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(71) **Applicant: VOLUMINA MEDICAL SA** [CH/CH]; Route de la Corniche 5, 1066 Epalinges (CH).

(72) **Inventors:** **BÉDUE**, Amélie; Chemin Jean Pavillard 18, 1009 Pully (CH). **BRASCHLER**, Thomas; Route de la Mouline 22, 1022 Chavannes-Pres-Renens (CH). **BERN-**

HARD, Armand; Av. Fantaisie 4, 1006 Lausanne (CH).

RIVIER, Laurence: Ch. en Purian 4, 1197 Prangins (CH).

(74) **Agent: DR. LUSUARDI AG (ASSOCIATION EPO NO. 1208);** Kreuzbühlstrasse 8, 8008 Zurich (CH).

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(54) Title: METHOD FOR SUCCESSIVE, PRESSURE-DRIVEN DISPENSATION OF SINGLE DOSES OF A MULTIPHASIC MIXTURE WITH CONTROLLED CONCENTRATION AND DOSE FROM A LARGER RESERVOIR TO SMALLER RECIPIENTS AND APPARATUS FOR PERFORMING THE METHOD

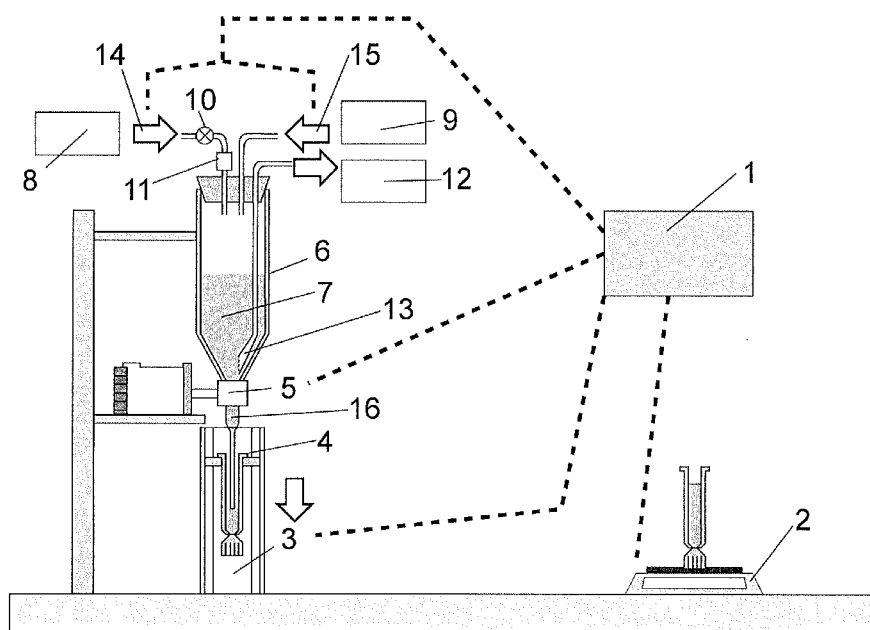


Fig. 1

(57) Abstract: The method serves for successive, pressure-driven dispensation of single doses of a multiphasic mixture comprising a fluid phase and a solid phase from a reservoir into single recipients, maintaining the composition of the mixture in the dispensed doses within pre-determined ranges. The method comprises the following steps: a) a pre-set range of the ratio between the fluid phase and solid phase of the multiphasic mixture is defined; b) a pre-set threshold value for the pressure P_{target} used to dispense the multiphasic mixture is defined; c) a pre-set target for the weight and/or volume dispensed is defined; d) weight and/or volume of the dispensed doses is measured after each dispense and is compared to the target weight and/or volume; e) deviation from

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target volume and/or target weight are compensated for by adjusting the pressure; f) the change of the pressure necessary to deliver the target volume or target weight is detected; g) an amount of fluid phase is added to the mixture remaining in the reservoir to restore the composition of the multiphasic mixture within the pre-determined range of ratio between the fluid phase and solid phase of the multiphasic mixture when the pressure exceeds the pre-set target value P_{target} .

Method for successive, pressure-driven dispensation of single doses of a multiphasic mixture with controlled concentration and dose from a larger reservoir to smaller recipients and apparatus for performing the method.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to a method according to the preamble of claim 1 and a device for performing the method according to the preamble of claim 27.

The invention relates in particular to methods for filling containers with liquids, suspensions or flowables, and more particularly for filling syringes or vials with heterogeneous mixtures while maintaining composition and dispensed dose within desired bounds.

2. Description of the Related Art

Different filling machines are available for filling a variety of products into a variety of containers. Syringe filling machines typically fill a liquid, or viscoelastic liquid into empty syringes. The main parameter to control is the amount filled, but other parameters such as the flawless filling with the avoidance of bubbles are also important.

Filling machines of various designs are well adapted to the filling of homogeneous, liquid, viscous or viscoelastic products, as well as powders. However, they show shortcomings when filling heterogeneous products, particularly products that can separate into a liquid and solid part. The aim of this invention is to describe technical solutions to the problem of phase separation during filling.

A variety of physical principles can be used to drive the substance to be filled from a reservoir to the target recipient. Piston-based volumetric pumps are a wide-spread technology. For instance, US5961303A describes servo-control of a volume displacement pump where predetermined cavities in rotating pistons accept and transmit flowable material in predetermined amounts. Such volumetric pumps typically have precise control over the pumped amount by design, the dispensed volume is indeed given by the geometrical features of the piston, and little backflow can occur due to precise mechanical design. However, with heterogeneous mixtures, there is no guarantee that the volume dosed by the pump has the same composition as the mixture in the reservoir. Indeed, while the overall volume is very precisely controlled, the composition is not and one component may be pumped preferentially. The pump also does not provide information about the composition being dispensed.

Peristaltic pumps are also used for volumetric dispensing. In this case, the physical properties of the flowable to be dispensed are more important than with volumetric displacement pumps, and calibration can be used to relate the movement of the pumping head to the volume being dispensed, as described in US4715786A. US6453927 further described the use of an additional flow line with lower flow rates to better control flow in precision peristaltic pump. Similarly, to volumetric pumps, there is no guarantee as to maintenance of composition upon dispensing of heterogeneous mixtures.

Auger screws are deeply grooved screws advancing material in the grooves when rotating. Augers are used for dosing, typically, albeit not exclusively, for powders. US4696329A describes retrocontrol on the rotation rate of the Auger as a function of the dispensed weight, as assessed by weighing a number of dispensed units and taking the average of the weights. With Auger screw dispensers, there is no guarantee as to maintenance of composition upon dispensing of heterogeneous mixtures.

Pressure or gravity driven flow along with flow control valves is another frequently used scheme. EP1847459A1 describes a multiport machine for filling bottles with liquids. The machine uses a plurality of electric valves to stop filling bottles placed under the valves, whenever a predetermined weight is reached in the bottle under the valve. The weights are measured with load cells, one per bottle. US9493254 describes topping, where additional pharmaceutical substance is added if the weighing after filling finds that not enough substance was dispense.

A critical element in the filling process is to control the driving force for advancing the fluid being filled as a function of the filling level. This is described in terms of turns of an Auger screw as a function of the achieved dispensed weight in US4696329A, in US2645447 in terms variation of the volume of volumetric filling chamber as a function of momentaneous density of powders, and in US4715786A regarding calibration of the rotation rate of a peristaltic pump head in order to dispense the desired amount of liquid. US3662517A uses photo-sensitive elements to interrupt filling when the desired level is reached. In pressure-driven filling, the control over the volume can be achieved by controlling the opening time, for example by closing the filling valve when a given target weight is reached (US3422916, EP1847459A1), or alternatively by using back-pressure from a sensing tube (US5161586, US3783913, US483209). Not only opening time, but also the pressure applied for filling can be controlled in feedback loops in order to adjust the amount dispensed (EP1754962A2, for dispensing viscous materials in PCB fabrication). US20040256022A1 generally proposes the use of strain gauges and associated electronic circuitry for monitoring weight during filling and adjusting filling parameters correspondingly, for instance by shutoff after reaching the desired weight. US7484345 teaches, *inter alia*, the use of a flow meter to monitor the rate of dispensing in real time. JP2022107632A teaches image

treatment for verification of successful filling. EP3466818B1 further describes removal of gas bubbles where at least two gas bubble sensors are used to enable precisely driving valves for the removal of gas bubbles and surrounding liquids during filling, enhancing control over the dispensed volume by removing gas bubbles.

While these teachings efficiently address the challenge of controlling the dispensed amount despite possible unanticipated variations in product or process parameters, they remain silent concerning the assessment of composition during filling in the case of filling heterogeneous mixtures.

On the other hand, viscosity sensing has been used to control fluid composition in various configurations. For example, US4445526A describes a sophisticated control system where proportions of phosphor, water and polyvinylalcohol are mixed in a common reservoir, and both specific gravity and viscosity are monitored and adjusted by retrocontrol on the relative addition rate of the three components such as to obtain a slurry of constant viscosity and specific gravity for automated television screen production. This method achieves desired compositional features, but needs a viscosity sensor in direct contact with the product and does not address control of dispensed mass. In a similar strategy, US4544489A describes addition of conditioning polymer to sewage to achieve specific viscous properties through feedback control. US2006118170A1 describes a control system with multiple control functions, to determine the addition of a gelling agent in real-time to continuously adjust viscosity as a function of sensed viscosity with minimal errors. WO2009032882A2 generically describes retrocontrol on the addition of a concentrate in a dilution machine through a number of parameters, among others viscosity and temperature. US2005286340 describes a continuous chemical blending system where feedback on a number of parameters can be used to adjust the ratio of the streams being blended.

US3024643 uses measurement of the pressure drop created by a fluid flowing through a narrowing to gauge its viscosity, in view of keeping a temperature constant by maintaining the viscosity constant. While permitting follow-up of viscosity in real-time, this invention does not permit to adjust composition. US4422085A exploits the link between specific gravity and viscosity in inkjet inks to estimate, and adjust by addition of solvent as triggered by the use of a floating element acting as a specific gravity sensor. This method also requires a sensor element in contact with the product, and is not adapted to viscoelastic solutions where displacement forces are large. US7331703B1 uses the torque on a mixing paddle by inkjet ink to estimate its viscosity and adjust it by retro-controlled fluid addition. While these methods do provide means for adjusting viscosity,

they require a sensor element in contact with the product which is not necessarily desirable and does not necessarily work with highly non-linear fluids.

CN113522101A describes a stirred tank for improved filling of heterogeneous fluids, with the option to fine tune filling rate by changing the stirring speed. Stirring improves homogeneity with gels able to sediment, but does not solve the issue of changes of concentration due to preferential pumping.

A problem arises in the filling of heterogeneous products in the form of liquids, solids, gels or mixtures thereof when the force or mechanism used to dispense preferentially advances one of the two components towards the receiving recipients. In this case, the filled units are enriched in this component, while the reservoir tank progressively becomes depleted, and subsequent units differ in composition even if the overall weight is precisely controlled. In particular, in solid-liquid or liquid-gel systems it can happen that the less viscous component, typically the liquid, is preferentially carried forward. The magnitude of the problem depends on the material being filled, it is especially pronounced for viscoelastic solid-liquid mixtures exhibiting large flow paths – large pores within suspended particles, or large inter-particle space or both.

BRIEF SUMMARY OF THE INVENTION

It is an object of the invention to provide a method for filling recipient units, like syringes or other containers with precisely known doses of a heterogeneous mixture.

It further provides means to monitor and/or prevent or correct inhomogeneity arising among units filled with a heterogeneous flowable prone to preferential delivery of one of its components - due to the pressure-dependent preferential advance of the fluid phase towards the recipients which leads to a depletion of the fluid phase in the remaining mixture of the reservoir and to a change in composition of the mixture being dispensed - without extraneous elements in contact with the product.

The invention has applications in medical, biomedical and pharmaceutical filling, but also in the food industry and elsewhere.

The invention solves the posed problem with a method comprising the features of claim 1 and with a device for performing the method according to the invention comprising the features of claim 27.

The advantage of the method according to the invention consists in the ability to maintain the initial composition of the multiphasic mixture and the dispensed doses within pre-determined ranges during the on-going dispensation of the multiphasic mixture.

Further advantageous embodiments of the invention can be commented as follows:

In a preferred embodiment a calibration of the relationship between the ratio between the fluid phase and solid phase of the multiphasic mixture and the pressure is performed to define the target pressure P_{target} prior to the start of the first dispense. If a calibration curve is known, then the actual composition can be controlled, at single given solid concentration or also at different concentrations for different fillings or different syringes in the same filling round. If just a single pressure and associated concentration is known, then it's possible to fill consistently to this concentration; if no prior information is known, it is possible to fill homogeneously to an arbitrary, unknown concentration by setting the pressure. The concentration can be measured afterwards, or, it may be enough to just be consistent.

In a further embodiment the method according to the invention comprises the following steps:

- A) defining a target value for the Pressure (P_{target}) to be used for the dispensing and defining a target value for the weight or volume to be dispensed;
- B) filling a reservoir with a multiphasic mixture;
- C) dispensing a dose of the mixture into a recipient using a first pressure P_1 ;
- D) measuring the weight or the volume of the dispensed dose;
- E) comparing the weight or volume measured in step D with the pre-determined target value for the weight or volume as defined in step A;
- F) adjusting the first pressure P_1 by a calculated amount ΔP to a different pressure $P_2 = P_1 + \Delta P$;
- G) repeating steps C-E using the adapted pressure P_2 for the filling of further recipients with doses of the mixture;
- H) optionally adopting one or more further pressure modifications according to step F;
- I) adding or subtracting a calculated amount of fluid phase, possibly zero, to the mixture for compensating the loss or the excess of fluid phase in the mixture, whereby the amount of fluid is calculated using the actual and target pressures .

This embodiment offers the advantage that calculation of the pressures based on algorithms makes the filling more reproducible. When a microcontroller is used, some sort of algorithm is required.

In a special embodiment fluid is only added when the pressure is above a threshold pressure P_{max} , distinct from and above the target pressure P_{target} .

Addition of fluid only above a threshold pressure, which is itself above the target pressure, is useful in algorithms where relatively large amounts of fluid are added at once (as illustrated in fig. 7). Indeed, if fluid is added at P_{target} , then the concentration of the solid content may become too

low because there is a “dip” in the solid concentration in the composition being filled after fluid addition. In other algorithms, the dip is anticipated (Smith correction) and it is not necessary to define a threshold pressure separately from the target pressure.

In a further embodiment fluid is withdrawn from the multiphasic mixture when the pressure is below the target pressure P_{target} . In cases where the solid concentration is too low in the reservoir, fluid withdrawal permits to increase the solid concentration. This can happen for example if the product was supplied with too little solid content at the outset of filling, or if a large portion of fluid was added.

In a further embodiment fluid addition and/or fluid withdrawal are only operated if the weight or volume of the dispensed dose is within the range of the target pressure P_{target} .

This allows to restring the addition and/or withdrawal of fluid to filling cycles where the target weight/volume ensures proper evaluation of the composition of the multiphasic mixture. Meeting the weight/volume target indicates that a stable, defined dispensing regime is reached, with a precise relation between solid content and pressure. Having reached such a stable operating regime means that the fluid compensation can be used advantageously.

The fluid phase may comprise one of the following substances: aqueous solutions, physiological saline (0.9% NaCl), buffers, pharmacologically acceptable solutions, hyaluronic acid, glycosaminoglycans, alginate, agarose, methylcellulose, carboxymethylcellulose, chitosan, anaesthetic solutions and solutions containing lidocaine.

The polymeric solutes have the advantage of adding viscosity to the fluid, reducing phase separation between solid and liquid. This further increases the precision of the method according to the invention.

The fluid phase may also comprise one of the following substances: water, isotonic solutions, isotonic buffers, hydrogels, solutions containing polysaccharides, deacetylated hyaluronic acid, hyaluronic acid modified with alkyne derivatives such as cyclooctynes, azide modified hyaluronic acid, thiolated hyaluronic acid, hyaluronic acid derivatives, hyaluronan oligosaccharides, heparosan and derivatives, polyfructose polyvinylalcohol, polyacrylates, nucleic acids, DNA, RNA, synthetic polymers, viruses, transfection agents, contrast agents, albumin, cell culture medium, xylocaine, bupivacaine, tetracaine, mepivacaine, rhopivacaine, mepivacaine and/or other anaesthetics of the -caine family; solutions containing antibiotics, penicillin, cephalosporine, tetracycline, amoxycylline, clavulanate, cephalixin, ciprofloxazine, metronidazole, azithromycine; organic solvents, in particular ethanol, isopropylalcohol, dimethylsulfoxide; oils,

triglycerides, lipid emulsions, fatty acids, oleic acid, linoleic acid, palmitic acid, or mixtures of all the aforementioned substances.

Lipid emulsions are advantageously filled by the present method according to the invention, because they show preferential fluid transport, particularly if the droplets are big.

The solid phase may comprise one of the following substances: porous scaffolds, porous scaffold particles, crosslinked polysaccharides, in particular porous crosslinked polysaccharides, crosslinked hyaluronic acid, crosslinked glycosaminoglycans, alginate crosslinked ionically, agarose, crosslinked carboxymethylcellulose, chitosan, decellularized tissue, decellularized adipose tissue.

Particularly the porous substances and the decellularized tissues are known for being affected by preferential transport and are advantageously filled with the present method according to the invention. If the liquid phase is sufficiently viscous, the problem may also disappear because the preferential fluid transport becomes negligible (viscosity-matching between solid and liquid). In many cases, adding sufficient viscosifying agent for successful filling is not possible because of problems in-vivo, such as inflammation or osmotic swelling.

The solid phase may also comprise one of the following substances:

foams, foam particles, hydrogels, hyaluronic acid crosslinked with butanedioldiglycid ether, hyaluronic acid modified with alkynes and azide moieties and crosslinked by the reaction of these groups, crosslinked deacetylated hyaluronic acid, hyaluronic acid crosslinked with disulfide bridges, divinylsulfone, crosslinked hyaluronic acid derivatives, crosslinked hyaluronan oligosaccharides, crosslinked heparosan and derivatives, alginate crosslinked with Ca^{2+} ions, Fe^{2+} or Fe^{3+} ions, Ba^{2+} ions, covalently crosslinked alginate, crosslinked polyfructose, (porous) crosslinked peptides, (porous) crosslinked proteins, decellularized plant material, decellularized human adipose tissue, porous silk particles, extracellular matrix, collagen, laminin, polyurethane foams and foam fragments, polyolefin foams and fragments. Polysaccharides, extracellular matrix, proteins, peptide precipitated in organic solvents, optionally crosslinked. Reconstituted cellulose as fibers, foam, foam fragments. Fibers, electrospun fibers: PLGA, PLA, polycaprolactones, polyurethane, polysaccharides, proteins. Extruded fibers such as regenerated cellulose, polysaccharides, proteins, peptides extruded into non-solvent, optionally crosslinked, or mixtures thereof, capsules, beads, DNA, RNA calcium hydroxyapatite, ice crystals, ceramics, frozen substances, solidified fats, oils, microparticles, silicone oil droplets, solid silicone particles, crosslinked cells, crosslinked tissue, living cells, organoids, vesicles, liposomes, capsules, capsules containing cells, lipid-loaded beads, PNIPAAm, thermosensitive materials, ice, insoluble or partially soluble salts.

Irregular structures tend to show preferential transport of fluid under pressure and other actuations. This is particularly true for foam-like structures, liquid emulsions, beads, fibers, irregular structures produced by precipitation of ionic polymers with multivalent cations, or by precipitation of polymers in organic solvents, or during cellulose regeneration in a coagulation bath, or during foaming or freezing, or also in natural tissues and cells or by precipitation of inorganic salts. These substances are thus advantageously filled by the present invention.

In a special embodiment the proportion of the weight or volume of the solid phase in relation to total heterogeneous product in the reservoir is between 0.05% and 95%, preferably between 0.1% and 50%, more preferably between 0.2% and 30%, most preferentially between 1% and 20%.

The solid-liquid compositions with both a substantial solid and liquid fraction are particularly prone to preferential transport of fluid in filling. They are dense enough so that the solid is retained in narrower parts of the conduits, while the fluid can still flow through interconnected pore space, yet the pores are big and interconnected enough to permit selective advancement of the fluid. Of note, the solid part here can also be a hydrogel, the meaning of "solid" here is that locally, it will not flow but remain contiguous.

In a further embodiment the multiphasic mixture is composed of several liquid phases and/or of several solid phases.

The simultaneous presence of solid and liquid phases predisposes to preferential advance, usually of the liquid phases, when pressure or another primary driving force is applied. Thus, such multiphasic systems are advantageously filled according to the method of the present invention.

In a special embodiment the multiphasic mixture is a viscoelastic material with an elastic modulus G' between 1Pa and 1Mpa, preferably between 10Pa and 100kPa and most preferably between 100Pa and 10kPa and/or a loss modulus G'' between 0.01Pa and 100kPa, preferably between 0.1Pa and 10kPa, and more preferably between 1Pa and 1kPa.

Viscoelastic materials undergoing preferential transport are advantageously filled with the method according to the invention. Moderately stiff materials can be filled with the present method, too hard ones would require excessive pressures.

In still a further embodiment the multiphasic mixture is biocompatible.

The materials in contact with the fluid are typically chosen to be resistant to sterilization and removal of endotoxins.

In a further embodiment of the method the viscosity of the multiphasic mixture is adjusted to render it injectable.

Injectable products need to be applied by actuation of a syringe and it is particularly helpful if they have a highly constant composition for the injecting physician to always apply the same manual procedure.

In a special embodiment the multiphasic mixture has a yield stress between from 0.1Pa to 100kPa, preferably between 1Pa to 10kPa, most preferably between 5Pa to 5kPa.

Many injectables do have a yield stress. Materials with yield stresses in the range of 0.1Pa to 100kPa can be filled with reasonable pressures, that is more than 100Pa and less than 2MPa, preferentially between 1kPa – 100kPa .

In a further embodiment the fluid phase has a viscosity between 0.0005 Pa·s to 10 Pa·s, preferably 0.0006 Pa·s to 0.1 Pa·s

Liquids with these viscosity ranges can surprisingly be filled without excessively high or low pressures.

In a further embodiment the fluid phase is a physiological saline solution or a solution of polysaccharides.

Polysaccharides make the liquid more viscous and facilitate homogenous filling.

In a further embodiment the fluid phase comprises a contrast agent.

The contrast agent permits X-ray quantification of the solid/liquid ratio, particularly when the contrast agent is excluded from the solid volume and the solid (or advantageously hydrogel) volume occupies a large fraction of the total volume.

In a further embodiment the solid phase has a yield strain between 0.1Pa to 100kPa, preferably between 1Pa to 10kPa and more preferably between 5Pa to 5kPa.

In a special embodiment the solid phase is hydrophilic.

Hydrophilic materials retain the fluid phase by capillarity, this prevents air entry into the heterogenous mixture when pressure is applied.

In a further special embodiment, the solid phase is porous. Porous materials are particularly prone to preferential advance of the fluid phase, and so can particularly benefit from fluid compensation. The mean diameter of the pores of the porous materials are purposefully in the range of 0,5 μm and 5 mm, preferably between 2 μm and 2 mm and more preferably between 5 μm and 1 mm.

Porous materials with relatively large pores are more prone to preferential advance of the fluid phase, and so can particularly benefit from fluid compensation.

In a further embodiment the pore fraction is in the range between 5% and 99.9%, preferably between 10% and 99.5% and more preferably between 30% and 99%.

Preferential fluid transport occurs particularly in solids with a large pore fraction and so filling of such materials is particularly difficult. In this sense, it is advantageous to use the method according to the invention with them.

The solid phase may comprise particles with the shape of beads, porous scaffolds and porous irregular scaffolds.

In a special embodiment the recipients are made of edible components.

Food items filled homogeneously into edible containers are advantageous for green technologies.

The invention is directed also to a device for performing the method according to the invention comprising:

- a) a reservoir for the multiphasic mixture to be dispensed,
- b) a dispensing element,
- c) a valve positioned between the reservoir and the dispensing element,
- d) a compensating fluid reservoir connected to the reservoir,
- e) a controller connected to a pressure regulation device connected to the reservoir where the controller is capable to adjust the pressure in such a way as to permit the device to dispense amounts close or identical to an amount of interest; and
- f) the same controller of step e) or a separate controller connected to a fluid delivery and/or subtraction device connected to the reservoir wherein the amount of fluid to be added or subtracted is calculated such as to return the pressure to a preset target value when the pressure deviates from this value.

In a special embodiment of the device a recording instrument records the measurements of the pressure and/or of the weights and/or volumes measured and/or the fluid addition or withdraws performed during the dispense. For recording quality control records for each device, it is important to keep track of the parameters used and measured for the filling of each syringe. In this way, observations made on particular syringes can be related to the parameters recorded, and/or downstream steps of in the fabrication procedure can be adjusted to the parameters measured. For example, the pressure recorded gives an indication of the solid concentration

present in given individual syringes, and the syringes can be sorted according to different solid concentration for different applications after the filling.

In a further embodiment of the device a pressure sensor is connected to the reservoir to continuously monitor the pressure while dispensing the multiphasic mixture and where an interrupter valve is positioned between the pressure regulator and the reservoir.

The drop of pressure in the closed reservoir can be used to judge the amount of liquid already dispensed, since the already dispensed liquid gives rise to a corresponding additional gas volume.

This permits to refine or define the opening time for achieving a more precise weight control.

Knowing the actual pressure in the reservoir without intervening tubing with gas flow permits better more precise estimation of the pressure acting on the multiphasic mixture and thus better estimation of the composition (solid content).

In a special embodiment the device further comprises a fluid withdrawal port connected to the reservoir.

This embodiment has the advantage that when the pressure is below the target pressure P_{target} .

It is possible to fluid is withdraw fluid from the multiphasic mixture. In this embodiment, not only too high concentrations of the phase or phases opposing higher flow resistance (usually the solid or hydrogel phase or phases) can be corrected by fluid addition, but also too low concentrations of this phase or these phases by withdrawal of the other phase through fluid withdrawal port.

A BRIEF DESCRIPTION OF THE DRAWINGS

Several embodiments of the invention will be described in the following by way of example and with reference to the accompanying drawings in which:

Fig. 1 illustrates a schematic representation of an embodiment of the device according to the invention.

Fig. 2 illustrates schematically the basic algorithm for pressure-driven filling of a heterogeneous product executed with the machine as shown in fig. 1 .

Fig. 3 shows a diagram showing calibration series for pressure feedback.

Fig. 4 shows a diagram with calibration linking the dispensing pressure to the composition being dispensed.

Fig. 5 shows an example of weights obtained in the first cycles of syringe filling.

Fig. 6 shows the pressures used to obtain the weights shown in Fig. 5.

Fig. 7 shows the pressures required for filling syringes with acceptable weight with the arrows indicating addition of constant amount of fluid each time.

Fig. 8 shows a comparison of the estimated composition between pressure-regulation only and pressure regulation and addition of fluid.

Fig. 9. Shows a comparison of different algorithms for regulating amount and composition when dispensing a heterogeneous product, with the horizontal lines representing common thresholds of acceptance: 10% for weight, 5% for compositional change for the 95% confidence intervals.

Fig. 10. Shows the relative efficiency of inventive algorithms.

Fig. 11 shows an embodiment for pressure-time filling.

Fig. 12 show an embodiment of electronic connectivity for a pressure-time filling machine.

Fig. 13 shows a recapitulation of cycle-to-cycle feedback.

Fig. 14 is a schematic representation of the primary feedback during the dispense cycle of the method according to the invention.

Definitions

Driving force: Force that is controlling the movement of the product feed. Among others, this can be pneumatic pressure, or mechanical movement such as the rotation rate of an Auger screw, peristaltic pumping head or piston.

Regulated driving force: Force that is controlling the movement of the product, under the control of a regulating controller.

Regulated pressure: Controlled pneumatic pressure used as the regulated driving force for the product feed.

Regulated rotation rate of auger: Controlled rotation of an Auger screw used as the regulated driving force for the product feed.

Regulated rotation of peristaltic pump head: Controlled rotation of peristaltic pump head used as the regulated driving force for the product feed.

Dispensing time: Time during which product is dispensed into receiving recipient

Regulated dispensing time: Dispensing time under the control of a regulating controller.

Primary process variable: The primary process characteristic that controls the amount of product being filled at its current composition, and at the same time holds information on product composition. This can be the driving force as applied intentionally, for instance the pressure, rotation rate of Auger screw, or the rotation rate of the peristaltic head. The primary process variable can also be the dispensing time, if the driving force is held constant, or a compound variable derived from both driving force and opening time if both are varied, such as the ratio between driving force and opening time.

Receiving recipient: Vial, syringe, bottle or other recipient into which controlled amounts of heterogeneous mixtures at controlled composition is dispensed.

Motorized valve: Flow control valve capable of interrupting or essentially interrupting the flow of product from the reservoir to the receiving recipient or receiving recipients.

Reservoir: Recipient containing the product to be dispensed, typically substantially larger than the unit dose to be dispensed.

Distributor: Nozzle, tube or assembly of nozzles and tubes used for delivering the product into the receiving recipient or recipients.

Parallel distributor: Distributor designed to deliver product to more than one receiving recipient simultaneously.

Dispensing element: Distributor or parallel distributor

Motorized stage: Stage capable of moving receiving recipients or parts or all of the distributing machinery during dispensing. A motorized stage is particularly advantageous for the rapid filling of high and slender receiving recipients such as syringes, with synchronization between the movement of the receiving recipient in the direction of the dispense.

Dispensed volume: The volume of product dispensed per receiving recipient. The dispensed volume can be measured by various techniques, for example by weighing or strain gauges measuring weight if specific density of the product remains substantially constant, or by various fill sensors such as interruption of an optical path, impedance or capacitive sensing, image process and other techniques known in the art. Depending on the technology used, the dispensed volume can be monitored in real-time (for example optical sensors, strain gauges) or after completion of the dispensing cycle (e.g. weighing on an external scale).

Primary feedback loop: Feedback loop controlling the driving force and/or opening time in such a way as to maintain the dispensed volume in a target range, and ideally substantially constant. The primary feedback loop can operate from filling cycle to filling cycle to adjust the driving force or opening time, or both, based on deviations from target in the previous cycle, or it can operate during the dispensing itself, for example by shutting off a motorized valve when a given fill level is reached.

Primary feedback algorithm: Algorithm used to correct the driving force and/or opening time during the primary feedback loop. The details of the primary feedback algorithm depend on the sensing methods for the dispensed volume and primary process variable.

Compensating fluid: Fluid that can be added to the product in the reservoir to correct its composition. In a preferred embodiment, the compensating fluid is a liquid, but it can generally be a flowable and as such can be a liquid, viscous liquid, viscoelastic liquid, powder, suspension, slurry, gel or mixtures thereof.

Compensating fluid reservoir: Container containing the compensating fluid.

Secondary feedback loop: Feedback loop using the primary process variable to maintain product composition constant. The secondary feedback loop triggers dispensing of compensating fluid or fluids to the product reservoir. In a typical application of filling of a heterogeneous solid-liquid mixture with preferential pumping of liquid during dispensing, the secondary feedback loop controls dispensing of the liquid component into the reservoir to keep the primary process variable and thus the solid-to-liquid ratio constant.

Secondary feedback algorithm: Algorithm used determine compensating fluid dispense in the secondary feedback loop.

Calibration data. Data acquired to establish the link between the primary process variable and the aspect of the composition of the product being dispensed to be controlled. For example, known linear or non-linear relation between the pressure and the absolute concentration of the polymer (dried to constant weight) in a heterogeneous mixture consisting of free fluid and swelled particles of the polymer.

Controlled dispensing of the compensating fluid: Dispense of the compensating fluid(s) into the product reservoir under the control of the secondary feedback loop.

Product: Material to be filled into receiving recipients.

Heterogeneous product: Product consisting of more than one component, which under conditions of filling can be at least partially separated from each other, leading to dispense of doses enriched in one or more components and correspondingly depleted in the others as compared to the reservoir.

Biphasic product: Product consisting of two component forming distinct phases, which under conditions of filling can be at least partially separated from each other, leading to dispense of doses enriched in one component and correspondingly depleted in the other as compared to the reservoir.

Homogeneous product: Product consisting of one or more components which are not separated under ordinary conditions of filling.

Homogeneity of dispensed product: Homogeneity of the dispensed product refers to maintenance of constant composition, or at least composition with predefined bounds for units acceptably filled.

Dispensing success criteria: Dispensing success criteria depend on the application, but for heterogeneous products will typically involve a first criterion on the volume or mass dispensed for each unit to be in a certain target range, and a second criterion on the composition being within certain limits. Supplementary criteria can be the absence or substantial absence of bubbles, horizontally level filling, absence of splattered droplets or others.

Elastic modulus: The elastic modulus G' is the elastic part of the viscoelastic response of a material measured in rheology. The measure can be performed in oscillatory shear rheology, at a frequency of 1Hz, with deformations in the range of 0.1% to 5%. The elastic modulus G' is

quantitatively evaluated as the in-phase component of the shear stress in oscillatory application of deformation.

Loss modulus: The loss modulus G'' is the viscous part of the viscoelastic response of a material measured in rheology. The measure can be performed in oscillatory shear rheology, at a frequency of 1Hz, with deformations in the range of 0.1% to 5%. The loss modulus G'' is quantitatively evaluated as the out-of-phase component of the shear stress in oscillatory application of deformation.

Detailed description of the invention

Embodiment 1: Setup and algorithm for pressure-driven filling of a heterogeneous product

The exemplary embodiment of the invention is based on pressure-driven filling. The aim is to fill a product consisting of heterogeneous mixture with a fluid and a gel-like component into syringes as receiving recipients despite preferred pumping of the fluid component of the heterogeneous mixture. To achieve this goal, a controller adjusts pressure to obtain filling of receiving recipients with a predetermined amount of product in a primary feedback loop. The evolution of the pressure necessary to obtain the desired dispensed volume for the receiving recipients is used to estimate the variation of composition being filled, as a higher proportion of gel-like material requires a higher pressure. The controller has a secondary feedback loop where a rise in pressure is countered by addition of supplementary compensating fluid. This allows to fill the receiving recipients not only with a predetermined dispensing volume, but also at a predetermined concentration of suspended heterogeneous material in the product.

The setup elements of a filling machine suitable for performing this preferred exemplary embodiment according to the invention is shown in Fig.1. The setup consists of a microcontroller 1 interacting with a scale 2 for monitoring dispensed weight, an optional motorized stage 3 to enable smooth dispense of viscous or viscoelastic flowables into a recipient 4, preferably a narrow syringe, a motorized valve 5 enabling precisely timed dispensing, and a reservoir 6 for the multiphasic mixture 7 to be dispensed. The microcontroller 1 is able to apply pneumatic pressure at will (from a pressure reservoir or source 8, using a pressure regulator 14) to the multiphasic mixture 7, and also to control fluid addition to the reservoir 6 from a fluid reservoir 9 (using a fluid delivery device 15). Optionally, an interruptor valve 10 is present between the regulated pressure reservoir 8, and also optionally, a pressure sensor 11 is present in vicinity or within the reservoir. If present, these elements are typically connected to the controller. Also, optionally, a fluid

withdrawal device 12 is present and can selectively withdraw fluid from the reservoir through a fluid withdrawal port 13. The fluid withdrawal port comprises a selectively permeable membrane or filter that allows withdrawal of the fluid phase or phases of the heterogeneous mixture constituting the product, shown as dashed line. If present, the fluid withdrawal device 12 is connected to the controller. During active filling, the multiphase mixture 7 flows through the dispensing element 16 and is dispensed into the recipient 4.

The invention uses a first “primary” feedback loop on a filling process variable such as pressure, time of opening of a valve, rotation rate of an Auger screw or peristaltic pump head in order to match the amount dispensed per unit to a pre-set target. The variable used to regulate the amount dispensed shall be referred to as the “primary process variable”. In the preferred embodiment shown in Fig. 1 the primary process variable is pressure.

The technical solution to the problem of monitoring changing composition is to use the value of the primary process variable, as adjusted by the primary feedback loop, to monitor relevant composition parameters. For instance, in solid-liquid mixtures, viscous or viscoelastic properties are often tightly linked to solid content, and in order to dispense a constant amount, increasing force is needed, leading to higher values of pressure, opening time, or rotation rate of Auger screw or peristaltic pump head required to meet the weight target. Therefore, by using pre-established calibration data regarding the link between the primary process variable and the composition of the dispensed material, the relevant compositional information can be retrieved for every unit filled. A first aspect of this invention is thus to monitor the composition of the dispensed flowable via the value of the primary process variable as controlled by feedback on the filled amount. This information is for example critical in respecting critical upper and lower boundaries for the concentrations in the composition being filled.

Beyond monitoring, the information on the compositional change can be used to correct the compositional change occurring over time. For instance, a tendency of increase in pressure during pressure-controlled filling as required to maintain constant weight indicates increasing sample solid content in a solid-liquid heterogeneous mixture, and can be corrected for by adding an amount of liquid calculated in such a way as to keep composition in the filled unit constant. In this way, small unit-to-unit variations in product consistency are corrected by the primary, typically rapid feedback loop, on the primary process variable. Changes in composition, typically arising more slowly, are corrected for by the secondary, typically slower feedback loop on the primary process variable, capable of detecting and correcting trending.

The detailed interplay between the feedback algorithms shall now be described with reference to Fig 1.

Fig. 2 outlines a basic method underlying this invention in the context of pressure-driven filling of syringes. The method can be subdivided into an initialization step (step 1 in Fig. 2) which is only executed once when setting up the machine, and the steps related to filling the syringe per se, which are repeated for each syringe (step 2-11 in Fig. 2)

In the initial step (step 1), the machine is set up physically and parametrized with initial values. These initial values can be actively entered by the user, or they can be derived from historical knowledge so that no user intervention is necessary, or a mixture of both. Key initial values are the pressure to be applied during the first filling cycle (P_1), the target weight to be dispensed (W_{target}), as well as update coefficients for the feedback loops. The valve opening time remains advantageously, but not necessarily, constant as this permits precise and constant synchronization between motorized stage movement and valve opening. Typical values for the valve opening time range from 10ms to 10000ms, more preferentially 20ms to 2000ms, even more preferentially from 50ms to 500ms and most preferentially from 100ms to 300ms. Step 1 also involves placing the volume of product to be dispensed into the reservoir, and may include a number of optional steps such as degassing, stirring, setting up of regulatory records, inspections, functionality tests and so forth.

Once the machine is set up and suitably parametrized, dispensing of heterogenous product into the syringes can be started. In the embodiment shown in Fig. 1, the product is dispensed into syringes one at a time, but it is understood that with minor differences, dispensing of products into several syringes in parallel is possible with self-evident minor changes to the method.

For each syringe to be filled, the user first carries out a few preparatory steps. The user first establishes the tare of the empty syringe (step 2). The user here can be a human, but it can also be a robotized system carrying the syringes from one part of the machine to another, or a robotized system as part of a larger, automated production facility. The tare can be established on an external balance and entered manually into the dispensing system, but preferentially, the tare is automatically read from the scale by the microcontroller of the dispensing system, upon confirmation by the user or by the known timing of the syringe placement in the case of a robotized system.

The user then places the syringes into the syringe holder on the dispensing machine (step 3). Weighing can also be performed by an integrated mechanism in the holder, for example by strain

gauges or by electromagnetic lifting and readout of the counterbalancing force. In this case, external weighing (step 2) is not necessary.

Once the syringe is stably placed into the syringe holder, the filling machine moves up the stage, which is motorized, into an upper position suitable for initiation of the dispense cycle (step 4). Typically, in this position, the dispensing nozzle reaches near open entry of the syringe, and more preferentially the nozzle is a tubular element reaching near the bottom of the syringe being filled. Confirmation for performing the vertical movement of the syringe can come from the user, or also by pre-programmed timing and/or sensor input confirming due placement of the syringe in a robotized system. When the motorized stage reaches the upper position, the system is ready for dispensing. In some cases, particularly with syringes with larger diameter or when filling into bottles or wide vials, the motorization may not be necessary.

Upon user command, or by detection of reaching the upper position, or by preprogrammed sequence, the dispense cycle is then initiated (step 5).

The dispense cycle is typically automated and fully directed by the controller, which is typically a microcontroller but can also be a programmable logic controller or a computer or the like. The automated tasks of the controller (step 6) involve applying the desired pneumatic pressure to the reservoir, opening the motorized valve for dispensing once the desired target pressure is reached. The opening of the valve is accompanied by initiation of the downward movement of the motorized stage, if such stage is present. The vertical movement of the motorized stage and thus the syringe placed on the holder needs to be tightly synchronized to the opening of the valve, accounting for latencies of both the valve opening and the motorized stage, and for acceleration and linear speed of the product being dispensed.

After execution of the dispensing, the motorized valve is closed, pressure released from the reservoir (step 7). The movement of the motorized stage is stopped at the unloading position. In some embodiments, not only pressure is released after the dispensing, but a slight vacuum, at a level compensating hydrostatic pressure of the product in the reservoir or slightly stronger, is applied. This enables the use of valves subject to minor leakage. Valves that have some minimal leak when closed are advantageous because they often require less torque to turn and enable faster operation. The commutation between pressure and vacuum in such embodiments is carried out by the microcontroller.

After completion of the dispense cycle, the filled syringe is removed from the holder (steps 8).

The filled syringe (or group of syringes) is then weighted. Weighting can again be on an external scale or using other means such as strain gauges or electromagnetic lifting. Subtraction of the

tare from the measured by permits to determine the actual net weight of heterogeneous product having been dispensed (W_{actual}).

The actual weight W_{actual} of the current cycle as well as the pressure applied in the current cycle (target or alternatively as monitored during the dispense cycle) serve as the basis for the machine's feedback algorithms. In an elementary feedback algorithm, the relative error between the actual weight (i.e. $(W_{\text{actual}} - W_{\text{target}})/W_{\text{target}}$) serves as the primary basis for adjusting the pressure of the next dispensing cycle (step 10). In Fig. 1, an elementary update formula taking only into account the present relative error is given, which amounts to using only the P term in a PID controller, but full PID controllers or model-based algorithms may be used as well. The coefficient α in the formula given in step 10 in Fig. 1 can have a value between 0.1 and 10, more preferentially between 0.15 and 1, and most preferentially between 0.2 and 0.4.

The update of the pressure from cycle to cycle is able to maintain the actual weight in close bounds with respect to the target weight for most syringes (>80% of the syringes, preferentially better than 85%, and most preferentially > 90%) for a bound of +/- 20% relative to target weight, preferentially +/- 15%, even more preferentially +/- 10% and most preferentially +/- 5%. To reduce the amount of rejected syringes, it is possible to operate the system in purge mode where instead of dispensing into syringes, heterogeneous product is dispensed into a recovery container. This is particularly useful for the initial cycles, when the pressure update algorithm tunes itself to the actual product being filled.

To maintain the concentration of the heterogeneous fluid being dispensed within its target range (within +/- 20% variation in solid-phase concentration, preferentially +/-10%, more preferentially +/- 5% and even more preferentially within +/- 2% and most preferentially within +/- 1%), step 11 provides fluid addition to compensate for preferential dispense of fluid phase. Fig. 1 provides an elementary fluid update algorithm, where concentration is re-adjusted based on proportional feedback between the target pressure and actual pressured needed to dispense the desired amount. For the fluid addition algorithm in Fig. 1 to be applicable, the remaining volume of heterogeneous product available in the reservoir is advantageously known. This is easily accessible by knowledge of the amount of product initially provided and the amount already dispensed. If this information is not available, instead a typical product volume can be assumed instead.

Embodiment 2: Determination of pressure feedback parameters

Fig. 3 contains an example dataset that can be used to configure the target pressure and the pressure feedback coefficient α . The calibration data itself is specific to the setup used and the

heterogeneous product to be dispensed, the coefficient α is normalized and its order of magnitude is common to many heterogeneous products. Data of the type shown in Fig. 3 can be acquired by dispensing heterogeneous material under conditions ensuring that the dispensed material has the desired composition.

To acquire the calibration data, the reservoir is filled with material with concentrations of the suspended solid phase typically superior to the targeted concentration, and dispense cycles are carried out. The concentration of the relevant constituent is measured on the dispensed materials by techniques known in the art (spectroscopy, drying to constant weight, conductivity and others). With a new heterogeneous product, it may take a few iterations of optimization until samples within the desired concentration range can be obtained, since initially, the relation between reservoir concentration and dispensed concentration is unknown. However, since increasing the concentration in the reservoir also leads to increasing concentrations in dispensed samples, the person skilled in the art will be able to carry out this optimization rationally.

Once samples in the desired range of concentration can be dispensed, the pressure is varied intentionally and corresponding changes in the dispensed weight recorded. This is shown in Fig. 3. By reporting relative deviation from the target dispensed weight as a function of relative deviation from the target pressure, the relative sensitivity of the dispensed weight to relative changes in pressure is established. This provides the value of the pressure feedback coefficient α as the inverse of the slope (the data in Fig. 3 is associated with a slope of about 3, and thus $\alpha=1/3=0.33$). In practice, there is some uncertainty in the value of α , and since exaggerated proportional coefficients in feedback regulation lead to oscillation, it may be necessary to decrease α to render the system stable, for example by 10% as compared to the primary calibration. The response of the dispensing machine to the change of pressure is immediate, such that even the simple feedback loop with only the proportional coefficient α stabilizes the dispensed volume stabilizes relatively quickly (in one embodiment, for extreme departures from target weight within 10-20 dispense cycles, otherwise within 4 or 5 cycles). Even so, it remains possible to improve the convergence by more sophisticated retrocontrol. For example, PID (proportional, integral, differential) coefficient values may be chosen instead of a sole proportional coefficient α . Optimization of such parameters is within reach of the person skilled in the art (a known method is for example the Ziegler-Nichols method; the necessary integral and differential error terms are calculated as simple sums and differences). The absolute value of the pressure corresponding to 100% of the target weight also provides useful information: this value can be used as an initial setting when starting to dispense from a freshly filled reservoir. Initial pressure values range from 100Pa to 2Mpa, more preferentially from 1kPa to 500kPa, and most preferentially from 10kPa to 100kPa, pressure values being relative to ambient atmospheric pressure. The pressure value associated with achieving the target pressure varies from product to product. It is not absolutely mandatory to dispose of an estimate of the initial pressure: the pressure update algorithm will by

itself find the pressure needed for dispensing the desired amount for as long as it lies within the capacity and safe operation domain of the machine. However, it is clear that if the initial pressure is far from the pressure needed to dispense the desired amount, reaching doses within target will take longer and more product will be wasted, such that generally, one will commence filling with a best-guess initial pressure instructed by historical calibration.

Embodiment 3: Determination of composition of the dispensed doses and feedback parameters for fluid addition

Fig. 4 shows an example calibration curve between compositional change, here measured as departure from a predefined target concentration of polymeric solid in a heterogeneous product being dispensed, and the pressure necessary to dispense the target amount. The calibration data is obtained during dispensing with active feedback on the pressure for reaching a target weight in place, and only samples where the target weight is achieved with the desired precision ($\pm 20\%$ relative to target weight, preferentially $\pm 15\%$, even more preferentially $\pm 10\%$ and most preferentially $\pm 5\%$) are used for constructing the calibration curve. Although the absolute values of such calibration curves are specific to the heterogeneous product being dispensed, the relative relations shown in Fig. 4 apply with minor variations to different products.

A surprising precision in the relation between the pressure and very minor changes in the composition of the product being dispensed can be seen in Fig. 4. This is all the more surprising as viscosity measurement of heterogeneous suspensions is known to be notoriously difficult. These suspensions typically display shear thinning or even defined yielding (i.e. materials with the characteristics of a Bingham plastic) or on the contrary, shear thickening, and viscosimetry in classical capillary viscosimetry is plagued by a host of problems ranging from clogging and irregular flow to near complete lack of reproducibility. Often, reasonable measurements can only be obtained in complex oscillatory rheometers, which are expensive and often little suited for per-dose measurements if for no other reason than the time necessary per measurement. Through the teaching of this invention, by the use of pressure-driven feedback loop to obtain regulated, highly reproducible flow conditions, the problem of viscosimetry of heterogeneous products, including ones with highly non-linear flow properties, is elegantly solved and provides a dose-per-dose quality control. It is in fact quite possible that the relation is even more precise than suggested in Fig. 4 since sampling and measurement of concentrations of small samples of heterogeneous product itself has limitations rooted in the imprecision of weighing or other detection method used.

By establishing calibration curves of the type shown in Fig. 4, desired bounds on the product composition are translated to corresponding bounds in the regulated pressure value.

Compositional precision in the range of a few percent (within +/- 20% variation in solid-phase concentration, preferentially +/-10%, more preferentially +/- 5% and even more preferentially within +/- 2% more preferentially within +/- 1% and most preferentially within +/- 0.5%) is easily achieved given the very high precision of present commercially available pressure sensors. For typical pressures in the range of 10kPa to 100kPa, a compositional change of 1% corresponds to a pressure change of over a 200Pa, knowing that commercial pressure sensors have sensitivities in the 1Pa range.

If desired, absolute viscosities can be calculated. For this, the system is by measuring the volume dispensed with calibration solutions with known viscosity commercially available, under identical machine setting and over a range of pressures. By using calibration curves thus established and using the linearity for the essentially Newtonian liquids provided as commercial calibration standards, a precise numerical value for the viscosity under dispensing conditions can be indicated for each dose dispensed.

To determine an optimal fluid correction coefficient β , the relative change in fluid composition necessary to compensate a given change in regulated pressure needs to be estimated. This information can be obtained from calibration curves such as the one shown in Figure 3. In the case of Fig. 3 an initial guess value for an optimal fluid correction coefficient β would be $\beta=0.36$.

Embodiment 4: Details on the fluid addition algorithm

As described in the formula in step 11 in Fig. 2, the fluid correction is minimalistic. Indeed, nothing is done until an upper pressure limit is reached. This pressure is typically chosen slightly below the upper limit of pressures associated with acceptable product composition. This means that the product composition slowly changes during dispensing, before it is corrected back to near optimal values by addition of fluid. Particularly if the reservoir is not stirred, there may be a lag between fluid addition and correction of product composition as sensed by change in regulated pressure; in this case, an elementary algorithm of fluid addition may add several doses of fluid before the regulated pressure drops below threshold, leading to over-correction. A simple measure to avoid this is to implement an inactivity period before the next fluid addition, regardless of momentaneous regulated pressure value.

Embodiment 5: Illustration of pressure and fluid feedback

Fig. 5 (weight) and Fig. 6 (pressure) provide an illustration of the pressure algorithm in detail during the first 30 dispense cycles. The steps taken in this practical example are as follows:

Cycles	Explanation
1&2	Purging cycles: remove air bubbles, fill nozzle. The pressure is kept constant at the initial value during these two purging cycles, $P_2=P_1=P_{\text{initial}}$. The initial pressure depends on the product and is typically established such that the dispensed weight will initially be as close to its target value as possible; typical values of initial pressure can be about 5kPa, about 10kPa, about 15kPa, about 20kPa, about 25kPa, about 30kPa, about 35kPa, about 40kPa, about 45kPa, about 50kPa, about 60kPa, about 70kPa, about 80kPa, about 90kPa, about 100kPa above ambient atmospheric.
3	In cycle 2, the dispensed weight was 0.41g for a target of 1.1g (horizontal line in Fig. 5). With an update coefficient of $\alpha=0.3$, the pressure P_3 was calculated to be $P_3=(1+(1.1-0.41)/1.1*0.3)*P_2=1.19*P_2$. Applying this increased pressure resulted in a dose of 0.37g being dispensed.
4	By application of the update algorithm, a pressure of $P_4=(1+(1.1-0.37)/1.1*0.3)*P_3=1.20*P_3$ was applied in the fourth cycle. This resulted in a dispense of 1.64g, now substantially above the target of 1.1g
5-10	In each subsequent step, the update algorithm is applied and pressure progressively adjusted to reach a dispensed weight near 1.1g
11-29	From cycle 11 on, the dispensed weight is stably with the target range, which was 0.95-1.25g for this example. From stabilization on, the fluid algorithm addition was in place, but the threshold for fluid addition, here set at 20% above the initial pressure was not reached up to cycle 29. Fluid addition is to be discussed below.

In the present example, no fluid was added up to dispense cycle 29. Fig. 7 shows a larger view on the filling episode, with several episodes of fluid addition. The table below provides an explanation on the different steps.

Cycles	Explanation
11-29	See above. Stable pressure regulation phase without exceeding the fluid addition threshold pressure
30	The fluid pressure exceeds the set threshold pressure of $1.2*P_{\text{initial}}$ for the first time. In this simple example, a target pressure of $1.07*P_{\text{initial}}$ was used (the fluid target pressure does not need to be identical to initial target pressure), for a β value of 0.36 and a constant $V_{\text{reservoir}}=220\text{mL}$, corresponding to about the initial heterogeneous product volume. This results in a fluid addition of 10mL according to the formula in step 11 of Fig. 2.

31	The pressure in this step is calculated based on the values before fluid addition (i.e. step 30), and so it also above $1.2 \cdot P_{\text{initial}}$. However, to avoid duplicate addition of fluid, no fluid is added.
32-40	The regulated pressure starts dropping, no fluid addition is required. By step 40, the pressure has dropped to about the anticipated target pressure of $1.07 \cdot P_{\text{initial}}$.
41-75	Rising regulating pressure indicates again rising concentration of solids in the dispensed heterogeneous product
76	The threshold pressure of $1.2 \cdot P_{\text{initial}}$ is exceeded. In this example, the fluid addition volume is kept constant at 10mL. No fluid is added in step 77 as before.
77ff.	The pressure and fluid regulation algorithms pursue, with fluid addition whenever the upper limit of pressure is reached. As constant volumes are added in this example, while the product volume decreases, the pressure drop after fluid addition becomes more important as the remaining heterogeneous product volume shrinks.

Embodiment 6. Comparison with and without fluid addition

Embodiment 6 compares dispensing cycles with and without fluid addition. Fig. 8 provides the estimated composition over successive filling cycles, with and without addition of compensation fluid. The composition is estimated through the pressure used for dispensing through a calibration curve (as in Fig. 4). The data for the fluid addition curve corresponds to Fig. 7; experiment was stopped for the case without fluid addition because the pressure became excessive, and both curves are reported to 125 dispense cycles, with 3 fluid additions of 10mL each in the case of the “Fluid addition” curve. Both curves are only from cycle 11 on, where stable weight allowed to convert pressure to target weight via calibration curve. (Fig. 7). Even though the algorithm used is crude (fluid addition only upon reaching a discrete threshold above intended overall target pressure, repeated addition of a constant volume of liquid, thus ignoring the change in reservoir content), the example shows the net effect: if no liquid is added, the preferential dispense of fluid leads to a relative accumulation of solid in the reservoir. In the example shown, the concentration of solid dispensed happened to be above target concentration already initially, and the situation becomes worse and worse over time. Fluid addition normalizes the concentration, approaching it towards the target level.

Embodiment 7. Algorithms for addition of compensation fluid and pressure regulation

Fig. 9 shows comparatively the relative efficiency of different algorithms for regulating dispensed amount and composition of a heterogeneous product, as obtained by fluid dynamic modelling of the dispense. The algorithms compared are briefly listed here and explained below.

- 1) "No regulation": This is dispensing according to the pressure-time method, well-known in the art: a constant pressure and time are set, and product is dispensed with constant settings during the filling process. As can be seen from Fig. 9, very substantial errors in both weight and composition are incurred in this way. Indeed, the concentration of the solid mounts in the reservoir as more liquid doses are dispensed. This leads to progressively smaller and more concentrated doses dispensed and ultimately to major error in both weight and composition.
- 2) "Pressure only": Regulating pressure to target a constant weight being dispensed addresses the problem of heterogeneity of dispensed weights satisfactorily. This is known in the art. The approach does however not improve the heterogeneity of product dispensed.
- 3) "Fluid only". Addition of compensation fluid to target a constant weight being dispensed addresses the problem of compositional change from dose to dose satisfactorily. However, while there is also some improvement in the weight, the variations remain clearly above satisfactory levels. Thus, controlling the fluid addition only does not lead to overall satisfactory results.
- 4) "Fluid only, Smith correction". The inventors observed a lag in time between addition of compensation fluid and changes in dispensed product weight in the "Fluid only" approach. To compensate for this lag, the Smith correction method was tried. Even though this further improves the compositional aspect, the variations in weight remain unacceptable large.
- 5) "Pressure and Fluid". The teaching of this invention is to use feedback on both pressure and addition of compensating fluid. While it seems at first glance mathematically impossible to derive a sensible feedback for two variables from a single readout value (the weight), the method of sequential feedback in this teaching still provides updated values for pressure and an amount of fluid to be added. In Fig. 9, the algorithm outlined in Fig. 2 was used, with a threshold pressure equal to the target pressure in step 11.
- 6) "Pressure and Fluid, Smith correction". In addition to the two feedback algorithms, the Smith correction was applied to the addition of compensation fluid. This improves the precision on weight, and quite dramatically improves the precision of composition (by about a factor of 2x, from over 3% error in composition to slightly over 1.5% error in composition in the present example).
- 7) "Pressure and Fluid, Smith correction and cross-feedback". Same algorithm as "Pressure and Fluid, Smith correction", and additionally correction from the Smith compensation term on the pressure to be applied in the next cycle. This anticipates the lowering of pressure by distribution of compensation fluid through the heterogenous product in the reservoir and leads to further substantial improvements in dispensed weight and possibly also a slight improvement in terms of compositional control.

Fig. 9 shows a clear cleavage between strategies using a single feedback loop and strategies using a double feedback loop as disclosed. Fig. 10 shows in more detail that different double feedback algorithms exhibit different efficiencies both in terms of compositional control and in terms of weight control. The differences in mass control in Fig. 9 and 10 are all statistically significant. In terms of compositional control, the introduction of the Smith correction has a highly significant impact, but not the difference between the conditions “Pressure and fluid, Smith correction” and “Pressure and Fluid, Smith correction, cross-feedback”.

Detailed description of the algorithms

1. “No regulation”: Description given above.
2. “Pressure only”: Pressure was updated based on the formula given in Fig. 2 $P_{n+1} = P_n \cdot (1 + \alpha \cdot (1 - W_{\text{actual}}/W_{\text{target}}))$, where P_{n+1} is the pressure to be applied in the subsequent cycle, P_n the pressure in the present cycle, α is the update coefficient, as given above, whereas W_{actual} and W_{target} are the actual and target weights for the dispense.
3. “Fluid only”. Pressure was kept constant in this algorithm, and the amount of compensating fluid to be added in the next cycle was calculated as $V_{\text{fluid}} = \gamma \cdot (1 - W_{\text{actual}}/W_{\text{target}}) \cdot V_{\text{product in reservoir}}$, where the right-hand side values are from the current cycle. We used here a best fit value of $\gamma = 0.04$ (preferentially between 0.001 and 1, more preferentially between 0.005 and 0.2, most preferentially between 0.01 and 0.1). For values of $V_{\text{fluid}} < 0$, $V_{\text{fluid}} = 0$ was used instead. The volume of heterogeneous product in the reservoir $V_{\text{product in reservoir}}$ was calculated from the initially known amount of heterogeneous product added and the sum of the already dispensed doses, via conversion through the known density of the heterogeneous product.

“Fluid only, Smith correction”. The Smith predictor treats the case of delayed responses in feedback loops. The Smith predictor theory is rather involved, but here, a facile implementation is possible based on the idea of compensating fluid deploying its effect exponential over time. We write: $V_{\text{fluid}} = \gamma \cdot (1 - W_{\text{actual}}/W_{\text{target}}) \cdot V_{\text{product in reservoir}} - V_{\text{latent}}$, where V_{latent} is the amount of fluid already added in previous cycles but modelled to not yet have had the time to cause a change in dispensed weight. A simple approach for estimating V_{latent} is to assume an exponential decay of the latent pool over time. In the discrete case of cycle-per-cycle calculations, the total latent volume can for instance be estimated from the volumes already added in the previous steps 1 to $n-1$, as follows:

$$V_{\text{latent}} = \sum_{i=1}^{n-1} V_{\text{fluid},i} \cdot k^{n-i}.$$

k , is a decay constant specific to the filling system being used, in the range $0 < k < 1$. k can be estimated by a person skilled in the art by analyzing the changes of weight being dispensed following a single addition of a defined amount of compensation fluid compared

to adding no fluid. For Fig. 9, $k=0.7$ was used (preferentially between 0.001 and 0.999, more preferentially between 0.05 and 0.99, most preferentially between 0.1 and 0.95).

4. "Pressure and Fluid". The pressure is updated as $P_{n+1}=P_n \cdot (1+\alpha \cdot (1-W_{\text{actual}}/W_{\text{target}}))$, as described above (« Pressure only », Fig. 2). Compensation fluid is added as

$$V_{\text{fluid}}=(P_n-P_{\text{target}})/P_{\text{target}} \cdot \beta \cdot V_{\text{product in reservoir}}$$

also as described above (Fig. 2). For $V_{\text{fluid}} < 0$, $V_{\text{fluid}}=0$ was used for Fig. 9 and 10 ; this amount to setting the threshold pressure for fluid addition equal to P_{target} .

5. "Pressure and Fluid, Smith correction". The idea of latency before action of added fluid is incorporated here by $V_{\text{fluid}}=(P_n-P_{\text{target}})/P_{\text{target}} \cdot \beta \cdot V_{\text{product in reservoir}} - V_{\text{latent}}$, again with $V_{\text{latent}} = \sum_{i=1}^{n-1} V_{\text{fluid},i} \cdot k^{n-i}$

6. "Pressure and Fluid, Smith correction and cross-feedback". For this algorithm, the pressure is also corrected for anticipated effects:

$$P_{n+1}=P_n \cdot (1+\alpha \cdot (1-W_{\text{actual}}/W_{\text{target}})) - V_{\text{entering}}/V_{\text{product in reservoir}}/\beta).$$

V_{entering} is an estimate of the compensating fluid that should deploy its effect in the next cycle. Within the model of an exponential decay of the latent pool, an estimate based on discrete geometric series is :

$$V_{\text{entering}}=\sum_{i=1}^{n-1} V_{\text{fluid},i} \cdot k^{n-1-i} \cdot (1-k) = V_{\text{latent}} \cdot \left(\frac{1}{k} - 1\right)$$

where the k is the decay constant as described above. The volume of compensation fluid to add can be estimated by:

$$V_{\text{fluid}}=(P_{n+1}-P_{\text{target}})/P_{\text{target}} \cdot \beta \cdot V_{\text{product in reservoir}} - \left(2 - \frac{1}{k}\right) \cdot V_{\text{latent}}$$

chosen such that a coefficient of -1 remains in front of V_{latent} for the fluid addition.

Embodiment 8: Implementation of the electronics of the control circuit

Fig. 11 shows an overview over a communication system that can be used for a pressure-driven filling machine according to the invention. The microcontroller 1 directs the operations of the machine. The microcontroller can be any microcontroller known in the art, provided it has a sufficient number of input and output pins. Communication 18 with higher-level user interface equipment 19 is optional, but if so, can be done through USB, wireless ethernet, Bluetooth or other communication channels as known in the art. In one embodiment, the dispensed volume is assessed by weighing (before and after dispense), with the microcontroller reading the appropriate weight from a laboratory or analytical grade scale 2 via serial communication 20, for example through RS232 communication. The microcontroller also drives, by means of appropriate drivers and amplifiers 19, the motorized valve 5 and the motorized stage 3 in order to provide appropriately timed and synchronized movements. The microcontroller also drives the fluid delivery device 15 (and possibly a withdrawal device, c.f. Fig. 1, label 12), for example by means of communication with a syringe pump or syringe pumps, or a peristaltic pump or pumps,

or a control valve regulating gravity-driven flow or flows, or any other suitable means to deliver and/or withdraw a known amount of fluid to the reservoir 6.

Fig. 12 shows details of an electronic implementation. In Fig. 12, IO means input/output, GPIO refers to general purpose input output pins, UART means Universal Asynchronous Receiver / Transmitter and refers to a standard protocol for serial communication, RS-232 is a Recommended Standard for serial communication (follow-up standards such as RS-485 or RS-422 can also be used, depending on equipment).

An Arduino Mega rev3 or any other microprocessor can be used as the central microprocessor. In the case of the Arduino Mega, it communicates through a built-in Atmel 16U2 chip and a USB cable with a tablet capable of displaying a user interface. The firmware in the microprocessor is for instance programmed in C++ as specific to the Arduino environment, through means known in the art, but any other programming language, human or machine, can be used. The user interface on the tablet can be programmed in any suitable language, for example Java or Kotlin for Android, or any other programming language, as known in the art. The presence of a user interface is useful for configuration and for recording of record data, including to document the dispensing characteristics for each unit dispensed, but it is otherwise optional to the functioning of the filling machine itself. The user interface can also be implemented on other electronic means than a tablet, for example mobile phone, desktop or laptop computers, as a web interface, as an interface exposing remote procedure calls or any other means known in the art. Alternatively, the machine can be run entirely by the microcontroller, optionally with a touch screen, for example by using a Raspberry PI instead of an Arduino. The communication between the user interface and the microcontroller can be implemented in any of the numerous means known in the art, a USB cable being a convenient example, other examples being Bluetooth, Ethernet, Wireless, infrared communication, radiofrequency communication, dedicated digital input/output pins, serial communication via RS-232 or related standards, and many more.

The choice of sensors and actuators, as well as the details of the communications between the microcontroller and the peripherals is to a large extent arbitrary. Fig. 12 shows a set of intermediate electronics along with sensors and actuators enabling a robust implementation of the present invention, but it is clear that any of the components can be exchanged by a multitude of functional equivalents or assemblies of functional equivalents. In particular, there are many stepper motors and linear drives, pressure sensors and also integrated digital pressure regulators, syringe pumps, valves and the like. The choice of the precise equipment depends in part on the heterogeneous product to be filled and the throughput intended, with rapid filling posing generally higher requirements on the electronics. Likewise, the voltage level shifters are typically implemented using a combination of discrete npn and pnp transistors and resistors, or alternatively using integrated, commercially available solutions, with a wide choice of suitable

components. Some exemplary transistors are indicated in Fig. 12 but a wide choice exists and the person skilled in the art will find suitable ways of constructing the communication scheme outlined in Fig. 12. In this respect, Fig. 12 outlines the general communication scheme, in practice, a precise layout will have to be constructed by the person skilled in the art, considering the practical characteristics such as the number and type of communication pins, stepper phases, power and current ratings, and so forth. These considerations are elementary and well-known in the art.

With regard to the microcontroller, it is important to note that timing is critical. The critical time scales are typically on the order of 1ms. This is long with respect to internal calculation cycles of modern microprocessors, operating in the MHz range or above, but not necessarily long with respect to communication delays with external equipment such as a user interface app on a tablet. In this respect, regarding firmware implementation, the person skilled in the art will need to give the necessary considerations regarding responsibilities, with time-critical elements being performed with minimal interruption.

With a constant dispensing time as given by a constant opening time of the motorized valve, it is noteworthy that the z-displacement can be easily calibrated in such a way that it is not quite sufficient to accommodate all the product that would be extruded if there were no syringe. The fact of going just slightly too slowly creates a backpressure and thus slows the flow of product. Since the backpressure is greater if for any reason more product is dispensed, the process becomes dominated by the mechanical movement of the z-stage, which can be controlled extremely precisely. It is advantageous to implement precise timing between mechanical movement of the motorized stage and opening of the dispense valve. Preferentially, the rate of downward movement is adjusted in such as to avoid product stretching (movement too fast), or a discrete bubble at the bottom of the syringe (movement initiated too early) and simultaneously avoiding product flow being impeded excessively (movement too slow, too late). Preferentially, the motorized stage movement is adjusted such that starting the downward movement of the motorized stage by a few milliseconds earlier just generates a small, isolated bubble at the bottom of the syringe, ensuring appropriate synchronization of the beginning of the movement of the motorized stage. The linear speed is advantageously adjusted such that the product flow is slightly, but not excessively impeded by the syringe. Preferentially, in the presence of the syringe, the amount dispensed is between 30% and 99.9% of the amount that would be dispensed into a distant waste recipient, more preferentially between 50% and 99%, and most preferentially between 70% and 95%. This approach preserves sensitivity of the amount being dispensed to the product composition, while taking substantial advantage of mechanical limitation of the amount dispensed and thus increasing precision. It is also noteworthy that constant dispensing

time enables facile calibration and execution of stereotypical, rapid movement, with filling times typically faster than 2s, preferentially 1s, more preferentially 0.5s and most preferentially 0.25s or less. Rapid filling often helps decrease effects of product separation.

Parallelization of filling into multiple vials can be used by means of a parallel distributor to achieve higher rates of filling per hour.

Primary feedback loop

In some embodiments, the primary feedback operates by using results from the previous cycle or cycles to adjust the upcoming cycle. This principle is shown in detail in Fig. 2 and is summarized in Fig. 12. In such cycle-to-cycle adjustment, process variable(s) is/are updated to correct for errors detected in the previous cycle. Proportional adjustment, but also more sophisticated Proportional-Integral-Differential (PID) algorithms are possible, and also model-based algorithms, for example anticipating diminishing hydrostatic with advancing filling in pressure-driven filling. A correction for lag in the effect of the fluid, for example by means of Smith-type predictors as outlined are also advantageous. Combinations of PID elements and model or lag elements are also possible.

In some embodiments, the primary feedback loop operates in real time, during the dispense cycle, as outlined in Fig. 12. The simplest primary feedback algorithm consists in stopping the dispensing when the target for the dispensed volume is reached. The necessary real-time information on the advancement of the filling can be obtained from weight information, but also from optical, impedance-based, or image-treatment based sensing, as known in the art. The pressure drop caused by the dispensed volume itself can be monitored in real-time, particularly if after pressure regulation, the connection to the pressure regulator is closed by a valve or if the pneumatic flow resistance in the tubing is sufficiently high to effectively temporally isolate the filling reservoir during the dispense period. The real-time part of the algorithm can be more sophisticated by anticipating valve response and sensing delays. In any case, feedback within the dispensing cycle can increase weight control beyond the possibilities offered by cycle-to-cycle control. However, regardless of whether primary feedback operates already within the dispensing process or exclusively regarding the next cycle, the information gained can be used for a secondary feedback as taught in this disclosure. Real-time and cycle-to-cycle feedback can also be combined, for instance, if real-time feedback indicates that the valve needs to remain open longer, in the next cycle, pressure can be correspondingly increased to regularize the ejection time.

For example, real-time feedback on the amount already filled can advantageously be used to control the closing of the motorized valve. The weight filled will be more precise since over- and underfilling is avoided in real time. The precise actual time used for filling, alone or advantageously along with the weighing, can then substitute for the weight information regarding

the adjustment of pressure. For example, if only 90% of the time was necessary to fill exactly the intended amount, then in the full time, about $1/0.9$, which is about 110% of the weight would have been obtained and the pressure needs to be adjusted correspondingly. Analogously, if in 90% of the time, 95% of the targeted amount was filled, in the full dispense time, some $95\%/0.9$, which is about 105%, would have been filled. Thus, supplementary or isolated information obtained during real-time control can substitute or complement the estimation of the dispensed amount in the context of this disclosure.

As in primary feedback based on the total dispensed amount of heterogeneous product observed after dispensing, different means of estimating the amount of product dispensed can be used in real-time as well. Some examples include the use of strain gauges, optical sensors, image processing, and also the monitoring the drop of pressure due to product dispense. Such information can be used along, or instead, or weight information for controlling the dispensing process itself, but also within the teaching of this invention for addition of compensating fluid.

Secondary feedback

The secondary feedback aims at keeping composition of the dispensed material constant. This composition is not necessarily the one present in the reservoir. It is indeed an important aim of this invention to dispense heterogeneous product with constant composition despite selective transport from the reservoir to the dispensing station. The secondary feedback can operate regardless of whether the primary feedback is done in real-time or in a cycle-to-cycle fashion. The dependency of the primary process variable on the composition being filled provides the necessary indication on composition in both cases. Like the primary feedback loop, the secondary feedback loop can involve simple proportional error correction, or feature PID control, or model elements, or mixtures of the approaches, and/or lag correction as discussed above. Model elements can typically also include correction for decreasing hydrostatic pressure upon advancement of filling, and accounting for heterogeneous concentration regions contributing to the primary process variable. For instance, the pressure necessary to perform pressure-driven filling within the opening time and to within dispensed volume target mostly depends on the product composition within the narrowest parts of the product path – which is typically the nozzle or tube used for filling of the syringes. Advantageously, the design of the reservoir amplifies this resistance compared to the resistance in the reservoir. Nevertheless, some resistance to product advancement also arises in the reservoir itself. By accounting for the mass balance and by making use of calibration data obtained with known product compositions in the different parts of the fluid path, the link between primary process variable and concentration of the product being dispensed can be refined and dose homogeneity improved. As product is being filled, the composition of each unit can be estimated from the calibration data between primary process variable and

composition, and the model updated regarding prevailing composition in the reservoir, and thus refinement of the estimation of the concentration being dispensed.

Many materials and particularly gel-like materials are highly non-linear and a good correlation between primary process variable and product composition is only achieved when the flow regime is tightly controlled. In a preferred embodiment, the secondary feedback is operated only when the dispensed volume is within the target range. Particularly along with constant dispensing time, this ensures tightly controlled and constant flow conditions and enables highly precise regulation of product composition.

The efficiency of the secondary feedback can be very high if the material being filled easily transmits changes in fluid composition across the reservoir. This is for instance the case with porous, elastic materials, since these materials will rapidly equilibrate pore pressure, particularly under the effect of repeated movement. In this case, simple addition of the fluid on top of the product in the reservoir is sufficient, and the invention obviates the need for stirring. In other cases, fluid addition near the bottom of the reservoir or stirring is required.

In some embodiments, fluid addition is performed in real-time during the dispense cycle as function of the momentaneous pressure and change rate in pressure, which is related to the momentaneous flow rate. In such an embodiment, fluid addition is typically performed near the bottom of the reservoir. Dispense of compensation fluid at different places in the reservoir is also possible, for example at the top of the product to compensate for the gross composition change, and with a secondary, more precise delivery path to the bottom of the reservoir for fine adjustment during within an individual dose.

Advantageously, the solid phase of the product is hydrophilic (contact angle measurements: preferentially between 0° and 60°), or in case the fluid phase is an organic solvent, has affinity towards the solvent (contact angle measurements: preferentially between 0° and 60°).

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the scope of the appended claims.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as

suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Reservoir

The aim of this invention is the control of composition and weight or volume of doses of heterogeneous product being dispensed. The regulated driving force, and in a preferred embodiment the regulated pressure required for dispensing acceptable doses in terms of weight/volume, reflects the flow resistance encountered by the product during dispensing. The entire amount of heterogeneous product in the reservoir contributes to this flow resistance, but advantageously, the reservoir is designed in such a way as to maximize the contribution of the dose being dispensed to the flow resistance, and concomitantly to minimize the contribution of the remainder of heterogeneous product in the reservoir. This is achieved through the design of the reservoir and also the motorized valve. The cross-sectional area in the reservoir is advantageously much larger than in the distributor (preferentially, cross-sectional area in the reservoir at least 2x larger, more preferentially at least 5x larger, even more preferentially at least 10x larger and most preferentially at least 50x larger). If the distributor branches, the cross-sectional area at the narrowest point is taken. In one embodiment, the distributor has an intentional narrow, giving rise to the principal resistance.

In some embodiments, not only is compensation fluid added, but the fluid phase can also be withdrawn from the heterogeneous product. In this case, the reservoir, or the distributor, are equipped with a filter through which the fluid phase can be withdrawn in specified amounts with minimal or without withdrawal of solid. For this purpose, the filter has a pore size smaller than 95% of the particles (by mass), preferentially smaller than 99% of the particles (by mass), preferentially smaller than 99.9% (by mass). The fluid withdrawal port is connected through tubing or the like to a device permitting to control withdrawal quantitatively, for example a pump.

Materials of components in contact with the product

The reservoir and the valve and the distributor can be made out of glass, quartz, borosilicate glass, stain-less steel, polypropylene, Teflon, nylon, silicone or any other material resistant to sterilization methods such as steam sterilization, gamma or X-ray irradiation, ethylene oxide, plasma treatment, ozone sterilization, UV treatment, and the like.

Distributor

In some embodiments, the distributor contains a grid or filter with openings with diameters comprised between 0.1mm and 5mm, more preferentially 0.2mm to 1mm. In some embodiments,

the distributor contains electrodes connected to an impedance measurement device or a particle counter, in some embodiments, the distributor contains a flow sensor, a camera for detecting foreign particles, a Hall sensor and a magnetic field.

Heterogeneous product (multiphasic mixture)

The heterogeneous product to be filled consists of at least two phases. Typically, one of the two phases is a liquid, a viscous liquid, a viscoelastic substance, a viscoelastic substance, a gel or a hydrogel, whereas there is at least another phase that is a solid, a viscoelastic solid, a gel, or a hydrogel. There is however also the possibility that both phases are selected from the group of liquids, viscous liquids, a viscoelastic liquid, a viscoelastic substances, gels or hydrogels, and form an emulsion or other non-fully miscible phase system, and there is also the possibility that at least one phase is a gas (filling of foams). In some embodiments, the heterogeneous product to be filled is injectable through at least through needles or cannulae of caliber 16G or with larger diameters, or at least through 20G cannulae or needles, or at least through 25G cannulae or needles, or at least through 27G cannulae or needles, or at least through 30G cannulae or needles, with maximal forces below 100N, preferentially below 50N, preferentially below 30N, and most preferentially below 20N required on the syringes into which the product is filled.

Examples of liquid phases are phases that can comprise water, aqueous solutions, physiological saline (0.9% NaCl), isotonic solutions, buffers, isotonic buffers pharmacologically acceptable solutions, hydrogels, solutions containing polysaccharides (for example hyaluronic acid, glycosaminoglycans, deacetylated hyaluronic acid, hyaluronic acid modified with alkyne derivatives such as cyclooctynes, azide modified hyaluronic acid, thiolated hyaluronic acid, hyaluronic acid derivatives, hyaluronan oligosaccharides, heparosan and derivatives, alginate, alginate partially crosslinked with divalent and multivalent ions, particularly with Ca^{2+} , Fe^{2+} or Fe^{3+} or Ba^{2+} ions, agarose, methylcellulose, carboxymethylcellulose, chitosan, polyfructose), polyvinylalcohol, polyacrylates, nucleic acids, DNA, RNA, synthetic polymers, viruses, transfection agents, contrast agents, soluble collagen, proteins, albumin, cell culture medium, anaesthetic solutions, solutions containing lidocaine, xylocaine, bupivacaine, tetracaine, mepivacaine, ropivacaine, mepivacaine and/or other caines, solutions containing antibiotics, penicillin, cephalosporine, tetracycline, amoxycilline, clavulanate, cephalexin, ciprofloxazine, metronidazole, azithromycine. Organic solvents such as ethanol, isopropylalcohol, dimethylsulfoxide. Oils, triglycerides, lipid emulsions, fatty acids, oleic acid, linoleic acid, palmitic acid, or mixtures thereof. The liquid phase can also be obtained from a biological extract, for example blood plasma, blood serum, platelet rich plasma, supernatant from centrifuged lipoaspirate, milk serum and the like. The biological extracts can be autologous, heterologous or xenologous.

Examples of solid phases are phases that can comprise one of the following substances: porous scaffolds, porous scaffold particles, foams, foam particles, hydrogels, crosslinked polysaccharides (including porous crosslinked polysaccharides) such as crosslinked hyaluronic acid, hyaluronic acid crosslinked with butanedioldiglycid ether, hyaluronic acid modified with alkynes and azide moieties and crosslinked by the reaction of these groups, crosslinked glycosaminoglycans, crosslinked deacetylated hyaluronic acid, hyaluronic acid crosslinked with disulfide bridges, divinylsulfone, crosslinked hyaluronic acid derivatives, crosslinked hyaluronan oligosaccharides, crosslinked heparosan and derivatives, alginate crosslinked ionically, alginate crosslinked with Ca^{2+} ions, Fe^{2+} or Fe^{3+} ions, Ba^{2+} ions, covalently crosslinked alginate, agarose, crosslinked carboxymethylcellulose, crosslinked chitosan, crosslinked polyfructose, (porous) crosslinked peptides, (porous) crosslinked proteins, decellularized plant material, decellularized tissue, decellularized adipose tissue, decellularized human adipose tissue, porous silk particles, extracellular matrix, collagen, laminin, polyurethane foams and foam fragments, polyolefin foams and fragments. Polysaccharides, extracellular matrix, proteins, peptide precipitated in organic solvents, optionally crosslinked. Reconstituted cellulose as fibers, foam, foam fragments. Fibers, electrospun fibers: PLGA, PLA, polycaprolactones, polyurethane, polysaccharides, proteins. Extruded fibers such as regenerated cellulose, polysaccharides, proteins, peptides extruded into non-solvent, optionally crosslinked, or mixtures thereof, capsules, beads, DNA, RNA calcium hydroxyapatite, ice crystals, ceramics, frozen substances, solidified fats, oils, microparticles, silicone oil droplets, solid silicone particles, crosslinked cells, crosslinked tissue, living cells, organoids, vesicles, liposomes, capsules, capsules containing cells, lipid-loaded beads, PNIPAAm, thermosensitive materials such as PNIPAAm modified polysaccharides or copolymers containing NIPAAm monomers, ice, reactive materials, or materials designed to react with in vivo, for instance by containing fibrinogen peptides or analogs reacting with activated factor XIII, with or without addition of exogeneous factor XIII, or by containing glutamine residues susceptible to be crosslinked by endogenous or exogeneous transglutaminase, of insoluble or partially soluble salts, solid or particulate fractions of living biological extracts such as liposuction extracts, and blood or milk cell or lipid concentrates. The biological extracts can be autologous, heterologous or xenologous.

The heterogeneous product can also be a processed or unprocessed biological extract, such as lipoaspiration material, blood, decellularized material, cultured cells, including co-cultures, and/or their matrix, cultured organoids including co-cultures and/or their matrix, and combinations of scaffold materials and cultured cells or co-cultures or organoids or co-cultured organoids. The origin of the biological extracts can be autologous, heterologous or xenologous.

The overall viscosity of the heterogeneous product can vary widely, from essentially infinite at low stress for materials that have a finite yield stress thus behaving as a Bingham plastic to values near the one of water (10^{-3} Pa*s). For injectable heterogeneous products, effective viscosities under injection conditions are typically in the range of 10^{-3} Pa*s to 10^3 Pa*s, more typically between 0.01Pa*s to 100Pa*s. The heterogeneous product may have viscoelastic properties, with an elastic modulus G' between 1Pa and 1Mpa, preferably between 10Pa and 100kPa and most preferably between 100Pa and 10kPa and/or a loss modulus G'' between 0.01Pa and 100kPa, preferably between 0.1Pa and 10kPa, and more preferably between 1Pa and 1kPa. In the case of viscoelastic heterogeneous products, they may be solid-like, with a ratio of G'/G'' in the low deformation limit between 1 and 10000, more preferentially 2 and 1000, and most preferentially 3 and 500. Alternatively, they may be liquid-like, with a ratio of G'/G'' in the low deformation limit between 10^{-4} and 1, preferably between 10^{-3} and 0.5 and more preferably between $2 \cdot 10^{-3}$ and 0.3.

In some embodiments, the properties of the heterogeneous product change over time. This can happen in biological samples because of ongoing enzymatic, chemical, biological or physical process, for example due to cell death, ongoing coagulation or on the contrary fibrinolysis, change in temperature, and the like. Non-living or non-biological heterogeneous products can also change over time, for example when polymerization is carried out during filling (for example, due to ongoing reaction between carboxylate groups and amines or hydrazides under the action of an activator such as a carbodiimide, or due to ongoing radical polymerization involving acrylates or acrylated monomers and radical initiators such as peroxide or ammonium persulfate and amine co-initiators such as tetramethylethylenediamine or amino acids, or due to ring opening polymerization or crosslinking between amines and epoxides, or due to ongoing click chemistry reactions such as the one between dibenzylcyclooctyne and azide or nitron moieties, or between strained or activated alkenes and tetrazine substituents). For effective compensation of absolute compositional change to be performed in such cases, it is necessary to either dispose of a priori knowledge on the time course of the anticipated changes, or to dispose of additional information such as spectroscopic, impedance-based or other sensor-based evaluation of ongoing change. Alternatively, the fluid addition algorithm may still be operated in the absence of such additional knowledge to obtain constant mechanical properties in the doses filled.

Examples

Example 1

A porous alginate biomaterial was synthesized as outlined in Bédier et al., Adv. Mater. 2021, 33, 2102350, and suspended in physiological saline at a concentration of 60mg/mL, constituting a heterogeneous product. The dispensing consisted in filling 5mL glass syringes having an internal

diameter of 1cm with a target weight of 5.5g. Syringes containing weights of 5.0g to 6.0g were considered acceptable for the future use of the product.

Briefly, 600mL of the product was poured into a glass reservoir with a maximum capacity of 1L. The reservoir for the compensation fluid delivery device was filled with 1L of physiological saline. The controller was parameterized as follows: An initial pressure of 50 000Pa was set to the controller to activate the filling of the first syringe. This corresponds also to the target pressure criteria to decide if additional physiological saline needs to be added in the reservoir or not and how much. The opening time of the motorized valve was set to 0.5s using the controller. The movement rate of the motorized stage holding the 5mL syringe was set to 14cm/s.

For the filling of the first 5mL syringe, the following was done: the empty 5mL syringe was weighted. The 5mL syringe was placed on the syringe holder of the motorized stage, and the motorized stage moved up such that the dispensing tube was positioned at the bottom of the 5mL syringe. Pressure was applied to the reservoir. When the pressure reached the desired 50kPa, the opening of the motorized valve was initiated. Once the motorized valve was starting to permit product flow, the vertical movement of the motorized stage was initiated at an acceleration of 4m/s^2 up to constant speed of 14cm/s and dispensing took place.

After dispensing, the weight of the filled 5mL syringe was recorded to be 6g, which was above the target of 5.5g. The following was calculated in order to calculate the pressure to use for the filling of the next 5mL syringe:

$$P = 50\,000 \cdot (1 + 0.3 \cdot (5.5 - 6.0) / 5.5) = 48\,636 \text{ Pa.}$$

Where $\alpha = 0.3$ is the pressure update coefficient.

The same steps were performed by using this new pressure and following the instructions described in Figure 2 for the filling of the second 5mL syringe. Of note, in this case, no fluid addition was required because the set pressure was initially too high to dispense the target weight.

Filling of the second 5mL syringe:

Same parameters than for the first syringe were used, except for the pressure. A pressure of 48 636 Pa was set. After dispensing, the weight of the filled 5mL syringe was recorded to be 5.7g, which was above the target of 5.5g. The following was calculated in order to calculate the pressure to use for the filling of the next 5mL syringe:

$$P = 48\,636 \cdot (1 + 0.3 \cdot (5.5 - 5.7) / 5.5) = 48\,105 \text{ Pa.}$$

Filling of the third 5mL syringe:

Same parameters than for the second syringe were used, except for the pressure. A pressure of 48 105 Pa was set. After dispensing, the weight of the filled 5mL syringe was recorded to be 5.3g, which was below the target of 5.5g. The following was calculated in order to calculate the pressure to use for the filling of the next 5mL syringe:

$$P = 48\,105 \cdot (1 + 0.3 \cdot (5.5 - 5.3) / 5.5) = 48\,629 \text{ Pa.}$$

Filling of the fourth 5mL syringe:

Same parameters than for the third syringe were used, except for the pressure. A pressure of 48 629 Pa was set. After dispensing, the weight of the filled 5mL syringe was recorded to be 5.2g, which was below the target of 5.5g. The following was calculated in order to calculate the pressure to use for the filling of the next 5mL syringe:

$$P = 48\,629 \cdot (1 + 0.3 \cdot (5.5 - 5.2) / 5.5) = 49\,424 \text{ Pa.}$$

Filling of the fifth 5mL syringe:

Same parameters than for the fourth syringe were used, except for the pressure. A pressure of 49 424 Pa was set. After dispensing, the weight of the filled 5mL syringe was recorded to be 5.2g, which was below the target of 5.5g. The following was calculated in order to calculate the pressure to use for the filling of the next 5mL syringe:

$P = 49\,424 \cdot (1 + 0.3 \cdot (5.5 - 5.2) / 5.5) = 50\,232 \text{ Pa.}$ This pressure is above the target pressure of 50 000 Pa defined at the beginning of the process, meaning that the heterogeneous product being dispensed has an increased content of porous alginate biomaterial. An amount of physiological saline calculated as follows $V = (50232 - 50000) / 50000 \cdot 0.2 \cdot 575 = 0.53 \text{ mL}$ was added correspondingly, 575 being the remaining volume in mL of heterogeneous product.

Filling of the sixth 5mL syringe:

Same parameters than for the fifth syringe were used, except for the pressure. A pressure of 50 232 Pa was set. After dispensing, the weight of the filled 5mL syringe was recorded to be 5.7g, which was above the target of 5.5g. The following was calculated in order to calculate the pressure to use for the filling of the next 5mL syringe:

$P = 50\,232 \cdot (1 + 0.3 \cdot (5.5 - 5.7) / 5.5) = 49\,684 \text{ Pa.}$ This pressure is below the target pressure of 50 000 Pa defined at the beginning of the process, meaning that the concentration of the porous alginate biomaterial has decreased and that no physiological saline needs to be added.

Example 2

Hydroxyapatite beads (40 micrometer diameter) were mixed with a solution of sodium hyaluronate of molecular weight of 100kDa, 0.25%, in physiological saline, at a bead volume fraction of 50%, to constitute an injectable, paste-like biomaterial. The material was filled into 1mL syringes, at a target weight of 1.2g, using an initial pressure of 80kPa and a target pressure of 85kPa. The compensation fluid consisted of 0.25% sodium hyaluronate in physiological saline, and was added as specified in Fig. 2 and illustrated by the example above. A compositional precision in terms of hydroxyapatite content of 1%, and a volumetric precision of 10% was reached.

Example 3

Agarose cryogel beads were produced as described in the literature (Macromol. Biosci. 2011, 11, 22–35) and suspended at a concentration of 80mg/mL in physiological saline. The material was filled into 2mL syringes, at a target weight of 2.2g, using an initial pressure of 10kPa and a target pressure of 10kPa. The compensation fluid consisted of physiological saline, and was according to the algorithm “Pressure and Fluid, Smith correction and cross-feedback”. A compositional precision concerning the content of insoluble polymeric material of 1%, and a volumetric precision of 5% was reached.

Example 4

Integra matrix wound dressing was minced to fragments of about 100 micrometer diameter and suspended at a concentration of 40mg/mL in physiological saline. The material was filled into 1mL syringes, at a target weight of 1.1g, using an initial pressure of 20kPa and a target pressure of 20kPa. The compensation fluid consisted of physiological saline, and was added according to the algorithm “Pressure and Fluid, Smith correction”. A compositional precision concerning the content of insoluble polymeric material of 2%, and a volumetric precision of 15% was reached.

Example 5

Gelfoam was minced to fragments of about 400 micrometer diameter and suspended at a concentration of 50mg/mL in physiological saline. The material was filled into 5mL syringes, at a target weight of 5.5g, using an initial pressure of 10kPa and a target pressure of 10kPa. The compensation fluid consisted of physiological saline, and was added according to the algorithm outlined in Fig. 2. A compositional precision regarding the content of insoluble polymeric material of 1%, and a volumetric precision of 20% was reached.

Claims

1. Method for successive, pressure-driven dispensation of single doses of a multiphasic mixture (7) comprising a fluid phase and a solid phase from a reservoir (6) into single recipients (4), maintaining the composition of the multiphasic mixture (7) in the dispensed doses within pre-determined ranges,

characterized in that

- a) a pre-set range of the ratio between the fluid phase and solid phase of the multiphasic mixture (7) is defined;
- b) a pre-set threshold value for the pressure P_{target} used to dispense the multiphasic mixture (7) is defined;
- c) a pre-set target for the weight and/or volume dispensed is defined;
- d) weight and/or volume of the dispensed doses is measured after each dispense and is compared to the target weight and/or volume;
- e) deviation from target volume and/or target weight are compensated for by adjusting the pressure;
- f) the change of the pressure necessary to deliver the target volume or target weight is detected;
- g) an amount of fluid phase is added to the multiphasic mixture (7) remaining in the reservoir (6) to restore the composition of the multiphasic mixture (7) within the pre-determined range of ratio between the fluid phase and solid phase of the multiphasic mixture (7) when the pressure exceeds the pre-set target value P_{target} .

2. Method according to claim 1, characterized in that prior to the start of the first dispense, a calibration of the relationship between the ratio between the fluid phase and solid phase of the multiphasic mixture and the pressure is performed to define the target pressure P_{target} .

3. Method according to claim 1 or 2, characterized by the following steps

- A) defining a target value for the Pressure (P_{target}) to be used for the dispensing and defining a target value for the weight or volume to be dispensed;
- B) filling a reservoir with a multiphasic mixture;
- C) dispensing a dose of the mixture into a recipient using a first pressure P_1 ;
- D) measuring the weight or the volume of the dispensed dose;
- E) comparing the weight or volume measured in step D with the pre-determined target value for the weight or volume as defined in step A;
- F) adjusting the first pressure P_1 by a calculated amount ΔP to a different pressure $P_2 = P_1 + \Delta P$;

G) repeating steps C-E using the adapted pressure P_2 for the filling of further recipients with doses of the mixture;

H) optionally adopting one or more further pressure modifications according to step F;

I) adding or subtracting a calculated amount of fluid phase, possibly zero, to the mixture for compensating the loss or the excess of fluid phase in the mixture, whereby the amount of fluid is calculated using the actual and target pressures .

4. Method according to one of the claims 1 to 3, characterized in that fluid is only added when the pressure is above a threshold pressure P_{max} , distinct from and above the target pressure P_{target} .

5. Method according to one of the claims 1 to 4, characterized in that fluid is withdrawn from the multiphasic mixture when the pressure is below the target pressure P_{target} .

6. Method according to one of the claims 1 to 5, characterized in that fluid addition and/or fluid withdrawal are only operated if the weight or volume of the dispensed dose is within the range of the target pressure P_{target} .

7. Method according to one of the claims 1 to 6, characterized in that the fluid phase comprises one of the following substances: aqueous solutions, physiological saline (0.9% NaCl), buffers, pharmacologically acceptable solutions, hyaluronic acid, glycosaminoglycans, alginate, agarose, methylcellulose, carboxymethylcellulose, chitosan, anaesthetic solutions and solutions containing lidocaine.

8. Method according to one of the claims 1 to 6, characterized in that the fluid phase comprises one of the following substances: water, isotonic solutions, isotonic buffers, hydrogels, solutions containing polysaccharides, deacetylated hyaluronic acid, hyaluronic acid modified with alkyne derivatives such as cyclooctynes, azide modified hyaluronic acid, thiolated hyaluronic acid, hyaluronic acid derivatives, hyaluronan oligosaccharides, heparosan and derivatives, polyfructose polyvinylalcohol, polyacrylates, nucleic acids, DNA, RNA, synthetic polymers, viruses, transfection agents, contrast agents, albumin, cell culture medium, xylocaine, bupivacaine, tetracaine, mepivacaine, rhopivacaine, mepivacaine and/or other anaesthetics of the -caine family; solutions containing antibiotics, penicillin, cephalosporine, tetracycline, amoxycilline, clavulanate, cephalexin, ciprofloxazine, metronidazole, azithromycine; organic solvents, in particular ethanol, isopropylalcohol, dimethylsulfoxide; oils, triglycerides, lipid emulsions, fatty acids, oleic acid, linoleic acid, palmitic acid, or mixtures of all the aforementioned substances.

9. Method according to one of the claims 1 to 6, characterized in that the solid phase comprises one of the following substances: porous scaffolds, porous scaffold particles, crosslinked polysaccharides, in particular porous crosslinked polysaccharides, crosslinked hyaluronic acid, crosslinked glycosaminoglycans, alginate crosslinked ionically, agarose, crosslinked carboxymethylcellulose, chitosan, decellularized tissue, decellularized adipose tissue.

10. Method according to one of the claims 1 to 6, characterized in that the solid phase comprises one of the following substances:

foams, foam particles, hydrogels, hyaluronic acid crosslinked with butanedioldiglycid ether, hyaluronic acid modified with alkynes and azide moieties and crosslinked by the reaction of these groups, crosslinked deacetylated hyaluronic acid, hyaluronic acid crosslinked with disulfide bridges, divinylsulfone, crosslinked hyaluronic acid derivatives, crosslinked hyaluronan oligosaccharides, crosslinked heparosan and derivatives, alginate crosslinked with Ca^{2+} ions, Fe^{2+} or Fe^{3+} ions, Ba^{2+} ions, covalently crosslinked alginate, crosslinked polyfructose, (porous) crosslinked peptides, (porous) crosslinked proteins, decellularized plant material, decellularized human adipose tissue, porous silk particles, extracellular matrix, collagen, laminin, polyurethane foams and foam fragments, polyolefin foams and fragments. Polysaccharides, extracellular matrix, proteins, peptide precipitated in organic solvents, optionally crosslinked. Reconstituted cellulose as fibers, foam, foam fragments. Fibers, electrospun fibers: PLGA, PLA, polycaprolactones, polyurethane, polysaccharides, proteins. Extruded fibers such as regenerated cellulose, polysaccharides, proteins, peptides extruded into non-solvent, optionally crosslinked, or mixtures thereof, capsules, beads, DNA, RNA calcium hydroxyapatite, ice crystals, ceramics, frozen substances, solidified fats, oils, microparticles, silicone oil droplets, solid silicone particles, crosslinked cells, crosslinked tissue, living cells, organoids, vesicles, liposomes, capsules, capsules containing cells, lipid-loaded beads, PNIPAAm, thermosensitive materials, ice, insoluble or partially soluble salts.

11. Method according to one of the claims 1 to 10, characterized in that the proportion of the weight or volume of the solid phase in relation to total heterogeneous product in the reservoir is between 0.05% and 95%, preferably between 0.1% and 50%, more preferably between 0.2% and 30%, most preferentially between 1% and 20%.

12. Method according to one of the claims 1 to 11, characterized in that the multiphasic mixture is composed of several liquid phases and/or of several solid phases.

13. Method according to one of the claims 1 to 12, characterized in that the multiphasic mixture is a viscoelastic material with an elastic modulus G' between 1Pa and 1Mpa, preferably between

10Pa and 100kPa and most preferably between 100Pa and 10kPa and/or a loss modulus G'' between 0.01Pa and 100kPa, preferably between 0.1Pa and 10kPa, and more preferably between 1Pa and 1kPa.

14. Method according to one of the claims 1 to 13, characterized in that the multiphasic mixture is biocompatible.

15. Method according to one of the claims 1 to 14, characterized in that the viscosity of the multiphasic mixture is adjusted to render it injectable.

16. Method according to one of the claims 1 to 15, characterized in that the multiphasic mixture has a yield stress between from 0.1Pa to 100kPa, preferably between 1Pa to 10kPa, most preferably between 5Pa to 5kPa.

17. Method according to one of the claims 1 to 16, characterized in that the fluid phase has a viscosity between 0.0005 Pa·s to 10 Pa·s, preferably 0.0006 Pa·s to 0.1 Pa·s

18. Method according to one of the claims 1 to 17, characterized in that the fluid phase is a physiological saline solution or a solution of polysaccharides.

19. Method according to one of the claims 1 to 18, characterized in that the fluid phase comprises a contrast agent.

20. Method according to one of the claims 1 to 19 characterized in that the solid phase has a yield strain between 0.1Pa to 100kPa, preferably between 1Pa to 10kPa and more preferably between 5Pa to 5kPa.

21. Method according to one of the claims 1 to 20 characterized in that the solid phase is hydrophilic.

22. Method according to one of the claims 1 to 21 characterized in that the solid phase is porous.

23. Method according to claim 22, characterized in that the mean diameter of the pores is in the range of 0,5 μm and 5 mm, preferably between 2 μm and 2 mm and more preferably between 5 μm and 1 mm.

24. Method according to claim 22 or 23, characterized in that the pore fraction is in the range between 5% and 99.9%, preferably between 10% and 99.5% and more preferably between 30% and 99%.

25. Method according to one of the claims 1 to 24, characterized in that the solid phase comprises particles with the shape of beads, porous scaffolds and porous irregular scaffolds.

26. Method according to one of the claims 1 to 25, characterized in that the recipients are made of edible components.

27. A device for performing the method according to one of the claims 1 to 26 comprising:

- a) a reservoir (6) for the multiphasic mixture (7) to be dispensed,
- b) a dispensing element (16),
- c) a valve (5) positioned between the reservoir (6) and the dispensing element (16),
- d) a compensating fluid reservoir (9) connected via a fluid delivery device (15) to the reservoir (6),
- e) a controller (1) connected to a pressure regulation device (14) connected to the reservoir (6) where the controller (1) is capable to adjust the pressure in such a way as to permit the device to dispense amounts of the multiphasic mixture (7) close or identical to an amount of interest; and
- f) the same controller (1) of step e) or a separate controller connected to a fluid delivery device (15) and/or subtraction device (12) connected to the reservoir (6) wherein the amount of fluid to be added or subtracted is calculated such as to return the pressure to a preset target value when the pressure deviates from this value.

28. A device according to claim 27, characterized in that a recording instrument records the measurements of the pressure and/or of the weights and/or volumes measured and/or the fluid addition or withdraws performed during the dispense.

29. A device according to claim 27 or 28, characterized in that a pressure sensor is connected to the reservoir to continuously monitor the pressure while dispensing the multiphasic mixture and where an interrupter valve is positioned between the pressure regulator and the reservoir.

30. A device according to one of the claims 27 to 29, characterized in that the device further comprises a fluid withdrawal port connected to the reservoir.

31. A device according to one of the claims 27 to 30, characterized in that the reservoir, including the valve (but not the motor) can be removed integrally from the device to permit aseptic filling.

AMENDED CLAIMS

received by the International Bureau on 12 March 2024 (12.03.2024)

1. Method for successive, pressure-driven dispensation of single doses of a multiphasic mixture (7) comprising a fluid phase and a solid phase from a reservoir (6) into single recipients (4), maintaining the composition of the multiphasic mixture (7) in the dispensed doses within pre-determined ranges,

characterized in that

- a) a pre-set range of the ratio between the fluid phase and solid phase of the multiphasic mixture (7) is defined;
- b) a pre-set threshold value for the pressure P_{target} used to dispense the multiphasic mixture (7) is defined;
- c) a pre-set target for the weight and/or volume dispensed is defined;
- d) weight and/or volume of the dispensed doses is measured after each dispense and is compared to the target weight and/or volume;
- e) deviation from target volume and/or target weight are compensated for by adjusting the pressure;
- f) the change of the pressure necessary to deliver the target volume or target weight is detected;
- g) an amount of fluid phase is added to the multiphasic mixture (7) remaining in the reservoir (6) to restore the composition of the multiphasic mixture (7).

2. Method according to claim 1, characterized in that the restoration of the composition of the multiphasic mixture (7) in step g) is performed within the pre-determined range of ratio between the fluid phase and solid phase of the multiphasic mixture (7) when the pressure exceeds the pre-set target value P_{target} .

3. Method according to claim 1, characterized in that fluid is only added when the pressure is above a threshold pressure P_{max} , distinct from and above the target pressure P_{target} .

4. Method according to claim 1, characterized in that prior to the start of the first dispense, a calibration of the relationship between the ratio between the fluid phase and solid phase of the multiphasic mixture and the pressure is performed to define the target pressure P_{target} .

5. Method according to claim 1 or 2, characterized by the following additional steps to be performed after step c):

- c2) filling a reservoir with a multiphasic mixture; and
- c3) dispensing a dose of the mixture into a recipient using a first pressure P_1 .

6. Method according to claim 5, characterized by the following additional steps to be performed after step f):

f2) adjusting the first pressure P_1 by a calculated amount ΔP to a different pressure $P_2 = P_1 + \Delta P$.

f3) repeating steps c2, d) and e) after having performed step f2 using the adapted pressure P_2 for the filling of further recipients with doses of the mixture and optionally adopting one or more further pressure modifications according to step f2; and

g2) performing step g) by adding or subtracting a calculated amount of fluid phase, preferably zero, to the mixture for compensating the loss or the excess of fluid phase in the mixture, whereby the amount of fluid is calculated using the actual and target pressures.

7. Method according to one of the claims 1 to 6, characterized in that fluid is withdrawn from the multiphasic mixture when the pressure is below the target pressure P_{target} .

8. Method according to one of the claims 5 to 7, characterized in that fluid addition and/or fluid withdrawal are only operated if the weight or volume of the dispensed dose is within the range of the target pressure P_{target} .

9. Method according to one of the claims 1 to 8, characterized in that the fluid phase comprises one of the following substances: aqueous solutions, physiological saline (0.9% NaCl), buffers, pharmacologically acceptable solutions, hyaluronic acid, glycosaminoglycans, alginate, agarose, methylcellulose, carboxymethylcellulose, chitosan, anaesthetic solutions and solutions containing lidocaine.

10. Method according to one of the claims 1 to 8, characterized in that the fluid phase comprises one of the following substances: water, isotonic solutions, isotonic buffers, hydrogels, solutions containing polysaccharides, deacetylated hyaluronic acid, hyaluronic acid modified with alkyne derivatives such as cyclooctynes, azide modified hyaluronic acid, thiolated hyaluronic acid, hyaluronic acid derivatives, hyaluronan oligosaccharides, heparosan and derivatives, polyfructose polyvinylalcohol, polyacrylates, nucleic acids, DNA, RNA, synthetic polymers, viruses, transfection agents, contrast agents, albumin, cell culture medium, xylocaine, bupivacaine, tetracaine, mepivacaine, ropivacaine, mepivacaine and/or other anaesthetics of the -caine family; solutions containing antibiotics, penicillin, cephalosporine, tetracycline, amoxycilline, clavulanate, cephalixin, ciprofloxazine, metronidazole, azithromycine; organic solvents, in particular ethanol, isopropylalcohol, dimethylsulfoxide; oils, triglycerides, lipid emulsions, fatty acids, oleic acid, linoleic acid, palmitic acid, or mixtures of all the aforementioned substances.

11. Method according to one of the claims 1 to 8, characterized in that the solid phase comprises one of the following substances: porous scaffolds, porous scaffold particles, crosslinked polysaccharides, in particular porous crosslinked polysaccharides, crosslinked hyaluronic acid, crosslinked glycosaminoglycans, alginate crosslinked ionically, agarose, crosslinked carboxymethylcellulose, chitosan, decellularized tissue, decellularized adipose tissue.

12. Method according to one of the claims 1 to 8, characterized in that the solid phase comprises one of the following substances:

foams, foam particles, hydrogels, hyaluronic acid crosslinked with butanedioldiglycid ether, hyaluronic acid modified with alkynes and azide moieties and crosslinked by the reaction of these groups, crosslinked deacetylated hyaluronic acid, hyaluronic acid crosslinked with disulfide bridges, divinylsulfone, crosslinked hyaluronic acid derivatives, crosslinked hyaluronan oligosaccharides, crosslinked heparosan and derivatives, alginate crosslinked with Ca^{2+} ions, Fe^{2+} or Fe^{3+} ions, Ba^{2+} ions, covalently crosslinked alginate, crosslinked polyfructose, (porous) crosslinked peptides, (porous) crosslinked proteins, decellularized plant material, decellularized human adipose tissue, porous silk particles, extracellular matrix, collagen, laminin, polyurethane foams and foam fragments, polyolefin foams and fragments. Polysaccharides, extracellular matrix, proteins, peptide precipitated in organic solvents, optionally crosslinked. Reconstituted cellulose as fibers, foam, foam fragments. Fibers, electrospun fibers: PLGA, PLA, polycaprolactones, polyurethane, polysaccharides, proteins. Extruded fibers such as regenerated cellulose, polysaccharides, proteins, peptides extruded into non-solvent, optionally crosslinked, or mixtures thereof, capsules, beads, DNA, RNA calcium hydroxyapatite, ice crystals, ceramics, frozen substances, solidified fats, oils, microparticles, silicone oil droplets, solid silicone particles, crosslinked cells, crosslinked tissue, living cells, organoids, vesicles, liposomes, capsules, capsules containing cells, lipid-loaded beads, PNIPAAm, thermosensitive materials, ice, insoluble or partially soluble salts.

13. Method according to one of the claims 1 to 12, characterized in that the proportion of the weight or volume of the solid phase in relation to total heterogeneous product in the reservoir is between 0.05% and 95%, preferably between 0.1% and 50%, more preferably between 0.2% and 30%, most preferentially between 1% and 20%.

14. Method according to one of the claims 1 to 13, characterized in that the multiphasic mixture is composed of several liquid phases and/or of several solid phases.

15. Method according to one of the claims 1 to 14, characterized in that the multiphasic mixture is a viscoelastic material with an elastic modulus G' between 1Pa and 1Mpa, preferably between 10Pa and 100kPa and most preferably between 100Pa and 10kPa and/or a loss modulus G'' between 0.01Pa and 100kPa, preferably between 0.1Pa and 10kPa, and more preferably between 1Pa and 1kPa.

16. Method according to one of the claims 1 to 15, characterized in that the multiphasic mixture is biocompatible.

17. Method according to one of the claims 1 to 16, characterized in that the viscosity of the multiphasic mixture is adjusted to render it injectable.

18. Method according to one of the claims 1 to 17, characterized in that the multiphasic mixture has a yield stress between from 0.1Pa to 100kPa, preferably between 1Pa to 10kPa, most preferably between 5Pa to 5kPa.

19. Method according to one of the claims 1 to 18, characterized in that the fluid phase has a viscosity between 0.0005 Pa·s to 10 Pa·s, preferably 0.0006 Pa·s to 0.1 Pa·s

20. Method according to one of the claims 1 to 19, characterized in that the fluid phase is a physiological saline solution or a solution of polysaccharides.

21. Method according to one of the claims 1 to 20, characterized in that the fluid phase comprises a contrast agent.

22. Method according to one of the claims 1 to 21, characterized in that the solid phase has a yield strain between 0.1Pa to 100kPa, preferably between 1Pa to 10kPa and more preferably between 5Pa to 5kPa.

23. Method according to one of the claims 1 to 22 characterized in that the solid phase is hydrophilic.

24. Method according to one of the claims 1 to 23 characterized in that the solid phase is porous.

25. Method according to claim 24, characterized in that the mean diameter of the pores is in the range of 0,5 μm and 5 mm, preferably between 2 μm and 2 mm and more preferably between 5 μm and 1 mm.

26. Method according to claim 24 or 25, characterized in that the pore fraction is in the range between 5% and 99.9%, preferably between 10% and 99.5% and more preferably between 30% and 99%.

27. Method according to one of the claims 1 to 26, characterized in that the solid phase comprises particles with the shape of beads, porous scaffolds and porous irregular scaffolds.

28. Method according to one of the claims 1 to 27, characterized in that the recipients are made of edible components.

29. A device for performing the method according to one of the claims 1 to 28 comprising:

- a) a reservoir (6) for the multiphasic mixture (7) to be dispensed,
- b) a dispensing element (16),
- c) a valve (5) positioned between the reservoir (6) and the dispensing element (16),
- d) a compensating fluid reservoir (9) connected via a fluid delivery device (15) to the reservoir (6),
- e) a controller (1) connected to a pressure regulation device (14) connected to the reservoir (6) where the controller (1) is capable to adjust the pressure in such a way as to permit the device to dispense amounts of the multiphasic mixture (7) close or identical to an amount of interest; and
- f) the same controller (1) of step e) or a separate controller connected to a fluid delivery device (15) and/or subtraction device (12) connected to the reservoir (6) wherein the amount of fluid to be added or subtracted is calculated such as to return the pressure to a preset target value when the pressure deviates from this value.

30. A device according to claim 29, characterized in that a recording instrument records the measurements of the pressure and/or of the weights and/or volumes measured and/or the fluid addition or withdraws performed during the dispense.

31. A device according to claim 29 or 30, characterized in that a pressure sensor is connected to the reservoir to continuously monitor the pressure while dispensing the multiphasic mixture and where an interrupter valve is positioned between the pressure regulator and the reservoir.

32. A device according to one of the claims 29 to 31, characterized in that the device further comprises a fluid withdrawal port connected to the reservoir.

33. A device according to one of the claims 29 to 32, characterized in that the reservoir, including the valve (but not the motor) can be removed integrally from the device to permit aseptic filling.

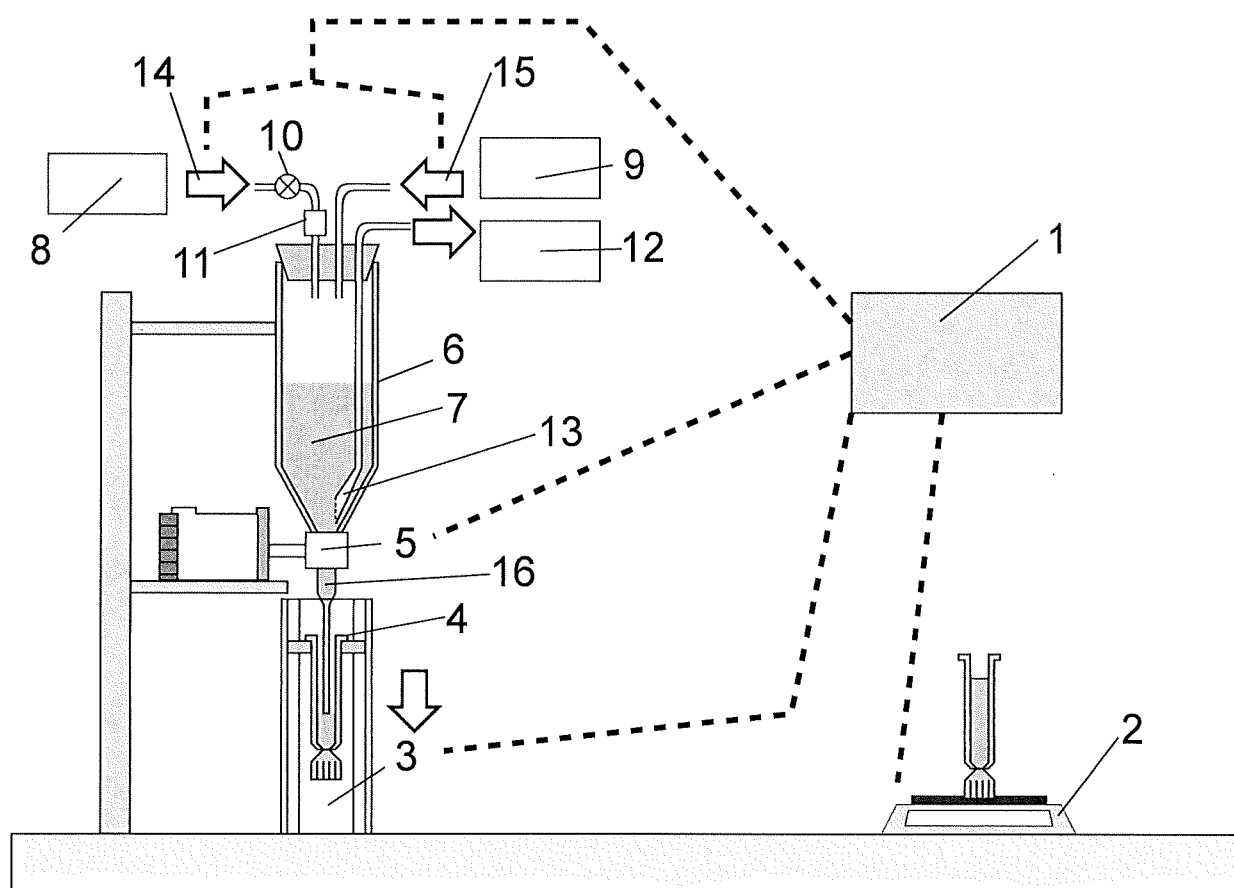


Fig. 1

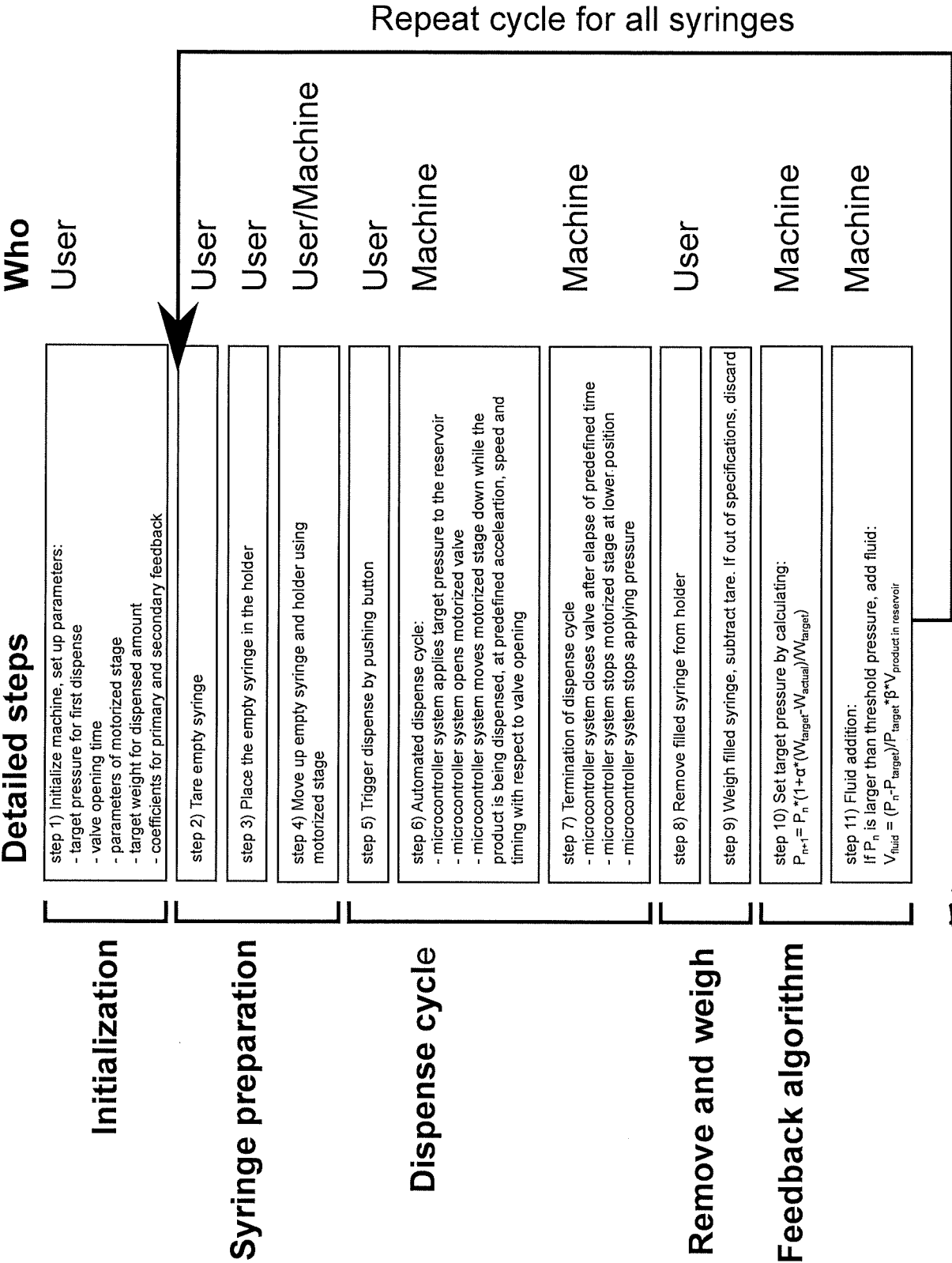


Fig. 2

Fig. 2

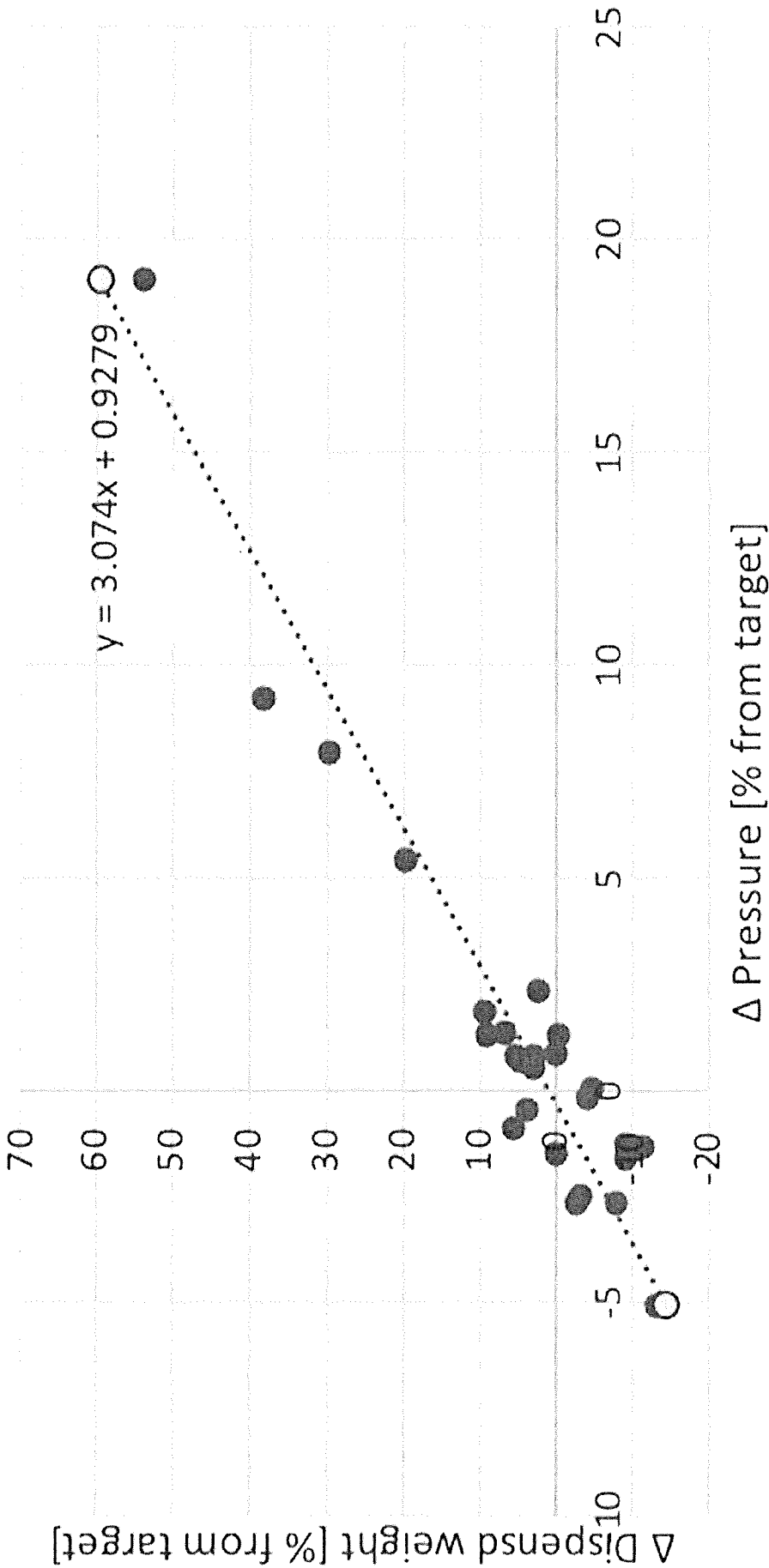
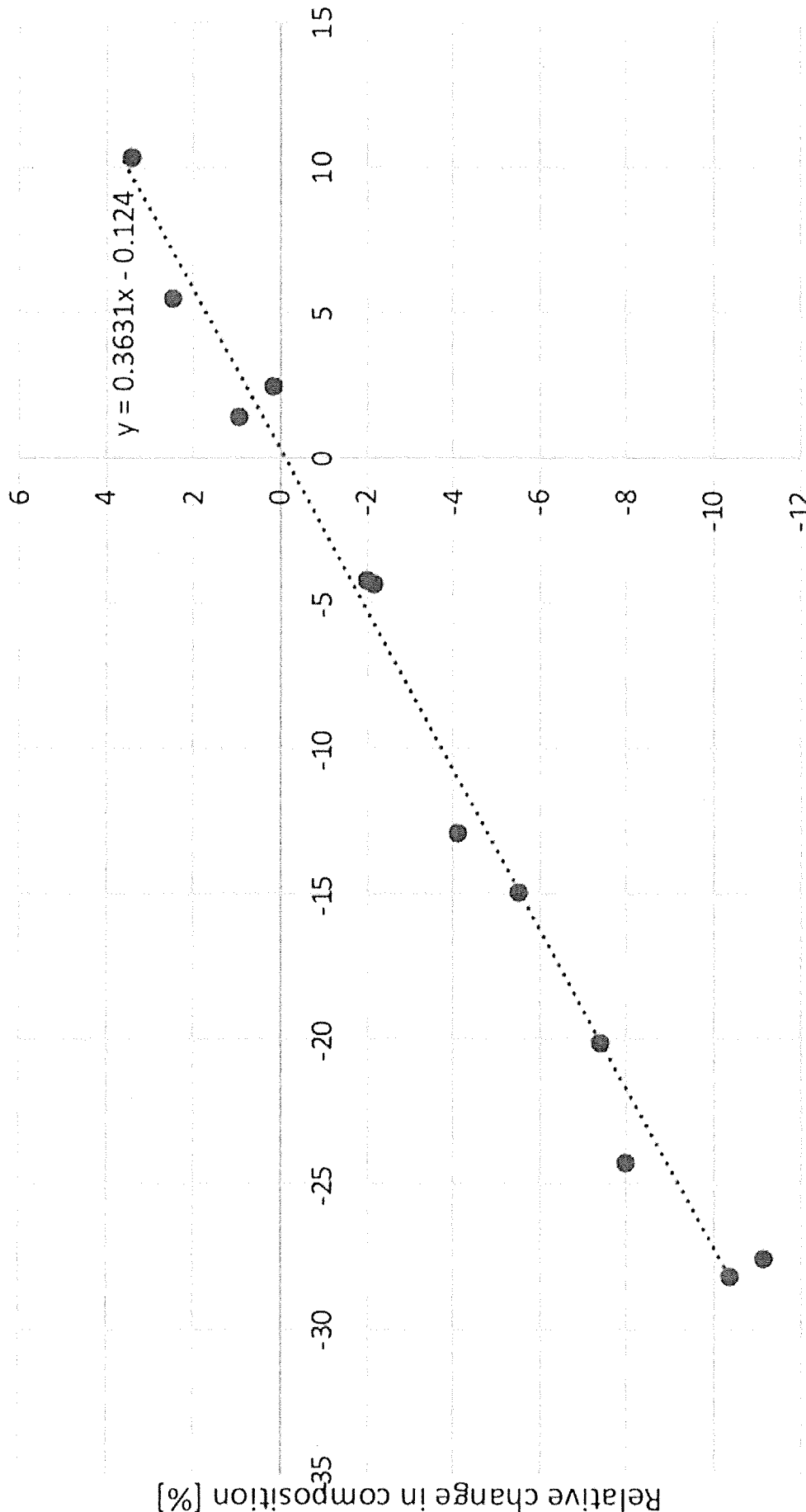


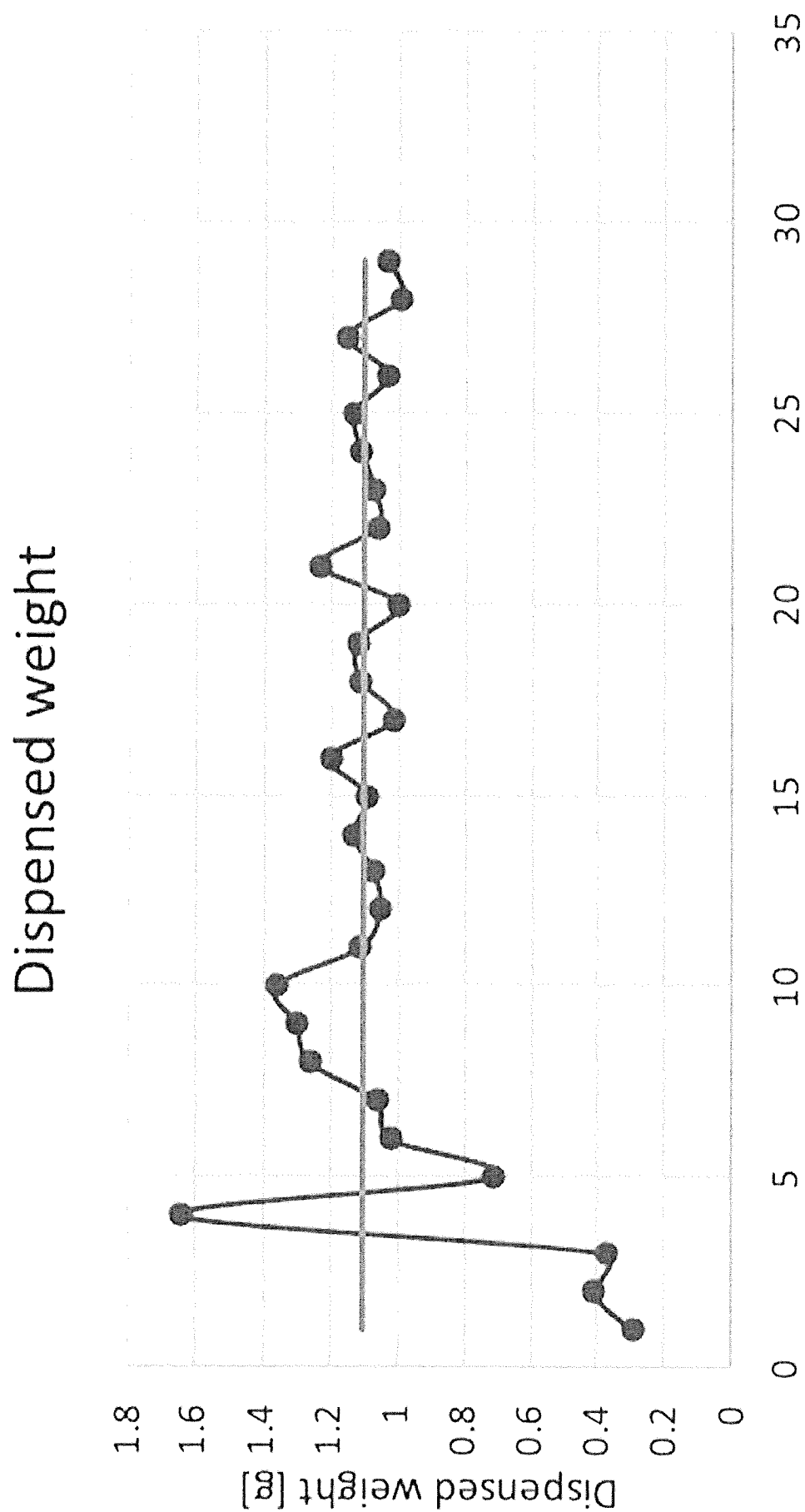
Fig. 3

Fluid feedback calibration



Relative change in pressure [%]

Fig. 4



Dispense Cycle #
Fig. 5

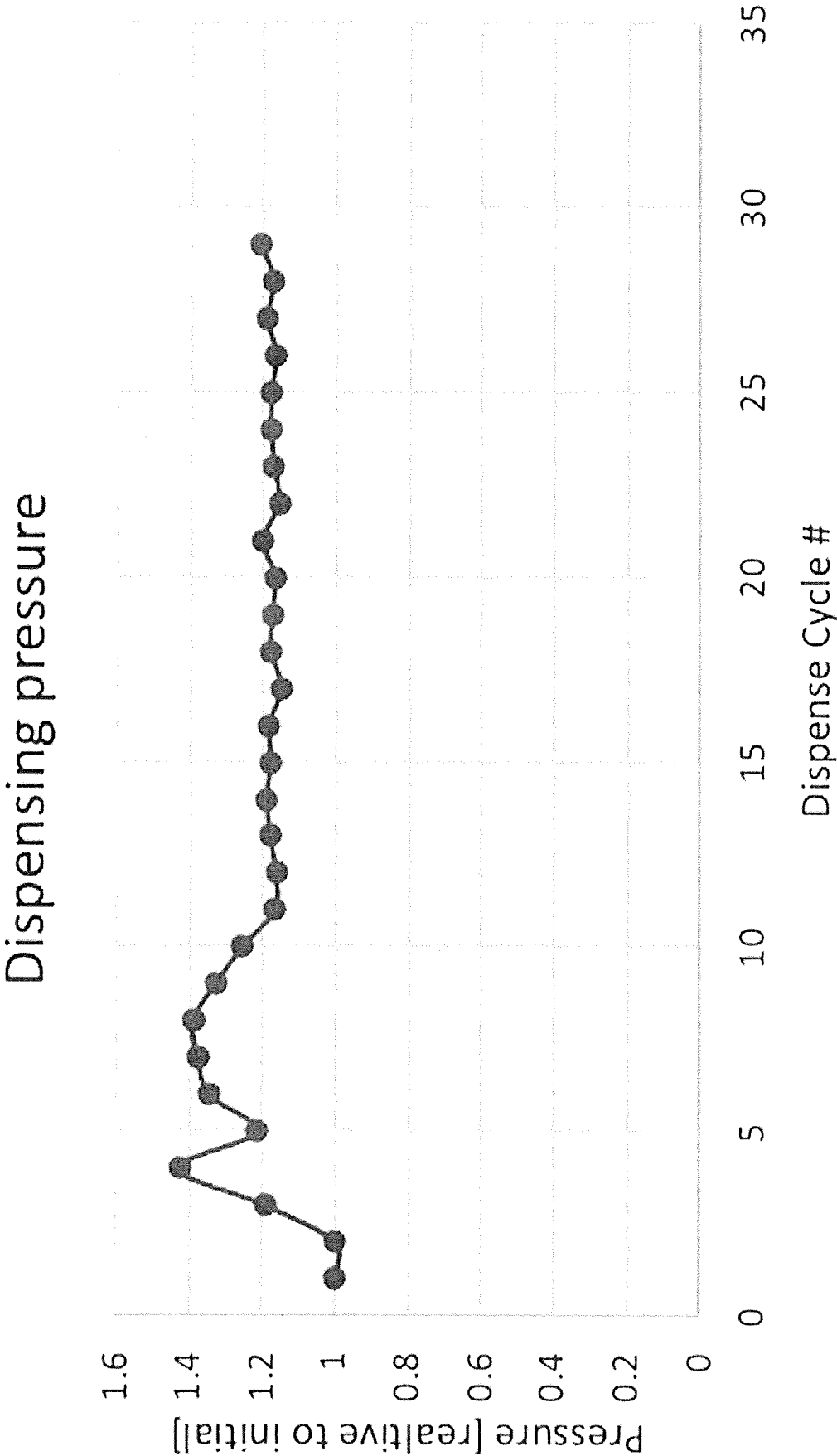
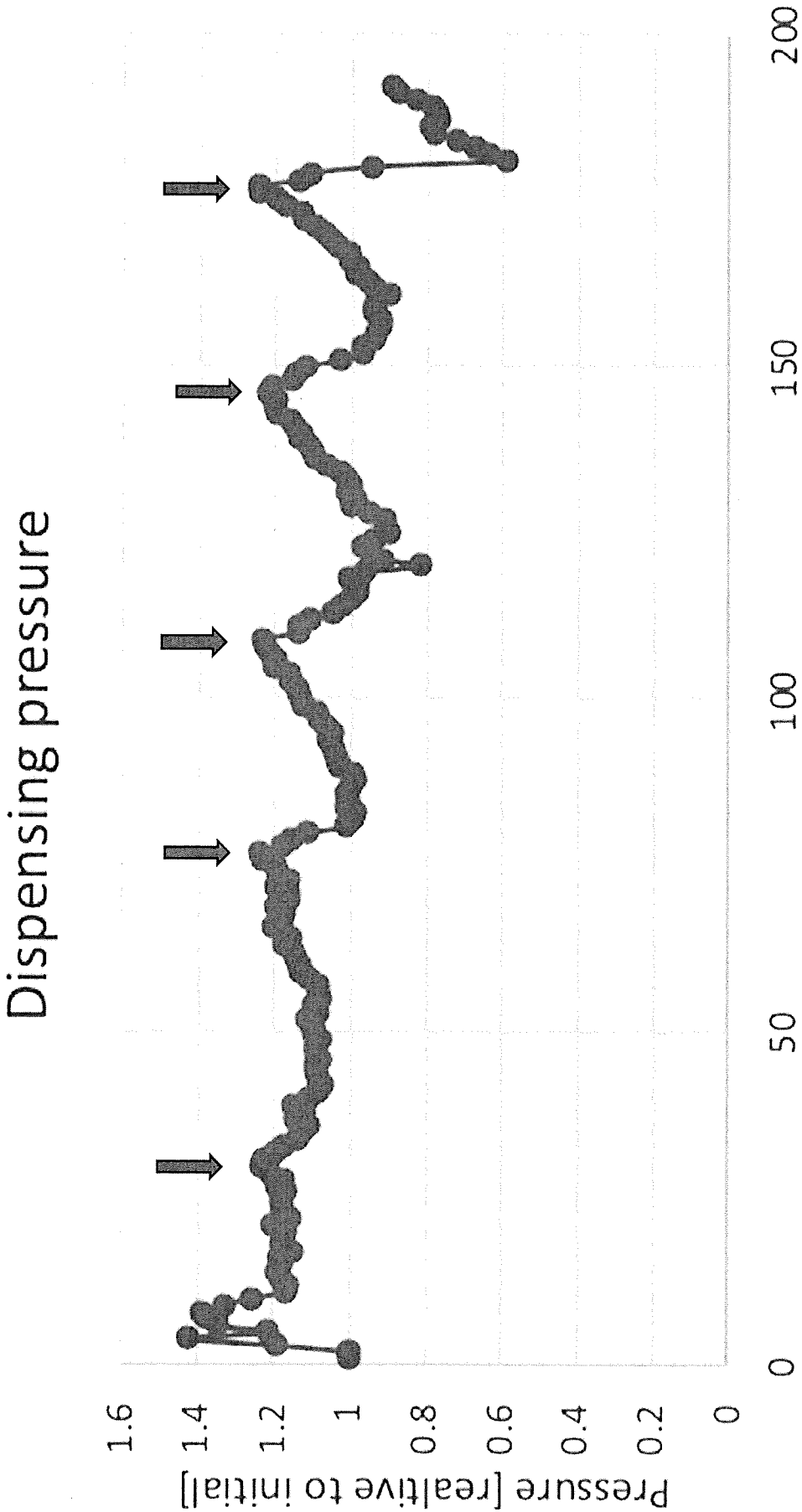


Fig. 6



Dispense Cycle #
Fig. 7

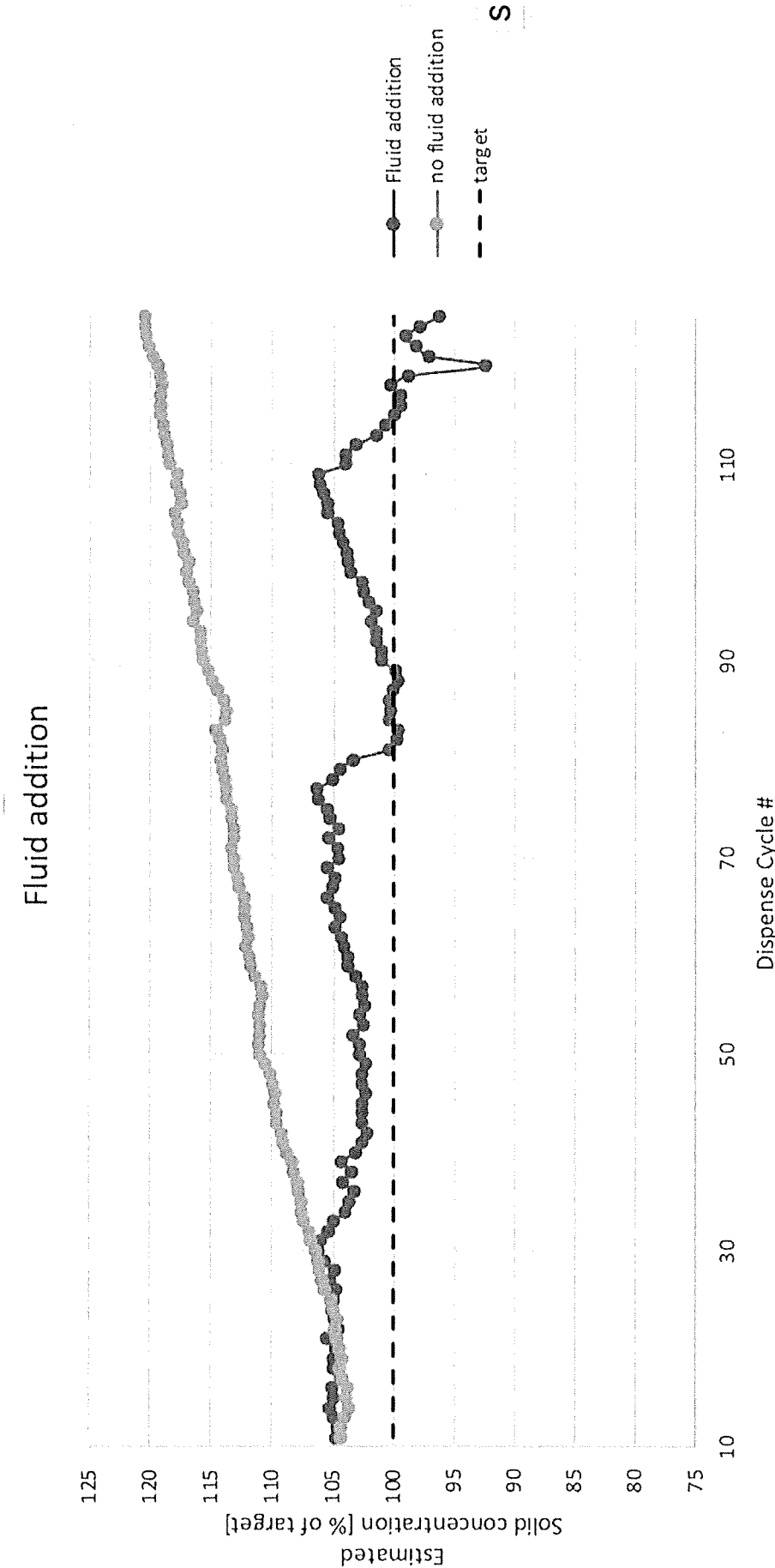


Fig. 8

95% confidence intervals for dispensed mass and concentration

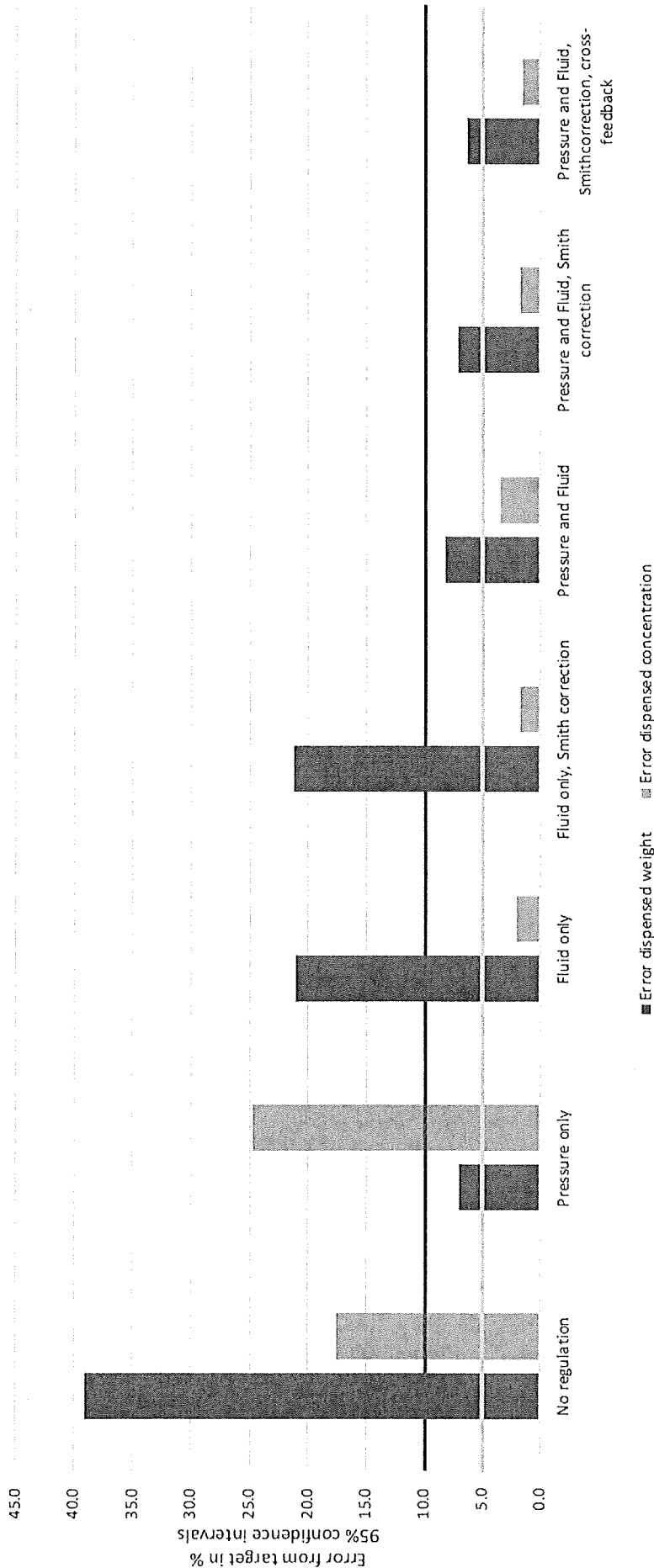


Fig. 10

95% confidence intervals for dispensed mass and concentration

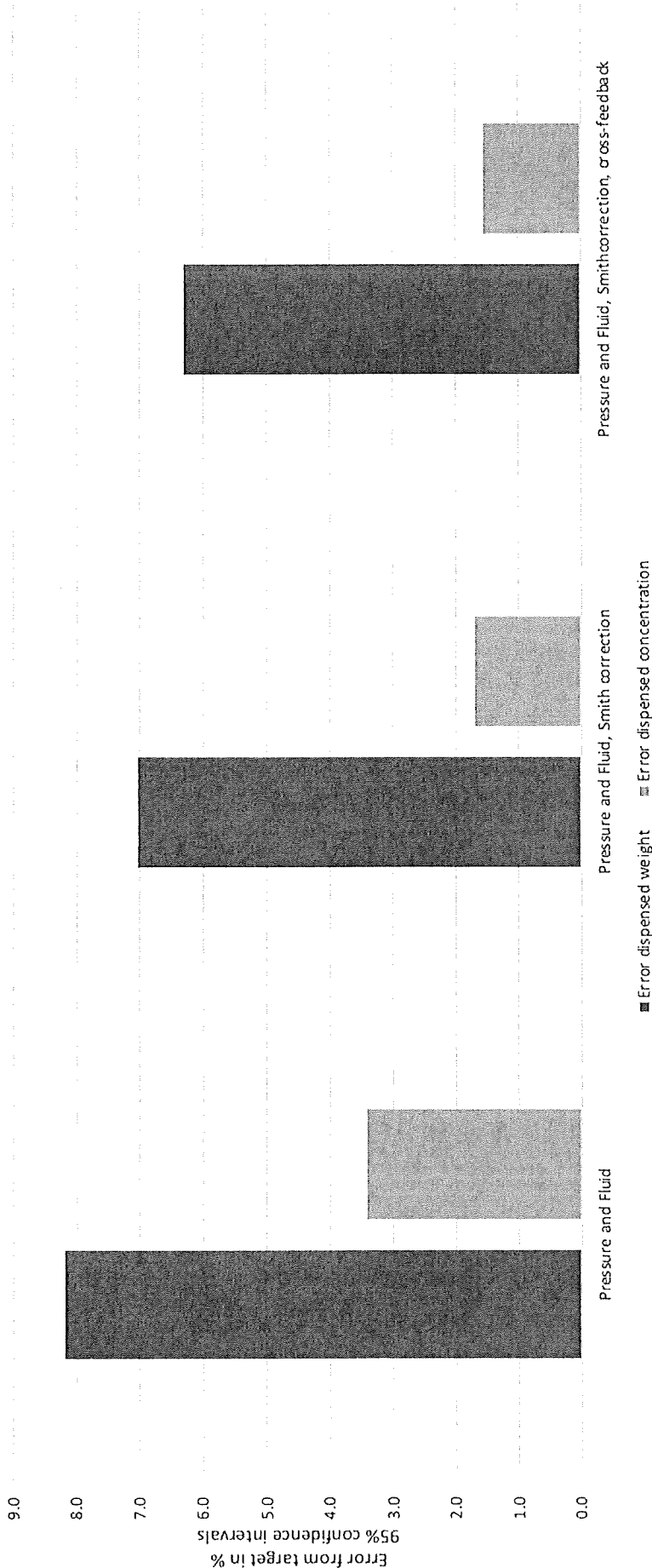


Fig. 10

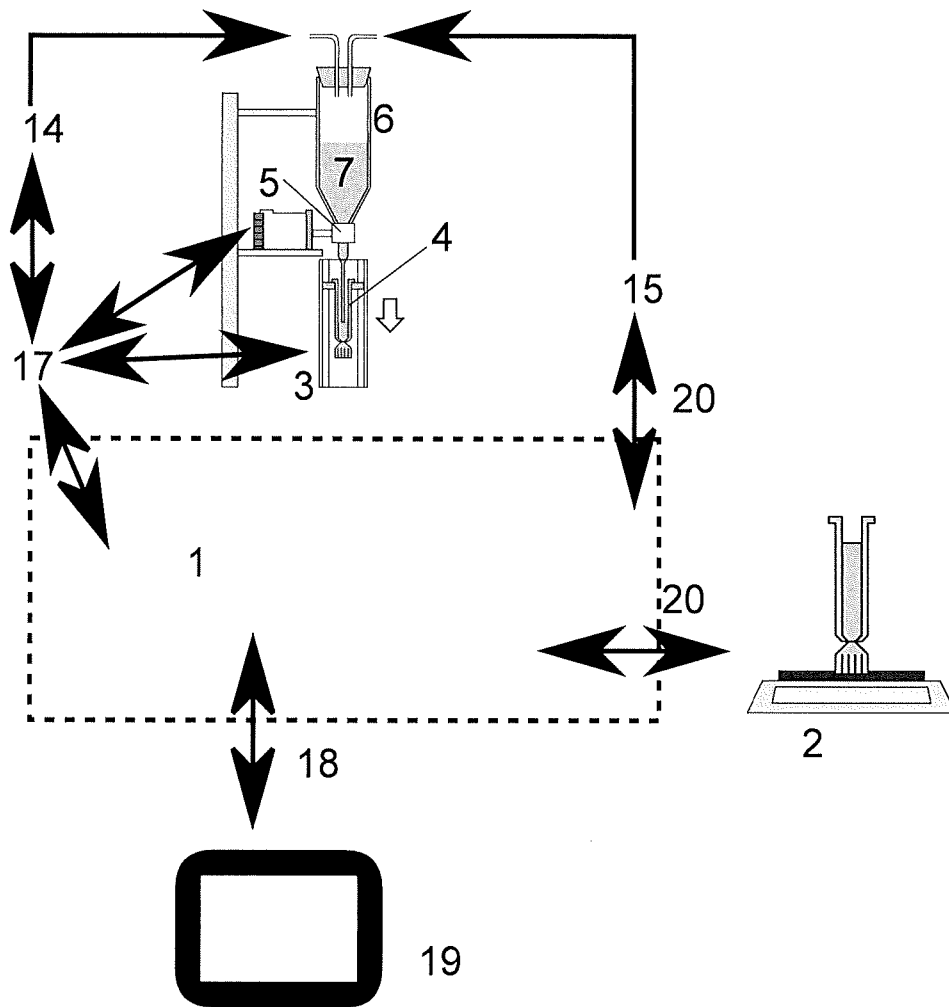


Fig. 11

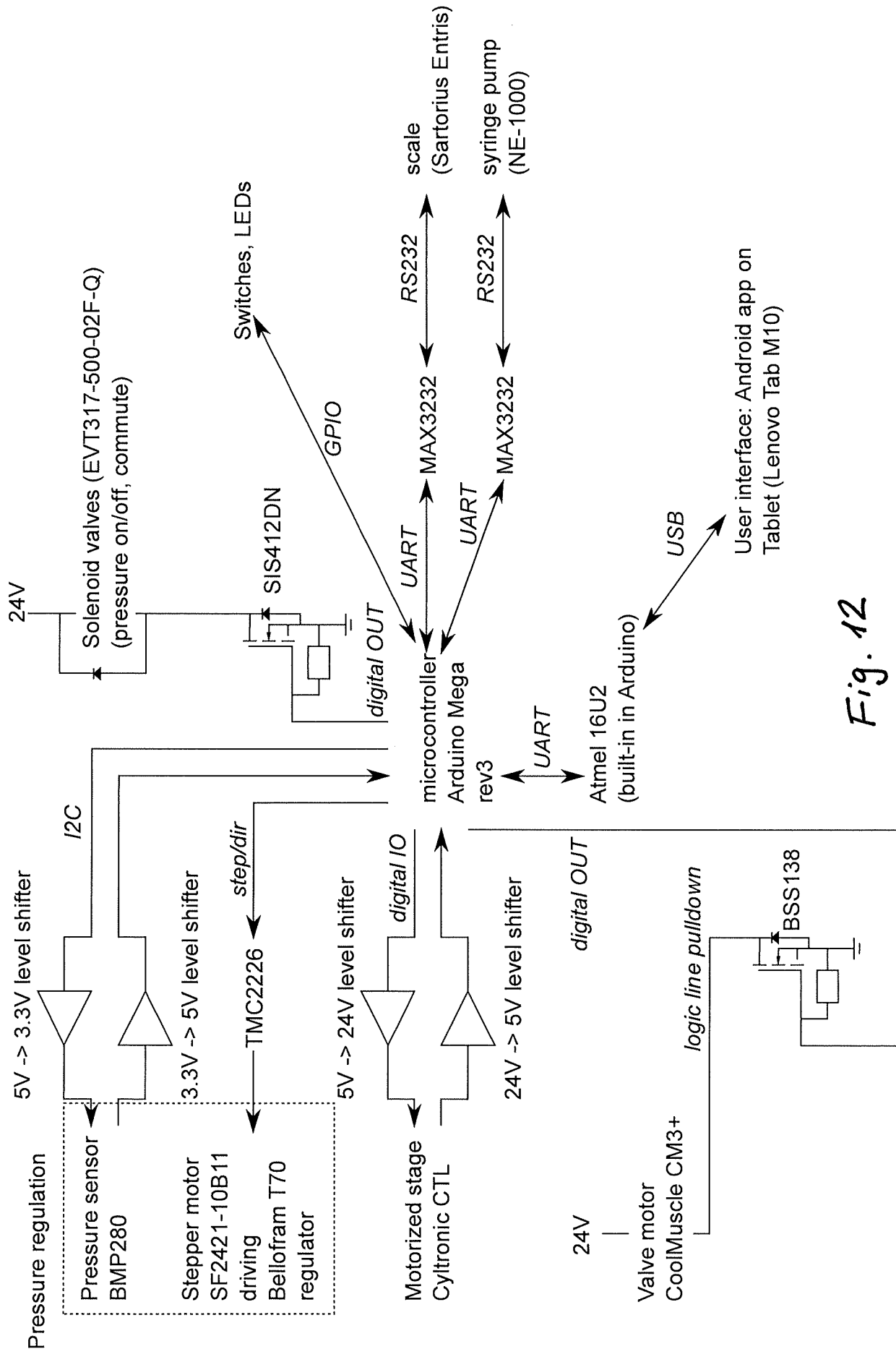
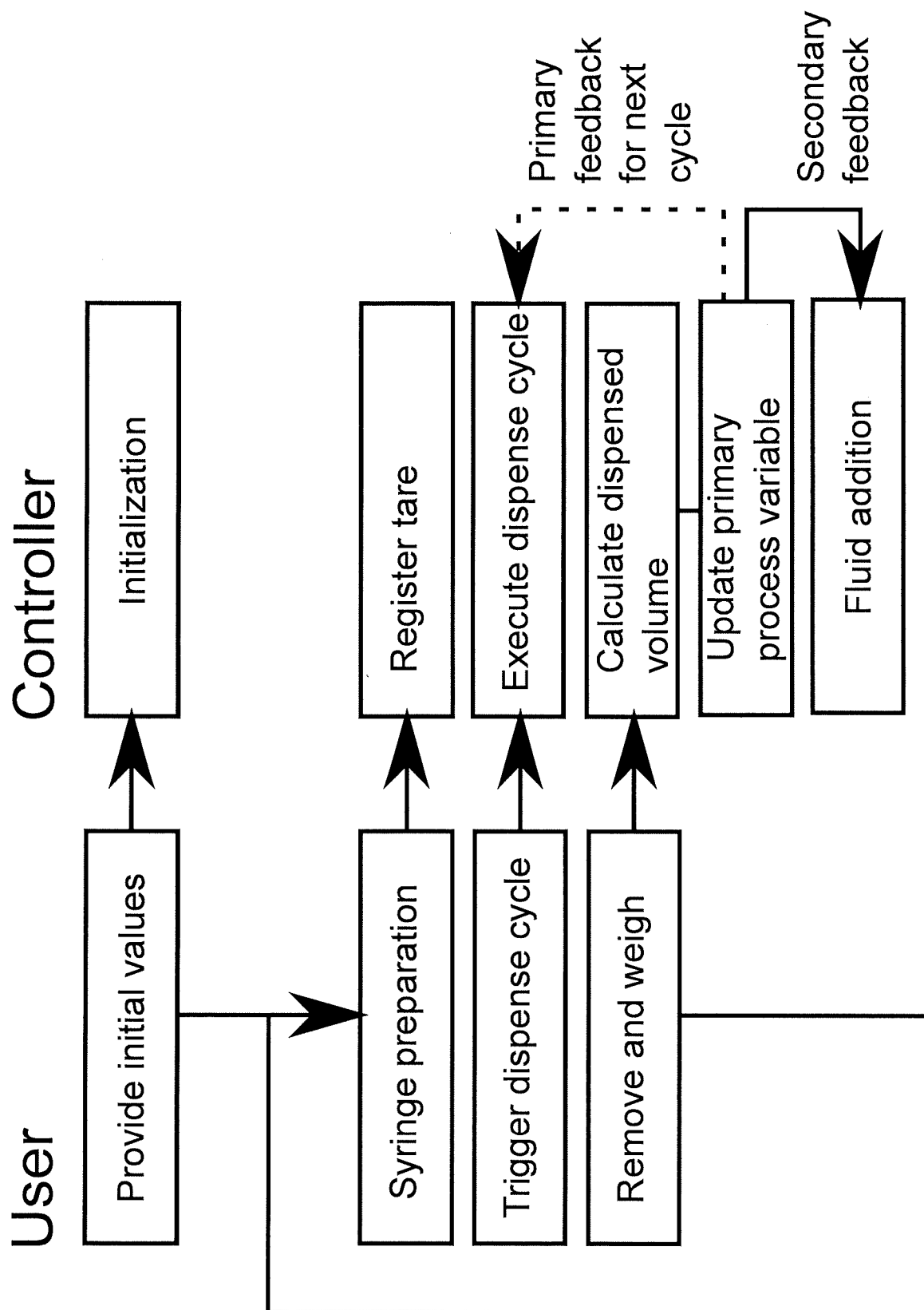


Fig. 12

*Fig. 13*

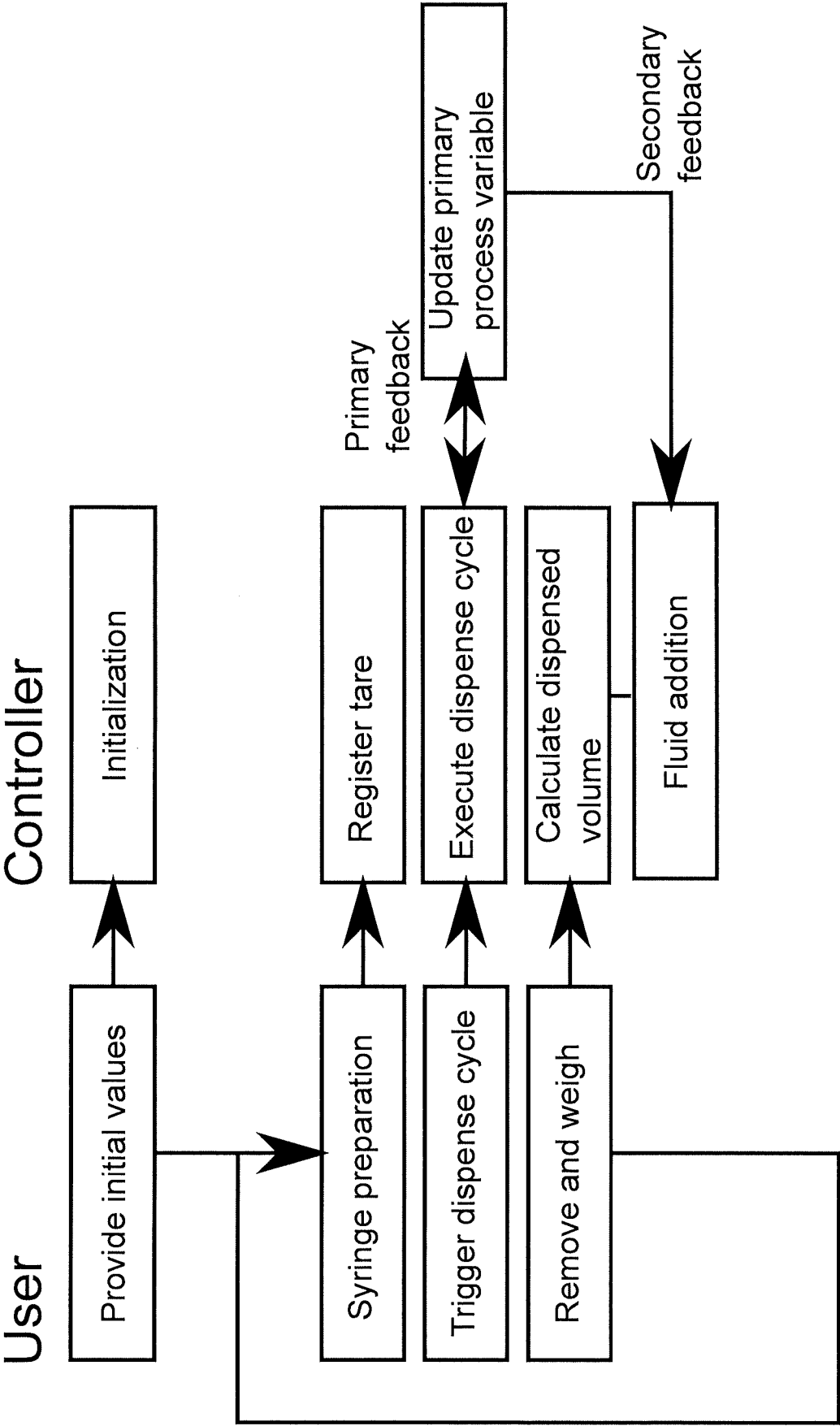


Fig. 14

INTERNATIONAL SEARCH REPORT

International application No
PCT/CH2023/050023

A. CLASSIFICATION OF SUBJECT MATTER INV. A61J1/20 A61M5/178 B65B3/00 B65B3/04 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) B65B A61M A61J		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2017/028130 A1 (PERAZZO NICHOLAS J [US] ET AL) 2 February 2017 (2017-02-02) paragraphs [0324] - [0326]; figures 1-4 -----	1-31
A	US 2022/370292 A1 (SETH AKHIL [US] ET AL) 24 November 2022 (2022-11-24) paragraphs [0072] - [0096]; figures 1, 2, 10, 11 -----	1-31
A	US 5 911 252 A (CASSEL DOUGLAS [US]) 15 June 1999 (1999-06-15) column 5, line 40 - column 6, line 51; figures 1-3A -----	1-31
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
5 January 2024		16/01/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Diamantouros, S

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/CH2023/050023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2017028130	A1	02-02-2017	NONE

US 2022370292	A1	24-11-2022	NONE

US 5911252	A	15-06-1999	NONE
