Immunodrop

Product Design Specifications

Product Design Specifications (PDS)

BME 200/300 Section 312
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Client

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Function

Collagen, and specifically Collagen Type I, is one of the most abundant proteins in the body, making up close to 90% of the structures within the extracellular matrix of a person. This makes it the perfect host for cell manipulation and transport in experiments or injections into patients [1]. Within laboratory settings, collagen is split into small beads and droplets using droplet generators and specifically engineered molds. Droplet generators employ syringes and syringe pumps to obtain a constant flow of collagen as well as certain oils, such as fluorinated oil, from another pump [1,2]. The device for Dr. Cristina Sanchez de Diego will generate collagen droplets containing T and B cells for use in an artificial lymph-node germinal-center model. This model will ultimately be used to study cancer-cell metastasis through the lymphatic system.

Client requirements

The client has the following requirements:

- Produce collagen droplets with a target volume of approximately 0.5 μL.
- Maintain the collagen solution at approximately 4 °C during droplet generation to reduce premature gelation and channel clogging.
- Fill the collagen gels with B and T cells and ensure that the collagen gel fully polymerizes at approximately 37 °C.
- Generate droplets automatically after activation without requiring continuous user intervention.
- A five- to ten-minute run-time was requested in order to keep up with the quick-paced nature of the lab.

Design requirements

1. **Physical and Operational Characteristics**
    a. **Performance requirements**
        i. The device should be autonomous in its operation, with the pumps being activated and the collagen droplets being produced and stored on the other end. New syringes of fluorinated oil and collagen should be easily accessible and replaceable when needed. The flow of each fluid used in the device- fluorinated oil, collagen, and a mixed-in or external surfactant- should all be simultaneous and at similar rates to properly produce collagen beads.
        ii. The device should be able to store excess collagen and keep it at 4 °C until the next use without fear of the collagen polymerizing while it is left in the device.
        iii. Bead collection should also be an automatic process, with a holding chamber designed to immediately initiate the process of incubation required prior to experimental use of the collagen microspheres. This will take place at 37 °C and should be implemented into the flow of the device naturally.
        iv. The device should operate at a rate and duration in accordance with the needs of the client currently specified to produce at least 300 collagen beads but more effectively closer to 600 collagen beads during each cycle. Additionally, this production cycle must

take place within a timeframe that increases the efficiency of the bead production process beyond the current timeframe required to individually hand-curate each microdroplet.

b. **Safety**
   i. All fluid-contacting components must be sterilized before experiments involving live cells to prevent culture contamination and user exposure to biological materials.
   ii. Syringes, tubing, and connections must remain below their manufacturer-specified pressure limits to prevent leakage, disconnection, or component failure [3].
   iii. The glass substrate must be inspected for cracks and handled carefully to prevent breakage, cuts, and exposure to sharp edges.
   iv. Heating and cooling units associated with the survival and incubation of B and T cell collagen beads should be diligently tested to remain within safe limits.
   v. All heated surfaces must be appropriately labeled.
   vi. Users must wear appropriate personal protective equipment and follow applicable laboratory and biological-safety procedures.

c. **Accuracy and Reliability**
   i. The accuracy of the droplet generator will be within a variable range of the 0.5μL specified value for collagen beads. Using tolerances and deviations stated in a previous publication from our client detailing a microfluidic droplet process, we predict the tolerance of this project to be about 0.5μL ± 0.23 μL. This could be caused by varying sizes of microfluidic channels or differing pressures calibrated within the device.

d. **Life in Service**
   i. The entire device should run for approximately 5-10 minutes, producing an ample amount of collagen droplets to fulfill the number of B and T cells used in each of the client's experiments. Molds need to be switched out after each use. However, the device should also keep the collagen at the requested temperature of 4 °C for up to a week, providing additional time for the client to wait before using the droplets. Additionally, any excess collagen not used in the first batch should be kept at 4 °C. This all leads to a life-in-service time of approximately one week, with the cooling mechanism being functional at almost all parts of the day if necessary.

e. **Shelf Life**
   i. With this device, failing parts, such as clogged syringes, damaged tubing, or faulty pumps, must be switched out easily without disassembling the entire system. Failing components like this have a wide range of timelines, with syringes remaining sterile for 3-5 years [4], while tubing used in the system will stay usable unless a leak or breakage occurs. Important and more expensive ones such as the cooling apparatus and the pumps should be able to withstand 8-12 years of use before requiring maintenance [5].

f. **Operating Environment**
   i. All procedures involving live cells must be performed aseptically in a biological safety cabinet by trained personnel.
   ii. Cell-free fabrication and proof-of-concept testing may be performed in an appropriate laboratory space by trained personnel.

iii. The collagen solution must be maintained at approximately 4 °C before and during droplet generation to limit premature polymerization, which could increase viscosity and clog the microchannels [6].
iv. Cell-containing droplets must be transferred aseptically to an incubator maintained at 37 °C and 5% CO_2.

g. **Ergonomics**
   i. The device should stay isolated from other laboratory equipment so as not to interfere with other protocols or testing. A collection dish, the syringe loading spots in the pumps, and the mold should all be easily accessible and independent of each other's places in the system. Overall, the system should be one piece of equipment, able to be moved by one person without any loose-hanging or free parts that need to be moved later. Because of this, weight is our largest ergonomic consideration, followed by the size of the system.

h. **Size**
   i. For the droplet generator, Ali et al.'s design may be used as a starting point rather than choosing the dimensions randomly. Their device used a 100 μm-wide collagen channel, 300 μm-wide oil channels, and a 75 μm nozzle where the droplets formed. This setup produced collagen droplets from about 100–1400 μm, depending on the pressure and operating conditions [7].
   ii. Another study by Hong et al. used a T-junction to generate collagen microspheres ranging from approximately 50–300 μm, with about 2% variation in size. Based on these studies, 100–300 μm is a reasonable starting range for the microspheres, but the channel dimensions should be finalized after deciding how many B or T cells we want per microsphere. This is important because the droplet size and cell concentration will determine the number of cells in each microsphere [8].
   iii. The device as a whole must fit inside a Class II Biological Safety Cabinet per the Centers for Disease Control and National Institutes of Health "Biosafety in Microbiological and Biomedical Laboratories," which states that all immune cells must be handled under Biosafety Level 2 conditions. This will help maintain sterility and protect the operator from fluidic leaks or pressurized tubing failures [9].

i. **Weight**
   i. 1–3 mg/mL of collagen [7].
   ii. The device must be able to be operated and maneuvered by one user. This gives the system a maximum weight of around 50 lb, so it is able to be moved by anyone.

j. **Materials**
   i. Materials contacting the cell suspension, including PDMS, glass, tubing, and syringes, must be biocompatible.
   ii. Autoclavable components should be autoclaved when appropriate and opened inside the biological safety cabinet.
   iii. Non-autoclavable components must be disinfected or sterilized using a method that does not damage the material or leave potentially harmful chemicals on the material surface.
   iv. Printed resin molds must be washed, dried, and UV post-cured according to the resin manufacturer's specifications before PDMS casting [10].

v. Finished PDMS components must not contain uncured resin or other residues that could inhibit PDMS curing or harm the cells.

k. **Aesthetics, Appearance, and Finish**

i. The generator should have a clean, transparent, and well-finished PDMS structure, with smooth and clearly defined microchannels so that we can easily see the flow and droplet formation during testing. PDMS is commonly used for microfluidic devices because it is optically transparent, biocompatible, flexible, and relatively easy to fabricate [11].

2. **Production Characteristics**

a. **Quantity**

i. One functional device is required for the client.

ii. Because each microfluidic chip will be single-use, the finalized design must allow chips to be fabricated repeatedly with consistent channel geometry and droplet-generation performance.

b. **Target Product Cost**

i. The target cost for the reusable device setup, excluding equipment and materials already supplied by the laboratory, is less than $100.

3. **Miscellaneous**

a. **Standards and Specifications**

i. The device is not considered a medical device under section 201(h) of the Food, Drug, and Cosmetics Act.

1. The act states a device is “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes” [12].

ii. The incubation device will require being heated to an appropriate incubation temperature, so ISO 7010-W017 must be considered.

1. ISO 7010‑W017 mandates the use of a standardized warning symbol to identify equipment presenting hazardous high‑temperature surfaces and to support consistent risk communication across laboratory and industrial environments. Proper implementation requires evaluating the equipment’s operating temperature, the likelihood of inadvertent contact, and the visibility and durability of the applied symbol. Thermal burn hazards and physical configurations that may impede recognition must be considered during risk assessment. ISO 7010 states that “the purpose of standardized safety signs is to draw attention rapidly and unambiguously to objects and situations affecting safety,” and requires application

in accordance with ISO 3864-1 and ISO 3864-4 to ensure uniform color, shape, and meaning [13].

iii. The device must comply with ISO 22916, a standard on interoperability requirements for dimensions and connections of microfluidic devices.
   1. The minimum distance of any hole from the side of the chip is 3mm. The total chip thickness can range from 0.8mm to 4mm. All ports must be at least 0.4mm in diameter. For ports 1.5mm apart center-to-center, the maximum port diameter is 0.7mm. For ports 3mm apart center-to-center, the maximum port diameter is 2.0mm. For ports 4.5mm apart center-to-center, the maximum port diameter is 3.5mm [14].

iv. The device must fit inside a Class II Biological Safety Cabinet per the Centers for Disease Control and National Institutes of Health "Biosafety in Microbiological and Biomedical Laboratories".
   1. This states that all immune cells must be handled under Biosafety Level 2 conditions. This will help maintain sterility and protect the operator from fluidic leaks or pressurized tubing failures [9].

v. The device and materials used must not kill the immune cells before testing or research occurs. Thus, the device must pass ISO 10993-5 in vitro cytotoxicity testing.
   1. This testing involves soaking the device's materials like PDMS and tubing in cell culture media at 37°C for 24 to 72 hours. Next, expose a standard cell line to this liquid and measure cell health using an MTT or XTT assay. The passing score is 70% cell viability. If the materials reduce cell survival by more than 30% compared to a control group, they are considered toxic and fail the test [15].

b. **Customer**

i. The client wants the device to maximize usable collagen-droplet output while minimizing operating time and user involvement.
   1. This includes vertically integrating the collagen and device cooling procedure, manual droplet fabrication process, and completed collagen bead incubation into a single automated cycle.
   2. A single control will initiate this cycle that then runs independently, producing the desired number/volume of beads.

ii. The device is intended for use by trained personnel in the client's research laboratory.

c. **Patient-related concerns**

i. N/A: The device is intended for laboratory research and will not involve patients. Sterilization requirements are addressed under Safety, Materials, and Operating Environment.

d. **Competition**

i. Micropillars are being implemented in microfluidics with a variety of impacts. In traditional droplet generators, micropillars can be used as structural support to prevent the delicate surface of microchannels from collapsing under stress. They are also used for flow regulation and sorting as a method of filtration. Finally, they are used to create parallel channels that exponentially increase the droplet generation rate in advanced chip designs. [16]

ii. Another competitive alternative is the spinning conical frustum mechanism that has been developed as a centrifugal way of creating extremely unique and ordered droplets without the use of microfabrication. [17]

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