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Microfluidic Bandage based on Diffusion Delivery

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Abstract- Over 400,000 people worldwide are living with Hemophilia A, a disease predominantly caused by deficiency of clotting factor VIII in the blood plasma. A localized application of the recombinant clotting factor VIII by integration with the contemporary bandage would help mitigate the damage caused by injuries in a hemophilia patient. The designed bandage would work on the principle of microfluidic diffusion delivery using a layer of membrane above which a microfluidic channel is present. The device was designed using a) Kinetic studies; b) Membrane Analysis; c) Finite element method. Hence an optimum design was achieved which provided maximum diffusion for minimum flow. The ease of application and the cheap manufacturing cost of the appliance, facilitates the large-scale production of this device at a low cost. This technique could further be extended to all drug delivery practices.

Keywords – Drug delivery, Microfluidic bandage, Bleeding disorder, PDMS membrane ,Clotting Factor

I. INTRODUCTION

Bleeding is the loss of blood due to damage to the blood vessel. Blood coagulation is a process that changes blood from a liquid into a gel forming a blood clot. It results in hemostasis cessation of bleeding. Blood coagulation is a result of 2 reactions – Platelet activation and the Coagulation cascade. These reactions are dependent on the concentration of platelets and 13 clotting factors present in blood plasma as specified by Davie and Earl[1].

Bleeding disorders is the result of the inability of blood to form proper blood clots at the site of blood vessel injury. These are caused by defects in platelets or blood clotting factors.

Hemophilia A, a bleeding disorder that affects more than 400,000 people worldwide is caused due to genetic deficiency in clotting factor VIII. It leads to prolonged bleeding even from common injuries.

Depending on the severity of the disease, Gilbert, Rosendaal and Aledort [2], classify Hemophilia A into three types. Individuals with less than 1% active factor are classified as having severe hemophilia, those with 1–5% active factor have moderate hemophilia, and those with mild hemophilia have between 5–40% of normal levels of active clotting factor.

Individuals with severe hemophilia often require regular treatment to prevent internal bleeding especially in joints, muscle, digestive tract, brain. In addition to that, they require special first aid and subsequent treatment in the event of any injuries to prevent superficial bleeding.

A. Traditional Methods

One of the most common methods of treatment of hemophilia is replacement therapy where concentrates of clotting factor VIII is injected into the vein to compensate for the deficiency in the bloodstream. Replacement therapies are classified into two types on the frequency of their administration. Demand replacement therapies are provided to stop immediate bleeding whereas prophylactic therapies which are administered on a regular basis

reduces the damage caused by bleeding even before first aid is received. However prophylactic therapies are more intensive and more expensive than demand therapies. According to Pier Mannuccio, DDAVP is conventionally used to treat mild Hemophilia A[3]. A literature research of 23 studies by Robson and Leung[4]showed that 4.3% of the patients showed side effects. Hypertension and Seizures were the predominant complications that were noted[5-8].

B. Concept

Microfluidic Bandage helps in the localized application of clotting factors by integration with a contemporary bandage. It consists of a layer of membrane above which a microfluidic channel is present. The user applies pressure on the bandage using a squeeze-chip which will cause the flow of fluid through the membrane into the wound site. The fluid contains a solution of recombinant factor VIII in blood plasma. Recombinant factor VIII is used to prevent infection associated with direct factor VIII transfusion. Bray and Gomperts proved that it doesn't have any side effects that is usually associated with desmopressin. [9]

C. Membrane

Polydimethylsiloxane (PDMS) Membrane is present above the microfluidic channel to enable the flow of liquid through it into the wound when the user applies pressure on the bandage using a squeeze-chip. It is a mineral-organic polymer (a structure containing carbon and silicon) of the siloxane family. PDMS is the most widely used silicon-based organic polymer and is particularly known for its unusual rheological (or flow) properties. PDMS membrane devices that are extremely flexible due to both the very low Young's modulus and the thickness of the membrane[10]. PDMS is optically clear, and, in general, inert, non-toxic, and non-flammable and anti-fouling properties. Due to the high permeability of PDMS, the membrane can be used to exchange gas or small molecules between two liquids or a gas and a liquid without direct contact.[11] It also has a higher mass transfer coefficient than compared to other membranes[12]

II. Experiment and Results

In this present work, it is employed a microfluidic channel which is coupled with a PDMS membrane. Due to the immense pressure applied by the fluid on the membrane, diffusion delivery takes place. The required factor VIII concentration for a hemophilic patient was initially determined by studying the kinetics of blood coagulation [16-17]. The fig. shows that a steady state concentration of 1 μM and flow velocity of 60 mm/s is to be maintained using the delivery system proposed. Keeping the concentration of component factor VIII in blood at normal values as found in people not suffering from hemophilia promises steady localized application of the component for a clotting time of a healthy human being. This hence facilitates in reducing the clotting time of a hemophiliac patient.

A. Kinetic Analysis

According to Butenas and Saulius[18], the concentration of Factor VIIIa in the blood of a healthy individual is around 1.22 nM. This concentration can be assumed to be uniform for all practical purposes. Assuming that the concentration of Factor VIIIa in a hemophilic individual is negligible, the desired Haemophilia A level increase can be calculated.

One IU (unit), as defined by the World Health Organization standard for blood coagulation factor VIII, human, is approximately equal to the level of factor VIII activity found in 1 mL of fresh pooled human plasma

Therefore the dose of Hemophilia Factor A in IU can be calculated by

$$\text{Dose AHF (IU)} = W \times D \times 0.5 \qquad \ldots.(1)$$

where,
W=Weight of body in kg
D=Desired AHF increase

The formula was used to find out the dose of Kogenate FS in terms of IU. Kogenate FS should be administered at the rate of 10mL per minute at a concentration of 1 IU.Using the standard IU data for Kogenate FS for a body weight of 80 kg, the concentration of the microfluid in the bandage was calculated to be 1 mM.[19]

B. Membrane Calculations

The general equation of mass transfer in liquid boundary layer can be generally given by:

$$J_i = K_l * (C_{i,b} - C_{i,w}) \qquad \ldots.(2)$$

Where,

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k_l is the boundary layer mass transfer coefficient,
$C_{i,b}$ the concentration of component I in liquid bulk,
$C_{i,w}$ the concentration in liquid at the liquid–membrane interface

Based on the solution-diffusion model[21], the flux of component i through the membrane (from membrane surface to permeate side) can be expressed as:

$$J_i = (D_m / L)* C_{i,m}(1 – (p_{i,d} / p_c)) \quad \ldots.(3)$$

Where,
Dm is the diffusion coefficient in the membrane
L the membrane thickness

Thus, by varying the concentration inlets and taking the out stream pressures as normal blood pressure range, pressure inlet can be modeled. The required pressure drop to be exerted on the system comes out to be 11000 Pa.

C. Flow Calculations

Hence a pressure of 11000 Pa must be exerted by the microfluidic system on the membrane. The microfluidic flow pattern was analyzed using the commercial software ANSYS 17.0 (licensed). The system is assumed to be in laminar, incompressible flow regime [22-24] and is assumed to be a 3-D model. The pressure domain is as given in fig. (1). Since the flow is in microfluidic scale it is to be assumed as completely laminar. The viscosity of the fluid is assumed to be as of plasma as 1.5 cF. The pressure hence obtained (fig 1) on the membrane due to the flow is parameterized versus the inlet velocity. The flow velocity is analyzed in the range of 0-100 mm/s and the respective pressure exerted on the membrane is calculated. A pressure above 11000 Pa is observed for velocities above 60 mm/s as seen in fig. 2. The optimum inlet velocity which is to be supplied to the system is hence acquired.

To apply such a velocity to the system, micro-pumps, syringe pumps, squeeze chips can be used. The specific advantage with the latter is that squeeze chips pave way for in-situ application for the device. Velocities upward of 600 µL/min can be achieved using a squeeze-chip[25]. Hence making it possible and practical for in-situ applications.

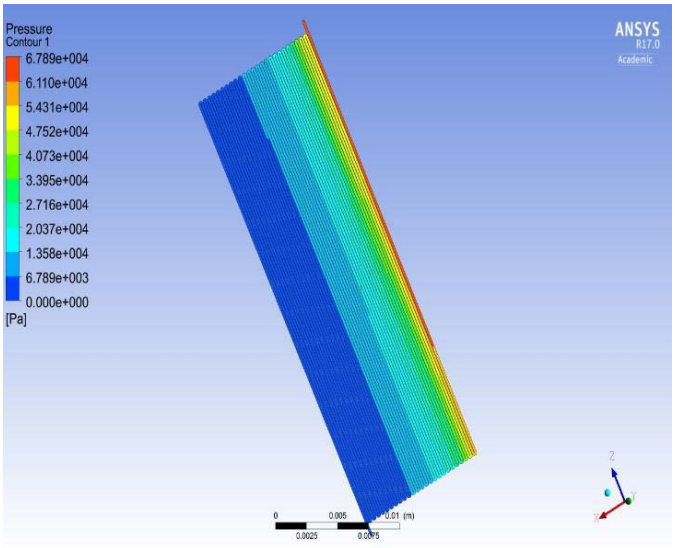

Figure 1. Pressure distribution at v=75 mm/s

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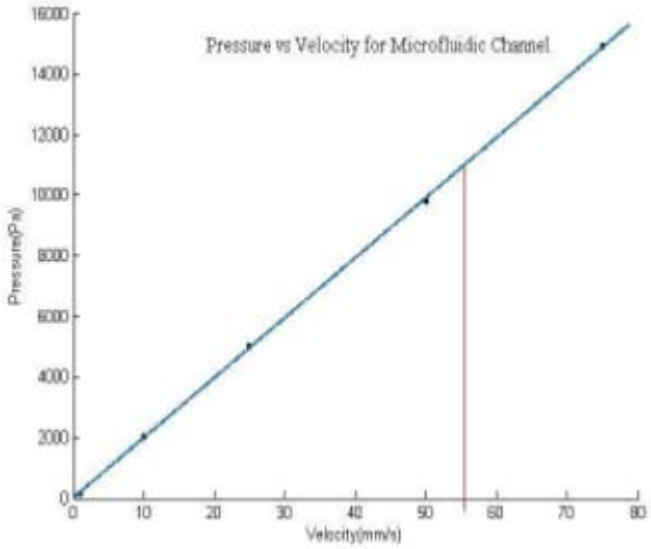

Figure 2. Pressure distribution for various velocities

II. DESIGN OF THE DEVICE

A. Membrane configuration and preparation

Membranes were configured in such a way that its thickness is minimum so that blood permeates through the membrane easily. The thickness of the membrane was found to be around 0.000003m(300 microns).

The study is aimed to provide a low-pollution and high-efficiency preparation method using water as a solvent.[29]The PDMS membrane is generally prepared on a wafer which will be used in a spin coater to realize the PDMS membrane. Before use, the wafer has to be cleaned. The wafer is first cleaned with acetone, then dried with air and then kept in an oven at 120℃ for 5 minutes.

The PDMS membranes were then prepared by solution casting method as given by Sun, De, Li, and Xu[25].For the preparation of unfilled PDMS membrane, a casting solution containing 17 wt% PDMS was prepared by dissolving PDMS, crosslinker (ethyl silicate) and curing agent (dibutyltindilaurate) in the solvent (n-heptane) with a ratio of 10:1:0.5 (in weight). The solution was subjected to homogenization by magnetic stirring of 3 hours; after the preparation of PDMS casting solution, it was poured onto the surface of thenon-woven fabric for 15 seconds. The PDMS coated flat sheet membrane was dried in the sterile room at room temperature for 24 hours, and then the cross-linked unfilled PDMS flat sheet composite membrane was prepared. The composite membranes with skin layers of variable thickness could be achieved by controlling the concentration of PDMS solution or the coating amount.

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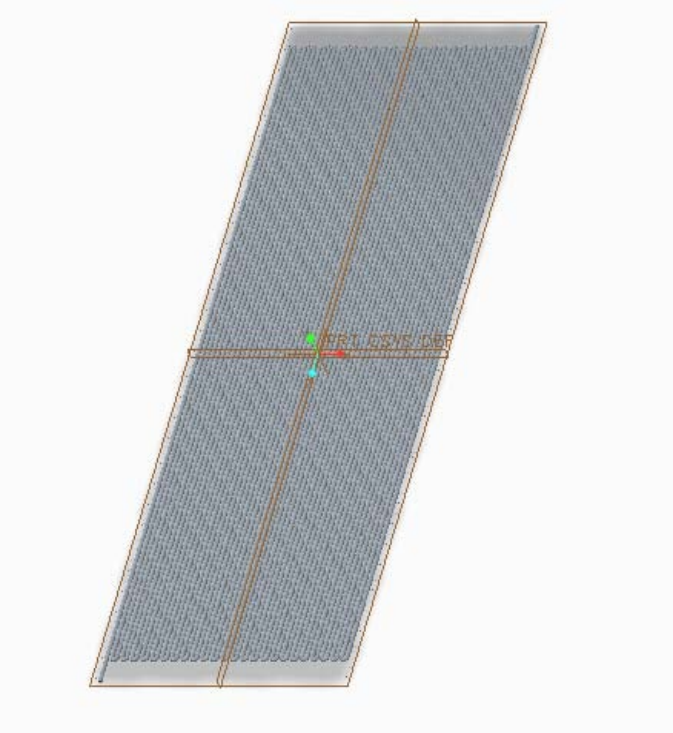

Figure 3. The optimum microfluidic channel design

B. Micro-channel configuration

The given microchannel is a semi-cylindrical in nature with a diameter of 10 µm. It is made of silicon material coated with the hydrophobic membrane to repulse the plasma and ensure smooth flow of liquid. The same is manufactured using lithography techniques[26-27]. There are over 20 such channels winding over to provide maximum pressure to the channel flow as shown in fig 3. The number of channels and the diameter was decided such that the pressure through the system is maximized. On decreasing the diameter of the system, due to constraints because of the viscosity of the fluid against the walls of the system, the net pressure generated decreases. However, increasing the diameter would also result in the same issue. Hence an optimum size is achieved accordingly after parameterizing the diameter through simulations.

C. Squeeze chip specifications

The squeeze chip[25] is a device which supplies the required flow rate to the channel. Since a flow velocity of 60-70 mm/s is to be generated, a series of squeeze chips and variations in flow channel diameters is employed.

D. Squeeze chip specifications

The plaster is such that it gives support to the membrane and microfluidic channel beneath. It shouldn't be poisonous and shouldn't cause deleterious effects to the user. The adhesive bandage designed by Lauritzen(1985) using acrylate serves the purpose at hand[31].

IV.CONCLUSION

The microfluidic bandage designed can serve as an in situ application for wounded hemophilic patients.The given device is found to provide sufficient delivery of the deficient factor VIIIa to the patients. In addition, it is easy to operate as it uses a basic push mechanism. The proposed microfluidic bandage that has been designed theoretically is to be further fabricated and experimentally analyzed. The devices could further be extended on to treat other bleeding disorders such as Hemophilia B and Von Willebrand disease.Therefore, microfluidic bandage with PDMS

membrane can attract great interest for application in many important drug delivery practices.Further work is also going on to study the working of this device in intravenous applications

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