FROM GLASS PIPETTES TO INTELLIGENT AUTOMATION: THE EVOLUTION OF LIQUID HANDLING TECHNOLOGIES

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Abstract

The precise manipulation of liquid volumes is a foundation stone of experimental integrity across the chemical and life sciences. This article covers the pipette's technological history from its primitive beginnings in industrial France in the eighteenth century to the modern era of intelligent automation and sonic dispensing. The shift from dangerous mouth pipetting to the mechanical revolution of air-displacement systems, the later incorporation of microprocessor control and the development of high-throughput robotic workstations are discussed in this study. This study highlights the ongoing importance of volumetric rigor in the pursuit of scientific reproducibility by connecting historical turning points with contemporary innovations like Acoustic Droplet Ejection (ADE) and AI-driven error correction.

Keywords: High-Throughput Screening, Laboratory Automation, Liquid Handling, Micropipette, Pipetting, Volumetric Analysis

1. Introduction

In the contemporary landscape of chemical and life sciences—including pharmacology, biochemistry and environmental monitoring—accurate measurement of liquid volumes is fundamental to experimental validity. The quantitative precision of liquid transfer directly determines the reliability, reproducibility, and comparability of experimental results. Consequently, precise volumetric measurement has become an indispensable component of modern laboratory practice.

Among the various instruments developed for this purpose, pipettes and burettes remain two of the most fundamental tools for precise liquid handling, particularly in titrimetric and solution-based analyses. Their ability to deliver accurately measured volumes has made them central to quantitative chemical experimentation and analytical procedures.

Pipetting, in particular, lies at the heart of laboratory science. Nearly every experiment in the life sciences—from classical titrations and biochemical assays to advanced techniques in genomics and molecular biology—requires precise measurement and transfer of liquids. For much of scientific history, however, liquid handling was labour-intensive, error-prone and sometimes hazardous. Early laboratory practices frequently relied on mouth pipetting and manually calibrated glassware, posing risks to both accuracy and user safety. The gradual transition from simple graduated glass devices to modern automated and digitally controlled liquid-handling systems reflects the broader technological evolution of laboratory science and the growing demand for precision and efficiency. Each technological innovation has attempted to increase measurement precision, experimental throughput and operator safety, thereby enabling new experimental possibilities and supporting the rapid expansion of fields such as molecular biology, pharmaceutical research and diagnostic science.

This review examines the historical origin and technological evolution of pipettes, highlighting key innovations that have shaped their development. Particular emphasis is placed on improvements in precision, ergonomics and safety, as well as on the role of this instrument in the advancement of analytical chemistry and laboratory pedagogy. To fully appreciate the significance of modern volumetric instruments, it is useful to consider how scientists initially approached the problem of measuring and transferring liquids. Long before the development of standardized laboratory glassware and calibrated devices, early experimenters relied on simple containers, rudimentary measuring techniques and empirical observations to estimate liquid quantities. Although these early practices were often imprecise, they laid the conceptual foundation for later developments in volumetric analysis. The following section therefore, explores the earliest methods of liquid measurement and the gradual emergence of quantitative approaches that ultimately led to the development of pipettes, burettes and other standardized volumetric instruments.

2. Early Methods of Liquid Measurement

Before the development of standardized laboratory glassware, liquid measurement relied on rudimentary and largely qualitative approaches. One of the earliest scientific principles applied to volume determination was the displacement method described by **Archimedes** around 250 BCE. This method was primarily used to determine the volume of irregularly shaped objects rather than for precise liquid transfer.

In ancient civilizations—including Rome, Greece and Babylon—measurement systems were designed to facilitate trade in commodities like wine and grain. The Roman amphora quadrantal and its subdivision, the sextarius (~546 mL), served as standardized units; however, these vessels were designed "to contain" rather than "to deliver". The intrinsic porosity of fired clay and inconsistencies in vessel geometry limited their suitability for reproducible scientific measurements.

Prior to the development of laboratory glassware, apothecaries and early experimentalists relied on simple containers such as cups, spoons, vials and graduated vessels. These methods were largely qualitative and lacked reproducibility, making precise chemical analysis difficult. The transition toward precise volumetric measurement occurred during the late eighteenth century with the development of volumetric analysis (titrimetry). Particularly, the French textile industry needed quick and accurate ways to evaluate the effectiveness of bleaching products based on chlorine. Traditional gravimetric procedures, which involved the laborious process of weighing samples and reagents, were too slow for the fast-paced demands of industrial quality control. This demand stimulated the development of dedicated volumetric instruments. In 1795, the French chemist François Descroizilles introduced one of the first precise liquid dispensers: he described a graduated cylinder for titrations "berrholli-mètre" and an "alcalimètre" for small volumes (SLAS, 2009). Gay-Lussac later coined the terms burette and pipette in 1824 during his work on the standardization of indigo solutions (SLAS, 2009). Throughout the 19th century, improvements – such as Mohr's self-feeding burette with a clamp and tip (1845) – refined volumetric measurement, but most pipetting remained manual and prone to error. Gay-Lussac's work formalized titrimetry as a quantitative analytical method and laid the foundation for modern volumetric liquid-handling tools.

The eighteenth century saw tremendous developments in volumetric glassware as analytical chemistry advanced and the necessity for accurate and consistent liquid measurements was felt. Improvements in glassblowing and the standardization of lab equipment allowed for the creation of specialized instruments like as burettes, pipettes and volumetric flasks.

One of the earliest forms of the pipette was the volumetric or transfer pipette, consisting of a narrow glass tube with a central bulb and a single calibration mark indicating the volume to be delivered. Further, the graduated pipette was developed to allow the measurement of variable liquid volumes. These pipettes contained a series of graduation marks along the length of the tube, enabling the user to deliver different volumes as required. Two principal forms eventually became common: The Mohr pipette, in which the graduations terminate before the tip and the serological pipette, where graduations extend to the tip and the final drop is expelled. These designs improved versatility in routine laboratory work while maintaining acceptable levels of accuracy.

3. Advanced and Specialized Pipettes

Despite their high accuracy, classical glass pipettes have several limitations such as fragility, fixed-volume calibration and heavy reliance on operator technique. For over 150 years, from the early 1800s until the mid-20th century, the standard method of liquid aspiration involved mouth pipetting, in which researchers drew liquid directly into the pipette by suction. This practice was not merely imprecise; it was a significant vector for laboratory-acquired infections and chemical poisoning. By the 1970s, evidence suggested that 40% of workplace infections were directly linked to mouth pipetting (Phillips & Bailey, 1966). Routine exposure to toxic chemicals, radioactive isotopes and pathogenic microorganisms ultimately led institutions such as the National Institutes of Health to formally prohibit the practice in 1984. The combination of safety risks, increasing experimental complexity and the need for reproducible, variable-volume measurement created strong pressure for innovation. These concerns directly motivated the development of mechanically actuated, air-displacement micropipettes—ushering in a new era of safer, more precise and ergonomically controlled liquid handling

The first meaningful advance in pipetting safety emerged in the mid-19th century with Louis Pasteur's introduction of a glass pipette fitted with a rubber bulb. These Pasteur pipettes (now commonly referred to as droppers) eliminated direct oral contact and reduced the risk of accidental ingestion. However, they were intended primarily for transfer rather than calibrated volumetric measurement and therefore offered limited quantitative precision.

A more mechanically sophisticated development followed with the Overlach syringe (1889), which incorporated a piston–cylinder mechanism to aspirate and dispense liquid. Although early designs employed asbestos-based pistons that degraded over time, the fundamental principle—a movable piston displacing a defined volume within a sealed cylinder—became the conceptual and mechanical foundation of the modern air-displacement micropipette.

The modern era of liquid handling truly commenced in 1957 with the invention of the first piston-driven micropipette with a replaceable plastic tip by Heinrich Schnitger. In the realm of modern biochemistry and biomedical research, the air-displacement micropipette has become the dominant tool for handling microliter volumes. These devices operate using a piston-driven vacuum mechanism: as the piston moves upward, a vacuum is created, drawing liquid into a disposable tip. Depressing the piston expels the liquid. The use of a disposable plastic tip eliminated cross-contamination between samples and simplified cleaning, while the air buffer prevented direct contact between the liquid and the piston mechanism (Klingenberg, 2005). In short Schnitger's "Marburg pipette" was the first piston-driven, tip-mounted micropipette. The invention immediately addressed safety and accuracy issues.

Commercialization soon followed when the Marburg pipette design was licensed to Eppendorf in Hamburg, leading to the launch of the first commercial micropipette system in 1961. Eppendorf introduced the first single-channel adjustable-volume micropipette, known as the Eppendorf Marburg model. The introduction of affordable, standardized single-use disposable polypropylene tips made these pipettes practical and widely accessible. However, for viscous or volatile liquids where an air cushion would lead to inaccuracies, positive-displacement pipettes are used, where the piston comes into direct contact with the liquid.

In 1969, Osmo Suovaniemi, a Finnish physician and entrepreneur, filed patents describing the first adjustable-volume micropipette featuring user-selectable volume settings and disposable plastic tips to minimize cross-contamination. This innovation markedly improved accuracy and precision compared with manual glass pipetting methods. Building on this concept, he subsequently developed the first multichannel pipettes. In 1973, through Labsystems (now part of Thermo Fisher Scientific), Suovaniemi patented and commercialized the Finnpipette, available in 4-, 8- and 12-channel formats (Metacelsus, 2024). These developments established variable-volume single- and multichannel micropipettes as global laboratory standards and marked a decisive transition from fixed-volume glass instruments to precision, user-adjustable air-displacement systems. In 1972, Warren Gilson and Henry Lardy at the University of Wisconsin–Madison developed a screw-mechanism pipette with a digital readout, leading to the patent of the Gilson Pipetman (1974). Gilson's design was the first "recognizably modern micropipette" with a true variable-volume setting (Miller, 2022). The commercial success and widespread adoption of adjustable micropipettes fundamentally changed laboratory practice across multiple disciplines.

4. The Transition to Microprocessor Control: The Electronic Pipette (1970s-1990s)

One of the most significant advances is the development of **electronic pipettes. Electronic pipettes incorporate** microprocessor-controlled systems that utilize stepper motors for precise plunger movement, allowing for controlled aspiration and dispensing of liquids. One of the earliest documented electronic pipetting systems was the mechanized, direct digital-control pipette developed by Nishi in 1972 for ultramicro chemical analyses (Nishi, 1972)

By the 1980s, portable, hand-held electronic pipettes had begun to emerge. The year 1984 is widely recognized as an important moment in electronic pipetting, when Magnussen and colleagues at Rainin Instrument (now part of Mettler Toledo) filed a patent for the world's first stepper-motor-driven electronic pipette, known as the Electronic Digital Pipette (EDP) (Magnussen, Jr et al., 1984). The patent described a self-contained automated device designed for pipetting and titration. Its key innovation included

- Integration of a motorized piston-drive system, microprocessor control and rechargeable battery into a compact handheld device

- Microprocessor-controlled programming of aspiration and dispensing parameters, ensuring controlled motor speed and optimal handling of liquids with varying viscosities to prevent air bubbles or splashing

- Multidispensing (repeater) function and protocol storage capability, allowing a large volume to be aspirated once and dispensed into multiple smaller aliquots, thereby increasing throughput and ensuring reproducibility

- Retention of manual pipette ergonomics while enabling programmable electronic operation

- Replacement of the high-force manual plunger with a low-pressure electronic trigger, minimizing strain and preventing musculoskeletal disorders among laboratory professionals

Biohit (Finland) commercialized one of the first successful electronic pipettes, establishing the company as a leader in this sector (Kontinen, 2014). Other companies (e.g. Titramat, Eppendorf) introduced competing models. Over time, additional innovations appeared, including hybrid pipettes that combined digital displays with manual piston mechanisms, as well as ultra-lightweight designs—for example, Gilson's Pipetman L series introduced in the 2000s. Electronic pipettes offered improved accuracy and precision by eliminating manual plunger depression and providing consistent aspiration and dispensing speeds.

Table 1. Milestones in Pipette History, micropipette to electronic pipette (1957–1984)

Year	Inventors	Key Innovation
1957	Heinrich Schnitger	Air-displacement micropipette (prototype)
1961	Heinrich Netheler (Eppendorf)	Commercial micropipette system
1971	Gilson & Lardy	Adjustable-volume pipette mechanism
1973	Osmo Suovaniemi	Multichannel pipette (4–12 tips)
1984	K. Magnussen et al. (Rainin)	Motorized electronic pipette patent

5. Automation and Robotic Integration (1980s-2000s)

As the scale of biological research expanded into genomics and drug discovery in the late 20th century, even the most efficient handheld pipetting could not meet the demands for high throughput and precision. The challenge led to the development of Automated Liquid Handling Systems (ALHS), commonly referred to as pipetting robots or workstations, which were designed to automate pipetting, transferring and dispensing samples in nanoliter to mililiter volumes. These systems range from compact benchtop units to massive, integrated workstations capable of processing hundreds of thousands of samples per day.

Early automation was semi-robotic, focusing on replacing the repetitive thumb action of pipetting with motorized syringe pumps. The Hamilton Company, founded by Clark Hamilton to produce syringes for gas chromatography, introduced the Digital Dilutor in 1971('Hamilton Company', 1975). This semi-automated, DC motor-driven device used two calibrated syringes as pistons, allowing for highly accurate dilution sequences otherwise impossible to achieve manually. Hamilton

and Tecan AG collaborated in the late 1970s on the AMICA system, a stopped-flow fluidics platform with microprocessor control (SLAS, 2009). Further, Hamilton 2000 and the Tecan Sampler 500 series were developed, featuring single pivotic arms moving along X, Y and Z axes. These platforms were capable of aspirating and dispensing from microplates using washable steel needles connected to syringe pumps.

By the early 1980s, liquid-handling automation evolved toward multi-arm and multi-channel architectures. Zymark's Z510 (1982) used a 3-axis robotic stage with syringe pumps, as part of the Zymate robotic lab system(SLAS, 2009). In 1986, Beckman Coulter launched the BioMek series, among the first robotic platforms to integrate pipetting with broader laboratory functions. The introduction of the Quadra96 by Tomtec in 1990 marked a significant breakthrough, as the first 96-channel pipetting head enabled true parallel liquid handling i.e processing an entire microplate at once. During the 1990s and 2000s, companies such as Beckman Coulter, Tecan, and Hamilton Company developed advanced automated liquid handling platforms (e.g., Biomek series, Freedom EVO, Microlab STAR). These systems featured interchangeable pipetting heads (8-, 96-, or 384-channel), plate stackers, integrated incubators, and sophisticated control software. Thus, fully automated execution of complex workflows—such as PCR setup and plate replication was possible without human intervention.

Key milestones in this evolution include

- Standardization of microplate architecture – 96, 384, 1536 wells, led to the development of high-throughput instrumentation designed for the simultaneous manipulation of multiple volumes."

- The emergence of High-Throughput Screening (HTS) fundamentally transformed experimental workflows by integrating robotic platforms to rapidly evaluate vast chemical libraries against biological targets. Research that previously required years of manual pipetting could now be completed in weeks or even days, significantly accelerating drug discovery and large-scale projects such as the Human Genome Project.

These early innovations established the foundational architecture for modern liquid-handling robots used in automated laboratories.

Table 2: Evolution of Major Automated Liquid Handling Platforms (1980–2025)

Year	Notable Platform	Key Innovation
1986	Beckman Biomek 1000	Modular liquid handling architecture
1990	Tomtec QUADRA96	First 96-channel simultaneous dispenser
2000s	Hamilton Microlab STAR	Air-displacement robotics with CO-RE technology
2010s	Labcyte Echo	Acoustic (tip-less) nanoliter dispensing
2017	Eppendorf VisioNize	IoT-enabled device and data management
2023	DISPENDIX I.DOT	Non-contact, pressure-driven microfluidic dispensing

6. Emerging Technologies: ADE, IoT and the Future of Nano-dispensing (2010s–2020s)

6.1 Intelligent Pipetting Systems

The rise of laboratory automation created the need for new verification protocols. Unlike manual pipetting, where the operator can visually detect errors, automated systems require integrated sensors and monitoring mechanisms to ensure accuracy and reliability. Consequently, recent developments have focused on the design of intelligent pipetting systems with built-in verification capabilities.

Bheemavarapu et al. developed an intelligent pipetting system incorporating differential pressure sensor to automatically detect common errors like clogs, bubbles, or missing tips. These platforms used real-time feedback control to adjust for variations in liquid properties and environmental conditions like temperature, humidity and atmospheric pressure (Bheemavarapu et al., 2018)

6.2 Acoustic Droplet Ejection and Tip-Free Dispensing

In the 2000s, tip-free liquid dispensing technologies emerged to enable ultra-low-volume handling and reduce contamination. The most prominent example is Acoustic Droplet Ejection (ADE), pioneered by Labcyte. ADE utilizes focused ultrasonic energy to move liquids and thus eliminates the need for a physical pipette tip.

- A transducer at the bottom of a source well emits focused sound waves into the liquid. When the acoustic pressure at the surface exceeds the surface tension of the fluid, a precise droplet (typically 2.5 to 25 nL) is "ejected" upward into an inverted destination plate.

- This contactless method minimizes cross-contamination, reduces plastic waste and supports highly miniaturized assays with significant reagent savings.

Other approaches, such as pressure-driven and microfluidic dispensers (e.g., DISPENDIX I.DOT), also enable on-demand nanoliter dispensing through nozzles or microfluidic systems, reflecting a growing trend toward sustainable, non-contact liquid-handling technologies

6.3 Smart / IoT/ AI Pipettes

In recent years, pipettes and liquid-handling workstations have become integral components of the smart laboratory ecosystem through the integration of digital connectivity and advanced automation.

Modern electronic pipettes incorporate wireless technologies such as Bluetooth, Wi-Fi and RFID for real-time data logging, calibration tracking and integration with electronic lab notebooks and cloud-based platforms. During the COVID-19 pandemic, several key technologies developed towards cloud-controlled liquid handlers which enabled researchers to design and monitor experiments without being physically present (Zucchelli et al., 2021). For example, platforms like Andrew Alliance's OneLab and Eppendorf's VisioNize platform allow remote monitoring and scheduling of pipetting tasks via the cloud(*VisioNize® Lab Suite*, 2022). These systems enable remote monitoring, automated scheduling and improved experimental traceability.

AI and machine learning Machine Learning (ML) algorithms have been integrated into electronic controllers to monitor droplet shape and velocity and piston resistance in real-time. If the system detects a change in viscosity (e.g., switching from an aqueous buffer to a glycerol-rich enzyme solution), the AI automatically recalibrates the motor speed to maintain volumetric accuracy without manual intervention. "Virtual laboratory assistants" are on the horizon: software agents that convert a researcher's protocol description into robot commands and even order reagents when stocks run low. Sensor-equipped pipettes are in development to measure tip attachment quality or liquid surface detection, further automating quality control.

6.4 Nanopipetting and Sub-microliter Precision

For ultra-low-volume applications, **high-resolution pipetting mechanisms** have been developed. Adjustable deamplification technologies enable precise control over minute volume changes, thereby extending the lower limits of conventional pipetting systems (Beroz et al., 2017). Deamplification technology operates on the principle that a relatively large movement of the control mechanism, such as a plunger or dial, is converted into an extremely small piston displacement, thereby minimizing the influence of user input on volume delivery. Furthermore, innovations such as **ink-jet–based nano-pipettors** achieve exceptional performance at microliter and sub-microliter scales, with reported coefficients of variation as low as 1–2% at 1 µL (Astle, 2005). These pipettes eject droplets of liquid using controlled thermal or piezoelectric pulses, similar to the operating principle of ink-jet printers. This level of precision is critical for the development of targeted drug delivery systems and high-resolution diagnostic sensors.

7. Current Commercial Landscape

The current pipette market is dominated by several established manufacturers, each offering comprehensive product lines spanning manual, electronic and automated systems.

Eppendorf remains one of the most recognized brands, recognized for precise, durable and ergonomic manual and electronic pipettes. Eppendorf's electronic pipettes feature programmable protocols, rechargeable batteries and intuitive interfaces.

Gilson is renowned for the industry-standard Pipetman manual series. Their electronic pipettes, including the programmable Pipetman Concept, offer advanced protocol programming and data management .

Rainin (now part of Mettler Toledo) produces both manual and electronic pipettes, specializing in ergonomic design to reduce repetitive strain. Their electronic pipettes feature microprocessor control and multiple pipetting modes.

Sartorius (formerly Biohit), established in 1980 is a pioneer in electronic pipetting. They offer a comprehensive range of liquid handling products, including electronic and mechanical pipettes, disposable tips and pipette maintenance and calibration services.

Beckman Coulter focuses primarily on automated liquid handling workstations, with its Biomek series representing a leading platform for high-throughput applications in drug discovery and genomics.

Tecan Group: A historical leader in modular automation. Platforms like Freedom EVO and Fluent offer hybrid liquid handling arms that can switch between air and liquid displacement.

8. Future Direction and Emerging Technologies in Pipetting

The future of pipetting and liquid handling is moving toward greater automation, digital connectivity and intelligent laboratory systems. Emerging "smart pipettes" equipped with sensors, wireless connectivity and integration with Laboratory Information Management Systems (LIMS) enable real-time monitoring, automatic data logging and improved quality control.

Artificial intelligence and machine learning are increasingly used to optimize liquid handling and error detection, predict maintenance needs. These support the development of autonomous "self-driving" laboratories capable of designing and executing experiments with minimal human intervention. Some companies are exploring agentic/AI systems that can autonomously design and execute pipetting protocols based on user goals (analogous to autonomous vehicles).

At the same time, new technologies such as acoustic droplet ejection and microfluidic platforms are enabling ultra-low-volume, non-contact dispensing and even replacing traditional pipetting in certain applications.

Open-source and low-cost automation platforms are expanding access to laboratory liquid-handling technologies. Inspired by systems such as Opentrons, researchers have developed open-source smart and digital pipettes to support affordable automation and self-driving laboratories. These initiatives, together with cloud-connected instruments, enable broader access to automation, remote monitoring and workflow management while fostering innovation through community collaboration.

Sustainability and ergonomics are also becoming key considerations, driving innovations such as reusable or biodegradable tips, reduced plastic waste and sensor-enabled pipettes that help prevent user strain.

Together, these developments point toward highly integrated, intelligent and environmentally conscious liquid-handling systems in future laboratories.

9. Conclusion

The evolution of liquid handling—from the handcrafted glassware of the 19th century to today's non-contact acoustic dispensing technologies—reflects a continuous pursuit for precise measurement. The early effort by François Descroizilles and Joseph Louis Gay-Lussac to standardize industrial chemistry has evolved into a highly sophisticated, digitally integrated framework that supports modern laboratory practice.

The shift from the manual skill of the chemist to the algorithm-driven accuracy of automated workstations has significantly reduced human-induced variability, thereby enhancing experimental reproducibility. As research advances into nanoliter-scale volumes and AI-enabled workflows, the fundamental principles of volumetric measurement established over two centuries ago continue to serve as the foundation of scientific progress. Ultimately, this technological progression ensures that even as sample sizes decrease and data complexity increases, the reliability and precision of experimental outcomes are maintained.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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