Establishing Metrology Standards in Microfluidic Devices

REPORT:

A2.2.1: A literature review of existing metrology and normative standards related to the flow properties and microfluidic devices

Work package 2

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This report was written as part of activity 2.2.1 from the EMPIR Establishing Metrology Standards in Microfluidic Devices (MFMET) project. The three-year European project commenced on 1st June 2021 and focused on providing a generic methodology of accurate measurement of a particular quantity in a microfluidic device by utilising standardised methods and reference documents, e.g. VIM & GUM. For more details about this project, please visit www.mfmet.eu

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The EMPIR initiative is co-funded by the European Union's Horizon 2020
research and innovation programme and the EMPIR Participating States

Contents

1. Scope

This document provides a literature review of existing metrology and normative standards related to the flow properties and microfluidic devices.
The flow quantities input from A2.1.3:

1- Flow rate (including fast changing flow rates)
2- Flow resistivity
3- Volume, such as internal volume, dead volume and droplet size

Activity number	Activity description	Partners (Lead in bold)
A2.2.1 M11	Using the flow quantities identified in A2.1.3, TUBITAK, DTI, NQIS, CETIAT, IPQ, CMI and BHT will perform a literature review of existing metrology and normative standards related to the flow properties and microfluidic devices.	**TUBITAK**, DTI, NQIS, CETIAT, IPQ, CMI, BHT

2. Normative References

ISO 10991:2009 Micro process engineering — Vocabulary

ISO 4006:1991 Measurement of fluid flow in closed conduits — Vocabulary and symbols

ISO 14511:2019 Measurement of fluid flow in closed conduits. Thermal mass flowmeters

ISO 9368-1:1990 Measurement of liquid flow in closed conduits by the weighing method — Procedures for checking installations — Part 1: Static weighing systems

ISO 4185:1980 Measurement of liquid flow in closed conduits — weighing method

ISO/TR 20461:2000 Determination of uncertainty for volume measurements made using the gravimetric method

ISO 8316:1997 Measurement of liquid flow in closed conduits — Method by collection of the liquid in a volumetric tank

ISO/TR 3313:2018 Measurement of fluid flow in closed conduits. Guidelines on the effects of flow pulsations on flow-measurement instruments

IEC EN 60601-2-24:2015 Medical electrical equipment - Part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers

AAMI TIR101:2021 Fluid delivery performance testing for infusion pumps

ISO 4787:2021 - Laboratory glass and plastic ware — Volumetric instruments — Methods for testing of capacity and for use

ISO 10790:2015 Measurement of fluid flow in closed conduits — Guidance to the selection, installation and use of Coriolis flowmeters (mass flow, density and volume flow measurements)

ISO 14511:2019 Measurement of fluid flow in closed conduits — Thermal mass flowmeters

ISO 5167:2003 Measurement of fluid flow by means of pressure differential devices inserted in circular cross-section conduits running full – Part 1: General principles and requirements

3. Flow Metrology Terms and Definitions

Flow Metrology terms and definitions are taken from the normative references given above. In brackets are written the corresponding references and the applicable clauses. The order is alphabetical.

3.1. Actual Flow (ISO 10991:2009-cd)

Output value of the master reference standard. Expressed in volume units over time units.

3.2. Buoyancy correction (ISO 4006:1991)

Correction to be made to the readings of a weighing-machine to take account of the difference between the upward thrust exerted by the atmosphere on the fluid being weighed and that exerted on the reference weights used during the calibration of the weighing machine.

3.3. Calibrated measuring (volumetric) tank (ISO 4006:1991)

Tank in which the relationship between the volume, for a known liquid at a given temperature, and the liquid level is known with accuracy by an independent calibration method.

3.4. Capillary force (ISO 10991:2009-cd)

Capillary action flowing of liquid inside microchannels without external actuators but only by adhesive force between liquid and channel material.

3.5. Cavitation (ISO 10790:2015)

Phenomenon related to and following flashing of liquids if the pressure recovers causing the vapour bubbles to collapse (implode)

3.6. Coriolis flowmeter (ISO 10790:2015)

Device consisting of a flow sensor (primary device) and a transmitter (secondary device) which measures mass flow and density by means of the interaction between a flowing fluid and the oscillation of a tube or tubes

3.7. Dead-volume (ISO 10991:2009-cd)

Portion of the internal volume of a system that is not part of a continuous flow-path. In this context dead signifies unmoving, stagnant, or un-swept. The dead volume is expressed in volume quantities such as mm^3 or microliter.

3.8. Differential pressure, Δp (ISO 5167-1:2003)

Difference between the (static) pressures measured at the wall pressure tappings, one of which is on the upstream side and the other of which is on the downstream side of primary device (or in the throat for a venture nozzle or a venture tube), inserted in a straight pipe through which flow occurs, when any difference in height between the upstream and downstream tappings has been taken into account.

3.9. Discharge coefficient, *C* (ISO 5167-1:2003)

Coefficient, defined for an incompressible fluid flow, which relates the actual flowrate to the theoretical flowrate through a device, and given by the formula for incompressible fluids

$$C = \frac{q_m\sqrt{1-\beta^4}}{\frac{\pi}{4}d^2\sqrt{2\Delta p\rho_1}}$$

The quantity $1/\sqrt{1-\beta^4}$ is called the “velocity approach factor1, and the product

$$C\frac{1}{\sqrt{1-\beta^4}}$$

is called the “flow coefficient”.

3.10. Diverter (ISO 8316:1997, ISO 4006:1991 and ISO 4185:1980)

A device which diverts the flow either to the gauging tank or to its by-pass without changing the flow-rate during the measurement interval.

3.11. Dynamic gauging (ISO 8316:1997 and ISO 4006:1991)

A method by which the net volume of liquid collected is deduced from gaugings made while liquid flow is being delivered into the gauging tank. (A diverter is not required with this method.)

3.12. Dynamic weighing (ISO 4006:1991 and ISO 4185:1980)

Weighing method in which the net mass of the fluid collected is deduced from weight measurements made while fluid flow is directed into the weighing-tank.

Note – A diverter is not required with this method.

3.13. Expansibility (expansion) factor, ε (ISO 5167-1:2003)

Coefficient used to take into account the compressibility of the fluid

$$\varepsilon = \frac{q_m\sqrt{1-\beta^4}}{\frac{\pi}{4}d^2C\sqrt{2\Delta p\rho_1}}$$

3.14. Flashing (ISO 10790:2015)

Phenomenon, which occurs when the line pressure drops to, or below, the vapour pressure of the liquid

Note 1 to entry: This is often due to pressure drops caused by an increase in liquid velocity.

Note 2 to entry: Flashing is not applicable to gases.

3.15. Flow rate (ISO 14511:2019)

Quotient of the quantity of fluid passing through the cross-section of a conduit and the time taken for this quantity to pass through this section

3.16. Flow profile (ISO 14511:2019)

Graphic representation of the velocity distribution

Note 1 to entry: The point flow velocity across the cross-section of a conduit is not constant. It varies as a consequence of upstream and downstream disturbances and with the Reynolds number of the flow stream. For a fully developed flow, the point flow velocity varies from 0 m/s at the pipe wall to a maximum value at the conduit center. The flow profile describes the variation of the flow velocity across the conduit cross-section and may be expressed mathematically or graphically

3.17. Flow sensor (primary device) (ISO 10790:2015)

Mechanical assembly consisting of an oscillating tube(s), drive system, measurement sensor(s), supporting structure, and housing

3.18. Flow stabilizer (ISO 8316:1997 and ISO 4185:1980)

A device inserted into the measuring system, ensuring a stable flow-rate in the conduit being supplied with liquid; for example, a constant level head tank, the level of liquid in which is controlled by a weir of adequate length.

3.19. Friction velocity, u* (ISO 4006:1991)

Square root of the quotient of the wall shear stress τ_o and the density of the flowing fluid,

$$u^* = \sqrt{\frac{\tau_0}{\rho}} = U\sqrt{\frac{\lambda}{8}}$$

3.20. Fully developed velocity distribution (ISO 4006:1991)

Velocity distribution that, once attained, does not vary from one cross-section of a fluid flow to another. It is generally attained at the end of a sufficiently long straight length of conduit.

3.21. Hydrodynamic resistance (ISO 10991:2009-cd)

Ratio of pressure drop over flow rate for a certain component or system.

3.22. Hydraulic diameter, Dh (ISO 4006:1991)

Four times the quotient of the wetted cross-sectional area and wetted premier

3.23. Hydrostatic pressure (ISO 10991:2009-cd)

Pressure that is exerted by a fluid at rest at a given height within the fluid, due to the force of gravity.

3.24. Infusion pump (IEC 60601-2-24:2012)

An equipment intended to regulate the flow of liquids into the patient under pressure generated by the pump.

Note 1 to entry: The Infusion Pump may provide one or more of the following types of flow:

type 1: continuous infusion;

type 2: non-continuous infusion;

type 3: discrete delivery of a bolus;

type 4: profile pump

3.25. Internal volume (ISO 10991:2009-cd)

Maximal total available volume comprised within a fluidic component, device or system under normal atmospheric pressure. The internal volume is the total of dead volume and swept volume.

3.26. Mass flow rate (ISO 14511:2019)

Flowrate in which the quantity of fluid is expressed as a mass.

3.27. Mean axial fluid velocity, U (ISO 4006:1991)

Ratio of the volume flow-rate (the integral over a cross section of the conduit of the axial components of the local fluid velocity) to the area of the measurement cross section

3.28. Mean flow-rate (ISO 4006:1991)

Mean value of flow-rate over a period of time

3.29. Micro pump (ISO 10991:2009-cd)

Miniaturized liquid or gas pumping equipment with capacity of lower than milliliter per minute flow rate.

3.30. Non-dimensional velocity, v* (ISO 4006:1991)

Ratio of the flow velocity at a given point to a reference velocity measured at the same time which may be at a particular point (for example the center-line velocity) of the mean axial fluid velocity.

3.31. Normalized volume flowrate, (GB) / standardized volume flowrate, (US) (ISO 14511:2019)

Flowrate for which the quantity of fluid is expressed in terms of volume, with the fluid density calculated at a known and fixed pressure and temperature condition

The values used to define these reference conditions (also known as “standard reference conditions”) are industry and country specific and therefore shall always be specified when these units are used. Typical reference conditions are 0 °C and 101,325 kPa.

3.32. Normalized velocity, (GB) / standardized velocity, (US) (ISO 14511:2019)

Flowrate for which the quantity of fluid is expressed in terms of the speed of flow, with the fluid density calculated at a known and fixed pressure and temperature condition

The values used to define these reference conditions (also known as “standard reference conditions”) are industry and country specific and therefore shall always be specified when these units are used. Typical reference conditions are 0 °C and 101,325 kPa.

3.33. Nozzle (ISO 5167-1:2003)

Device which consists of a convergent inlet connected to a cylindrical section generally called throat.

3.34. Orifice plate (ISO 5167-1:2003)

Thin plate in which a circular opening has been machined.

3.35. Pressure drop (ISO 10991:2009-cd)

Difference of pressure between two positions in the flow path.

3.36. Pressure ratio (ISO 5167-1:2003)

Ratio of the absolute (static) pressures at the downstream pressure tapping to the absolute(static) pressure at the upstream pressure tapping.

3.37. Pulsating flow of mean constant flow rate: (ISO 4006:1991, ISO/TR 3313:2018)

Flow in which the flow-rate in a measuring section is a function of time but has a constant mean value when averaged over a sufficiently long period of time.

Two types of pulsating flow are found, i.e.

- Periodic pulsating flow

- Randomly fluctuating flow

3.38. Relative flow stability (ISO 10991:2009-cd)

Coefficient of variation, standard deviation of the flow rate divided by the average flow rate. Expressed as a percentage

3.39. Regular velocity distribution (ISO 4006:1991)

Distribution of velocities which sufficiently approaches a fully developed velocity distribution to permit an accurate measurement of the flow-rate to be made.

3.40. Reynolds number, Re (ISO 4006:1991)

Dimensionless parameter expressing the ratio between the inertia and viscous forces. It is given by the formula

$$Re = \frac{Ul}{u}$$

Where

U is the mean fluid velocity across a defined area

l is a characteristic dimension of the system in which the flow occurs

υ is the kinematic viscosity of the fluid

3.41. Response time (ISO 10991:2009-cd)

Interval of time between the set point step change the moment the flow has increased x% of is intended rise or x% of its intended fall

3.42. Swept volume (ISO 10991:2009-cd)

Portion of a volume that is part of the flow path.

3.43. Static gauging (ISO 8316:1997 and ISO 4006:1991)

A method by which the net volume of liquid collected is deduced from measurements of liquid levels (i.e. gauging), made respectively before and after the liquid has been diverted for a measured time interval into the gauging tank, to determine the volume contained in the tank.

3.44. Static weighing (ISO 4006:1991 and ISO 4185:1980)

Weighing method in which the net mass of the fluid collected is deduced from the tare and gross weights determined respectively before and after the fluid has been diverted for a measured time interval into the weighing-tank.

3.45. Steady flow: (ISO 4006:1991, ISO/TR 3313:2018)

Flow in which parameters such as velocity, pressure, density and temperature do not vary sufficiently with time to affect the required accuracy of the measurement.

3.46. Syringe or container pump (IEC 60601-2-24:2010)

Infusion Pump intended for controlled infusion of liquids into the patient by means of one or more single action syringe(s) or similar container(s) (e.g. where the cartridge/bag is emptied by positive pressure applied to the cartridge/bag) in which the delivery rate is indicated in volume per unit of time or units related to drug dosage.

3.47. Transmitter (secondary device) (ISO 10790:2015)

Electronic control system providing the drive electrical supply and transforming the signals from the flow sensor to give output(s) of measured and inferred parameters

3.48. Universal head loss coefficient, λ (ISO 4006:1991)

Ratio of the pressure loss a flow, along a length of conduit equal to the hydraulic diameter, to the dynamic pressure calculated from the mean axial fluid velocity. It is given by the formula

$$\Delta p = \lambda \frac{l}{D_h} \times \frac{1}{2} \rho U^2$$

3.49. Unsteady flow: (ISO 4006:1991, ISO/TR 3313:2018)

Flow, which may be laminar or turbulent, in which such as velocity, pressure, density and temperature fluctuate with time.

3.50. Venturi Nozzle (ISO 5167-1:2003)

Device which consists of a convergent inlet which is a standardized ISA 1932 nozzle connected to a cylindrical part called the “throat” and an expanding section called the “divergent” which is conical.

3.51. Venturi tube (ISO 5167-1:2003)

Device which consists of a convergent inlet which is conical connected to a cylindrical part called the “throat” and an expanding section called the “divergent” which is conical.

3.52. Volumetric flow rate (ISO 10991:2009-cd)

Volume of fluid which passes per unit time.

3.53. Volumetric infusion controller (IEC 60601-2-24:2010)

An equipment intended to regulate the flow of liquid into the patient under positive pressure generated by gravitational force in which the delivery rate is indicated by the ME Equipment in volume per unit of time.

3.54. Volumetric infusion pump (IEC 60601-2-24:2010)

Infusion Pump in which the delivery rate is indicated in volume per unit of time or units related to drug dosage, but excluding syringe or container pumps.

3.55. Zero offset (ISO 10790:2015)

Indicated flow when there are zero flow conditions present at the meter

Note 1 to entry: This could be due to mechanical or electrical noise superimposed on the sensor output but equally could be due to installation effects such as torsional loading caused by improper torqueing of the flange bolts or temperature extremes creating deflection of the pipeline.

3.56. Zero stability (ISO 10790:2015)

Variation of the flowmeter output at zero flow after the zero adjustment procedure has been completed, expressed by the manufacturer as an absolute value in mass per unit time

4. Flow - rate

4.1. Primary methods

Micro and nano-flow rate primary measurement methods are described in the first deliverable of the “Metrology for Drug Delivery II” project, available at https://drugmetrology.com/wp-content/uploads/2020/10/MeDDII-D1_V1-1.pdf

This report includes the description of the following methods and their associated uncertainty budgets:

- Gravimetric method
- Optical method: meniscus tracking
- Optical method: pendant drop
- MicroPIV/MicroPTV
- Displacement method

These methods are intended to be used when the best accuracy in flow measurement is needed, or in case of a flow meter or flow generator calibration.

4.1.1. Gravimetric Method

4.1.1.1. Test Procedure (IEC 60601-2-24:2010 and AAMI TIR 101)

The gravimetric test system shown in Figure 1 and 2 can be used to determine the accuracy of flow devices. The test time and calibration points should be chosen by the user depending on the application.

The test solution should be 0.9% Normal Saline or distilled water of grade 3 (or better) according to ISO 3696, unless there is a compelling reason to choose a different clinically relevant fluid. The density of the test solution can be determined using the Tanaka formula. The test solution temperature should be measured in the source container at the start of the test and at the balance at the end of the test. The average of the two temperatures should be used to determine the density of the test solution [7].

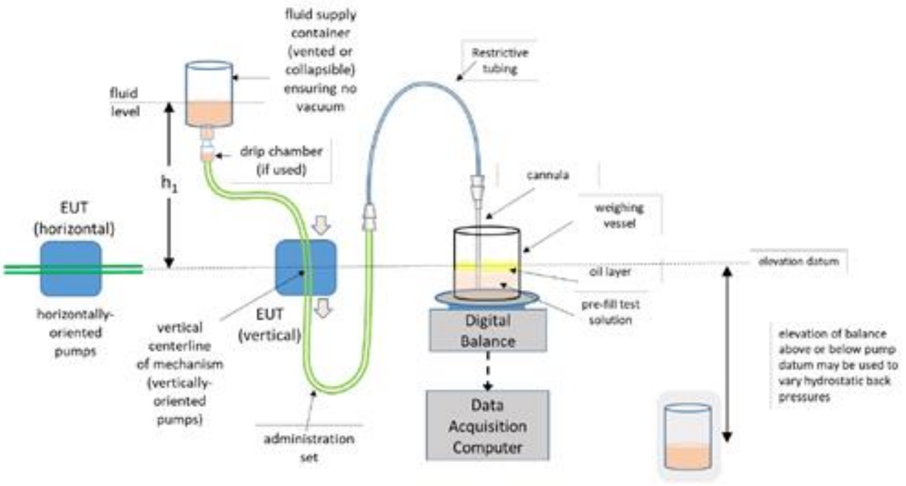

Figure 1. Test apparatus for volumetric infusion pumps and volumetric infusion controllers

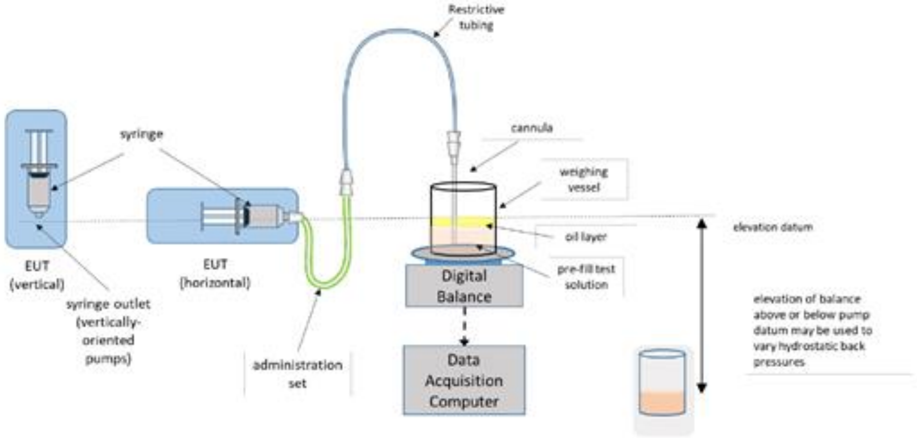

Figure 2. Test apparatus for syringe or container pumps

Set height (collapsible bag, vented container) in accordance with the Manufacturer's instructions for use. The needle shall be positioned below the liquid surface. The mean center line of the pumping chamber to be at the same height as the tip of the needle.

4.1.1.2. Calculation of flow-rate

The set-up in Figure 1 or Figure 2 can be used to measuring the flowrate of any microfluidic device. The equations given in ISO 4185 should be used with corrections including the needle for buoyancy, evaporation and surface tension effects. In that case volume flow rate [1, 2]:

$$q_V = \frac{1}{t_f - t_i}\left[\left((I_L - I_E) \times (1 - \left(\frac{D_{tube}}{D_{tank}}\right)^2)\right) \times \frac{1}{\rho_W - \rho_a} \times (1 - \frac{\rho_a}{\rho_p}) \times [1 - \gamma(T - 20)]\right] + \delta q_{evp} \qquad (4.1)$$

Calculation of mass flow-rate (ISO 4185:1980)

The mean mass flow-rate during the filling time is obtained by dividing the real mass m of the liquid collected by the filling time t:

$$q_m = \frac{m}{t} = \frac{m_1 - m_0}{t} \times \frac{1 - \frac{\rho_a}{\rho_p}}{1 - \frac{\rho_a}{\rho_W}} \qquad (4.2)$$

Where

q_m mass flow-rate

m mass

t time

ρ_w density of liquid

ρ_a density of air

ρ_p density of standard weights

If necessary, t is corrected in accordance with the described procedure in the standard (ISO 4185) to take into account the diverter timing error. The final term in this equation is a correction term introduced to take into account the difference in buoyancy exerted by the atmosphere on a given mass of liquid and on the equivalent mass in the form of weights made, for example, of cast iron, used when calibrating the weighing machine.

Calculation of volume flow-rate (ISO 4185:1980)

The volume flowrate is calculated from the mass flow-rate, and from the density of the liquid at the temperature of operation, as read from standard tables or calculated from the formula 6.3:

$$q_V = \frac{q_m}{\rho_w t} = \frac{m_1 - m_0}{\rho_w t} \times \frac{1 - \frac{\rho_a}{\rho_p}}{1 - \frac{\rho_a}{\rho_w}} \qquad (4.3)$$

Where

q_v volume flow-rate

4.1.2. PIV/PTV

Particle Image Velocimetry (PIV) is a non-invasive, full field optical measuring technique, which has become dominant tool for obtaining velocity information about fluid motion. In PIV experiments, the fluid of interest is seeded with tracer particles, which are illuminated by a sheet of bright light. The positions of these particles at different times are recorded on a camera. Then, by measuring the particle displacements, the motion of the fluid can be ascertained. Generally, PIV means the accurate, quantitative measurement of fluid velocity vectors at a very large number of points simultaneously.

Micron resolution particle image velocimetry (µPIV) is a modification of PIV in order to access the small scales of microfluidic devices. In a typical particle image velocimetry (PIV) experiment, a light sheet formed by a laser is used to illuminate only a section of the flow, where the thickness of the light sheet is smaller than the depth of focus of the image recording system. In most cases, this approach is impractical for micro-PIV, and instead so-called volume illumination is applied. Here, the whole volume of the flow is illuminated, and now the depth of focus of the microscope objective defines the measurement region.

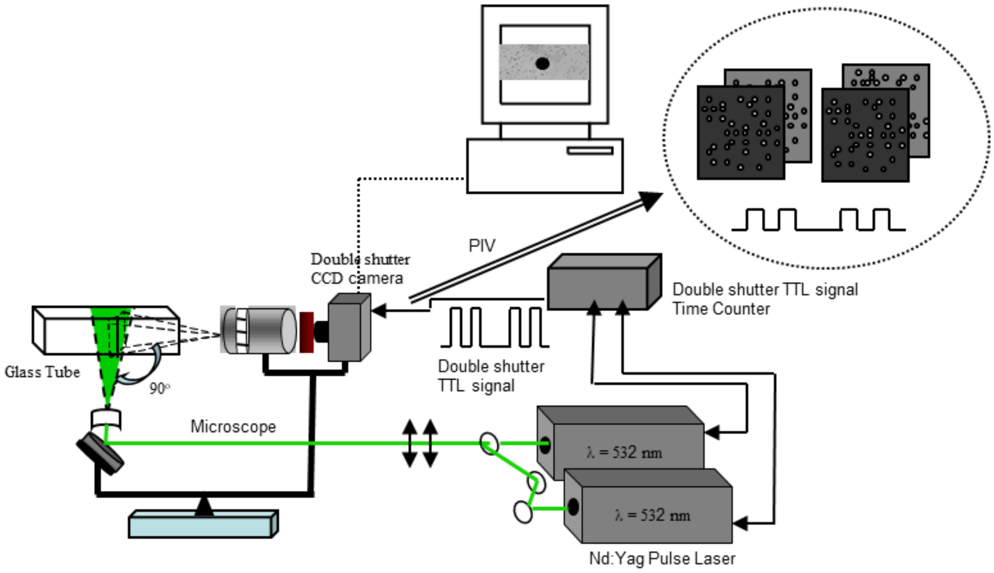

Figure 3. Micro PIV setup

Particle Tracking Velocimetry (PTV) is another widely used approach for flow velocity analysis. The major difference between PTV and PIV is that the later ascertains flow velocity fields by tracking individual particles rather than using cross correlating interrogation volumes, as is done in PIV. The nearest neighbor search with geometrical constraints and binary-image cross correlation between regions around particles of consecutive frames are frequently used particle tracking methods [9].

When there is a flow the positions of the tracer particles have slightly changed in the two consecutive recordings. The tracer particles with velocity *v* have shifted by a certain displacement Δs;

$$v = \frac{\Delta s}{\Delta t} = \frac{\Delta s}{t_2 - t_1} \qquad (4.4)$$

The two digital images are sent to a PC, where they are stored together with the time information. In a successive evaluation step the particle displacement Δs is digitally evaluated from the image pair.

4.2. Secondary methods

Flow rate can be measured using a dedicated flow meter. Commercially available flow meters for low flow rates are mainly based on the following principles:

- Coriolis
- Thermal difference
- Pressure differential

A flow meter is used by placing the instrument in series with the system, device, or object (such as a tube or channel) through which the liquid flows. The flow measurement accuracy can be influenced by liquid properties changes (such as the liquid density), ambient conditions changes, and any other influence factor which may affects the flow or the measuring device performances. In any case, the calibration of the flow meter is required in order to know the measurement accuracy.

4.2.1. Coriolis Flowmeter (ISO 10790:2015)

Coriolis flowmeters operate on the principle that inertia forces are generated whenever a particle in a rotating body moves relative to the body in a direction towards or away from the centre of rotation. This inertial force is called the Coriolis force.

A Coriolis flowmeter is an electromechanical system which consists of a flow sensor and a transmitter. The Coriolis flowmeter sensor is the primary mechanical part while the transmitter provides control and signal processing.

Coriolis flowmeters directly measure fluid mass flow rate and density at metering conditions. However, there are applications where the advantages of a Coriolis flowmeter would be very beneficial, but the desired measurement is volume at metering conditions. Coriolis flowmeters can be effectively used for volume flow measurement.

Calibration by using Coriolis flowmeter:

The flow shall be kept stable to within ±5 % of the selected flow rate for the duration of the calibration test at that flow rate. Variations in fluid temperature and pressure should be minimized during the calibration process. For a single run, the temperature should be held constant to within 1 °C, and to within 5 °C for the entire duration of the calibration. The fluid pressure within the test rig should be kept sufficiently high to avoid flashing or cavitation in the flowmeter and/or in the vicinity of the flowmeter. Depending on the Coriolis flowmeter design, the performance can be affected by variations in fluid density and viscosity. In these cases, test fluids should be used having properties that are the same or similar to the process fluid for which the flowmeter is intended.

4.2.2. Thermal Mass Flowmeter (ISO 14511:2019)

TMF meters generally use for gas and fall into two basic design categories:

a) capillary TMF meters (CTMF meters);

b) full bore TMF meters, consisting of the following two types (ITMF meter):

1) insertion type;

2) in-line type.

A typical CTMF meter consists of a meter body and flow sensor. The flow sensor is mounted integrally into the meter body. A defined portion of the gas flow from the meter body is diverted through the (bypass) flow sensor, through which the gas flowrate is measured. TMF meter is often combined with a flow controller downstream to the sensing sensor so as to obtain a mass flow controller.

A typical ITMF flowmeter consists of two temperature sensors. An amount of heating power P is applied to one of the sensors, causing its temperature to rise to a measured value T_2. The other sensor measures the gas temperature T_1. The gas mass flowrate can be determined from the temperature difference between the heated sensor and the gas ($\Delta T = T_2 - T_1$) and the amount of heating power P applied.

4.2.3. Pressure Differential Flowmeter (ISO 5167-1:2003)

The principle of the method of measurement is based on the installation of a primary device (such as orifice plate, a nozzle or a venture tube) into a pipeline in which a fluid is running full. The installation of the primary device causes a static pressure difference between the upstream side and the throat or downstream side of the device. The flowrate can be determined from the measured value of this pressure difference and from the knowledge of the characteristics of the flowing fluid as well as the circumstances under which the device is being used.

The mass flowrate can be determined, since it is related to the differential pressure:

$$q_m = \frac{C}{\sqrt{1-\beta^4}} \varepsilon \frac{\pi}{4} d^2 \sqrt{2\Delta p \rho_1} \qquad (4.5)$$

Except for the case of venture tubes, C may be dependent on Re, which is itself dependent on q_m. In such cases the final value of C, and hence q_m, has to be obtained by iteration.

The cavitation and compressibility effects is important for the pressure differential flowmeter in microflow. The orifice cavitation number σ is defined as:

$$\sigma = \frac{2(P_{down} - P_v)}{\rho V^2} \qquad (4.6)$$

where P_{down} is the static pressure downstream the orifice and P_v is the local vapor pressure. The threshold is $\sigma \approx 0.3$ needed to start cavitation in micro-orifice liquid flows. The cavitation number should be higher than threshold.

The relevance of compressibility effects was checked with the Mach number defined as:

$$Ma = \frac{V}{a_S} \qquad (4.7)$$

where a_s is the liquid sound velocity. The Mach number should be below of 0,3 to neglect compressibility effects and assume incompressible flow conditions [8].17

The pressure differential flowmeters need constant flowrates, not pulsating flow. The flow is considered as not being pulsating when;

$$\frac{\Delta p'_{ms}}{\Delta p} \leq 0{,}1$$

Where

$\Delta p'$ is the fluctuating component of the differential pressure,

$\Delta p'_{ms}$ is the root mean square value of $\Delta p'$

$\Delta p'$ can only be measured accurately using a fast-response differential pressure sensor [ISO 5167-1:2003].18

4.3. Comparison of instantaneous and mean flow-rates (ISO 8316:1997)

It should be emphasized that only the mean value of flow-rate for the filling period is given by the volumetric method. Instantaneous values of flow-rate as obtained on another instrument or meter in the flow circuit may be compared with the mean flow-rate only if the flow is kept stable during the measurement interval, by a flow-stabilizing device, or if the instantaneous values are properly time-averaged during the whole filling period.

5. Flow Resistance (Hydrodynamic Resistance)

Flow resistance**,** also called hydrodynamic resistance or just microfluidic resistance, corresponds to the opposition that a fluidic element, like a pipe, offers to a flow through itself. Each element of a microfluidic circuit offers some resistance to the flow which is translated into a drop of pressure. The pressure drop according to the desired flow rate in the flow system can be calculated by using the Hagen-Poiseuille equation:

$$\Delta P = QR_H \tag{5.1}$$

Where ΔP is the pressure difference, or drop, between two points of the system, Q is the flow rate and R_H is the hydraulic resistance.

It can be demonstrated that the pressure drop associated with any section of microchannel only depends on the flow rate, the dimensions of the channel and the dynamic viscosity of the fluid itself. The flow resistor expressions for the most typical channel cross sections are as follows. These are, respectively: circle, rectangle and square shapes [3, 4]:

$$R_{Hc} = \frac{8\mu L}{\pi r^4} \qquad R_{H,rec} = \frac{12\mu L}{1-0{,}63\left(\frac{h}{w}\right)}\left(\frac{1}{h^3 w}\right) \qquad R_{H,sq} = \frac{12\mu L}{1-0{,}917\times 0{,}63}\left(\frac{1}{h^4}\right) \tag{5.2}$$

where:

r is the radius of the circle.

μ is the dynamic viscosity.

L, h, w the length, height and width of the channel.

The assumptions for this theoretical model are the following:

- Small Reynolds number,
- Incompressible fluid,
- Unidirectional flow,
- Steady flow along the channel.
- Small fluid mass per distance unit, so gravity is negligible.

6. Volume

6.1. Calculation of volume using the gravimetric method (ISO 4787:2021)

For the conversion of the balance reading of the mass m to volume *V* at the reference temperature, a correction for the liquid's density and air buoyancy is necessary. The calculation of the liquid volume at the reference temperature is given in Formula (6.1).

$$V_{ref} = (I_L - I_E) \times \frac{1}{\rho_W - \rho_A} \times \left(1 - \frac{\rho_A}{\rho_B}\right) \times \left[1 - \gamma\left(t_W - t_{ref}\right)\right] \qquad (6.1)$$

where

V_{ref} is the calculated volume at the reference temperature, in ml;

I_L is the balance reading of the weighing vessel after liquid delivery, in g;

I_E is the balance reading of the weighing vessel before liquid delivery, in g ($I_E = 0$ in case the balance was tared with the weighing vessel);

ρ_A is the density of air, in g/ml, see Formula (6.2) below;

ρ_B is the actual or assumed density of the weights used to calibrate the balance, in g/ml;

NOTE Stainless steel weights of density 8,0 g/ml are typically used for balance calibration.

γ is the coefficient of cubic thermal expansion of the material of which the volumetric instrument tested is made, in reciprocal degrees Celsius;

t_w is the temperature of the water used in the test, in degrees Celsius

t_{ref} is the reference temperature, in degrees Celsius

Formula (6.2) for air density can be used at temperatures between 15 °C and 27 °C, barometric pressure between 600 hPa and 1 100 hPa, and relative humidity between 20 % and 80 %.

$$\rho_A = \frac{1}{1000} \times \frac{0{,}34848 \times P - 0{,}009 \times h_r \times 10^{(0{,}061 \times t)}}{t + 273{,}15} \qquad (6.2)$$

where

ρ_A is the air density, in g/ml;

t is the ambient temperature, in °C;

P is the barometric pressure, in hPa;

h_r is the relative air humidity, in %.

The relative uncertainty of this formula is $2{,}4 \times 10^{-4}$. At other environmental conditions, Formula (6.2) shall be replaced with the current CIPM air density equation.

The density of pure water is normally calculated using formula given in the literature. Formula (6.3), as published by Tanaka, provides a good basis for standardization:

$$\rho_W = a_5 \times \left[1 - \frac{(t_W + a_1)^2 \times (t_W + a_2)}{a_3 \times (t_W + a_4)}\right] \qquad (6.3)$$

where

ρ_W is the density of water, in g/ml

t_W is the water temperature, in °C

a_1 = -3,983035 °C

a_2 = 301,797 °C

a_3 = 522528,9 $(°C)^2$

a_4 = 69,34881 °C

a_5 = 0,999974950 g/ml

Note: a5 is the maximum density value of SMOW water in one atmosphere (at 3.98 °C). Many users of water rely on tap water instead of SMOW. Thus, a_5 must be changed accordingly to reflect the density of the water used. Also, the correction due to air content in the water can be done according to the following formula described in [5]:

$$\Delta\rho = s_0 + s_1 t \quad \text{g/mL} \tag{6.4}$$

Where:

t = water temperature, in °C

s_0 = -4.612×10-6 g/mL

s_1 = 0.106×10-6 g/mL°C

The full equation of state for water provided by the International Association for Properties of the Water Substance (IAPWS) can also be used to determine the density of the used water and a formula based on this equation is given in [6]. This provides an alternative to the Tanaka formula and should be used at temperatures above 30 °C.

6.2. Regression analysis (ISO/DIS 23783-2:2021)

The Gravimetric Regression Method (GRM) is suitable for the measurement of very small liquid volumes, between 0,005 µl and 1 µl. The method is based on a gravimetric balance as primary measurement device.

This method is intended to be used for non-contact liquid delivery devices (e.g., dispensing valves, acoustic, or inkjet-type dispensing) that deliver the liquid volume as free flying droplet or jet to the balance receptacle.

The key difference to traditional gravimetric methods used for the measurement of larger volumes is the determination of the target volume: a series of balance readings is recorded over a period of time before and after the device under test has delivered the liquid to be measured into the receptacle on the balance. The measurement result of the delivered test liquid is then determined as the difference between two linear regression lines fitted to the recorded balance data before and after the liquid delivery. This method allows measurement of balance drift due to evaporation and other disturbances of the measurement (e.g., by vibrations during the data acquisition), so that these can be compensated for in the measurement calculation

6.3. Evaporation (ISO/DIS 23783-2:2021)

During method validation it shall be determined whether measurement results need to be corrected for evaporation. If evaporation needs to be taken into account, the effect shall be determined experimentally and compensated mathematically. The error due to evaporation shall also be reflected in the determination of the measuring system uncertainty, if reported.

6.4. Droplet size (ISO/DIS 23783-2:2021)

The droplet size can be determine by imaging liquid droplets in flight by a suitable digital optical setup, such as a calibrated high-speed camera or a stroboscopic imaging system. From the acquired grey-scale images of the droplet, the size and shape of the outline of the droplet is determined by conversion to a black and white image by the image processing algorithm described in G.6.4. The three-dimensional volume of the droplet is then reconstructed by rotating the two-dimensional projection extracted from the image around the axis defined by the flight path of the droplet, assuming rotational symmetry of the droplet shape.

7. References

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