

MIXER FOR PARTICLE SUSPENSIONS INSIDE BAGS

Technical Field

The technical field of the invention is mixing of fluid and particles to create a suspension within a closed bag as an aseptic process. For example, the technology can be deployed for mixing live cells within a blood transfer bag for biomedical product manufacture.

Background

Regenerative medicine and advanced cell therapies are emerging medical therapeutic technologies that build on manipulation of live, human derived cells to create constructs, deliver immunogenic responses or stimulate repair responses in the patient body. While some of these techniques can deliver many doses to multiple patients from a single source of cell (allogeneic products,) there is growing recognition that processing and delivering cells derived from the patient or matched donor is safe and efficacious. To produce patient or matched donor specific cell products (autologous products) typically requires small batch processing.

To obtain regulatory approval, to make cell therapies widely available to patients, requires the equipment and process used to prepare the cell products be deemed safe and reliable, in addition to proving safety and efficacy of the particular therapy. A product specific, closed system has many benefits for cell product production. Such systems are designed for a dedicated function, i.e. a single production process for a specific cell product or set of cell products derived from the single production process. Such dedicated functionally closed systems are designed to deliver an aseptic processing environment for the medical product through close materials traceability and qualified sterilization protocols. Single use aseptic processing systems are assembled using a range of common disposable (one off use) components such as fluid bags and tubes.

Functionally closed processing systems commonly present the cell product inside single use bags where they are accessed by tubing connections integrated with the bag. Aseptic processing is achieved by employing pre-sterilised fluidic assemblies and conducting all operations without exposing the fluid contents to the open air.

There is often a need to mix cell suspensions because cells will settle if not disturbed and tasks such as aliquoting final doses rely on an homogeneous cell suspension to assure sufficient and consistent cells quantities per patient dose within a controlled fluid volume.

Traditionally mixing techniques have relied on personnel manipulating the bag containing the cell suspension in a "mixing procedure". Inconsistent outcomes from manual methods led to the development of automated mixing devices. Automated mixing devices used a mechanism to rock or squeeze the bag to cause movement of fluid within the bag.

Mixing devices act on the bag to relocate the fluid in a systematic way intended to achieve the mixing function. Different mixing devices support the fluid in bag in different orientations and squeeze the fluid in the bag in different ways. Such devices can have some inconsistency in mixing, or regions of the bag where fluid movement is inadequate, allowing components to settle or separate. Inconsistency in mixing be more likely where fluid bags are under or over filled compared with an optimal volume range for the bag and mixing device combination.

Fluid bags for biomedical products are typically accessed through tubing ports positioned at the bottom of the hanging bag. This enables all fluid in the bag to be drained. A problem with inadequate mixing is that some particles may cease to be suspended and settle to the bottom of the bag. Settling can also occur while mixing is ceased, for example during a setup phase or fault. It can be difficult to resuspend such settled particles. Settled particles can at least negatively affect consistency in concentration of particles in fluid dispensed initially compared to a later time. Settling particles can potentially block tubing ports.

There is a need for alternative automated mixing devices.

Summary of the Invention

According to one aspect of the present invention there is provided a mixing system comprising:

- a support for a flexible bag holding fluid for mixing;
 - a paddle mechanism comprising at least two opposing paddles configured to engage opposing sides of the bag supported by the support;
 - a paddle driving mechanism; and
 - a control system,
- wherein the paddle mechanism is arranged to engage with a portion of the bag proximate a bottom edge and only extending partially across the bag, such that actuation of the paddle driving mechanism causes movement of the paddles to compress the bag and displace the fluid across and upward through the bag from the portion of the bag engaged by the paddles, and

the control system controls actuation of the paddle driving mechanism.

In some embodiments the control system controls the paddle driving mechanism to perform repeated displacement and release cycles which creates a recirculating flow of fluid within
5 the bag.

In some embodiments the recirculating flow of fluid within the bag across the bottom of the bag acts to resuspend any settled particles.

10 In some embodiments the paddle drive mechanism is configured to cause the paddles to oscillate and includes paddle cycle speed control. In some embodiments the speed control enables the control system to vary paddle cycle speed.

In some embodiments the control system varies paddle cycle speeds based on mixing
15 requirements to perform any one or more of:
homogenise partly immiscible fluids,
create an homogeneous suspension, or
sustain a suspension.

20 In an embodiment, where required paddle cycle frequency is low, the control system intermittently actuates the paddle drive mechanism with a timed dwell between each mix cycle such that mixing action occurs at a speed supporting active mixing.

Some embodiments further comprising a mixer counter configured to count displacement
25 and release cycles of the paddles. In some embodiments the control system monitors the mixer counter and implements a mixer count trigger, whereby transition to a next stage of a mixing protocol is triggered based on the mixer counter cycle count.

In some embodiments the paddle mechanism includes a force limiting mechanism.
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In some embodiments the control system includes a communication module.

According to another aspect of the present invention there is provided a mixing system comprising:

35 a support for a flexible bag holding fluid for mixing;
a paddle mechanism comprising at least one paddle configured to engage with the bag supported by the support;

a paddle driving mechanism; and

a control system,

the paddle mechanism comprising at least one paddle configured to be disposed on a first side of the bag to engage with a portion of the bag proximate a bottom edge and only extending partially across the bag, and a surface disposed on an opposite side of the bag such that actuation of the paddle driving mechanism causes movement of the at least one paddle to compress the bag and displace the fluid across and upward through the bag from the portion of the bag engaged by the at least one paddle, and

the control system controls actuation of the paddle driving mechanism.

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Some embodiments further comprise a temperature controlled plate arranged to contact the bag for heat exchange between the plate and contents of the bag.

Embodiments of the mixing system described above may be integrated into an aseptic (or even non-aseptic) processing system. For example, embodiments of the mixing system may be included in a housing as a component of a processing circuit for an aseptic system. In an alternative embodiment the may be configured to connect to an aseptic system and the mixing system controller receive mixing control instructions from the processing system controller to enable mixing control by the processing system.

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According to another aspect of the present invention there is provided a mixing method for implementation using a mixing system having a paddle mechanism arranged to engage with a portion of a flexible bag holding fluid proximate a bottom edge and only extending partially across the bag, the method comprising the steps of:

performing repeated displacement and release cycles which creates a recirculating flow of fluid within the bag,

each displacement and release cycle including actuation of the paddle mechanism to cause compression of the bag and displacement of the fluid across and upward through the bag from the portion of the bag engaged by the paddle mechanism, and subsequent release.

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In some embodiments the recirculating flow of fluid within the bag across the bottom of the bag acts to resuspend any settled particles.

Some embodiments of the method including varying displacement and release cycle speeds based on mixing requirements to perform any one or more of:

homogenise partly immiscible fluids,

create an homogeneous suspension, or
sustain a suspension.

In some embodiments where required paddle cycle frequency is low, intermittently
5 performing displacement and release cycles with a timed dwell between each cycle such
that mixing action occurs at a speed supporting active mixing.

Some embodiments of the method include counting displacement and release cycles of the
paddles, monitoring a mixer count trigger, and transitioning to a next stage of a mixing
10 protocol based on the cycle count fulfilling the mixer count trigger.

Brief Description of the Drawings

An embodiment, incorporating all aspects of the invention, will now be described by way of
example only with reference to the accompanying drawings in which
15 Figure 1 is a representative block diagram of the system;
Figure 2a is a representative illustration of a system embodiment;
Figure 2b is a side view of the system of figure 2a, and illustrates the paddle mechanism in
an open or released state, without a bag in place;
Figure 2c is a side view of the system of figure 2a, and illustrates the paddle mechanism in a
20 closed or compressed state, without a bag in place;
Figure 2d represents on the illustration of figure 2a where the cross section for figure 2f is
taken.
Figure 2e is a side view of the system of figure 2a, and illustrates the paddle mechanism in
an open or released state, with a bag in place;
25 Figure 2f is a side view of the cross section indicated in figure 2d and illustrates the paddle
mechanism in a closed or compressed state, with a bag in place;
Figure 2g is a perspective view of the system of figure 2a, and illustrates the paddle
mechanism in a compressed state, with a bag in place;
Figure 2h is another perspective view of the system of figure 2a, and illustrates the paddle
30 mechanism in a compressed state, with a bag in place;
Figure 2i is another perspective view of the system of figure 2a, and illustrates the paddle
mechanism in an open or released state, with a bag in place;
Figure 2j is another perspective view of the system of figure 2a, and illustrates the paddle
mechanism in an open or released state, with a bag in place;
35 Figure 3a and figure 3b illustrates adaption of the system to different sized bags;

- Figure 4a is a representation of fluid flow created in the bag by the movement of paddles to the compressed state;
- Figure 4b is a representation of fluid flow created in the bag by movement paddles to the released state;
- 5 Figure 4c is a representation of fluid flow acting to scour the bottom of the bag;
- Figure 5a and 5b are representative comparative examples of the difference in bag interference created by paddles in embodiments of the present invention (figure 5a) versus an example representing paddle configuration known in the current art.
- Figure 6a and 6b are representative block diagrams of a side view and top view of an
- 10 alternative arrangement for the mixing device.
- Figure 6c is an example of a commercial concept of the embodiment as shown in Figures 6a and 6b and using the same reference numerals.
- Figure 7a and 7b are representative block diagrams of examples of integration of a mixing system into a processing system.
- 15 Figure 8 is a flowchart providing an example of a method of operating an embodiment of the mixing system.

Detailed Description

- 20 Disclosed herein is a mixing technique and associated device design that creates fluid flow within a fluid bag which reduces accumulation of particles which may settle out of suspension. Figure 1 presents a block diagram of the key components of the mixer system 100, which include a support 110 for a flexible bag 120 holding fluid for mixing, a paddle mechanism 130, a paddle driving mechanism 140, and a control system 150.

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- The support 110 is a bag supporting structure arranged to hold an aseptic process bag 120 containing fluid and particles to engage with the paddle mechanism. Such processing bags 120 are known and comprise a flexible bag typically with associated tubing, which is sterilised and designed for one off use. The support can include a hook, peg, clamp, or
- 30 other mechanism to hang or otherwise support the bag 120 for engagement with the paddle mechanism 130.

- The support 110 can be mounted on a housing which supports the paddle mechanism 130 and houses the control system 150, and paddled drive mechanism 130. Alternatively, the
- 35 bag mechanism may be freestanding, positioned adjacent the paddle device such that the supported bag 120 appropriately engages with the paddles (which will be described in

further detail below). The bag supporting structure of some embodiments can be adjusted to accommodate different sized bags.

5 In the illustrated embodiment, the paddle mechanism 130 is configured to engage opposing sides of a bag 120 supported by the support 110. The paddle mechanism 130 is driven by the paddle driving mechanism 140 to squeeze the bag 120, actuation of the drive mechanism is controlled by the control system 150. When the bag 120 is correctly positioned, the paddle mechanism engages 130 with a bottom portion of the bag only extending partway across the bottom of the bag 120. The paddle mechanism is designed to 10 compresses and release the engaged portion of the bag 120. For example, a reciprocating motion of paddles on either side of the bag squeezing (compressing) and releasing the bag between the paddles. Compression displaces fluid across and upward through the bag from the portion of the bag engaged by the paddle mechanism. Fluid flows back into this portion of the bag once the compression is released. Repeating cycles of compression and release, 15 and the associated repetition of displacement and flow back, creates a recirculating flow within the bag 120. This recirculating flow is effective for maintaining particles in suspension. This recirculating flow can also have an advantageous effect of scouring the bottom of the bag, to reduce particle settling. This scouring effect can also promote resuspension of settled particles.

20 Testing has proven the combination of compressing only part of the bottom of the bag and repeating cycles of compression and release has proven highly effective relative to pre-existing designs. It has been observed in testing of prototype embodiments by the applicant that the fluid flow within the bag created by the mixing motion actively flushes the lower 25 region of a hanging bag where particles that have settled congregate. Such settled particles can be difficult to resuspend. For some fluids such particles are notoriously difficult to resuspend. It has also been observed in the tested prototype embodiments that the fluid flow within the bag created by the mixing motion induces a large-scale circulation from top to bottom creating an evenly dispersed suspension.

30 It has also been observed in the tested prototype embodiments that the mixing motion is not sensitive to the fluid volume in the bag since it physically displaces a small portion of the bag capacity, allowing a common mixer design to service a broad range of bag sizes and fluid volumes.

35 Further, as only a small portion of the fluid in the bag is displaced during each compression action on the bag, the force and power required to conduct effective mixing is substantially

reduced relative to those methods that attempt to lift a large portion of the fluid in the bag before releasing it. Reduced force and power of the mixing function enables inherently safe mixing devices incorporating safety features to be accessed by personnel without exclusion barrier guarding.

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An embodiment of the paddle mechanism will now be described with reference to figures 2a-2j, for ease of reference the same reference numerals are used when referring to the same elements in different drawings. In this embodiment the mixer device housing 155 is mounted on a single pole 280. A pair of paddles 210 that oscillate between an open and closed state extend from the housing 155. The bag 120 of fluid and particles to be mixed is hung from the support comprising an arm 285 and a hook 290 to position the bottom of the bag near the bottom of the paddles 210 when they are closed. In some embodiments the arm 285 and height of the hook 290 may be adjustable to accommodate different sized bags. Figures 3a and 3b illustrate use of the mixer system 200 with different sized bags 120, 320. As can be seen in figure 3b the system can be adjusted to alter the relative position of the arm 285 relative to the housing 155 to accommodate the longer bag 320. In some embodiments this may be through raising the arm 285 relative to the housing 155. In an alternative embodiment the support may be fixed and the housing 155 able to be repositioned on the pole 280 to adjust the position of the arm 285 relative to the paddles 210. An embodiment may use an adjustable height bag hanging hook to set the bottom of bag relative to the paddles.

The paddle mechanism comprises two paddles 210 disposed to be on opposite sides of a bag 120 when this is correctly positioned. In this embodiment the paddles are substantially rectangular, however other shapes may be used, such as square, elliptical or other shapes configured to engage with a portion of the bag proximate the bottom edge and one side. The paddles each have two lower arms 220 and two upper arms 225 to connect the paddle to two shafts 235 (an upper shaft and a lower shaft), mounted such that relative rotation is allowed between the arms 220, 225 and shafts 235. The shafts 235 connect to cranks 230 which are driven by the motor (not shown) of the paddle driving mechanism 140, the motor being located within the housing. The cranks are operably connected to the motor to be driven in an oscillating manner. Figure 2b shows an initial or rest position of the paddles. The cranks 230 are driven, by operation of the motor, to partially rotate in the directions as indicated in figure 2b to the position shown in figure 2c, this causes the paddles 210 supported by the arms 220, 225 to move in the direction as indicated in figure 2b to the compression position shown in figure 2c. On release the paddles 210 and other components return to the rest position as shown in figure 2b. The effect of this movement to

compress the portion of the bag 120 between the paddles is illustrated in figures 2d-2j, where figures 2e, 2i and 2j show the bag and paddles in the rest position from different perspectives, and figures 2f-2h show the bag and paddles in the compression position, figure 2e showing a cross section of the device 200 and bag 120 taken through line A-A of figure 2d. From these figures it should be apparent that in the paddles engage the bag in a lower quadrant, and the bag is compressed (in other words squeezed) between the paddles thereby displacing the fluid in the bag from the region between the paddles.

The motor of the paddle driving mechanism can be actuated to repeat movements between the rest position and compression position by the control system in accordance with a mixing protocol. Reciprocating motion of the paddles can be controlled to be any one or more of periodic, oscillating motion, variable, or pulsed with pauses between actuation of the paddles.

Each of the cranks 230 has a shaft which extends into the housing to engage with a gearing system connected to the drive motor to drive. In some embodiments the gearing system is configured to translate rotational movement of the motor into oscillating movement of the cranks. In alternative embodiments the motor may be driven in forward and reverse direction to drive oscillating movement of the cranks, translating to oscillating movement of the paddles 210. In an embodiment the motor is intermittently driven to cause rotational movement to the compression or displacement position (shown in figure 2c), and in absence of the motor driving force allowed to relax back to the initial or release position (shown in figure 2b). In other alternative embodiments the motor is driven in forward and reverse directions to drive reciprocating movement of the paddles.

Figures 4a-4c illustrate the fluid motion created in the bag arising from the paddle motion mixing action. Figure 4a highlights the fluid flow in the bag 120 away from the zone squeezed by the closing paddles 210. During the compression phase of the paddle cycle fluid lower in the bag is displaced outward 410 along the base of the bag and upward due to the side of the bag, fluid also flows upward 415 away from between the paddles 210. Figure 4b highlights the fluid flow in the bag when the paddles open. As the paddles 210 return to the initial position, fluid flows 420 downward and along the bottom of the bag into the space created by the retreating paddles, and also downward 425 to refill the space between the paddles 210. The different flow trajectories due to only partial coverage of the bottom of the bag 120 by the paddles 210 can cause turbulence in the fluid which can be beneficial to mixing. Repeated actuation of the paddles can also create a recirculating fluid flow.

Figure 4c illustrates how the fluid flow scours (dislodges) particles from the bottom of the bag because of the partial coverage of the lower bag. Due to only partial coverage of the bottom of the bag, part of the fluid returning to the space between the paddles will flow along the bottom of the bag. This can reduce settling of particles (also referred to as sedimentation) at the bottom of the bag. Movement of fluid along the bottom of the bag can also aid in stirring up particles which may have settled (for example during storage, setup, or a pause in processing etc.) so these can become re-suspended through the mixing process. There can also be advantages in mixing efficacy due to different directions of fluid flow causing turbulence with the bag, which aids mixing and maintaining particles in suspension.

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The control system 150 controls the paddle driving mechanism to perform repeated displacement and release cycles which creates a recirculating flow of fluid within the bag. The control system includes a processor and memory configured to control the paddle driving mechanism, for example the processor may be microprocessor, for programmable hardware such as a programmable logic controller (PLC), or field programmable gate array (FPGA). The memory can include volatile and non-volatile memory, for example using solid state memory in processor circuits or conventional processor and memory boards.

The control system may be programmed with instructions for actuations of the paddle drive mechanism for execution of one or more mixing protocols. Each mixing protocol may define a series of mixing stages, for example defining for each stage time periods and frequencies for actuation of the paddles, or specify a number of actuations to perform and pause times between each actuation. For example, mixing protocols executable by the system may be designed for homogenising partly immiscible fluids, creating an homogeneous suspension, or sustaining a suspension. In an example, an homogenising state where a fast continuous mixing cycle executed for a controlled number of cycles (a cycle being a paddle compressions and release of the bag) can be used initially to mix particles in suspension media to form an homogeneous suspension. The homogenising state can be followed by a sustaining state using a relatively slower or pulsed mixing cycle to maintain the particles in suspension. For example, an homogenising state may use a cycle rate of one or more cycles per second, and a sustain state, may use a pulsed cycle where a mix cycle occurs over 1 second every 3 to 5 seconds. A sustain state may also use a slower continuous cycle rate, for example one cycle every 2 seconds. The cycle rates and whether pulsed or continuous cycles are used for various mixing states will vary between embodiments based on variable values for mixture parameters. Mixture parameters may include measures of any physical property which may affect mixing such as volume, particle size, particle density, carrier liquid viscosity, temperature etc. Some chemical properties may also be taken into

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consideration. It should be appreciated that mixing protocols may vary widely based on the mixture parameters and mixing objective. For example, forming an homogeneous mixture can have different mixing requirements (i.e. higher cycle frequency and longer duration) than simply maintaining particles in suspension, in other words preventing particles from settling.

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In some embodiments the paddle drive mechanism is configured to cause the paddles to oscillate. The oscillation can be reciprocating motion between compression and release states of the paddles, with paddles moving at a constant speed for a specific cycle frequency. The paddle drive mechanism can include any one or more of paddle speed control, paddle

10 cycle speed control (frequency control), variable speed control. Embodiments can enable the controller to control system to vary paddle cycle speed. In some embodiments the control system varies paddle cycle speeds based on mixing requirements to perform any one or more mixing protocols.

- 15 In some embodiments where required paddle cycle frequency is low, the control system intermittently actuates the paddle drive mechanism with a timed dwell between each mix cycle such that mixing action occurs at a speed supporting active mixing.

In some embodiments the controller includes a mixer counter configured to count

20 displacement and release cycles of the paddles. Such embodiments can also implement a count trigger, where actions can be triggered based on cycle count. For example, a stage of a mixing protocol may specify a number of mixing (compression and release) cycles, and completion of this specified number of mixing cycles triggers a change in operation of the system. In an example, the control system monitors the mixer counter and transition to a

25 next stage of a mixing protocol is triggered based on the mixer counter cycle count.

A mixer count trigger may also be utilised to trigger operation of another system or operation external to the mixing system, for example initiating or stopping a processing phase in a connected system, trigger input from another system, or initiate outputting of fluid from the

30 bag, etc. In such embodiments the mixer count trigger may cause a signal to be sent to the other system, and the connected system takes action responsive to the trigger signal. In an alternative embodiment the control system for the mixer system may be integrated with the control system for the connected processing system, and the mixer count trigger used directly to affect the processing protocol. In an example a dispensing system, connected in

35 line with the mixing system and relying on correct mixing of the product, may be paused by the control system while the paddle mixing system completes the pre-determined number of

mixing cycles. On completion of the pre-determined number of mixing cycles the mixer count trigger signals to the dispensing system to proceed.

5 In some embodiments the controller may include a communication module and receive instructions to control mixing operations via the communication module from another device or system. The communication module may use wired or wireless data transfer techniques in various embodiments. In an embodiment conventional transceiver hardware, software and protocols may be used. Alternatively, embodiments may be developed compatible with
10 proprietary communication protocols. The communication system may be utilised to integrate the mixing system with a processing system that utilises mixing at some stage in its processing to enable integrated process control. The communication system may also be utilised to download or upload data logs where the controller is programmed to log data during processing.

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In the embodiment illustrated in figures 2a-2h, the configuration of the paddle mechanism and crank and shaft drive method mean that the paddles operate in an upward swinging motion. This motion will slightly push the bag up to the hook rather than drag it down during compression. However, alternative embodiments are also envisaged as being applicable to
20 this disclosure. For example, the paddle mechanism may be configured for horizontal reciprocating or oscillating motion only.

An embodiment may include only one paddle which acts against one side of the bag to compress the bag against a fixed surface. For example, a single paddle may be mounted on
25 the housing with a plate opposite (instead of another paddle) in a fixed position, with a gap to receive the bag between the plate and the paddle when the paddle is in a rest or non-compression state. Such a mechanism could utilise a similar paddle and paddle drive mechanism as illustrated in figure 2a with one paddle replaced by a fixed plate, and the drive mechanism altered to provide a longer horizontal linear travel for the paddle to compensate
30 for having only one paddle.

Alternatively, for an embodiment having only one moving paddle, the paddle may be mounted parallel to the housing with a fixed plate mounted opposite. The fixed plate being connected to the housing along on vertical edge only at a distance allowing a gap to receive
35 a bag between the fixed plate and paddle in a rest position. In this embodiment the paddle drive mechanism may be configured for direct horizontal linear movement of the plate, for example using a piston type mechanism or other linear actuator, moving the paddle away

from the housing and toward the fixed plate during the compression phase of the cycle and back toward the housing in the release phase of the cycle.

- 5 In the embodiment shown in figure 2a, the paddle mechanism extends orthogonally relative to the housing. However, this relative orientation is not essential and other orientations are contemplated. For example, the paddle mechanism may be configured to extend parallel to the housing. Different orientations may require alteration to the paddle mechanism and driver from the examples disclosed herein.
- 10 An example of an alternative embodiment is illustrated in the representative block diagrams of figures 6a and 6b, which represent a side view and top view of an alternative arrangement for the mixing device 600. An example of how this may be implemented in a commercial embodiment is shown in figure 6c. This embodiment of a mixing device 600 includes a fixed plate 630 that supports a fluid bag 620 at an angle. The fixed plate is oriented at an angle
- 15 relative to a horizontal plane that is sufficient for liquid to flow toward the bottom of the bag 620 by influence of gravity, but allows the bag to lie supported in place on the plate. The angle also allows draining of the fluid from the bag 620 through one or more tubes 625 at the bottom of the bag. In an alternative embodiment the bag may be supported upright, against a vertical surface. A paddle 610 is arranged to overlie a portion of the bottom of the bag 620 and is driven by a paddle drive mechanism toward the fixed plate to compress this bottom
- 20 portion of the bag to displace liquid upward and outward from under the paddle, and then release so fluid flows back to this portion. Repetitions of this compression and release cycle creating a circulating flow within the bag, as described above.
- 25 In some embodiments the plate 630 can be temperature controlled to facilitate temperature management of the liquid in the bag. For example, the temperature control may be for cooling or heating the contents of the bag 620. In some embodiments the plate may have a region 660 that is temperature controlled. For example, a region where a heating coil or heat exchange fluid pathways are embedded in or otherwise carried by the fixed plate. Any
- 30 suitable temperature control mechanism may be used to control temperature of the plate for heat exchange between the plate and the bag to adjust temperature of the contents of the bag. For example, to maintain liquid in the bag within a target temperature range during mixing.
- 35 In an embodiment, a pressure plate 640 is provided to press the bulk of the liquid in the bag against the temperature controlled plate 630. In the example of figure 6a, the pressure plate 640 is placed over the bag 620 attached by clamps 645 to the fixed plate (or housing 630) at

a distance above the plate 630 that is set to provide slight compression of the bag and prevent all liquid in the bag pooling at the bottom of the bag due to gravity, while still allowing for liquid to be moved by operation of the paddle 610.

- 5 Using the pressure plate in this manner can improve temperature control characteristics by increasing the surface area of the plate covered by the liquid by the pressure plate reducing pooling at the bottom of the bag. The pressure plate may also provide some insulation against ambient temperature.
- 10 The pressure plate 640 can have a cutout in the paddle region to accommodate the paddle. Alternatively, an embodiment may be provided where the paddle operates from under the pressure plate. The pressure plate may have thinner region proximate the paddle to reduce risk of interference with the pressure plate. In an alternative embodiment, the paddle may operate from below the bag, compressing the bag against the pressure plate. In an
- 15 embodiment the pressure plate can be held in place (for example using clamps, clips or other fastenings) a fixed distance above the fixed plate. In the embodiment illustrated in figure 6a the pressure plate 640 is supported by arms (not shown) attached to clips 645. The arms can be adjustable to allow the plate to compensate for the volume in the bag 620. The mixer paddle 610 in this embodiment works through a clearance gap in the pressure
- 20 plate 640.

- In an alternative embodiment the pressure plate may be supported in a manner that allows for limited movement, for example using an elasticised or resilient spring mounting. Such
- 25 embodiments may be useful where the mixing is performed simultaneously with dispensing of liquid from the bag or filling the bag, and the volume in the bag may change significantly during mixing. Similarly, this embodiment may be advantageous in an application where contents of a fluid bag need to be thawed from frozen, as the geometry of the bag may changes as the liquid therein melts. Mixing during thawing may improve thawing efficiency. Further as components of a mixture may thaw at different rates, and therefore be prone to
- 30 separating during thawing, mixing can recombine separated components to reform the original mixture composition.

- In the block diagram example of figure 6a the fixed plate 630 is supported by a housing 630, which may also house a paddle drive mechanism 650, and controller with a user interface
- 35 660. However, this is not essential, for example the fixed plate may be mounted on a stand, and the plate angle may be adjustable.

In the embodiment shown in figure 6c, the paddle drive mechanism 650 is a piston type drive mechanism. The paddle moves linearly toward and away from the fixed plate 630 to effect mixing.

- 5 To avoid restrictive guard protection for the mixing system, the exposed mixing paddles must meet the Australian standards specification UL61010-1 section 7.3.4 "Limitation of force and pressure" to be non-hazardous for operators. A major advantage of embodiments of this invention is that reduced force is required to mix product in the bag since the mixing action displaces a small volume relative to the known prior art at the relevant priority date.

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Embodiments of the paddle driving mechanism can include a force limiting mechanism for operator safety. For example, a pre-loaded force limiting device may be included in the paddle actuation mechanism that protects human operators from injury if fingers are caught between the paddles. For example, a mechanical spring or gas spring controlled force

- 15 limiting device can provide this primary safety function.

The force limiting mechanism is designed to inhibit further movement of paddles if a preconfigured threshold force is applied on the paddles.

- 20 In some embodiments the control system may also be configured to reverse movement of the paddles where a paddle force threshold is exceeded. An electronic control system can also be configured to detect such events and respond to minimise user exposure in addition to the primary safety system. For example, one or more pressure sensors in the paddles or support surface may be used to monitor force applied and detect when the threshold is
- 25 exceeded. Alternatively, monitoring the drive motor for fault conditions may be used. For example, variation in load torque may be used as an indicator of paddle force and variation outside of an anticipated range indicate interference with paddle movement due to obstruction. Drive motor power consumption, movement, or movement resistance may also be monitored and used as indicators of paddle fault conditions or triggering safety cutoff of
- 30 the motor.

The force limiting device may vary for different configurations of paddle drive mechanisms.

- As discussed above, the disclosed system can be used with different sized fluid bags. The
- 35 size of the paddles relative to the bag is not critical, provided the paddle mechanism only partially covers the width of the bag.

- Figure 5a and 5b illustrate the difference in bag and fluid displacement between the current invention, figure 5a, and an example showing bag coverage by paddles equivalent to that of existing bag mixer art, figure 5b. As should be apparent from the illustrative example of Figure 5b, that currently known compression type mixers which have paddles extending across the whole width of the bag are required to elevate (displace upward) the entire contents of the bag, the required displacement could be around 1/3 of the bag height. This restricts the volume of liquid that can be present in the bag and demands substantial force and power for active mixing.
- 10 In contrast the mixer of the current invention (figure 5a) only needs to lift around 25% of the liquid each cycle. This has an advantage of dramatically reducing force and power requirements for mixing compared with prior art mixing systems for equivalent bag size and fluid volume. This can also have an advantage of relaxing constraints of bag fill levels.
- 15 A further advantage of embodiments of the present invention is that the only partial coverage of the bottom of the bag means that the bag can be arranged such that at least one output line located at the bottom of the bag will not be occluded when the paddles are closed, so fluid can be drawn from the bag when mixing is taking place. For example, sustaining an homogenous suspension during dose dispensing operations.
- 20 As mentioned above, embodiments of the mixing system may be used with or integrated into a processing system. Figures 7a and 7b are block diagrams of some examples of integration of the mixing system with a processing system. In the example of figure 7a, the mixing system is integrated into the same housing or cabinet as the processing system 710, in this example the processing system 710 housing is configured to support one or more input fluid bags 740 and a mixing fluid bag 760 in engagement with one or more paddles 770 driven by a motor drive system (not shown) within the housing under control of the processing system 710 controller (not shown). Processing system flow paths 720 connect the input fluid bag(s) 740, mixing fluid bag 760, and one or more output 750 paths provide a processing fluid circuit, through which fluids may be moved by operation of a pump 730 (such as a peristaltic pump) under control of the system controller. The system controller may also control valves (for example pinch valves) of the fluid processing system flow paths to control flow of fluid through the system. The output 750 paths may connect to one or more containers or bags for collection of output products, or to another separate processing system. The processing system controller in this embodiment is configured to control all of the components of the processing system, including the mixing system paddle drive motor, to execute one or more processing processes or protocols. It should be appreciated that the
- 35

processing system can be an aseptic processing system, enabling fully autonomous execution of a processing process.

5 In the example of figure 7b, the mixing system 780 is separate to the processing system 710', for example configured to be set up proximal to the processing system cabinet to enable the mixing system 780 to support a mixing fluid bag 760 connected in the processing circuit for the processing system. This embodiment may be suitable for a processing system configurable to perform a variety of processing processes, not all of which require mixing, or where mixing is an optional step for the processing. The mixing system 780 may be set up
10 adjacent the processing system 710' cabinet on a bench or a stand. In some embodiments a stand for the mixing system may be physically attached or attachable to the processing system cabinet. Any suitable arrangement that allows a mixing fluid bag 760 connected into the processing circuit to be operably engaged by the mixing system 780 is contemplated within the scope of the invention.

15 The controller 790 of the mixing system 780 is independent of the processing system 710' controller. In some embodiments the mixing system may be manually switched on or otherwise controlled by a human operator, for example this may be suitable for a process where constant mixing is required. In some embodiments an operator may be able to set a
20 timer or mixing program for execution of a mixing process with timing coordinated with the processing system process, but independently controlled by the mixing system. In alternative embodiments the mixing system controller 790 may be configured to receive instructions from the processing system controller to control the mixing process. For example, the mixing system controller may be provided with a data communication module
25 configured to connect to the processing system controller via a wired (e.g. data cable, USB, ethernet or optical fibre) or wireless (e.g. WIFI, infra-red, Bluetooth) data connection. The mixing system controller may receive "start" and "stop" trigger signals for a pre-programmed automated mixing operation or mixing sequence. Alternatively, the external system
30 controller may provide signals to control the mixing process, for example controlling paddle oscillation speed, pulsing, changes in speed or temperature control (for embodiments where the mixing system includes such functionality) during execution of the processing process.

It should be appreciated that the circuit comprising the fluid bags 740, 760 and processing flow paths 720 for an aseptic process is typically provides as a kit configured for the process
35 and processing system with the fluid processing circuit pre-connected to provide a closed sterile environment, the kit may also include output containers. As such, the kit can be configured to include paths for the fluid mixing bag of sufficient length to accommodate a

mixing system 780 placed near the processing system 710'. For example, the mixing system 780 may be adjacent the processing system 710' cabinet on a bench or a stand. In some embodiments a stand for the mixing system may be physically attached or attachable to the processing system cabinet. Any such kits which enable connection of the mixing bag into the fluid processing system flow paths, providing a processing fluid circuit to enable movement of fluid through the system by operation of the system pump 730 are contemplated within the scope of the present disclosure.

It should be appreciated that the mixing system described herein may be utilised with a variety of different processing systems, or for a mixing operation alone. Examples of processing systems which may be integrated with or used with the disclosed mixing system can be found in the applicant's own prior patent applications publication nos. WO2018/204992, WO2019/140491, and WO 2023/272360.

Figure 8 is a flowchart of an example of a mixing process which can be implemented using a mixing system as described herein. In a setup phase 810 a flexible mixing bag, connected into a fluid circuit is attached to the support of the mixing system arranged to engage with the paddle mechanism. The bag positioned so that the paddle or paddles are arranged to engage with a portion of a flexible bag holding fluid proximate a bottom edge and only extending partially across the bag. If fluid bag is not already holding fluid, fluid may be pumped to the bag 820. Performing repeated displacement 830 and release 840 cycles which creates a recirculating flow of fluid within the bag. Each displacement and release cycle including actuation of the paddle mechanism to cause compression of the bag 830, which causes displacement of the fluid across and upward through the bag from the portion of the bag engaged by the paddle mechanism. Subsequent release of the compression 840 allows fluid to flow back into the previously compressed portion of the fluid bag. Repeating these cycles creates a recirculating flow of fluid within the bag across the bottom of the bag which acts to resuspend any settled particles.

The mixing system processing may include counting the displacement and release cycles, once the count is met the mixing process may be ended or proceed to a next processing step 850, for example a change in mixing speed or pulsing operation. The mixing process can include counting displacement and release cycles of the paddles, monitoring a mixer count trigger, and transitioning to a next stage of a mixing protocol based on the cycle count fulfilling the mixer count trigger.

The mixing process can include varying displacement and release cycle speeds based on mixing requirements. For example, processing may require differing speeds to homogenise partly immiscible fluids, create an homogeneous suspension, or sustain a suspension.

- Where required paddle cycle frequency is low, the mixing processing can include
- 5 intermittently performing displacement and release cycles with a timed dwell between each cycle such that mixing action occurs at a speed supporting active mixing.

It will be understood to persons skilled in the art of the invention that many modifications may be made without departing from the spirit and scope of the invention.

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It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

- 15 In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or
- addition of further features in various embodiments of the invention.

20

Claims:

1. A mixing system comprising:
 - a support for a flexible bag holding fluid for mixing;
 - a paddle mechanism comprising at least two opposing paddles configured to engage
 - 5 opposing sides of the bag supported by the support;
 - a paddle driving mechanism; and
 - a control system,
 - wherein the paddle mechanism is arranged to engage with a portion of the bag
 - proximate a bottom edge and only extending partially across the bag, such that actuation of
 - 10 the paddle driving mechanism causes movement of the paddles to compress the bag and
 - displace the fluid across and upward through the bag from the portion of the bag engaged by
 - the paddles, and
 - the control system controls actuation of the paddle driving mechanism.
- 15 2. The mixing system of claim 1, wherein the control system controls the paddle driving mechanism to perform repeated displacement and release cycles which creates a recirculating flow of fluid within the bag.
3. The mixing system of claim 2, wherein the recirculating flow of fluid within the bag
- 20 across the bottom of the bag acts to resuspend any settled particles.
4. The mixing system of any one of claims 1 to 3, wherein the paddle drive mechanism is configured to cause the paddles to oscillate and includes paddle cycle speed control.
- 25 5. The mixing system of claim 4, wherein the speed control enables the control system to vary paddle cycle speed.
6. The mixing system of claim 5, wherein the control system varies paddle cycle speeds based on mixing requirements to perform any one or more of:
- 30 homogenise partly immiscible fluids,
- create an homogeneous suspension, or
- sustain a suspension.
7. The mixing system of claim 5 or 6, wherein where required paddle cycle frequency is
- 35 low, the control system intermittently actuates the paddle drive mechanism with a timed

dwel between each mix cycle such that mixing action occurs at a speed supporting active mixing.

8. The mixing system of any one of claims 1 to 7, further comprising a mixer counter
5 configured to count displacement and release cycles of the paddles.
9. The mixing system of claim 8, wherein the control system monitors the mixer counter and implements a mixer count trigger, whereby transition to a next stage of a mixing protocol is triggered based on the mixer counter cycle count.
10
10. The mixing system of any one of claims 1 to 9, wherein the paddle mechanism includes a force limiting mechanism.
11. The mixing system of any one of claims 1 to 9, wherein the control system includes a
15 communication module.
12. A mixing system comprising:
a support for a flexible bag holding fluid for mixing;
a paddle mechanism comprising at least one paddle configured to engage with the
20 bag supported by the support;
a paddle driving mechanism; and
a control system,
the paddle mechanism comprising at least one paddle configured to be disposed on
a first side of the bag to engage with a portion of the bag proximate a bottom edge and only
25 extending partially across the bag, and a surface disposed on an opposite side of the bag
such that actuation of the paddle driving mechanism causes movement of the at least one
paddle to compress the bag and displace the fluid across and upward through the bag from
the portion of the bag engaged by the at least one paddle, and
the control system controls actuation of the paddle driving mechanism.
30
13. A mixing system as claimed in claim 12, further comprising a temperature controlled plate arranged to contact the bag for heat exchange between the plate and contents of the bag.
- 35 14. A mixing method for implementation using a mixing system having a paddle mechanism arranged to engage with a portion of a flexible bag holding fluid proximate a

bottom edge and only extending partially across the bag, the method comprising the steps of:

performing repeated displacement and release cycles which creates a recirculating flow of fluid within the bag,

- 5 each displacement and release cycle including actuation of the paddle mechanism to cause compression of the bag and displacement of the fluid across and upward through the bag from the portion of the bag engaged by the paddle mechanism, and subsequent release.

- 10 15. The mixing method of claim 14, wherein the recirculating flow of fluid within the bag across the bottom of the bag acts to resuspend any settled particles.

16. The mixing method of claim 15, including varying displacement and release cycle speeds based on mixing requirements to perform any one or more of:

- 15 homogenise partly immiscible fluids,
create an homogeneous suspension, or
sustain a suspension.

17. The mixing method of any one of claims 14 to 16, including, where required paddle
20 cycle frequency is low, intermittently performing displacement and release cycles with a timed dwell between each cycle such that mixing action occurs at a speed supporting active mixing.

18. The mixing method of any one of claims 14 to 17, including counting displacement
25 and release cycles of the paddles, monitoring a mixer count trigger, and transitioning to a next stage of a mixing protocol based on the cycle count fulfilling the mixer count trigger.