartridge samples are taken from port D. After cartridge samples are taken from port H.

2. Test Methods Performed

Total Hemoglobin and Hematocrit – pRBCs samples were analyzed for total hemoglobin (Hb) and hematocrit (Hct) on a Cell-Dyn Emerald Hematological Analyzer. The measured values were used to calculate percent hemolysis of red blood cells.

Plasma Free Hemoglobin Assay – pRBCs samples were assayed for plasma free hemoglobin (PFH) using a reagent kit purchased from Catachem Inc. (Bridgeport, CT) . Absoprtion at 600nm was measered using a BioTek Synergy Mx plate reader. Values obtained from the assay were used in conjunction with total Hb and Hct values, to calculate percent hemolysis of red blood cells using the following formula:

$$\% \text{ Hemolysis} = (100\text{-Hct})(\text{PFH g/dl})/(\text{Hb g/dl})$$

Sodium (Na+) and Potassium (K+) Concentrations – pRBCs samples were analyzed for Na+ and K+ levels using a Nova Biomedical Stat Profile Critical Care Xpress chemistry analyzer.

Osmotic Fragility (OF) – pRBCs samples were assayed for the measurement of osmotic fragility. The assay calculates the percent of buffered saline at 50% hemolysis of red blood cells. The assay was performed using various percentages of phosphate buffered saline and measuring absorbance on a BioTek Synergy Mx plate reader.

Phosphatidylserine (PS) –pRBCs samples were assayed for measurement of the externalization of PS on red blood cell membranes. A fluorescein insothiocyanate (FITC) Annexin IV Apoptosis Detection Kit purchased from BD Life Sciences was used and the anlysis was performed on a BD Life Sciences FACS Aria III cell sorter.

> Flow cytometry method: To test for PS, cells were labeled with BD Biosciences FITC Annexin V using an apoptosis detection kit. Cells treated with N-ethylmaleimide (NEM) were used as positve control for PS. Fresh RBCs were unstained or labled with Annexin V for a control. Data were acquired and analyzed uing FACSDiva (version 6.1.3) software. Mean channel fluorescence (MCF) was determined from 10,000 gated events using 488 nanometer channel. Instrument was aligned and calibrated. Percent PS was determined from gated RBCs.

Adenosine Triphosphate (ATP) – pRBCs samples were assayed for measuremnt of ATP using a CellTiter-Glo Luminescent Cell Viability Assay kit purchased from Promega Corporation (Madison, WI). Luminescense was measured using a BioTek Synergy Mx plate reader.

Raw data were statistically analyzed using a two-sided paired t-test as recommended by the bio-statistician, and power analysis was calculated. Groups with a sample size of 10 achieve 29% power to detect a mean of paired differences with moderate effect size of 0.5 (assumed) and a significance level (alpha) of 0.05000. Covariate adjusted least square means were computed along with their 95% confidence intervals and reported for treatment groups. All statistical analyses were performed using PASS 11 software.

3. Results

No statistical significant difference between pre-infusion samples and post-infusion samples (both high-flow and low-flow) were found except osmotic fragility of pre-infusion samples versus low-flow samples (See Table 1). The fluid warmer was not found to significantly damage pRBCs by any measured parameter with one exception – an increased osmotic fragility of low-flow samples. Despite this increase, however, osmotic fragility values are still within the normal range acceptable for pRBC transfusion.

Although no significant damage was found to RBCs, there were concerns of possible stagnant areas in the cartridge. These concerns were based from a practice run with the fluid warmer and using pRBCS. A technical error on the part of a technician resulted in the fluid warmer overheating and extremely damaged pRBCs. Attempts to flush the cartridge with normal saline to remove damaged RBCs were unsuccessful.

Following this incident, Rocky Research performed a series of experiments and found stagnant areas in the SPC design (see pg 13-18 of this report). Rocky Research redesigned the SPC using a single helical channel design, which was used in the bench performance testing by UNSOM.

Table 1: Mean for feasibility study using packed Red Blood Cells.

Tests	Pre-infusion	Low Flow	High Flow
Osmotic Fragility (% Buffered Saline @ H50)	0.39 +/- 0.04	0.4* +/- 0.04	0.39 +/- 0.04
% Hemolysis	0.25 +/- 0.16	0.24 +/- 0.15	0.24 +/- 0.17
K+ (mmol/L)	20.9 +/- 11.2	19.5 +/- 9.35	20.4 +/- 7.97
Na+ (mmol/L)	143.2 +/- 5.66	143 +/- 5.41	143.1 +/- 3.78
ATP (Umol/gHb)	0.66 +/- 0.15	0.66 +/- 0.16	0.65 +/- 0.18
% Phosphatidylserine	1.34 +/- 0.575	1.43 +/- 1.30	1.62 +/- 1.13
% Hematocrit	60.1 +/- 7.70	60.2 +/- 6.74	61.5 +/- 6.70

* p value < 0.05

+/- values are Standard Deviation values

Single Helical Channel SPC Feasibility Study

1. Study Design and Set Up

A feasibility study was performed to determine if RBCs were damaged by single helical channel SPC or adhered to the inside wall of the cartridge. Extracellular potassium, percent hemolysis, and phosphatidylserine (PS) externalization were used as markers to determine global cellular damage of RBCs. Hematalogical parameters such as RBC count and hematocrit were used as indicators of possible cell adherence to SPC wall. Cluster of differentiation 47 (CD47) expression was also measured as a marker of cell health.

All units of pRBCs were collected in CPD anticoagulant with Additive Solution 1 – Adsol (AS1) and purchased from Biological Specialties, Corp. (Colmar, PA). Units of pRBCs were shipped overnight in appropriate shipping containers maintaining temperatures between 2 – 6°C. A temperature-monitoring device was shipped with pRBCs to confirm temperature range was maintained. Prior to use, pRBCs units were gently mixed by inverting bag thirty times. Sixty-two units of pRBCs were divided into two study groups; group 1 was transfused at 40 mL/minute and group 2 at 20 mL/minute to simulate two clinically relevant transfusion rates. Units of pRBCs (stored between 6 - 8 days to simulate fresh RBCs. Expiration date for pRBCs stored in CPD-AS1 was 42 days) were run through Rocky Research Portable Fluid Infusion Warmer via intravenous (IV) tubing. The fluid warmer was run on AC power. The IV tubing set up consisted of a macrobore 100" Y-type filtered blood set (0.12'' ID, Hospira) that was spliced into two sections. The blood tubing sections were reconnected via 3/16" luer connectors with an 18" section of silicone tubing (#16; 1.6 mm wall thickness, 3.1 mm inner diameter; Langer Instruments, Alpharetta, GA) in the center. Then the Y-type blood tubing set was spiked into a unit of pRBCs with the silicone tubing threaded through a Longer BT300-2J peristaltic pump head (Langer Instruments) with the other end of the IV blood tubing connected to the inlet port of SPC. Two LifeShield™ TwinSite™ 32" extension sets (Hospira) with Clave™ y-sites were connected together with one end of the extension set connected to the outlet port of the SPC and the other end connected to waste container (See figure 25). Flow rates were controlled by peristaltic pump. Pre-infusion samples were collected from the tubing port located directly upstream from the SPC. Post-infusion samples were collected from the tubing port located directly downstream of the SPC. Tubing lines were flushed with copious amounts of normal saline between runs, if running more than a unit of pRBCs per day.

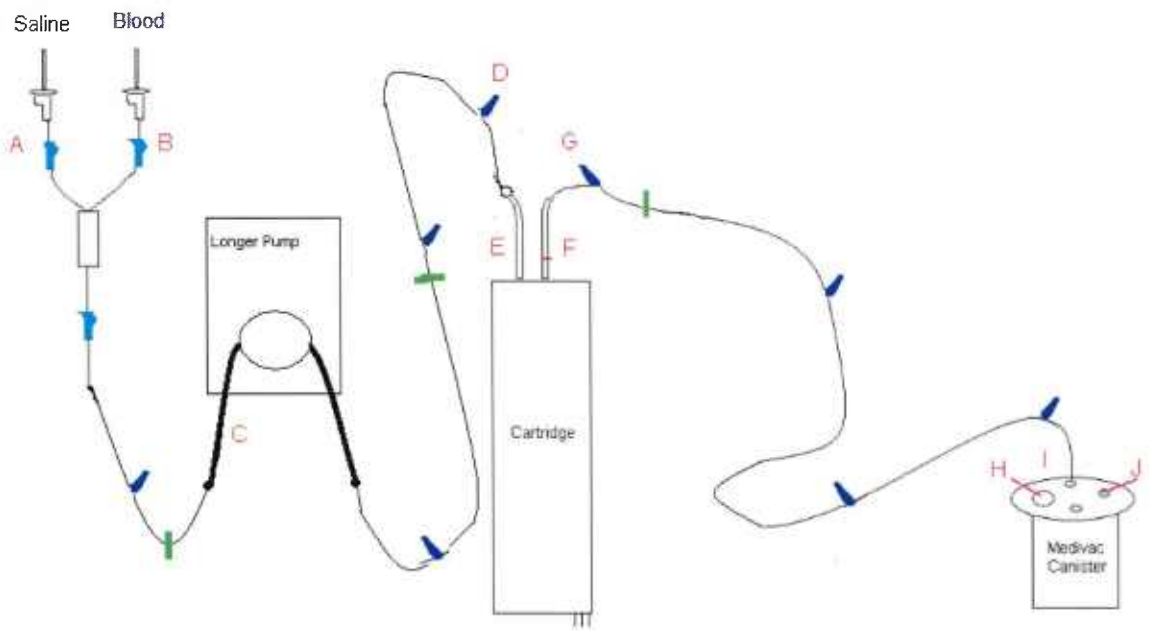


Figure 25: Feasibility Study Tubing Setup. A-control saline flow, B-control blood flow, C-silicone tubing for pump, D-pre-infusion sampling port, E-in line to cartridge, F-out line from cartridge, G-post-infusion sampling port, I-waste container.

2. *Test Methods Performed*

Extracellular potassium, percent hemolysis, PS externalization are frequently used as markers for indicating the presence of RBC damage. In a red cell storage lesion study performed by Seghatchian and Krailadsiri[1], the group concluded that the combination of potassium levels, plasma hemoglobin, and supernatant Annexin V is a better indication of global cellular damage. Kamel et al.[2] also used potassium levels, percent hemolysis, PS externalization, and CD47 expression as indicators of cell damage for a study on effects of storage time of pRBCs. CD47 appears to play a role as a marker of self on RBCs and sends a negative signal to macrophages when the RBC is normal, which protects it from phagocytosis.[2] Percent hemolysis, potassium concentration and PS were selected by UNSOM because they are known global indicators of red blood cell damage. CD47 was measured as a marker of cell health. Hematalogical parameters such as RBC count and hematocrit were used as indicators of possible blood cell loss due to adherence to SPC wall.

1. Extracellular K+ – pRBCs samples collected in the feasibility study were analyzed for K+ levels using a Nova Biomedical Stat Profile Critical Care Xpress chemistry analyzer.

2. Hematological parameters – pRBCs samples were analyzed for RBC count and hematocrit using an Abbott Emerald Cell-Dyn hematological analyzer.

3. Phosphatidylserine (PS) Externalization–samples of pRBCs were assayed for externalization of phosphatidylserine on red blood cell membranes. Cells were analyzed by flow cytometry (BD Life Sciences FACSAria III cell sorter)

   Flow cytometry method: RBCs were labeled with allophycocyanin (APC) conjugated anti-glycophorin A in order to isolate the RBC population. To test for PS, cells were labeled with BD Biosciences FITC Annexin V using an apoptosis detection kit. Approriate isotype negatives controls were used. All antibodies were purchased from BD Biosciences. Cells treated with N-ethylmaleimide (NEM) were used as positve control for PS. Fresh RBCs were unstained or labled with both Annexin V and anti-glycoprotein A anitibody for a control. Data were acquired and analyzed uing FACSDiva software (version 6.1.3). Mean channel fluorescence (MCF) was determined from 10,000 gated events using both 488 and 633 nanometer channels. Instrument was aligned and calibrated. Percent PS was determined from gated RBCs.

4. CD47 Expression – pRBCs samples collected in the feasibility study were assayed for externalization of the integrin associated transmembrane protein CD47 on red blood cell membranes. Cells were analyzed flow cytometry.

   Flow cytometry method: RBCs were labeled with allophycocyanin (APC) conjugated anti-glycophorin A in order to isolate the RBC population. To test for CD47, cells were labeled with BD Biosciences anti-human CD47 labled with phycoerythrin (PE). Approriate isotype negatives controls were used. All antibodies were purchased from BD Biosciences. Cells treated with NEM were used as a control for CD47. Fresh RBCs were

unstained or labled with both anti-human CD47 and anti-human glycoprotein A anitibodies for a control. Data were acquired and analyzed uing FACSDiva (version 6.1.3) software. MCF was determined from 10,000 gated events using both 488 and 633 nm channels. Instrument was aligned and calibrated. Percent CD47 was determined from gated RBCs.

5. Phosphatidylserine (PS) Externalization/CD47 Expression- samples of pRBCs collected in the feasibility study were assayed for externalization of phosphatidylserine on red blood cell membranes and expression of CD47. Cells were analyzed by laser scanning microscopy (LSM; Nikon A1R Laser Scanning Inverted Confocal Microscope (Nikon, New York, NY).) to confirm flow cytometry findings (See figure 26).

LSM method: RBCs were labeled with Brilliant Violet (BV) 421 conjugated anti-glycophorin A in order to identify RBC population. To test for PS, cells were labeled with BD Biosciences FITC Annexin V apoptosis detection microscopy kit and anti-human CD47 labeled PerCP-Cy5.5. All antibodies were purchased from BD Biosciences. Cells treated with NEM were used as a control for PS/CD47. Fresh RBCs were unstained (negative control) or labled with Annexin V, anti-human CD47, and anti-human glycoprotein A anitibody for a positive control. Cells were fixed with 3% paraformaldehyde. A cell prep was placed into a glass bottom dish (MatTek Corp., Ashland, MA) and viewed on the confocal micoscope. Images and data were acquired using Nikon NIS Elements Software (version 4.10) while viewing the 405- 450, 488-530, and 640-680 (Excitation-Emmision) nanometer channels.

The NIS Elements Software was used to analyze the data. An elliptical region of interest (ROI) was placed around the first 20 single, isolated RBCs. After the ROIs are placed, the software was used to take automated measurements of the fluorescent intensities of the cells. Fluorescent readings from unstained RBCs were used to correct for background and autofluorescence. The mean and standard deviation (STD) on the intensity of each fluorescent channel was calculated. The mean + 2 STD was used to correct each cell sample for background and autofluorescence. RBCs with fluorescence intensities greater than 1 were counted as positive. All positive cells for each wavelength were counted. Annexin V and CD47 positive cells were divided by the number of CD235 positive cells to give Percent RBCs positive for Annexin V (apoptotic) and CD47 (healthy RBCs).

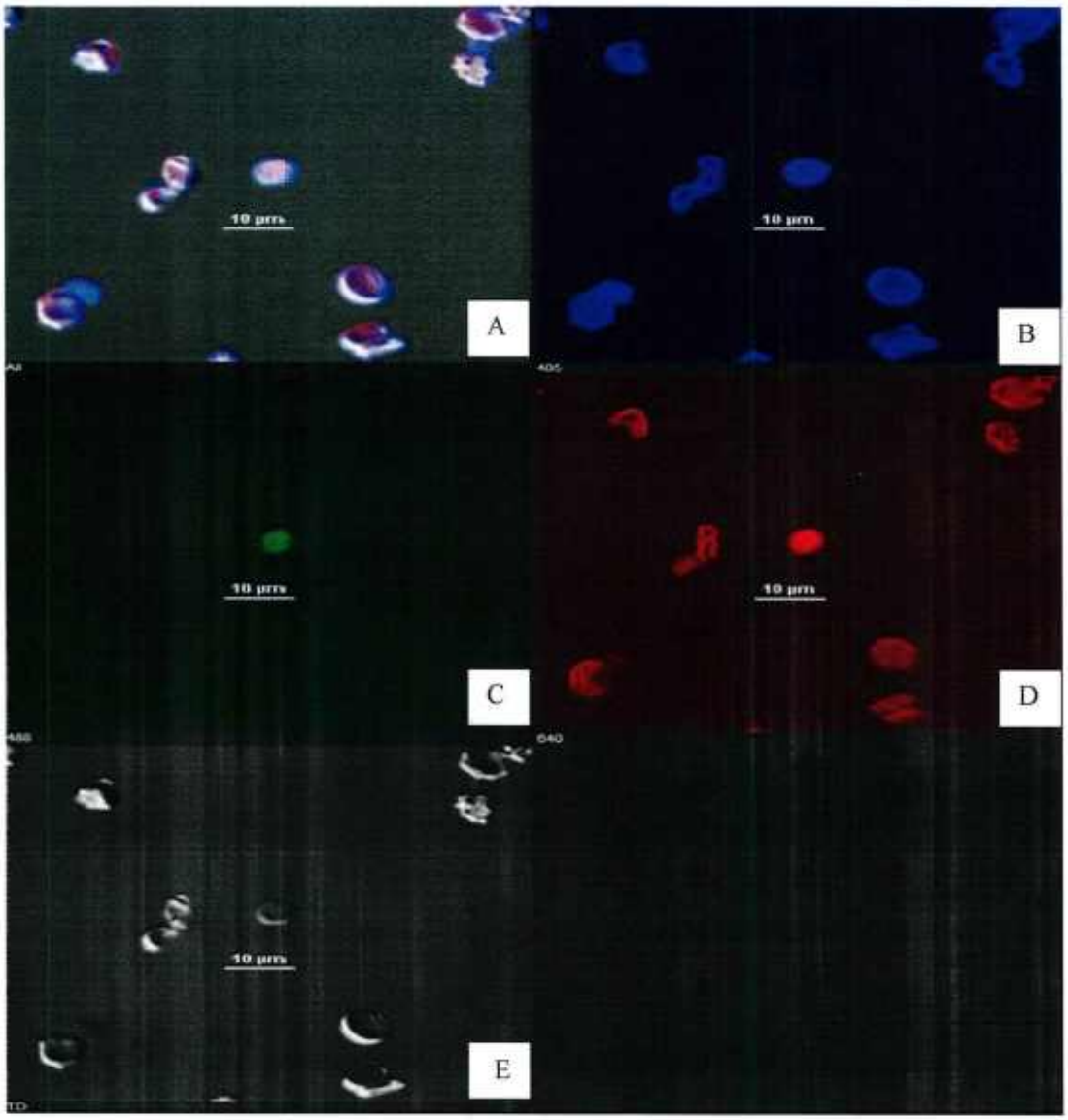


Figure 26. Fluorescence-imaging of human erythrocytes labeled with anti-human glycophorin A – BV421, anti-human CD47- PerCP-Cy5.5, and Annexin V-FITC. (A) Cells with transmitted light and excited using 405nm, 488nm, 640nm channels. (B) Erythrocytes, (C) Annexin V positive cells. (D) CD47 positive cells, and (E) Cells with transmitted light only.

6. Percent Hemolysis- Values obtained from plasma free hemoglobin assay were used in conjunction with total Hb and Hct values, to calculate percent hemolysis of red blood cells using the following formula:

$$\% \text{ Hemolysis} = (100\text{-Hct})(\text{PFH g/dl})/(\text{Hb g/dl})$$

a. Plasma Free Hemoglobin Assay - pRBCs samples were assayed for plasma free hemoglobin (PFH) using a reagent kit purchased from Catachem Inc. (Bridgeport, CT). Absoprtion at 600nm was measered using a BioTek Synergy Mx plate reader. Values obtained from the assay were used in conjunction with total Hb and Hct values, to calculate percent hemolysis of red blood cells using the above formula:

b. Total Hemoglobin and Hematocrit – pRBCs samples were analyzed for total Hb and Hct on a Cell-Dyn Emerald Hematological Analyzer. The measured values were used to calculate percent hemolysis of red blood cells.

All data are presented as a group means + standard deviation. Normality tests were carried out before further analysis. Statistics were performed using ANOVA and paired t test. A p-value <0.05 was considered statistically significant. Analyses were conducted using Statistical Analysis System (SAS) (version 9.3) software.

3. *Results*

- Output temperatures from the SPC, as shown in Table 2, report that the pRBCs are being delivered at or above normothermia. Temperatures at a low flow rate are slightly higher, likely due to the longer time in the SPC to warm the pRBCs.

- No statistical significant difference between pre-infusion samples and post-infusion samples (both 20 ml/min and 40 ml/min) were found for percent hemolysis, PS externalization, or CD47 expression (See Table 3). Potassium concentration was statistically significant for group 1 (40mL/min), the post samples showed a decrease in potassium. The percent hemolysis for both groups did not exceed the FDA guidelines; the accepted level of hemolysis must be less than 1% for units of pRBCs. The fluid warmer was not found to significantly damage pRBCs by any measured parameter.

- Both RBC count and hematocrit were statistically significant for group 1 and 2 (See Table 3). RBC count and percent hematocrit showed a decrease in post samples. A reduction in RBC count and percent hematocrit may indicate a possible blood cell loss.

Table 2: Temperatures of the SPC pre- and post-infusion

Temperatures (°C)	Pre-Infusion		Post-Infusion	
	In	Out	In	Out
Low Flow	26.96 ±1.44	38.75 ±2.33	26.69 ±1.22	38.61 ±0.40
High Flow	21.76 ±0.94	38.29 ±0.19	21.78 ±1.28	38.17 ±0.14

Table 3. Mean and Percent change values for feasibility study using packed Red Blood Cells

Test	Flow Rate 20 ml/min			Flow Rate 40 ml/min		
	Pre Sample	Post Sample	% Change	Pre Sample	Post Sample	% Change
Potassium Levels (mmol/L)	20.9 ± 3.45	20.5 ± 3.54	-1.91	21.3 ± 4.13	20.8* ± 3.95	-2.35
RBC Count (10^6/µL)	6.62 ± 0.534	6.56* ± 0.552	-0.906	6.71 ± 0.607	6.63* + 0.611	-1.19
% Hematocrit	60.4 ± 3.46	60.0* ± 3.54	-0.662	60.0 ± 3.69	59.4* ± 3.73	-1.00
% Hemolysis	0.131 ± 0.097	0.140 ± 0.105	6.87	0.075 ± 0.034	0.080 ± 0.045	6.67
% CD47 by Flow Cytometer	96.0 ± 4.2	96.6 ± 4.1	0.625	95.3 ± 5.17	95.8 ± 4.90	0.525
% PS by Flow Cytometer	5.8 ± 2.3	6.0 ± 2.6	3.4	8.1 ± 3.09	7.4 ± 2.91	-8.6
% CD47 by LSM	100 ± 0	100 ± 0	0	99.8	100 ± 0.898	0.200 ± 0
% PS by LSM	3.5 ± 6.2	4.6 ± 7.6	31	13.4 ± 12.2	21.6 ± 24.4	61.2 ± 29.6

* p value < 0.05
+/- values are Standard Deviation values
Zeros were imputed for divide by zero formula errors

Bench Performance Study – Comparison of Rocky Research Portable Fluid Infusion Warmer

1. Continuous Power Study Design and Set up

Bench performance study was performed to compare three Rocky Research Portable Fluid Infusion Warmer prototypes run on AC power. The purpose of the study was twofold. First, determine if there were statistical similarities among prototypes in heating capabilities and allow interchanging of devices during various bench performance testing if necessary. Second, determine if prototypes heating ability

was consistent for future manufacturing purposes. The same SPC was used on all three prototypes. Set up consisted of submerging one end of #16 silicon tubing (1.6 mm wall thickness, 3.1 mm inner diameter; Langer Instruments, Alpharetta, GA) into a pan of distilled water and threading the tubing through a Longer BT300-2J peristaltic pump head (Langer Instruments) with the other end connected to the inlet port of SPC. Hospira pre-pierced Y-site 32" extension set was connected to the outlet of SPC with the other end attached to a 1 liter graduated cylinder. Thermocouples (Type T, Omega, Stamford, CT) were placed at the inlet and outlet sites of the SPC for monitoring temperature. A peristaltic pump was adjusted to 210 rpm to maintain a constant flow rate. Each test was run for 1 hour in triplicate per prototype. Data for the outlet temperature was collected every 15 seconds using Labview (Version 7.1) software .

All data are presented as a group means + standard deviation. Normality tests were carried out before further analysis. Statistics were performed using ANOVA. A p-value <0.05 was considered statistically significant. Analyses were conducted using Statistical Analysis System (SAS) (version 9.3) software.

Results:

No statistical significant difference between prototypes heating capabilities using continuous electrical power for outlet temperature measurements (See figure 27).

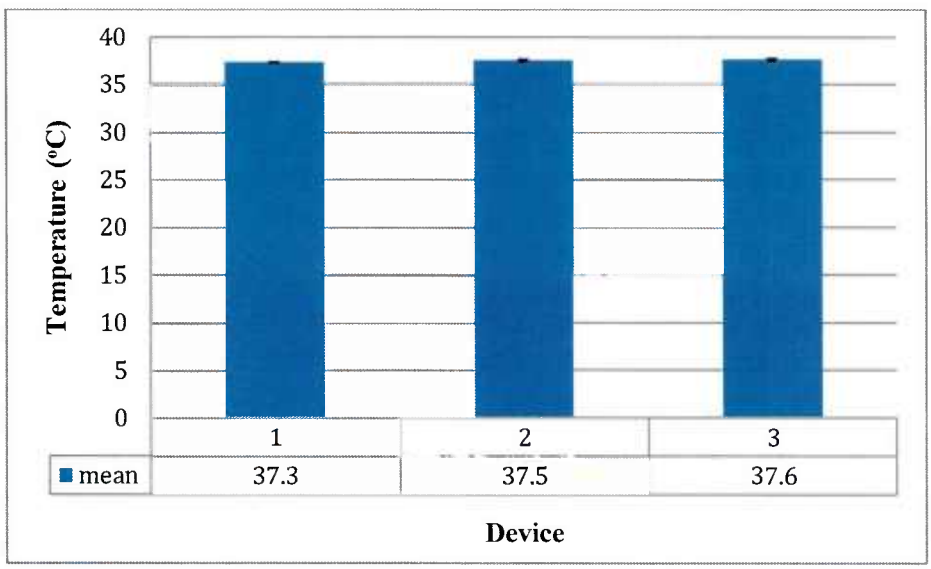


Figure 27. Fluid Warmer bench performance testing comparing prototypes outlet temperature

2. *Thermal Battery Power Study Design and Set up*

Bench performance study was performed to compare three Rocky Research Portable Fluid Infusion Warmer prototypes run on thermal battery. The purpose of the study was to determine if there were statistical similarities among prototypes in heating capabilities and battery capacity. The same SPC was used for all three prototypes. The following set up was used to simululate a clinical field setting: Tubing set up consisted of 100" Y-type filtered blood set (0.12'' ID, Hospira), connected to the inlet port of cartridge. Two pre-pierced Y-site 32" extension sets (Hospira) were connected together with a bubble trap in the center. One end of the extension set was connected to the outlet port of the SPC and the other end was connected to 14 gauge catheter. The catheter end was placed inside a 1 Liter graduated cylinder for

calculating flow rates by using a stop watch. Each test was started ten minutes after the prototype's battery recharged and cooled down period ended. Pressure bags were used to push distilled water through the warmer at 300 mm Hg. Thermocouples (Type T, Omega, Stamford, CT) were placed at SPC's inlet and outlet sites as well as the catheter for monitoring temperature. The run was ended when the temperature of the distilled water dropped below 32°C. Five runs were completed for each prototype. Data for the inlet, outlet, and catheter temperatures were collected every 15 seconds using Labview (Version 7.1) software. Flow rate was calculated based on time recordings every 100 mLs. The time and total volume of fluid passing through fluid warmer was recorded at the end of experiment for determining the thermal battery capacity of prototypes.

All data are presented as a group means + standard deviation. Normality tests were carried out before further analysis. Statistics were performed using ANOVA. A p-value <0.05 was considered statistically significant. Analyses were conducted using Statistical Analysis System (SAS) (version 9.3) software.

Results

No statistical significant difference between prototypes heating capabilities or flow rates using thermal battery power (See figures 28 and 29). Under the test conditions described above, the thermal battery capacity allowed an average mean of 2.1 liters of fluid to be warmed over a period of 12 minutes. The fluid outlet temperature was measured at $\geq 32^{0}$C for 100% of time and at $\geq 35^{0}$C for 78% of time.

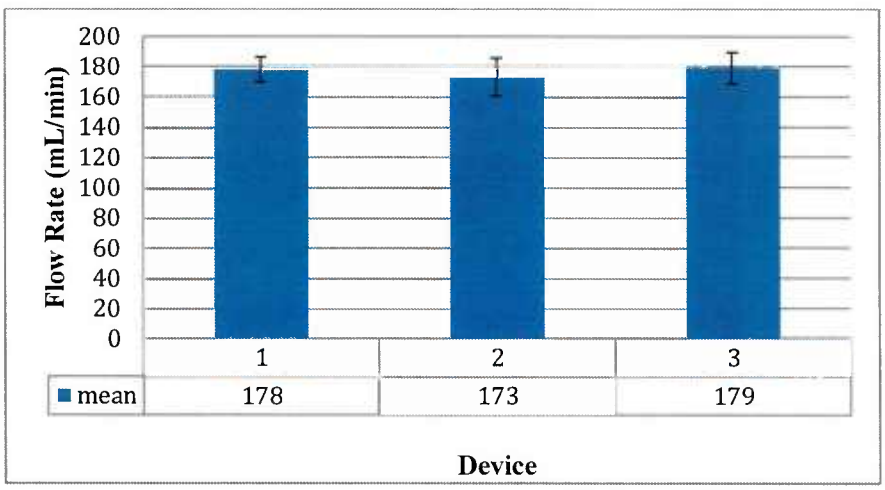


Figure 28. Fluid Warmer bench performance testing comparing prototypes average flow rate. Devices were run on thermal battery.

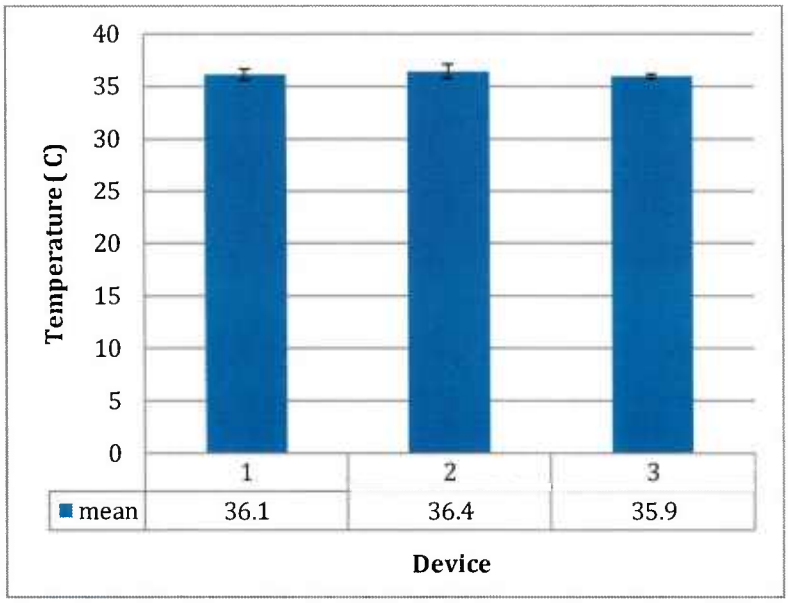


Figure 29. Fluid Warmer bench performance testing comparing prototypes average outlet temperature. Devices were run on thermal battery.

Bench Performance Study – Comparison Single Patient Cartridges

The comparison between cartridges was performed to determine if they were all identical in terms of heat transfer and flow rate. The purpose was same as discussed in the bench performance study comparing prototypes ran on continuous power. It was to demonstrate consistency for future manufacturing of SPCs and allow interchanging of SPCs in bench performance testing, if no statistical difference was shown between SPCs. This was necessary if one of the SPCs stopped functioning due to excessive repeated use or possibility of leaking. The SPCs were designed for single use, although cartridges were found to hold up generally well to repeated use. There were a few SPCs that leaked during the single helical channel feasibility study and were replaced as needed with new cartridges.

Ten cartridges and one prototype were used in this study. Set up consisted of submerging one end of #16 silicon tubing (1.6 mm wall thickness, 3.1 mm inner diameter; Langer Instruments, Alpharetta, GA) into a pan of distilled water and threading the tubing through a Longer BT300-2J peristaltic pump head (Langer Instruments) with the other end connected to the inlet port of SPC. Two pre-pierced Y-site 32" extension sets (Hospira) were connected together with a bubble trap in the center. One end of the extension set was connected to the outlet port of the SPC and the other end was connected to 14 gauge catheter. The catheter end was placed inside a 1 Liter graduated cylinder for calculating flow rates by using a stop watch. Thermocouples (Type T, Omega, Stamford, CT) were placed at SPC's inlet and outlet sites for monitoring temperature. Peristaltic pump was adjusted to 210 rpm to maintain a constant flow rate and AC power was used to ensure continuous power to device. Each test was run for 1 hour in triplicate per cartridge. Data for inlet, outlet, and catheter temperature was collected every 15 seconds using Labview (Version 7.1) software. Flow rate was calculated based on time recordings every 1 liter.

All data are presented as a group means + standard deviation. Normality tests were carried out before further analysis. Statistics were performed using ANOVA. A p-value <0.05 was considered statistically significant. Analyses were conducted using Statistical Analysis System (SAS) (version 9.3) software.

Results

No statistical significant difference between cartridges heating capabilities or flow rate using thermal battery power (See figure 30 and 31).

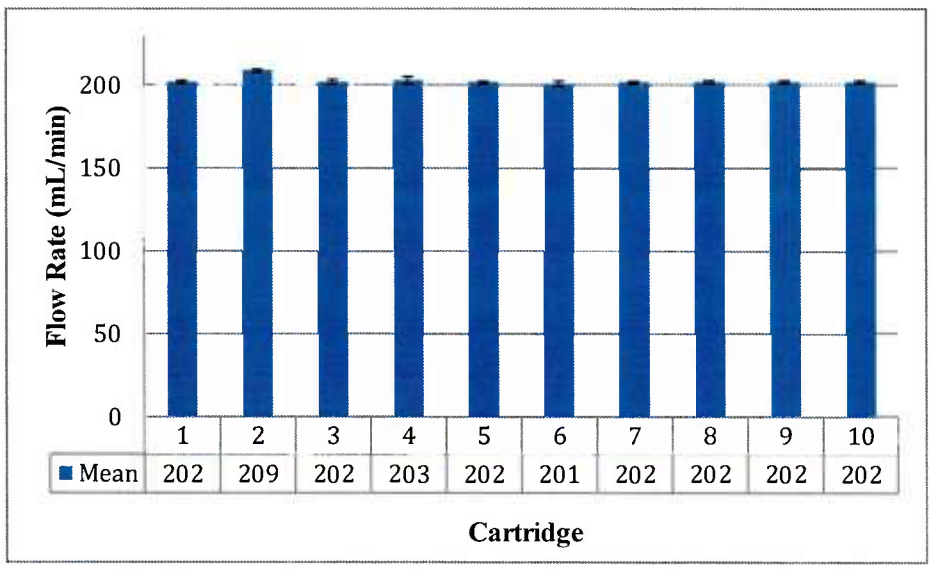


Figure 30. Fluid Warmer bench performance testing comparing cartridges flow rate

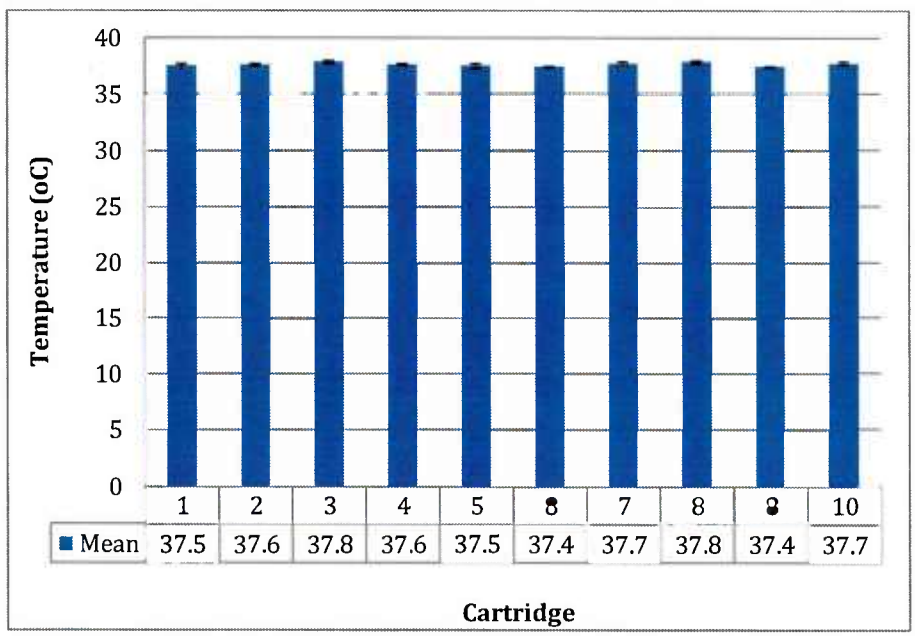


Figure 31. Fluid Warmer bench performance testing comparing cartridges outlet temperature

Bench Performance Study – Comparison of Rocky Research Portable Fluid Infusion Warmer to other commercial fluid warmers

The primary objectives of this study were twofold. First, compare the performance of Rocky Research Portable Fluid Infusion Warmer to currently available warmers used by the military. Second, demonstrate thermal battery proof-of-concept by examining the device's warming capabilities. A study performed by Dubick et al.[3] evaluated four commercial fluid warming devices for use in forward surgical and combat areas. Rocky Research prototype was ran under the same testing conditions described in the study and the data obtained from the prototype was compared to the published data reported in Dubick's study. The published study compared the Level 1 Model 1000 (Level 1 Technologies), FMS 2000 (Belmont Instruments, Billerica, MA), Thermal Angel (Estill Medical Technologies, Dallas, TX), and Ranger (Arizant Healthcare, Eden Praire, MN). In the published study, all the commercial devices were run at low and high flow rates; except the Level 1 was run at high flow rate.

Rocky Research's prototype was evaluated with lactated Ringer's solution (LR) on thermal battery power. The solution was used at two temperatures (ambient [20 – 21°C] and cold [4 – 10°C]). The LR solution was run through the warmer at two different pressures (150 and 300 mm/Hg) using a hand operated pressure bag and connections were made using standard IV tubing (100" Y-type filtered blood set (0.12" ID), and two connected pre-pierced Y-site 32" extension sets, Hospira) connected to an 18-gauge catheter. The two pressures will be designated as low and high flow rates. Temperature probes were placed 5 inches from inflow to warmer and outflow port of warmer as was described in Dubick's study. The run was ended when bag of LR was empty. Eight runs were completed for each test. Data for the inlet and outlet temperatures were collected every 1 second using Labview (Version 7.1) software. Flow rate measurements were taken for each test run. This was accomplished using a graduated cylinder and timer. The following measurable outcomes were analyzed: time for instrument to reach a steady temperature (warm-up time), change in temperature between inlet and outlet fluid temperature, average flow rate, percent of time temperature readings were greater than or equal to 32°C or 35°C at each flow rate. The two temperature points were chosen to meet minimum clinical standard (32°C) and the preferred clinical temperature (35°C).

All data are presented as a group means + standard error. Normality tests were carried out before further analysis. Statistics were performed using ANOVA and one way t test. A p-value <0.05 was considered statistically significant. Analyses were conducted using Statistical Analysis System (SAS) (version 9.3) software.

Results

- Comparison of Rocky Research prototype physical characteristics to Thermal Angel, Ranger, Level 1, and FMS 2000 (See Table 4). Rocky Research is the only portable device that may be operated by either high density thermal battery or AC power. Rocky Research prototype falls in the middle of the four devices relative to weight and size.
- Rocky Research prototype's thermal characteristics are compared to commercial IV fluid warmers (See Table 5). Rocky Research prototype was similar to Ranger in warm up time and priming volume. The prototype was similar to Thermal Angel's flow rates.

- Rocky Research prototype effective warming was compared to commercial devices (See Table 6). Both the time to reach average outlet temperature and change in temperature between inlet and outlet ports was evaluated.
    - Rocky Research prototype was statistically significant in reaching average outlet temperature faster than Thermal Angel with all test conditions, except it was similar at low flow rate using ambient LR. The prototype was significantly faster than Ranger using cold LR at both low and high flow rates, but similar using ambient LR at the two flow rates. The prototype was significantly faster than Level 1 at high flow rate using cold LR and significantly slower than Level 1 at high flow rate using ambient LR. The prototype was similar to FMS 2000 with all test conditions, except it was significantly slower at high flow rate using ambient LR.
    - Rocky Research prototype significantly had a greater temperature change from inlet to outlet ports than Thermal Angel with all test conditions except it was similar at low flow rate using ambient LR. The prototype significantly had less change than Ranger and Level 1 with all test conditions, except it was similar to Ranger at low flow rate using ambient LR. The prototype had significantly less change than FMS 2000 with all test conditions, except it was similar using ambient LR with both flow rates.
- Rocky Research prototype had a statistically significant lower flow rate at two different pressures compared to other devices (See figures 32 and 33).
- Rocky Research prototype average outlet temperature was compared to the commercial devices (See figures 34 and 35). The prototype had a significantly higher outlet temperature than Thermal Angel with all test conditions. It also had significantly higher outlet temperature than Ranger with all test conditions except it was similar using ambient LR at low flow. The prototype was significantly higher outlet temperature than Level 1 at high flow rate using both ambient and cold LR. The prototype was significantly higher outlet temperature than FMS 2000 using ambient LR at high flow rate. It was significantly lower than FMS 2000 using cold LR at high flow rate and similar at the low flow rate using both ambient and cold LR.
- Compared proportion of time the outlet port temperature was $\geq 32^{\circ}C$ or $\geq 35^{\circ}C$ between Rocky Research prototype and other commercial devices (See figure 36, 37, 38, and 39).
    - The proportion of time the outlet port was $\geq 32^{\circ}C$ for the prototype compared to Thermal Angel was significantly higher for all test conditions, except it was similar when using ambient LR at high flow rate. The prototype was similar to Ranger and FMS 2000 for all test conditions.
    - The proportion of time the outlet port was $\geq 35^{\circ}C$ for the prototype compared to Thermal Angel was significantly higher for all test conditions. The prototype was similar to Ranger and FMS 2000 at low flow rate using ambient and cold LR. It was significantly higher than Ranger and Level 1at high flow rate using cold LR. Rocky Research device was significantly lower than FMS 2000 at high flow rate using cold LR.

Table 4. Physical Characteristics

	Rocky Research	Thermal Angel	Ranger	Level 1	FMS 2000
Mass, lb (Kg)	21.5	0.56; battery 6.65	7.44	64	26
Dimensions Inches (L x W x H)	17 X 10 X 8	9 X 2.75 X 4.5	10 X 7.5 X 4.5	48 X 13 X 10	13.5 X 7.5 X12
Power Requirements	110 – 120 V, 50/60 Hz or Thermal Battery	12 V battery	100 – 120V, 50/60 Hz	110 V, 50/60 Hz	115 V, 50 – 400 Hz
Battery	Yes	Yes	No	No	Yes w/out heat
AC	Yes	No	Yes	Yes	Yes
Battery Recharge Time	25 minutes	14 hours	–	–	8 hours

AC, alternating current

Table 5. Fluid Warmer Thermal Characteristics

	Rocky Research	Thermal Angel	Ranger	Level 1	FMS 2000
Temperature set point	37°C	38°C	41°C	41.7 ± 0.3°C	37.5°C (50 – 500 mL/min 39°C (10 – 50 mL/min)
Over-temperature alarm	42°C	–	43°C	44.9 ± 0.1°C	42°C
Under-temperature alarm	–	–	33°C	–	–
Over-temperature cut-off	–	–	46°C	–	–
Flow rates (mL/min)	2 – 200*	2-150	100 – 500 (high flow set)	40 - 500	10 – 500, 2.5 and 5 (no heat)
Warm-up time	1 - 3 minutes	45 seconds	< 2 minutes	4 – 8 minutes	15 seconds
Priming Volume (mL)	112	25	120	56	230

*variable with tubing set up and catheter size

Table 6. Warming Effectiveness of Each Device at Each Flow Rate

	Cold LR	RT LR
High Flow Time to reach average temperature at outlet (s)		
Rocky Research Prototype	86 ± 16[a,b,c]	160 ± 18[a,c,d]
Thermal Angel	320 ± 6	287 ± 17.6
Ranger	173 ± 18	177 ± 18
Level 1	247 ± 20	93 ± 28
FMS 2000	80 ± 15	60 ± 0
High Flow Change in temperature from inlet to outlet port (°C)		
Rocky Research Prototype	25.4 ± 0.19[a,b,c,d]	15.8 ± 0.3[a,b,c]
Thermal Angel	15.8 ± 0.3	13.9 ± 0.4
Ranger	28.7 ± 3.3	17.1 ± 0.06
Level 1	29.7 ± 0.2	16.7 ± 0.3
FMS 2000	32.1 ± 0.3	16.3 ± 0.01
Low Flow Time to reach average temperature at outlet (s)		
Rocky Research Prototype	107 ± 14[a,b]	160 ± 23
Thermal Angel	337 ± 26	163 ± 71
Ranger	213 ± 33	173 ± 33
FMS 2000	73 ± 9	97 ± 14.5
Low Flow Change in temperature from inlet to outlet port (°C)		
Rocky Research Prototype	25.8 ± 0.3[a,b,d]	16.3 ± 0.8
Thermal Angel	20.3 ± 0.5	14.8 ± 2.7
Ranger	31.1 ± 0.4	18 ± 0.1
FMS 2000	31.3 ± 0.8	16.4 ± 0.1

Data are expressed as mean ± Standard Error (Rocky Research Prototype N = 8, other devices N = 3).
RT = Room Temperature
[a] $p < 0.05$ from Rocky Research vs. Thermal Angel
[b] $p < 0.05$ from Rocky Research vs Ranger
[c] $p < 0.05$ from Rocky Research vs. Level 1
[d] $p < 0.05$ from Rocky Research vs. FMS 2000

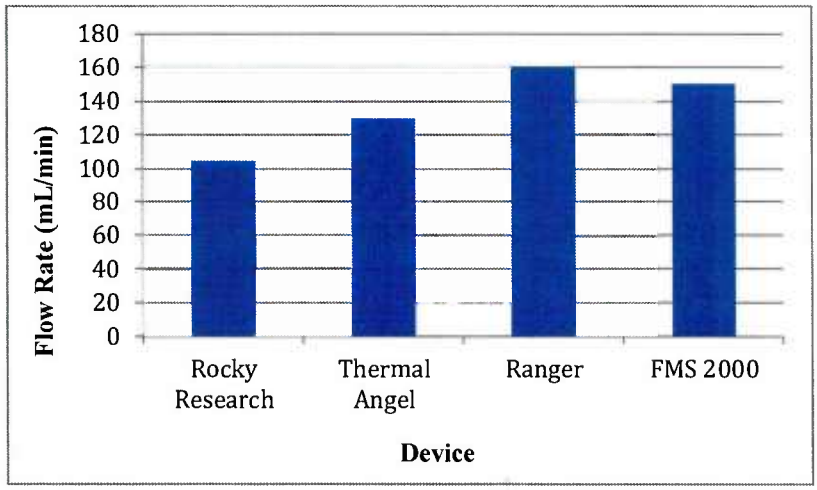


Figure 32. Rocky Research prototype comparison to commercial devices at low flow rate (150 mm Hg). $p < 0.05$ Rocky Research vs. all commercial devices.

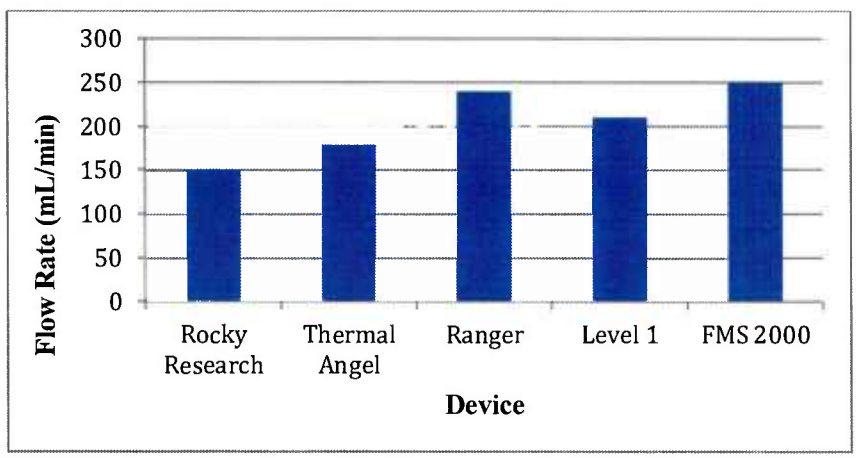


Figure 33. Rocky Research prototype comparison to commercial devices at high flow rate (300 mm Hg). $p < 0.05$ Rocky Research vs. all commercial devices.

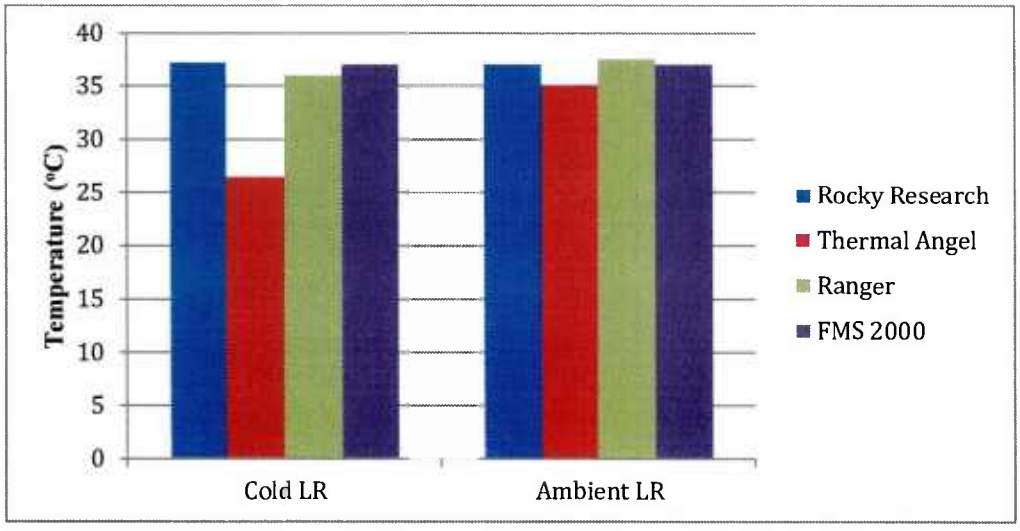


Figure 34. Rocky Research protctype comparison to commercial devices outflow temperature at low flow rates (150 mm Hg). $p < 0.05$ Rocky Research vs. Thermal Angel with ambient and cold LR. $p < 0.05$ Rocky Research vs. Ranger with cold LR. The Level 1 was excluded from low flow testing.

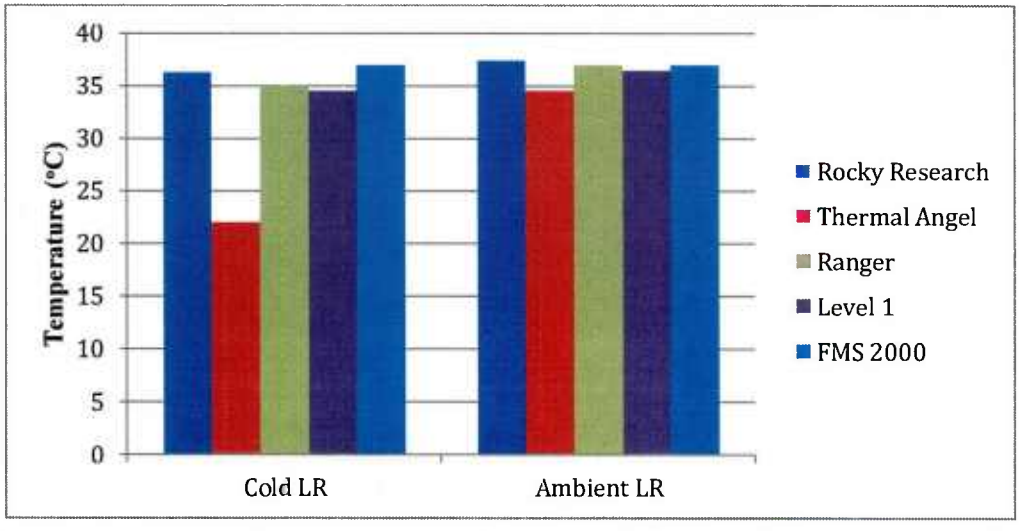


Figure 35. Rocky Research protctype comparison to commercial devices outflow temperature at high flow rates (300 mm Hg). $p < 0.05$ Rocky Research vs. all commercial devices with ambient and cold LR.

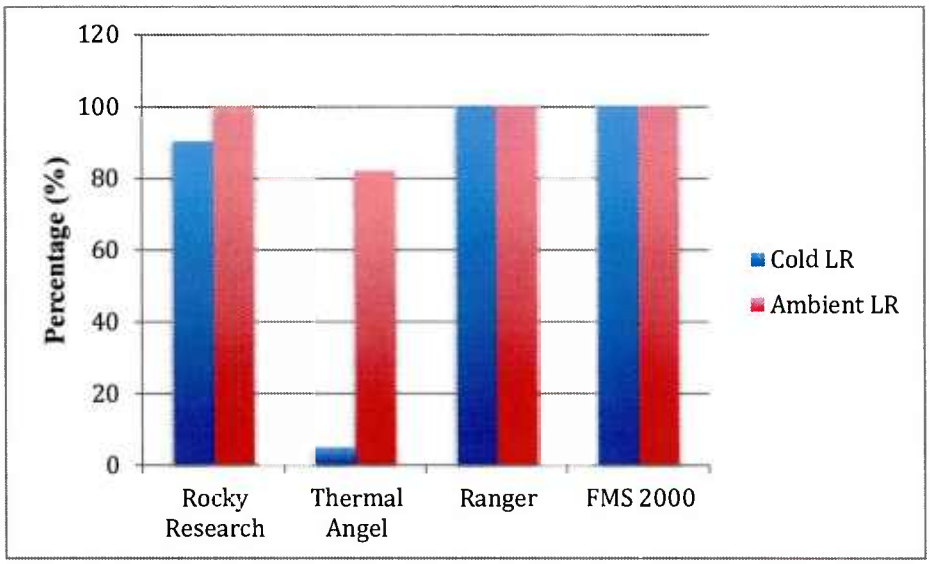


Figure 36. Rocky Research prototype comparison to commercial devices at low flow (150 mm Hg). Comparing proportion of time that the temperature at outlet port $\geq$ 32°C. $p < 0.05$ Rocky Research vs. Thermal Angel with ambient and cold LR. The Level 1 was excluded from low flow testing.

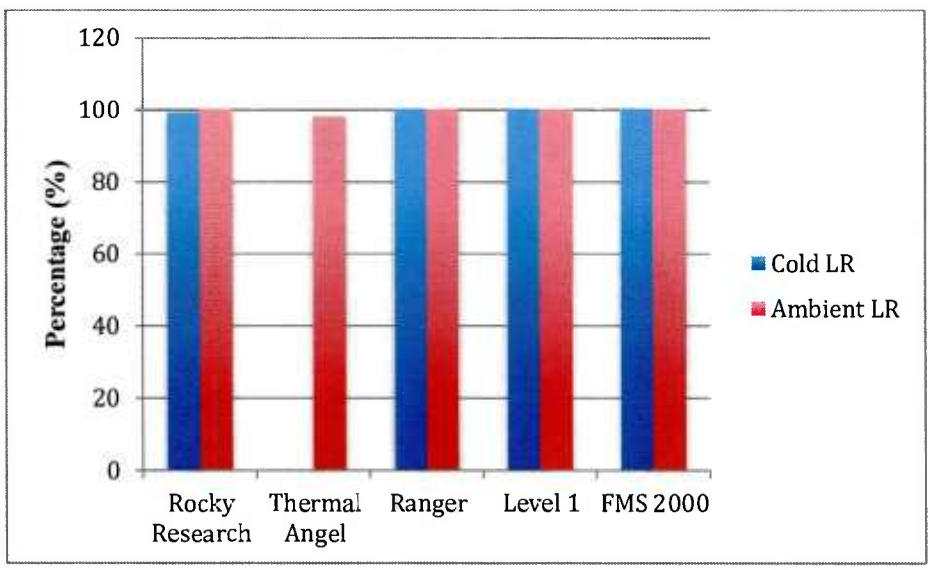


Figure 37. Rocky Research prototype comparison to commercial devices at high flow rate (300 mm Hg). Comparing proportion of time that the temperature at outlet port was $\geq$ 32°C. Thermal Angel was 0% with cold LR. $p < 0.05$ Rocky Research vs. Thermal Angel with cold LR

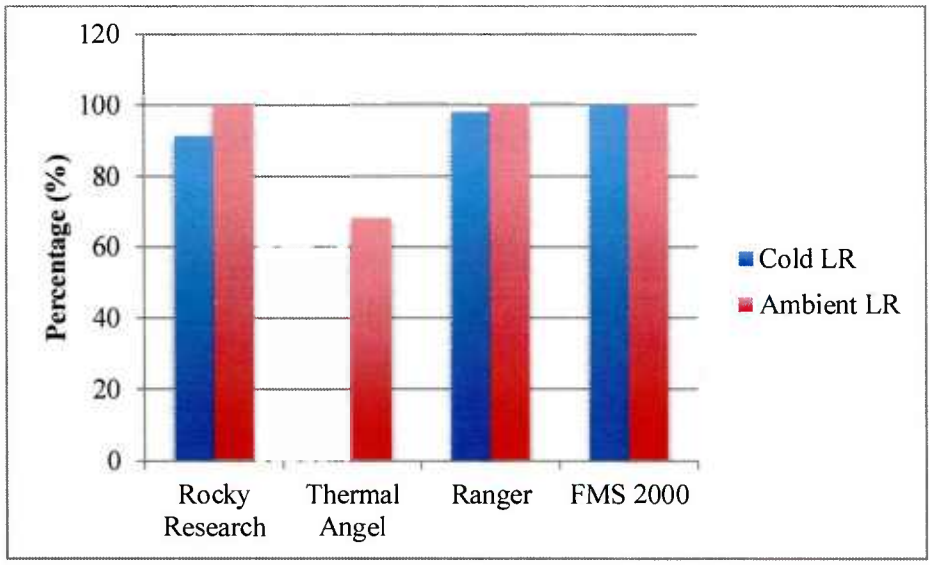


Figure 38. Rocky Research prototype comparison to commercial devices at low flow (150 mm Hg). Comparing proportion of time that the temperature at outlet port ≥ 35°C. Thermal Angel was 0% with cold LR. $p < 0.05$ Rocky Research vs. Thermal Angel with ambient and cold LR. The Level 1 was excluded from low flow testing.

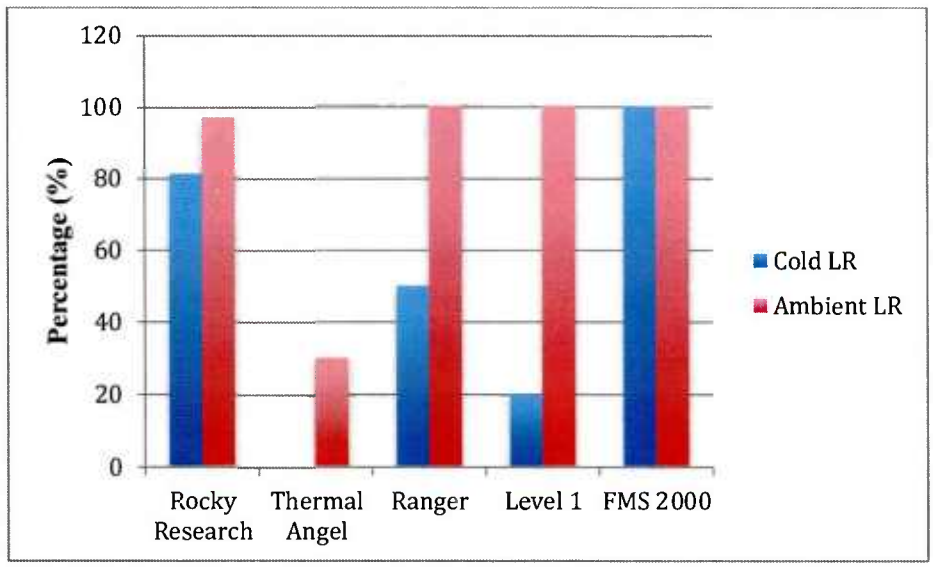


Figure 39. Rocky Research prototype comparison to commercial devices at high flow rate (300 mm Hg). Comparing proportion of time that the temperature at outlet port was ≥ 35°C. Thermal Angel was 0% with cold LR. $p < 0.05$ Rocky Research vs. Thermal Angel with ambient and cold LR. $p < 0.05$ Rocky Research vs. Ranger, Level 1 and FMS 2000 with cold LR.

TECHNICAL ISSUES

UNSOM and Rocky Research

UNSOM and Rocky Research recognized the need to work with an established company who specializes in medical temperature management products to assist in finishing work and commercializing of portable infusion fluid warmer. Two companies were approached during the second year of this project with the hope that one of the companies would be interested in a partnership. Each company sent representatives to meet with Rocky Research and UNSOM to discuss the possibility of a partnership. Both companies declined the offer of partnership after several months of discussions. In conversations with independent medical device consultants, several consultants had indicated the current economic environment has not been conducive to development of new devices and many commercial companies are not accepting outside projects.

Rocky Research

Several complications arose causing a delay in the delivery schedule while assembling the fluid infusion warmer prototypes. Multiple system components required redesign in order to improve system performance, reliability, safety and ease of use. Essential device components were no longer obtainable from the manufacturer due to manufacturer design changes. Specifically, the evaporator/condenser coil modifications implemented resulted in the coil no longer being able to withstand the operating pressures of the appliance. Consequently, a custom coil had to be designed, fabricated, and acquired. Furthermore, the original machine shop utilized to fabricate the new helical channel SPCs went out of business, resulting in a new shop having to be identified and a substantial time delay in the cartridge delivery schedule. Furthermore, several issues associated with the PCB redesign resulted in a delay of the prototype fabrication schedule.

The problematic issues associated with a multi-flow channel single patient cartridge heat exchanger were a significant setback. It required that the heat exchanger be revamped and optimized to alleviate the stagnant zones and mitigate the possibility of overheating the fluid or restricting flow. The new helical channel design allowed for a reliable method in ensuring air has been purged from the system before infusion. Elaborate investigation into optimizing a new flow channel design required a significant amount of time, ensuring that the new cartridge design was safe and effective in terms of maintainable flow rates and optimum heat transfer into the infused fluid.

A discrepancy was encountered between the outlet temperature read by the previous rapid infusion warmer prototype and the actual fluid outlet temperature being monitored via data acquisition. It was found that this incongruity could be attributed to a variance in the measured resistance on the thermistor at the outlet of the SPC. The discrepancy required extensive investigation into the root cause of the observed behavior. Primarily, identifying whether the origin of the problem was software or hardware related. A plausible explanation for the increased resistance on the thermistor, causing temperature reading accuracy to deviate, correlates to repetitive use. If the cartridge is not completely drained after bench top testing the outlet temperature thermistor is submerged in water. If the water penetrates the epoxy on the leads of thermistor it can result in corrosion of the thermistor material and subsequently increase resistance. Since cartridges are designed for a single use, degradation of thermistor accuracy for practical infusion implementations is unlikely. Even so, separate thermistors of higher accuracy have been identified and obtained for future cartridge implementation and evaluation. With the problem isolated to the thermistor on the cartridge, methodology for appropriately addressing the issue has been attained. Specifically, calibration of each thermistor on each cartridge is a necessity before utilization to ensure proper temperature readings.

Identifying and acquiring a new evaporator/condenser coil required a substantial amount of time. Not having a reliable source for a coil has prolonged the latest prototype fabrication significantly. Without the coil, the primary components of the heating subassembly could not be assembled. A large effort has been put into developing a new coil with little impact on the design, sizing, and spacing of other system components. Rocky Research worked closely with the manufacturer of the coils to expedite final prototype assembly. Even so, prototype assembly was delayed approximately 4 weeks until the coils were acquired, a significant delay.

The fabrication shop that machined the initial prototypes of the new helical SPC design went out of business shortly after initial product delivery. Resultantly, Rocky Research was forced to look elsewhere for a machine shop capable of producing the cartridges. The down time required to find a facility capable of reliable cartridge fabrication was significant, and once a new shop was identified a low quantity run had to be implemented for quality assurance purposes. Upon evaluating the cartridges, and deeming them acceptable, a larger quantity of SPCs was acquired. The implications of the process resulted in a substantial time delay.

Completely redesigning the control board required a considerable amount of time. After the board was redesigned it had to be evaluated for functionality and reliability before prototype assembly could ensue. With several issues identified during board assembly complete prototype fabrication had to be postponed until the issues could be addressed, resulting in a delay to the schedule.

UNSOM

Assay optimization for the analysis of whole blood has revealed that several of the proposed tests required fresh whole blood. Testing of > 24 hour old whole blood does not produce replicable test results. UNSOM had approached United Blood Services (UBS) and the American Red Cross, as potential sources of fresh whole blood (FWB). However blood bank regulations prevent the release of FWB prior to viral testing (48hr minimum). A viable source of FWB was not secured and several of the proposed tests were not optimized.

CONCLUSION/ FUTURE DIRECTION

The Rocky Research Portable Fluid Infusion Warmer prototype has been elaborately modified during the last three years. These refinements have led to a much improved device. Fabricated prototypes have been demonstrated to achieve objective infusion heating capacities, infusion rates, and the ability to accurately maintain target fluid temperature. Modifications have been implemented to the SPC as well as the functioning system in order to achieve such results. The PCB and control logic have been completely redesigned to better accommodate a cohesively functional product. Although the appliance has been drastically improved, there is still room to augment performance and reliability of the device. Future system implementations would inevitably incorporate modifications to enhance cartridge integrity along with ease and repeatability fabrication.

Four fluid warmer prototypes were delivered to UNSOM for bench performance testing and SPC's pRBCs feasibility testing. Three of the prototypes were used for bench performance studies and the fourth prototype was used for feasibility testing. Bench performance studies were performed on the fluid warmers and SPCs by evaluating flow rate and average outlet temperature. Three prototypes were evaluated by both thermal battery and AC power. All three units were similar in their ability to warm fluids to $\geq 37^{\circ}C$ by AC power and $\geq 36^{\circ}C$ by thermal battery respectively. Battery capacity was similar amongst the prototypes as well. SPCs were similar in heat transfer capabilities and pressure drop.

During the commercial device comparison study, Rocky Research's proof- of-concept thermal battery's heating capabilities generally performed better than or equal to other commercial fluid warmers (Thermal Angel, Ranger, Level 1, and FMS 2000) using all test conditions. The only exception was the FMS 2000 under two test conditions. In reaching average outlet temperature the prototype was approximately 1 minute and 40 seconds slower than FMS 2000 when using ambient fluid at high flow rate. Proportion of time the average outlet temperature was $\geq$ 35°C using cold LR at high flow rate, the prototype was 19% lower than FMS 2000. Rocky Research was the only portable device that may be operated by either high density thermal battery or AC power. Rocky Research's prototype fell in the middle of the four devices relative to weight and size. The prototype was unable to reach the flow rates achieved by the other commercial devices. However, tubing set ups may be varied to achieve higher flow rates.

A feasibility study was performed on the redesigned single helical channel SPC to determine safety and efficacy in using pRBCs. Extracellular potassium, percent hemolysis, and PS externalization were used as markers to determine global cellular damage of RBCs. CD47 expression was also measured as a marker of cell health. The SPC exhibited no measurable damage to RBCs. Hematalogical parameters such as RBC count and hematocrit were used as indicators of possible cell adherence to SPC's internal wall. There was a statistically significant decrease in RBC count and hematocrit indicating cell loss. Rocky Research plans to anodize the surface of the SPC which may correct this problem.

Several FDA working documents were created for future 510(k) submission. An FDA 510(k) preliminary review for Rocky Research Portable Fluid Infusion Warmer was compiled by a medical device consulting company. The review identified detailed information required to show Substantial Equivalence. User Requirements, Product Specification, and Biocompatibility Plan working documents were created by medical device consultants for the fluid warmer. An FDA consulting firm was hired to assist UNSOM in setting up a quality system to meet CFR Title 21 Part 820 requirements.

Currently, investors are being sought to continue funding the prototype's progress towards commercialization. Engineers at Rocky Research are acquiring type III colorless hard anodized cartridges with a standard thickness of 0.001'' and a conservative thickness of 0.002'' for pursuing further biocompatibility analysis. An FDA approved integrated medical device company will be selected to build a finalized Portable Fluid Infusion Warmer for further FDA testing with the ultimate goal of achieving future FDA 510K approval.

PRODUCTIVITY

Conference

Jones, M. Portable High Speed Blood and Fluid Transfusion Equipment: A Feasibility Study. The American College of Surgeons' Committee on Trauma 2012 Resident Trauma Papers Competition, 2011 Dec 3; Los Angeles, CA.

REFERENCES

1. Seghatchian J, Krailadsiri P. Red Cell storage lesion assessed by the levels of potassium, haemoglobin and Annexin V in supernatants. Tranfus Apher Sci. 2002 Apr; 26(2):139-43.

2. Kamel N, Goubran F, Ramsis N, Ahmed AS, Effects of storage time and leucocyte burden of packed and buffy-coat depleted red blood cell units on red cell storage lesion. *Blood Transfus* 2010; 8:260-6.

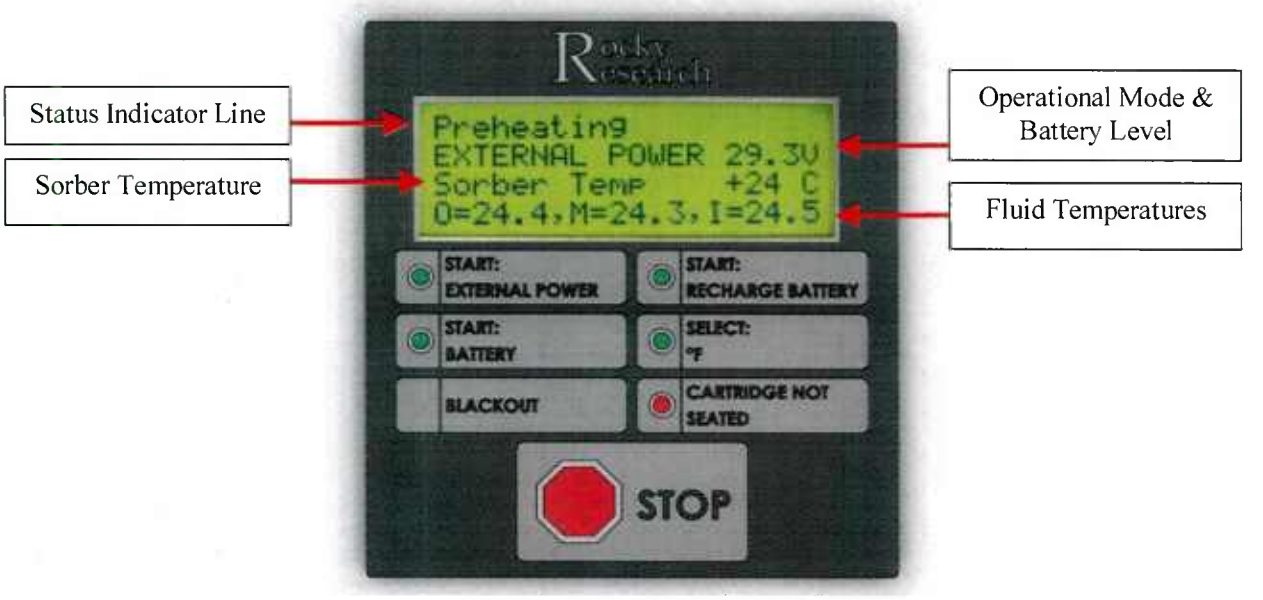
3. Dubick MA, Brooks DE, Macaitis JM, Bice TG, Moreau AR, Holcomb JB. Evaluation of commercially available fluid-warming devices for use in forward surgical and combat areas. Mil Med. 2005 Jan; 170(1):76-82.

Appendix A

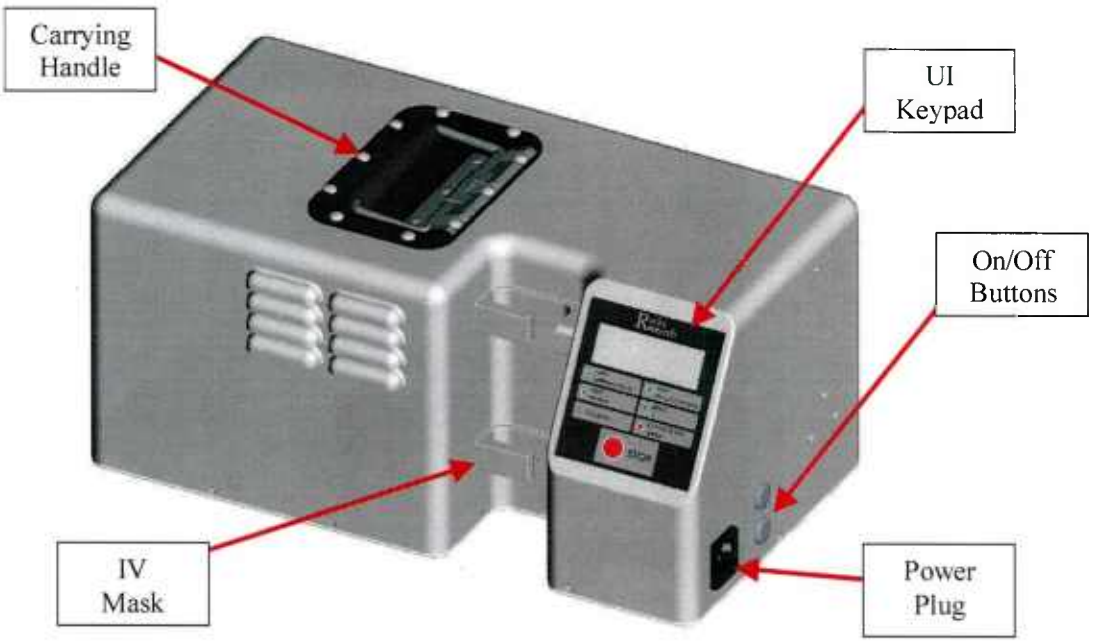
Portable Fluid Infusion Warmer
Operating Instructions

The user interface for the fluid infusion warmer is depicted below. The power on and off buttons are located on the right side of the unit and are labeled accordingly. The four line LCD display portrays relevant information pertaining to the status of the appliance. Such implications are pertinent to informing the user as to the state and operating mode of the device. The top line of the display is a status indicator line to alert the user as to the current status of the device. It is also a prompt to the user to inform them when certain tasks should be implemented, such as the start of fluid flow when preheating is complete. Furthermore, the status indicator line is where errors are presented and provides information to the user as to whether or not the SPC is properly seated. The second line of the display provides two sets of information. First, it informs the user as to the operational mode of the device, "READY", "EXTERNAL POWER", "BATTERY", "RECHARGING", or "COOLING DOWN". It also provides to the user the available voltage from the DC battery. A fully charged battery should indicate an available voltage of approximately 29.3V. The fourth line of the LCD display is to inform the user of fluid temperatures throughout the SPC during an infusion. "O" indicates outlet temperature, "M" indicates the fluid temperature at the center point of the path of the cartridge, and "I" is indicative of the fluid temperature as it enters the appliance. Under most operating circumstances the outlet temperature will yield the hottest fluid temperature. There are circumstances however, such as preheating and low flow rates, when the outlet temperature is not necessarily the hottest temperature, and for that reason all three temperatures are depicted on the display. The most prevalent temperature is the outlet temperature because it is closest to the temperature that the fluid will enter the patient. The device has been designed, developed, and implemented to regulate outlet fluid temperature at 37°C. Due to thermal gradients in the sorber, the hottest location of the SPC for stagnant flow is generally located at the center. For that reason, the outlet temperature is controlled to 37°C, but the hottest fluid temperature is modulated not to exceed 42°C, dangerously close to the possible hemolyzation temperature of blood at 45°C. Furthermore, the audible alarm is triggered if fluid temperature at any location in the cartridge reaches the 42°C mark. The system is designed to eliminate the possibility of fluid exceeding the 42°C temperature under any and all operating conditions.

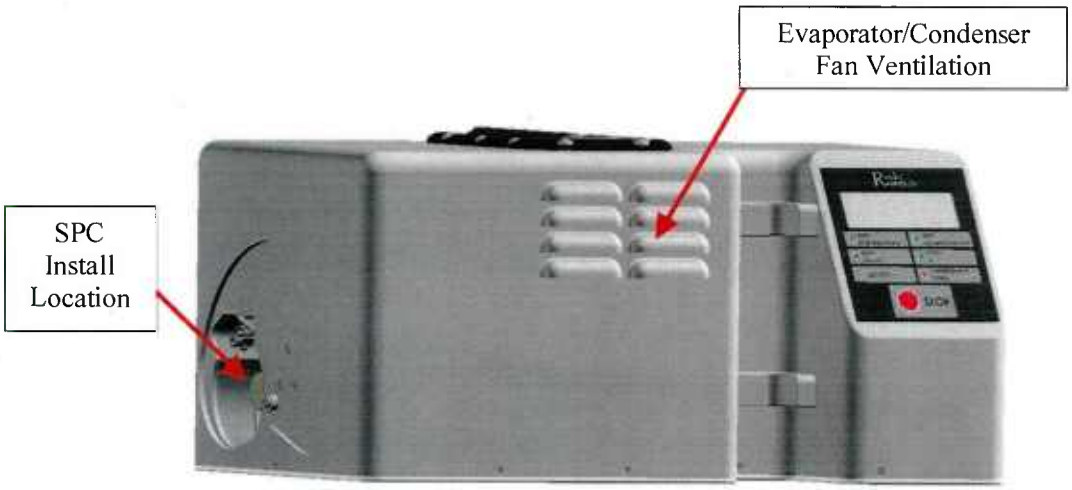
When the appliance is connected to external power the back light is continuously illuminated. When operating on battery power, if the device is inactive for 3 minutes following any user input the device will power off. Operating from either mode, if the user wishes to eliminate the backlighting from the LCD display they can do so by selecting the "Blackout" button. Toggling the "Blackout" button will allow the user to alternate between dimming and illuminating the backlight of the display.



Fluid infusion warmer user interface



Fluid Infusion Warmer Case



Powering on the Device

To power on the portable fluid infusion warmer select the "ON" button located on the right hand side of the case. When power is turned on to the device the LCD will display "Rocky Research" on the Status line, "Bloodwarmer" on the operational mode line, and the software version on the sorber temperature line. The LED's on the keypad will be individually illuminated in a scroll through process to ensure proper functionality. The sequential order for the LED illuminations is external power, battery, recharge battery, select F, and then cartridge not seated. Additionally, the audible alarm will beep three times to inform the user the alarm is fully operational. If the alarm does not beep or the LED's on the keypad don't cycle the appliance should be further evaluated before operation.

Installing a SPC

Medical tubing can be configured and attached to a SPC before or after the cartridge is installed on the fluid infusion warmer. If the medical tubing is connected before the cartridge is installed on the device extra precautions should be taken to ensure that the tubing does not get kinked, or restrict flow in any way when the cartridge is connected.

1) Open the heat shield on the case that isolates the sorber from the atmosphere by pivoting the shield door to the right.
2) Unfasten the knob utilized to support and secure the top end of the sorber to the case. The knob is spring loaded; upon unthreading the spring force will hold the latch in an open position.
3) Slide the cartridge onto the sorber. The cartridge should sit snugly over the sorber without pushing down with excessive force. Unwarranted force can instigate damage to the electrical contacts of the cartridge and compromise the integrity of the cartridge. The handle of the SPC should be utilized in order to tightly force the SPC onto the sorber.
4) When proper contact with the cartridge to the appliance is accomplished the status line on the LCD will display nothing. If a contact is compromised the line will display which contact is missing, where "in" portrays the inlet temperature, "mid" portrays the middle temperature, and "out" depicts the outlet infusion temperature.
5) Once the cartridge is properly seated, secure the end of the sorber by closing the support knob.

6) The case cover must be open when the cartridge is installed to accommodate connecting of the medical tubing.

Removing a SPC

SPCs are single use devices and must be interchanged between infusion patients. Removing the cartridge consists of the following procedure:

1) Unscrew the threaded knob supporting the sorber and cartridge.
2) Use the handle to pull the cartridge off of the sorber without utilizing excessive force.
3) If the cartridge is tightly installed utilize a thumb as leverage on the top of the sorber, do not tug on the handle or apply excessive force due to the risk of breaking the handle.
4) Remove the medical tubing once the cartridge has been removed from the sorber. DO NOT remove the medical tubing while the cartridge is installed on the sorber. Risk of fluid contamination to the appliance is a critical concern.

Heating utilizing external power

To implement an infusion utilizing AC power the appliance must be plugged into external power. If the device is not connected to an external power source, and the user attempts an infusion by selecting the "Start: External Power" button, the user will be prompted on the status line with a message stating, "Plug into Ext. Power". If the device has external electrical power available, the device will go into a preheating state. When the hottest fluid temperature, as determined by the three thermistors located down the length of the SPC, reaches 34°C the status line will instruct the user to start flow. Upon the user initiating flow, and flow detected by the appliance, the status line will go to "Flow Detected". "Flow Detected" indicates an active control state. The appliance will stay in this mode until the stop button is pressed. Upon pressing the stop key the device will go back to a ready state awaiting further user input. A step by step procedure for performing an infusion utilizing external power is presented:

1) Turn the appliance on by selecting the "ON" button located on the right side of the device. Powering on the device will initiate a quick test sequence to ensure proper system functionality as described above in (Powering on the Device).
2) Ensure the operation mode depicts "READY", then install a single patient cartridge on the absorber of the fluid infusion warmer (refer to Installing a SPC).
3) Connecting the medical infusion tubing to that of the cartridge and prime the cartridge.
4) Select the "Start: External Power" button. The appliance will go into a preheating state and "Preheating" will be displayed on the status indicator line of the screen.
5) When the status indicator line displays "Start Flow" initiate flow. Initiating fluid flow before preheating is complete will force the device into an active control mode just as if preheating had been achieved. Starting an infusion before preheating is complete should be done only under the guidance and discretion of qualified medical personnel.
6) When flow is started the device will recognize flow and the status line will indicate "Flow Detected". The indicator implies an active control mode for the device and the appliance will automatically regulate infusion fluid delivery temperature. Continue the infusion as deemed appropriate for the medical application at hand. 750 W of heating power is available utilizing the electrical heaters, providing enough heat input to accommodate a water fluid flow rate of 325

cc/min neglecting heat losses. A flow rate above 325 cc/min will undoubtedly result in a degradation of obtainable fluid infusion temperature from the targeted 37°C.

7) Once the infusion is complete select the "STOP" button on the bottom of the keypad to cease heat input to the SPC. The appliance will cycle back to a "READY" mode awaiting further user input. Fluid flow should be haltered through the SPC before selecting the "STOP" button.

Heating utilizing TES

To implement an infusion utilizing the thermal battery the appliance must be unplugged. If the device is connected to an external power source, and the user attempts an infusion by selecting the "Start: Battery" button, the user will be prompted on the status line with a message stating, "Unplug Ext. Power". If the appliance is unplugged, the device will go into a preheating state. When the hottest fluid temperature, as determined by the three thermistors located down the length of the SPC, reaches 34°C the status line will instruct the user to start flow. Upon the user initiating flow, and flow detected by the appliance, the status line will go to "Flow Detected". "Flow Detected" indicates an active control state. The appliance will stay in this mode until the stop button is pressed. Upon pressing the stop key the device will go back to a ready state awaiting further user input. A step by step procedure for performing an infusion utilizing external power is presented:

1) Turn the appliance on by selecting the "ON" button located on the right side of the device. Powering on the device will initiate a quick test sequence to ensure proper system functionality as described above in (Powering on the Device).
2) Install a single patient cartridge on the absorber of the fluid infusion warmer (refer to Installing a SPC).
3) Connecting the medical infusion tubing to that of the cartridge and prime the cartridge.
4) Select the "Start: Battery" button.
5) A series of clicking sounds will be emitted from the device. The sound originates from pulsating of the solenoid valve utilized to control ammonia flow during and absorption and is entirely normal. The appliance will go into a preheating state and "Preheating" will be displayed on the status indicator line of the screen.
6) When the status indicator line displays "Start Flow" initiate flow. Initiating fluid flow before preheating is complete will force the device into an active control mode just as if preheating had been achieved. Starting an infusion before preheating is complete should be done only under the guidance and discretion of qualified medical personnel.
7) When fluid flow is started the device will recognize flow and the status line will indicate "Flow Detected". The indicator implies an active control mode for the device and the appliance will automatically regulate infusion fluid delivery temperature. Continue the infusion as required for the utilized application or until the loss in TES capacity results in the infused fluid temperature dropping below acceptable temperature as allocated by medical personnel. Although the device will control infusion temperatures to 37°C, sufficient delivery temperature is at the discretion of the user once the storage capacity diminishes below that required to regulate at target temperature.
8) Once the infusion is complete select the "Stop" button on the bottom of the keypad to cease heat input to the SPC. The appliance will cycle back to a READY mode awaiting further user input. The system must be recharged before again being utilized in heat battery mode.

Recharging the System

In order to recharge the TES system the SPC must be removed from the device. If a cartridge is installed and the user attempts a recharge they will be prompted with a message from the status line of the display stating, "Remove Cartridge". External electrical power must also be available in order to implement a recharge of the TES system. If external power is not available the user will be informed via the status line indicator with a message stating, "Plug into Ext. Power". Once the cartridge has been removed the user is capable of implementing a system recharge.

1) Ensure external power is available by plugging in the device.
2) Remove the SPC from the unit (refer to Removing a SPC).
3) Select the "Start: Recharge Battery" button.
4) An initial click will be heard inside the appliance, indicative of the solenoid valve opening allowing for the passage of ammonia vapor out of the sorber and back to the reservoir.
5) The sorber recharge algorithm is implemented to detect when the system is fully recharged. The sorber will consistently reach temperatures of 195°C, so it is critical that the user does not come in contact with the sorber during a TES recharge.
6) After the sorber is recharged the appliance, especially any METAL COMPONENTS WILL BE VERY HOT. Do not touch any system components until the cool down is complete.

Cool Down Mode

1) THE DEVICE CANNOT BE UTILIZED for an infusion until Cool Down mode is complete. Furthermore, an SPC should not be placed on the appliance until cool down has commenced.
2) The appliance will go into a cooling down immediately upon the conclusion of a recharge. The status indicator line of the appliance will display "Cooling Down".
3) Upon entering cool down mode a small fan will turn on to circulate heat accumulated in the inner heat shield of the appliance to the ambient environment.
4) Cool down will conclude once the sorber temperature drops to 35°C, a safe temperature for implementing another infusion.
5) If a cool down is unintentionally interrupted before completion, the user can force a manual cool down by implementing the following procedure:
    i. Select the "Blackout" button and hold it down.
    ii. Without releasing the "Blackout" button turn off the power to the device.
    iii. Still holding the "Blackout" button, turn the power pack on to the device.
    iv. Release the "Blackout" button, the device should instantaneously initiate a cool down and the user should hear the small fan operating to produce airflow across the sorber.

NOTE: A cool down can only be instigated if the sorber internal temperature is above 35°C.

Additional Functionality and Buttons

The sequence for actively initiating cool down consists of holding down the blackout button, turning the unit off, power the unit back on, then releasing the blackout button.

Requested capability in terms of enhancing operation discreetness has been incorporated into the current fluid infusion warmer prototypes via the "Blackout" mode. Selecting the "Blackout" button allows the user to turn off the backlighting of the LCD display. Full system functionality is still available in blackout mode. The objective of the blackout button is to allow users to operate the device covertly, so that in a combat situation the appliance does not reveal the users location. Switching between blackout mode and normal operational mode is achievable by selecting the button. If the button is toggled back and forth the unit will dim and illuminate the display.

The device is capable of toggling the display temperature between degrees Celsius and degrees Fahrenheit via the "Select: °F" button. By default all temperatures are portrayed in units of degrees Celsius. Press the "Select: °F" button to display the temperature in degrees Fahrenheit. The LED associated with the "Select: °F" button on the keypad is illuminated when the units are in degrees Fahrenheit. The unit labeling is presented on the right side of the Sorber temperature line, the third line of the display. Press the button again to switch display temperature units back to degrees Celsius. The LED light on the keypad will turn off upon doing

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
10/14/2013	Final Technical Report	01 Jun 2010 - 30 Jun 2013

4. TITLE AND SUBTITLE
High Speed Blood and Transfusion Equipment

5a. CONTRACT NUMBER

5b. GRANT NUMBER
N00014-10-1-0869

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Fildes, John, MD (PI)
Browder, Timothy, D., MD (Co-PI)
Rockenfeller, Uwe, PhD (Rocky Research)
Khalili, Kaveh (Rocky Research)
Hoffmann, Ryan (Rocky Research)

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Nevada System of Higher Education DBA
University of Nevada, Reno
204 Ross Hall MS 325
Reno NV 89557-0240

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of Naval Research
300 5th Ave., Suite 710
Seattle, WA 98104-2398

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
Report prepared in cooperation with Rocky Research (1598 Foothill Dr., Boulder City, NV. 89005)

14. ABSTRACT
Many patients become hypothermic after severe injury due to environmental exposure during transportation and during resuscitation efforts following trauma. A portable fluid infusion warmer prototype has been designed, built and refined for administering fluid or blood components into the body at or above body temperature of 37 degrees Celsius to avoid hypothermia. This proof-of-concept device incorporates a high density thermal battery technology to allow for rapid fluid warming in the absence of external power sources. The device is capable of heating 1 liter of fluid from 4 to 37 degree Celsius at infusion rates from 2 - 200 mL/min utilizing thermal battery system or operated indefinitely on AC power.

15. SUBJECT TERMS
Hypothermia, Fluid Warmer, Trauma, Military

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			ONR
U	U	U	UU	67	19b. TELEPHONE NUMBER *(Include area code)*