Section A-Research paper
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Mesenchymal stem cells Extraction Automatic device

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Abstract – Mesenchymal stem cells (MSCs) is a form of regenerative medicine that utilizes the body's natural healing mechanism to treat various conditions. MSCs are used to renew and repair diseased or damaged tissue mostly it is used in the treatment of various orthopaedic, cardiovascular, neuromuscular and autoimmune conditions. Stem cells are present in all of us, acting like a repair system for the body. However, the number of stem cells decreases by increasing age due to this the required amount of stem cells are not delivered to the injured area. The main goal of stem cells is to amplify the natural healing process and repair system of the patient's body. In order to develop an effective automatic device that can extract MSCs from bone marrow blood concentration (thick blood) using automatic microcentrifugation and density gradient separator to isolate MSCs from other cell types. This device can isolate MSCs from other cell types with high purity and efficiency. However, this device reduces the risk of contamination of stem cells from bacteria and viruses as compare with manual extraction methods. This automatic device significantly improved the yield and purity of MSCs, and reduced the time and human efforts required in the extraction process.

Keywords*:* Mesenchymal stem cells extraction, MSCs extraction automatic device, Bone marrow extraction, stem cells extraction Etc.

1. Introduction

Mesenchymal stem cells (MSCs) has multipotent properties and self-renewal capability that why it used as a novel therapy for many diseases[1]. The extraction of mesenchymal stem cells (MSCs) are currently increase in medical industries for clinical trials to find out their potential in immune regulation and tissue regeneration[2]. Human bone marrow is the most common source of MSCs for clinical uses and trials[3]. It is very difficult to generate sufficient numbers of stem cells for medical and clinical uses[4]. To achieve more number to steam cells high volume of bone marrow blood concentration are taken from donors[5], [6]. The extraction of mesenchymal stem cells (MSCs) and other type of cells from blood concentration by manual methods is very difficult also it increases the chances of contamination from bacteria and viruses. There are lots of other devices and kit available which is used in manual extraction process. There is no single automatic device available which extract the cells from blood concentration fully automatically without human interaction. The objective of MSCs extraction automatic device is to reduce contamination of stem cells and increase purity also reduce the time taken in extraction process. The main feature of this device is it require less volume (6ml to 10 ml) of bone marrow to achieve adequate therapeutical dose of MSCs. This device has some unique and novel mechanism which make it fully automatic that is “Needle slider” “Automatic sample collection tube holder”, “Automatic microcentrifuge unit” and “Automatic cell culture dish holder”.

2. Materials and methods

Design of MSCs extraction automatic device

The designing of this device is done in 3D CAD software solidworks. This device is very easy to handle and use. The outer dimension of this device is 300 x 255 x 240 mm. It is fully air tight which prevent the contamination and maintain its internal hygiene. This device has some unique and novel mechanism which make it fully automatic. Below is the detail expiation of this device. Also, the detail explanation of unique (Novel) mechanisms that is “Needle slider” “Automatic sample collection tube holder”, “Automatic microcentrifuge unit” and “Automatic cell culture dish holder”.

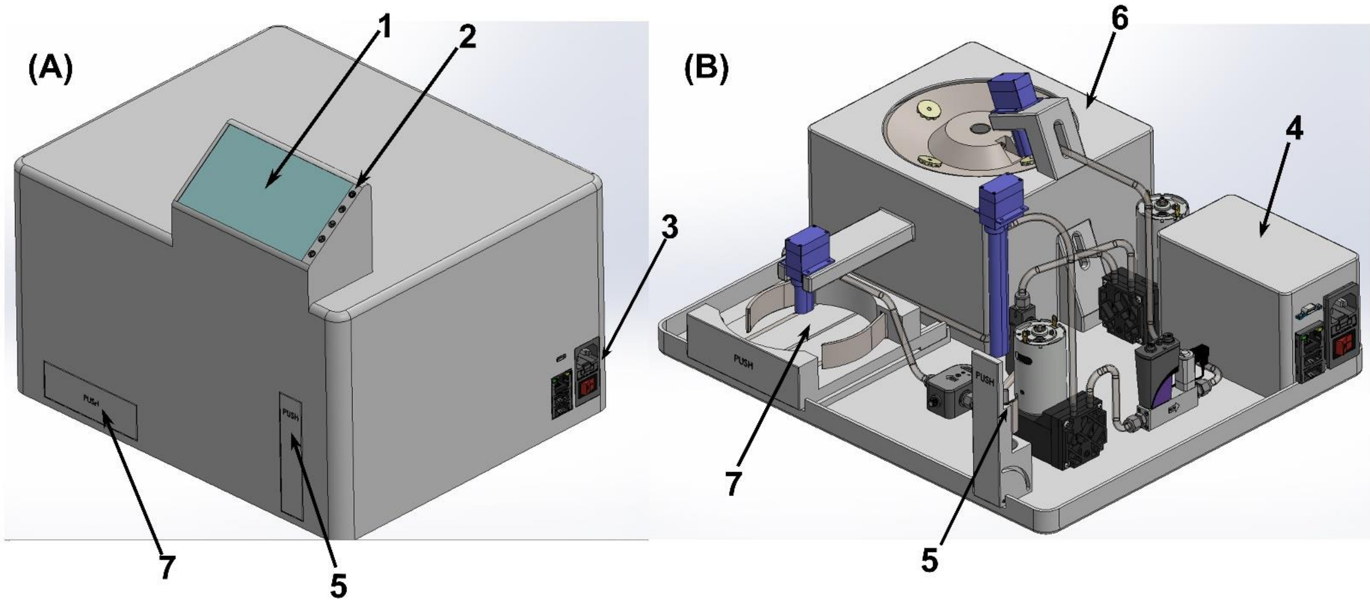

Figure 1 – (A)Isometric view (with top body), (B)isometric view (without top body) of MSCs extraction automatic device.

2.1. Display

In the above **Figure 1**(A) the point 1 is indicating the touch display. This touch display which is used to control and manage the task. The touch of this display is good responsive. its response in all condition like wet hands and wearing gloves etc. The touch display size is 5 inch (4.5 x 2.5 inch).

2.2. Power and control buttons

In the above **Figure 1**(A) the point 2 is indicating the power and control buttons. These buttons are made from soft silicon. The top button is display power button to turn on the display and others are mainly used to preform repetitive and special task.

2.3. Power input socket and data transfer ports

In the above **Figure 1**(A) the point 3 is indicating the power input socket and data transfer port. There is a main power supply button, power input socket, USB port, Ethernet Port LAN (Local Area Network).

2.4. Power distribution and control box

In the above **Figure 1**(B) the point 4 is indicating the power distribution and control box. It required 220-volt AC supply. It has AC to DC converter module which convert 220volt AC to 12 Volt DC, DC servo motor driver and control board. All electrical component is running on DC power supply. All electrical component is controlled by this unit.

2.5. Gripper Pad

This device has unique design gripper pad as it shows in **Figure *2***(B). The purpose of these pads is to avoid skidding and provide more grip with the surface even on wet surface. These gripper pads are designed in innovative way that it covers more area on the floor (surface) and provided more grip. Each pad has three-line contact with surface which restrict the linear movement in any direction. These pads are made from silicon rubber which absorb vibration easily.

2.6. Back Flap

There is a removeable lid which is back flap as it shows in **Figure *2***(A). The purpose of this flap is to change the microcentrifuge tube (**Figure 7**A) when its required. This flap is air tight so it prevents air contamination. It is very easy to use. To open it by simply just grab the hand of it and pull outside and to close it just push it inside.

2.7. Silicon rubber ring

In the **Figure *2***(A) R3 is the silicon rubber ring. The purpose of this ring is to make whole device air tight to prevent air contamination and maintain hygiene. This ring is all around the opening of back flap (**Figure *2***A).

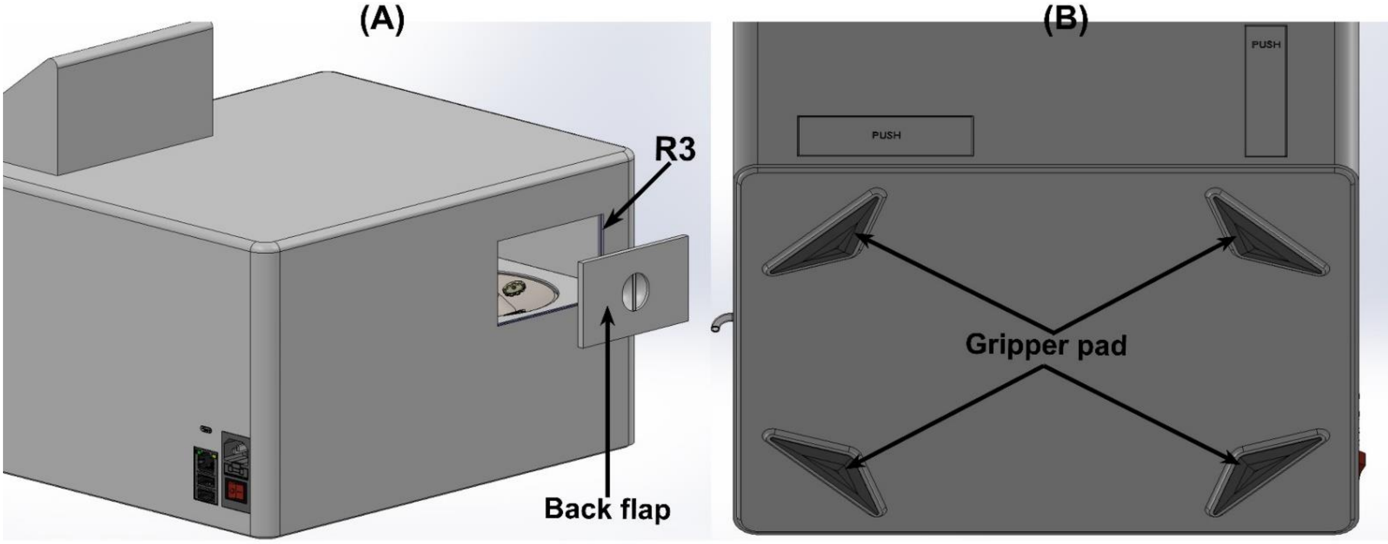

Figure 2 - (A)Back isometric view showing back flap, (B)bottom isometric view showing gripper pad of MSCs extraction automatic device.

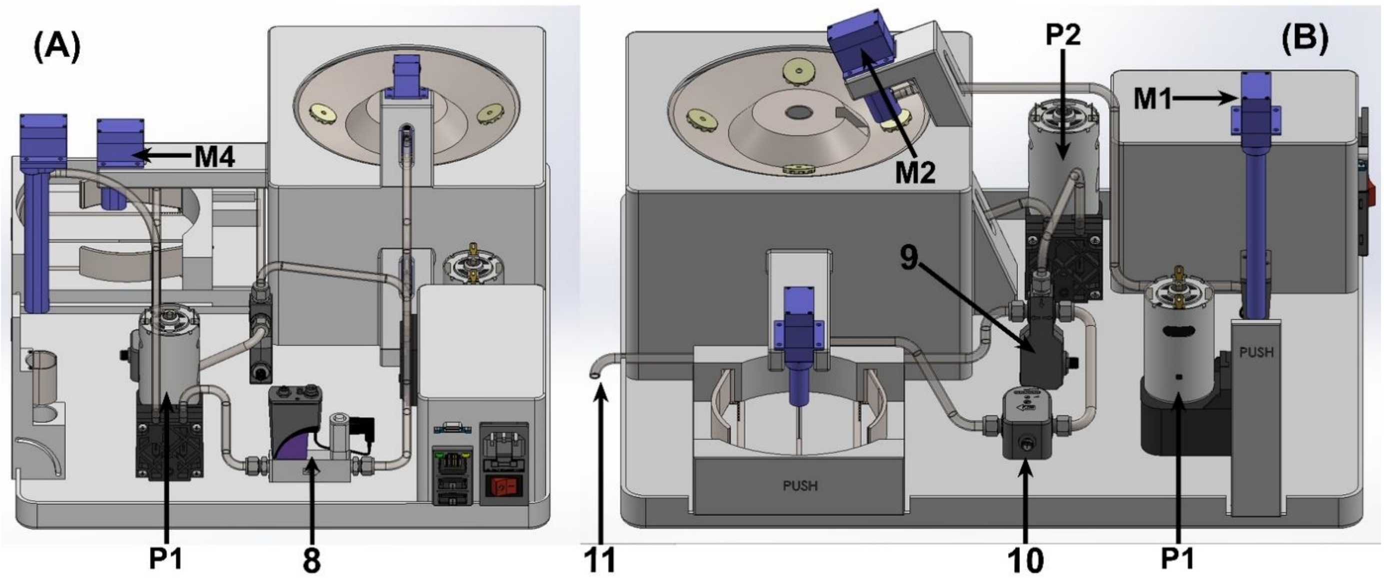

Figure 3 - (A)Side isometric view, (B) front isometric view of MSCs extraction automatic device.

2.8. Needle Slider

Usually large gauge needle is used to reduce the damage of blood cells during sampling, and laboratory tests that require whole blood cells, most commonly hypodermic needle and syringe are used for collecting blood sample[7]. The point M1(**Figure *3***B), point M2(**Figure *3***B), point M3(**Figure 8**A), point M4(**Figure *3***A) is indicating the needle slider. It is the unique (Novel) design with the combination of DC gear motor, screw shaft and 16-gauge needle with ball screw. This unique mechanism gives linear movement to needle that is in and out movement (**Figure 6**A, B). Each needle slider has a different length screw shaft and needle with ball screw according to requirement. Each needle slider has a cleaning block which help to clean needle every time when it moves in and out. When screw shaft rotates by DC gear motor it moves the ball screw which is attached to the needle and needle get the linear motion. This needle slider work on the principle of vacuum extraction tube systems for collecting blood from sample collection tube (**Figure 6**A) to reduces the risk of direct exposure of blood.

2.9. Mass flow pump

The point P1(**Figure *3***A) and point P2(**Figure *3***B) is indicating the mass flow pump. These two pumps flow the liquid mass from sample collection tube (**Figure 6**A) to the automatic microcentrifuge unit(**Figure 1**B-6) and further from automatic microcentrifuge unit(**Figure 1**B) to the automatic cell culture dish holder(**Figure 1**B-7). These mass flow pumps run on 12volt DC power supply. Each pump has a DC motor, gearbox, centrifugal pump box.

2.10. Mass flow sensor and controller

In the above **Figure *3***(A) the point 8 is indicating the mass flow sensor and controller. The propose of this sensor is to sense and control the flow between mass flow pump P1 (**Figure *3***A) and needle slider (**Figure *3***B-M2). This sensor distributes the liquid mass one by one in all four-microcentrifuge tube (**Figure 7**A) in control manner. This sensor required 12volt DC power supply to run.

2.11. Cell separator

In the above **Figure *3***(B) the point 9 is indicating the cell separator. The propose of this sensor is to separate plasma, buffy coat (mononuclear cells), ficoll and red blood cells on the basses of density gradient separator. In this sensor there is one input and two output according to density of liquid and type it separate mononuclear cells (MSCs) and transfer to the volume controller (**Figure *3***B-10). The input port of this sensor is connected to the outport port of mass flow pump (**Figure *3***B-P2) and one output port of this sensor is connected to the drain pipe and other is connected to the volume controller(**Figure *3***B-10). Both outputs can be used to get two different liquid. It requires 12volt DC power supply to run.

2.12. Volume controller

In the above **Figure *3***(B) the point 10 is indicating volume controller. The propose of this sensor is to calculate the volume of liquid solution which came from cell separator (**Figure *3***B-9) and transfer to the needle slider(**Figure *3***A-M4). This sensor gives the reading in millilitre(ml). It requires 12volt DC power supply to run.

2.13. Drain pipe

In the above **Figure *3***(B) the point 11 is indicating the drain pipe. This drain pipe is connected to one discharge port of cell separator separate (**Figure *3***B-9). The purpose of drain pipe is to move out unnecessary liquid and mass from device.

2.14. Automatic sample collection tube holder

Blood collection devices which having low hygiene and quality are the main source of pre-analytical error in laboratory testing, accurate laboratory testing requires high hygienic and air tight devices[8]. The **Figure 1**(A, B) and **Figure 4**(A) point 5 is showing the automatic sample collection tube holder. It has unique mechanism to hold any size of sample collection tube. It is fully automatic and easy to use. Automatic sample collection tube holder is hygienic also it prevents contamination while collecting sample from sample collection tube.

2.14.1. Holder

In the **Figure 4**(B) H1 are the two holders. The purpose of this holders is to hold the sample collection tube in the center of assembly. This holder has unique arc shape design which is capable to holed any size of sample collection tube. Each holder has a one torsion spring (**Figure 4**B-S1).

2.14.2. Torsion spring

In the **Figure 4**(B) S1 are the double-torsion spring and in the **Figure 5**(B) S2 is single torsion spring. The purpose of S1 torsion springs is to give angular movement to the holder. Each S1 torsion spring are attached with each holder (**Figure 4**B-H1) to give them angular movement. The purpose of S2 torsion springs (**Figure 5**B) is to give angular movement to the assembly of automatic sample collection tube holder.

2.14.3. Silicon rubber ring

In the **Figure 4**(B) R1 is the silicon rubber ring. The purpose of this ring is to prevent air contamination from bacteria and viruses and maintain hygiene. This ring is all around the opening of automatic sample collection tube holder.

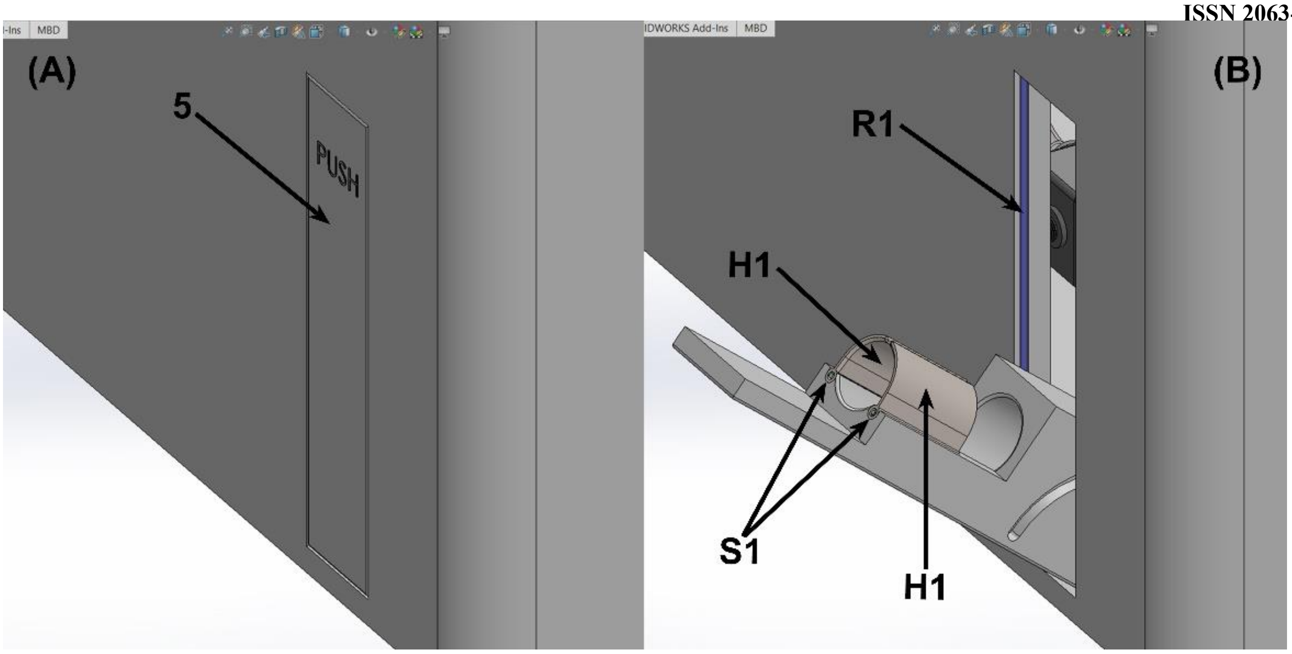

Figure 4 - (A)Closed position view, (B) open position view of automatic sample collection tube holder.

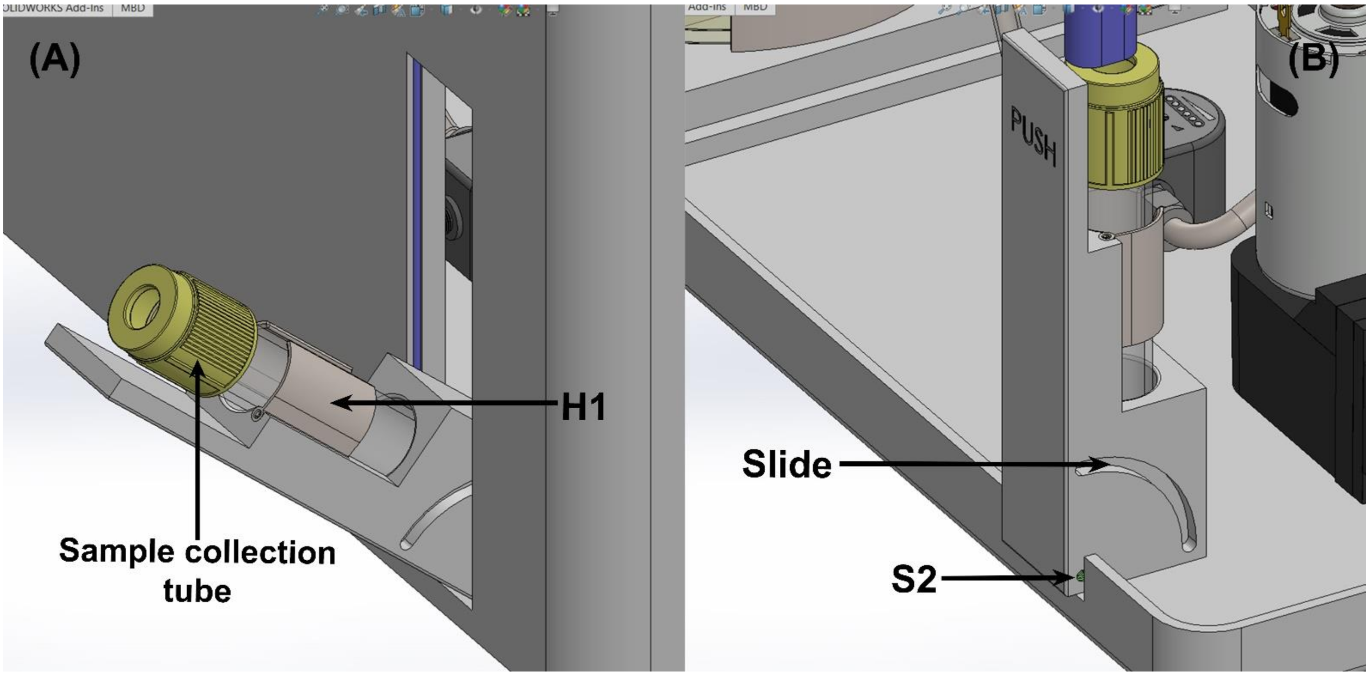

Figure 5 - (A)Open position with sample collection tube, (B) closed position with sample collection tube of automatic sample collection tube holder.

2.14.4. Working of automatic sample collection tube holder

This is the fully automatic unique (novel) mechanism. The purpose of this mechanism is to hold the sample collection tube (**Figure 5**A) in center to collect the sample. When the “push” button (**Figure 4**A) is slightly press by finger the whole assembly get unlock and came out at the angle of 50-degree (**Figure 4**A) this is the open position and to close it we have to push on “push” button (**Figure 5**B) assembly get lock(**Figure 5**B) this is the close position. The opening and close mechanism is taking place by torsional spring (**Figure 5**B-S2, **Figure 6**A-S2) and the slide(**Figure 5**B). The torsional spring S2 have the potential energy which converted in to mechanical energy further give angular momentum to the assembly. The slide (**Figure 5**B) have an arc grove which make an angular path for travelling the assembly. Both the holders H1 are always in close position (**Figure 4**B-H1) due to both torsional spring S1. The torsional spring S1 have the potential energy which converted in to mechanical energy further angular momentum to the holders H1. When we insert the sample collection tube in the assembly, Both the holders H1 came out according to the size of tube and hold it in the center of assembly.

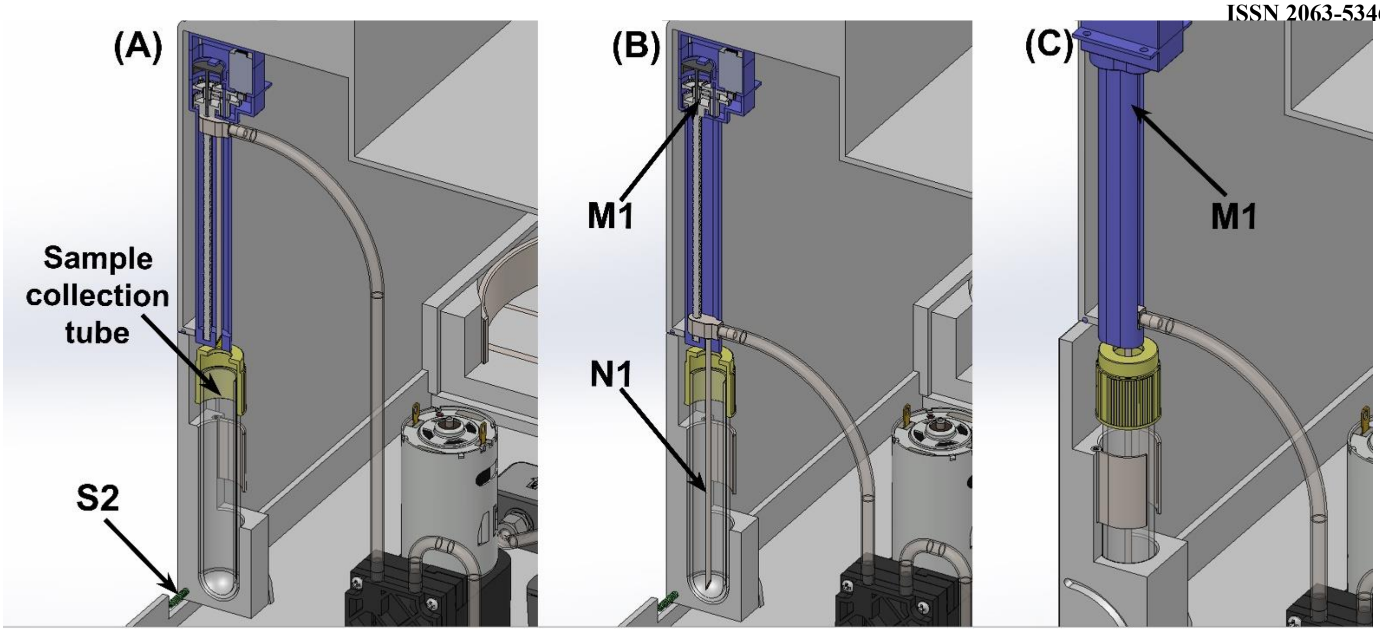

Figure 6 - (A), (B) Cut section view in closed position of automatic sample collection tube holder, (C) closed position view of automatic sample collection tube holder.

When automatic sample collection tube holder assembly get closed (**Figure 6**A). The needle slider M1(**Figure 6**B) came in action and start the rotating its screw shaft which push the needle N1 to the outside of needle slider further in the inside of sample collection tube to collect the sample. Every time when needle goes inside the sample collection tube it gets clean by cleaning block. After completing one cycle with one sample the whole system has to be clean to maintain the hygiene. It is very easy to clean whole system we just have to insert sample collection tube filled with cleaning liquid and that liquid pass through out system and clean it.

2.15. Automatic microcentrifuge unit

The microcentrifuge is normally used in research laboratories to break the solution in its components by applying high relative centrifugal force (g-force) for relatively short time intervals, usually 0.2-2.0 ml size micro tubes are used in microcentrifuge[9].The **Figure 1**(B) and **Figure 7**(A) point 6 is showing the automatic microcentrifuge unit. It has a fully automatic unique novel mechanism which isolate the mononuclear cell from whole bone marrow solution. It has two needle slider which fill the bone marrow solution into microcentrifuge tube also empty the solution after centrifugation process. It is very easy to use and hygienic also.

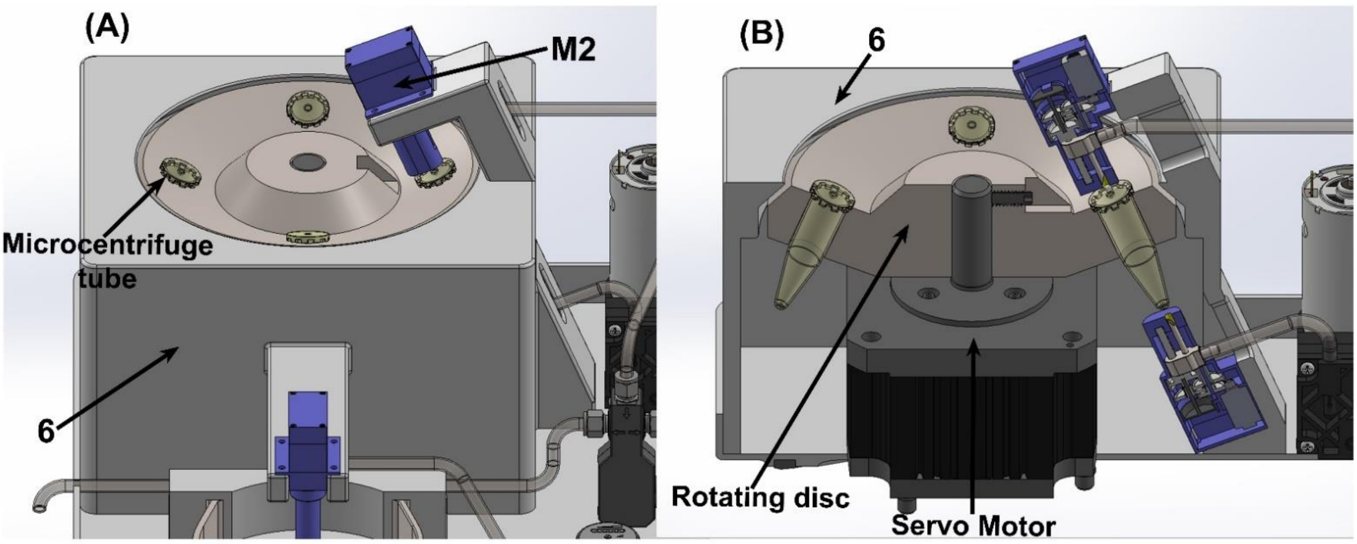

Figure 7 - (A)Isometric view of automatic microcentrifuge unit, (B)front cut section views of automatic microcentrifuge unit.

2.15.1. Microcentrifuge tube

In the **Figure 7**(A) and **Figure 8**(A) transparent color tubes are showing that is microcentrifuge tubes. These microcentrifuge tubes have innovative novel design. It has thin membrane at the top and bottom of same material. These thin membranes are in conical shape which automatically get close to prevent any leakage. There are four microcentrifuge tubes. These tubes are replaceable it is very easy to replace from back flap (**Figure *2***A). These tubes are easy to clean and hygienic also.

2.15.2. Rotating disc

In the **Figure 7**(B) and **Figure 8**(B) is showing rotating disc. This rotating disc has innovative novel design which is stable at high RPM. This disc is made from stainless steel which maintain the momentum at high RPM. It has four holes at a particular angle.

2.15.3. Servo motor

In the **Figure 7**(B) and **Figure 8**(B) is showing servo motor. This is high RPM servo motor. It run on DC power supply 12 Volt. There is servo driver in power distribution and control box (**Figure 1**A-3) which give the power supply to it to run it at high RPM. This servo motor achieves 5000 RPM maximum.

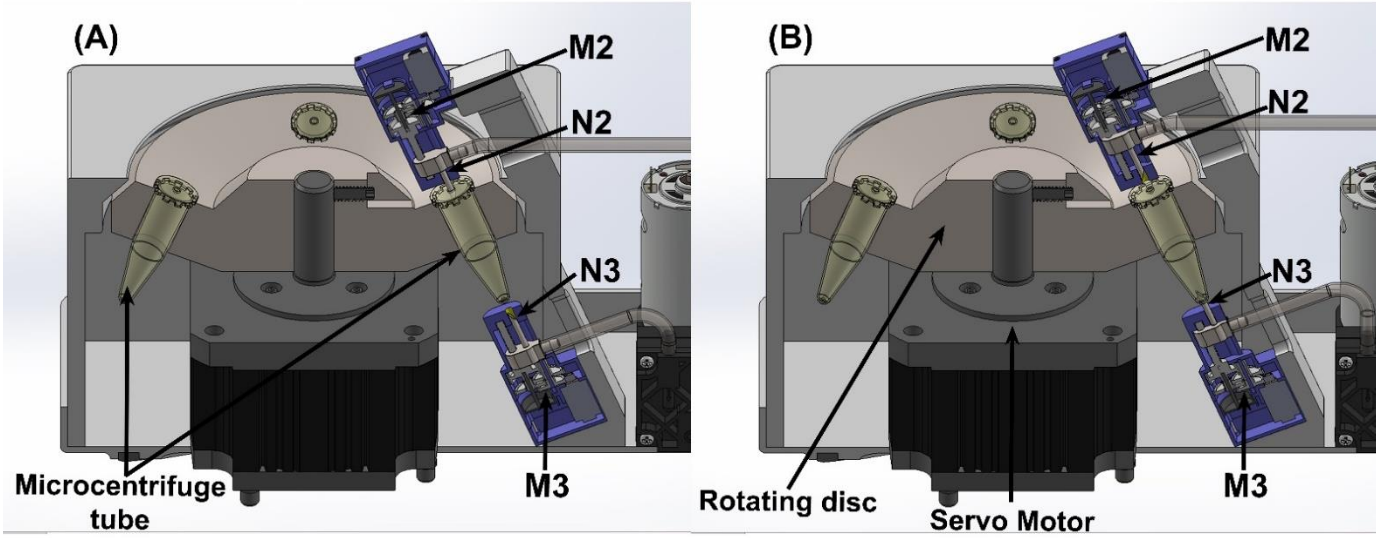

Figure 8 - (A), (B)Front cut section views of automatic microcentrifuge unit.

2.15.4. Working of automatic microcentrifuge unit

This is the fully automatic unique (novel) mechanism. The purpose of this mechanism is to isolate the mononuclear cell from whole bone marrow solution by centrifugation process. The working of this mechanism is unique and simple. The bone marrow solution(blood) came from mass flow sensor and controller (**Figure 3**A-8) to needle slider M2. Needle slider M2 insert the needle N2(**Figure 8**A) into microcentrifuge tube and fill it. After filling all four tubes one by one centrifugation process start at defined RPM, RPM can be adjusted by touch display (**Figure 1**A-1). After completing centrifugation process needle slider M3 insert the needle N3(**Figure 8**B) into microcentrifuge tube from bottom. After that mass flow pump P2(**Figure 3**B) start and it extract the solution from microcentrifuge tube and send it to cell separator(**Figure 3**B-9). Cell separator separate plasma, buffy coat (mononuclear cells), ficoll and red blood cells and send required part of solution to volume controller (**Figure 3**B-10). Volume controller calculate the volume of solution which came from cell separator (**Figure 3**B-9) and transfer to the needle slider M4 (**Figure 3**A).

2.16. Automatic cell culture dish holder

A simple cell culture dishes are disposable or reusable circular containers which is used in cell culture growth and propagation, cell and tissue culture dishes are available in different sizes, materials, and surface modifications[10].The **Figure 1**(A, B) and **Figure 9**(A) point 7 is showing the automatic cell culture dish holder. It has unique mechanism to hold any size of cell culture dish. It is fully automatic, easy to use and hygienic also.

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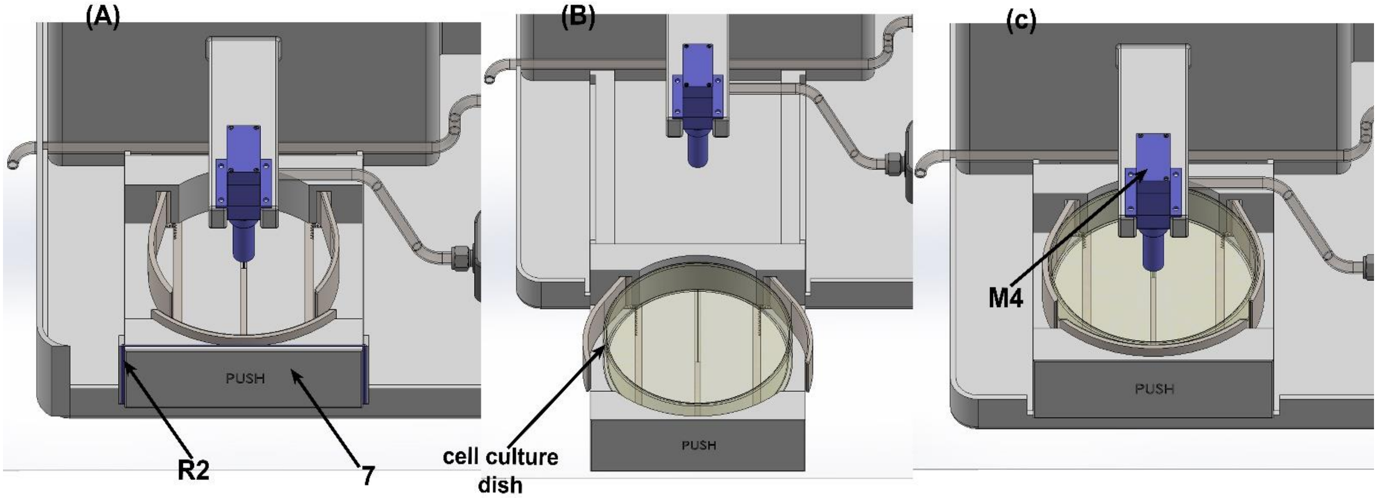

Figure 9 - (A) Closed position view, (B) open position view with cell culture dish, (C) Closed position view with cell culture dish of automatic cell culture dish holder.

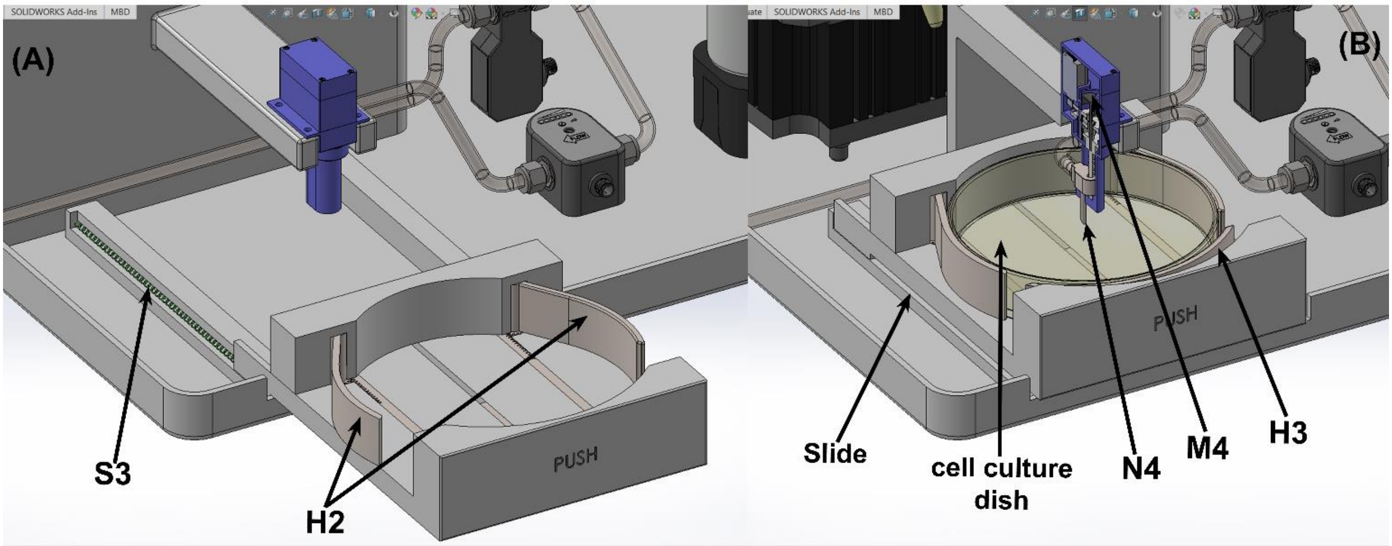

Figure 10 - (A)Open position view, (B) Closed position view with cell culture dish of automatic cell culture dish holder.

2.16.1. Holder

In the **Figure 10**(A) H2 are the two holders and H3 **Figure 10**(b) these are total 3 holders. The purpose of this holders is to hold the cell culture dish in the center of assembly. This holder has unique arc shape design which is capable to holed any size of cell culture dish. Both holder H2 has gear (**Figure 11**-H2) at the bottom. Holder H3 has rack gear (**Figure 11**A-H3) at the bottom on both sides. The bottom part of H2 and H3 are working as rack and pinion gears (**Figure 11**A, B). This rack and pinion mechanism of H2 and H3 can hold any size of cell culture dish in the center of assembly.

2.16.2. Spring

In the **Figure 10**(A) S3 are the two spring on both side (**Figure 11**A). The purpose of S3 Springs is to push automatic cell culture dish holder assembly outside. There are another two spring S4(**Figure 11**A) on bottom of holder H3. The purpose of S4 springs is to release holder H3 to take cell culture dish out from assembly.

2.16.3. Spring Thread

In the **Figure 12**(A, B) S5 is spring thread. The purpose of spring thread S5 is to pull and lock the holder H3 to hold the cell culture dish in the center of assembly. One end of this is connected to the base and other end is connected to the holder H3(**Figure 12**(A, B).

2.16.4. Silicon rubber ring

In the figure-9(A) R2 is the silicon rubber ring. The purpose of this ring is to prevent air contamination from bacteria and viruses and maintain hygiene. This ring is all around the opening of automatic cell culture dish holder.

2.16.5. Slide

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There are two different slides in automatic cell culture dish holder assembly. First slide is showing in the **Figure 10**(B) the purpose of this slide is to give stability and linear movement to the whole assembly also this slide lock and unlock the assembly. The second slide is showing is the **Figure 11**(B) the purpose of this slide is to give stability and linear movement to the holder H3.

2.16.6. Working of automatic cell culture dish holder

This is the fully automatic unique (novel) mechanism. The purpose of this mechanism is to hold the cell culture dish (**Figure 9**B) in center to dispense the mononuclear cells (MSCs) in cell culture dish. When the “push” button (**Figure 9**A) is pressed the whole assembly get unlock and slide outside(**Figure 9**B) automatically this is the open position and to close it we have to push on “push” button (**Figure 9**B) to slide inside and assembly get lock(**Figure 9**C) this is the close position. The opening and close mechanism is taking place by spring S3(**Figure 10**A, **Figure 11**A) and the slide(**Figure 10**B). The spring S3 have the potential energy which converted in to mechanical energy further give linear moment to the assembly. The slide (**Figure 10**B) have a linear grove which make a linear path for travelling the assembly. When the assembly slide inside a tension is developed in spring thread S5 (**Figure 12**B) which further pull the holder H3 and both spring S4. When holder H3 slide inside, the bottom part of it work as rack gear(**Figure 11**A) this transfer its linear motion into rotation with the pinion gear of both holder H2(**Figure 11**B) further a torque is developed in both the holders H2 and they grab the cell culture dish (**Figure 10**B). Both the holder H2 and H3 are work together to hold the cell culture dish in center.

After dispensing mononuclear cells (MSCs) in cell culture dish. To take the dish out, we have to slightly press the “push” button the whole assembly get unlock and slide outside which reduce the tension in spring thread S5 (**Figure 12**A) further both the spring S4 push holder H3 (**Figure 11**A) outside. Holder H3 slide outside which release cell culture dish (**Figure 9**B) further with the rack and pinion gear mechanism of both the holder H2 and H3 give torque to the holder H2and Holder H2 (**Figure 9**B) release the cell culture dish.

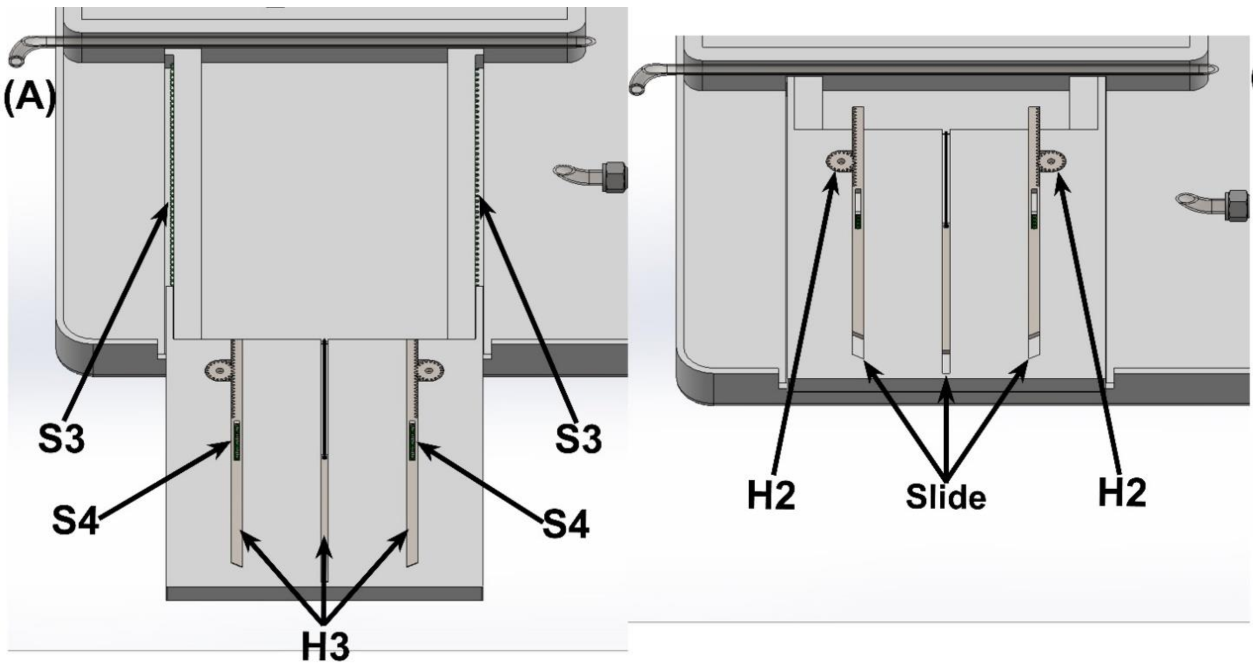

Figure 11 - (A) Top cut section open position view, (B) Top cut section closed position view of automatic cell culture dish holder.

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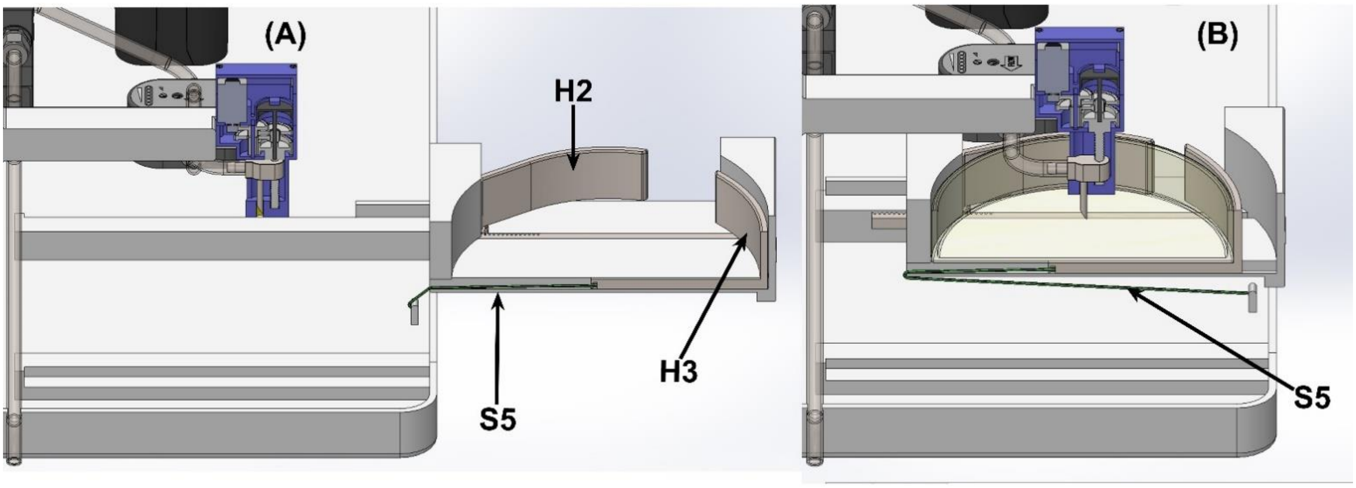

Figure 12 - (A) Side cut section open position view, (B) Side cut section closed position view of automatic cell culture dish holder

3. Working of MSCs extraction automatic device

This device has four unique novel mechanisms that is “Needle slider” “Automatic sample collection tube holder”, “Automatic microcentrifuge unit” and “Automatic cell culture dish holder” which makes the working of this device very simple and easy to use. This device required 220-volt AC power supply. After giving the power supply, the main power supply button (**Figure 1**A-3) need to be turn on after that to turn on display a display power button (**Figure 1**A-2) need to be press. Display turn on and we need to give input to preform required process. A warning sign appear on display which says “Insert simple collection tube and cell culture dish”. First sample collection tube needs to be inserts for that we need to press “Push” button (**Figure 4**A), automatic sample collection tube holder assembly came out (**Figure 4**B). A sample collection tube filled with bone marrow blood need to be insert in “automatic sample collection tube holder” (**Figure 5**A) and need to press “Push” button to slide it inside (**Figure 5**B). To inserts cell culture dish, we need to press the “push” button (**Figure 9**A-7) the whole assembly get unlock and slide outside automatically (**Figure 9**B). After placing cell culture dish again, we have to push on “push” button (**Figure 9**B) and slide it inside and assembly get lock (**Figure 9**C).

When automatic sample collection tube holder assembly get closed (**Figure 6**A). The needle slider M1 (**Figure 6**B) came in action and insert the needle N1 inside the sample collection tube (**Figure 6**B) to collect the sample. The mass flow pump P1 (**Figure *3***A) sucks all the solution and send it to needle slider M2 (**Figure *3***B, **Figure 7**A) by passing through the mass flow sensor and controller (**Figure *3***A-8). The needle slider M2 insert the needle N2 (**Figure 8**A) into microcentrifuge tube and fill the solution in all four tubes one by one by defined quantity in control manner. After filling all tubes, centrifugation process starts at defined RPM in automatic microcentrifuge unit (**Figure 7**A-6). RPM can be adjusted by touch display (**Figure 1**A-1). After completing centrifugation process needle slider M3 insert the needle N3 (**Figure 8**B) into microcentrifuge tube from bottom. After that mass flow pump P2 (**Figure *3***B) sucks and send it to cell separator (**Figure *3***B-9). Cell separator separate plasma, buffy coat (mononuclear cells), ficoll and red blood cells, the required part of solution sanded to volume controller (**Figure *3***B-10). Volume controller calculate the volume of solution which came from cell separator (**Figure *3***B-9) and transfer to the needle slider M4 (**Figure *3***A, **Figure 10**B). A needle N4 came out from needle slider M4 (**Figure 10**B) and dispense solution in cell culture dish (**Figure 10**B).

After dispense solution in cell culture dish a beep sound starts running and a notification came on display “Process completed take out the dish” and we have to press the “push” button (**Figure 9**C) the whole assembly get unlock and slide outside automatically (**Figure 9**B) and take out cell culture dish from assembly (**Figure 10**A). In the end we have to push on “push” button to slide back inside and assembly get lock (**Figure 9**A). For miniating the hygiene and reduce the contamination the whole system needs to clean. Cleaning of this device is very easy we just have to insert cell culture dish (**Figure 10**B) and sample collection tube filled with cleaning liquid solution than we have cleaning command from touch display and that liquid pass through out system and clean it.

4. Result

The designing of this device is done in 3D CAD software solidworks. This device is very easy to handle and use. It is fully air tight which prevent the contamination and maintain its internal hygiene. This device solves the problem related to extraction of mesenchymal stem cells (MSCs) from any blood concentration by making whole process automatically also it increases purity and reduce the time taken in extraction process. This device has some unique and novel mechanism which make it fully automatic. is “Needle slider” “Automatic sample collection tube holder”, “Automatic microcentrifuge unit” and “Automatic cell culture dish holder” these are unique (Novel) mechanisms which make this device fully automatic.

5. Discussion

In this work, MSCs extraction automatic device developed in 3D CAD software. This device solves the problem related to extraction of mesenchymal stem cells (MSCs) from any blood concentration by making whole process automatically also it increases purity and reduce the time taken in extraction process. This device reduces the chances of contamination of stem cells from bacteria and viruses as it is fully air tight and the whole process of extraction is completed fully automatically inside the device. The main feature of this device is, it requires less volume (6ml to 10 ml) of bone marrow to achieve adequate therapeutical dose of MSCs. This device has some unique and novel mechanism which make it fully automatic that is “Needle slider” “Automatic sample collection tube holder”, “Automatic microcentrifuge unit” and “Automatic cell culture dish holder”. This device has fully automatic cleaning system also which maintain the hygiene of it.

6. Acknowledgment

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