

## A REVIEW ON AUTOMATED LIQUID HANDLING SYSTEM FOR LABORATORY

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### ABSTRACT

In laboratories, liquid handling is a crucial procedure that involves automatically transferring precise amounts of liquids for a variety of tasks, including pipetting, dilution, mixing, and sample preparation. By effectively improving the accuracy, precision, and reproducibility of experimental workflows, automated liquid handling systems (ALHS) help reduce the errors, complications, and challenges associated with manual methods of liquid handling. They have revolutionized the life sciences by supporting research in numerous fields. Automated tools are quickly replacing outdated manual technology. These laboratory settings are expensive and complex. Accessing such technologies is difficult, particularly in emerging or impoverished nations. Robotic equipment for liquid handling devices can help in a variety of fields and carry out several duties. We believe that our labs will be equipped with cutting-

edge robotic technology in the upcoming years, revolutionizing the scientific landscape.

**KEYWORDS:** Laboratories, Liquid Handling, Robotic Equipment.

### INTRODUCTION

Molecular biology, drug development, genomics, proteomics, and other life sciences researchers have benefited from the development of automated liquid handling systems (ALHS) by improving the efficiency, accuracy, and reproducibility of experimental workflows, cutting down on cost, time, and error, and resolving a number of significant

bottlenecks related to manual liquid handling devices.<sup>[1]</sup> Processes in biotechnology and the life sciences depend on effective liquid handling methods. The highest level of precision must be maintained across the many stages of the workflow in drug discovery, proteomics, genomics, and diagnostics. False positives, poor clinical assays, and product loss in medication manufacturing can result from irregularities in precision and accuracy.<sup>[2]</sup> Nowadays, tools like mass spectrometry, acoustic droplet ejection, lateral flow assays (LFA), NMR spectrometry, filter-aided sample preparation (FASP), and For improved performance, ALHS can be combined with electro bioluminescence. Additionally, new tools and methods are appearing that improve experimental procedures even more. A survey estimates that the global market for automated liquid handling was worth 1,181.82 million USD in 2022 and is expected to grow to a size of about USD 2,580.45 million by 2032. The market for automated liquid handling is expected to reach USD 6.34 billion by 2035, up from USD 2.82 billion in 2023, according to another report. According to these reports, automated liquid handling is in high demand and will only grow in popularity.<sup>[1]</sup>

Modern industrial sectors employ automated liquid filling systems to save time, minimize liquid waste, obtain an identical amount of fluid for each filling process, and preserve liquid quality. Changes in the filling system's specifications, including the kind of liquid, container type, and any further setup required, are easily monitored and controlled.<sup>[3]</sup> Laboratory discovery of compounds and medications has increased at a never before seen pace since the advent of ALHS in the study of proteins, genes, drugs, and pharmaceutical companies. 19,116 genes in humans code for proteins. There are species with more than that. The structure, function, quantity, and identification of proteins in an organism must therefore be ascertained through a number of experiments.<sup>[1]</sup> A vital component of many life science investigations, especially those involving genomic and proteomic analysis, is liquid handling. Protein or DNA solution samples must be dispensed into microwells or onto substrates for this type of study; further synthesis and analysis procedures frequently call for the dispensing of additional solutions.<sup>[4]</sup> Applications in genetics, including DNA extraction, purification, isolation, sequencing, genotyping, and bio-active array preparation, are carried out by automated liquid handling systems. Along with other proteomics tasks, ALHS also does protein purification, crystallization, expression, and other processes.<sup>[1]</sup>

In the biological sciences, laboratory automation is nothing new. Liquid-handling robots have been employed for years by major pharmaceutical companies for high-throughput drug

discovery and development. Robots have made it possible to quickly screen millions of molecules in order to identify a single potential medication. Robots are capable of precisely dispensing tiny amounts of extremely valuable and delicate bio-active materials.<sup>[5]</sup>

In all sectors of the biotechnology and pharmaceutical industries, research facilities, diagnostic and hospital labs, academic institutions, and others, liquid handling is a crucial procedure. Drug development, proteomics, clinical diagnostics, genomics, and many more areas are among the numerous sectors in which laboratories might employ the systems. As the number of tests conducted for target screening and other research purposes has grown rapidly, there is a greater need for low-volume, high-throughput liquid handling technology. The majority of large and medium-sized life sciences research labs worldwide now depend on ALH systems for workflow.<sup>[7]</sup>

The use of these devices in routine laboratory experiments has grown in popularity due to recent developments in liquid handling lab automation<sup>1</sup>. Along with making lab automation liquid handling devices easier for non-experts to use, significant advancements in accuracy and precision have broadened their application. Scientific workflows have changed as a result of numerous innovations that allow scientists to conduct high throughput experiments without sacrificing accuracy or precision. They can also better utilize their time by concentrating on intricate tasks and analyses rather than time-consuming procedures that are prone to human error.<sup>[8]</sup>

## ABOUT LIQUID HANDLING

Liquid handling, despite its seeming simplicity, is crucial for labs worldwide. In the majority of tests, innumerable, minuscule liquid samples are examined for specific characteristics. The lab can still use samples less than 1 micro liter ( $\mu\text{L}$ ) to screen for illnesses, detect contaminants, and multiply DNA for additional testing. But for a lab, handling liquids might take a lot of time. Although a 1  $\mu\text{L}$  sample would be a practical way to use a liquid for a single test, testing apparatus typically has space for dozens or even hundreds of samples, each of which requires a liquid transfer. In order to accomplish their liquid handling objectives, labs frequently combine automated and manual pipetting.<sup>[9]</sup>

## CONTENT

Various Manual Liquid Handling Techniques

**1. Pipetting-** In many laboratory settings, including academic, clinical, industrial, and

regulatory ones, handling liquids is a widespread practice. In most labs where handling micro- to milliliters of liquids is necessary, micro-pipettes are an essential tool. Most people are aware that there are differences in pipetting. Guides showing proper pipetting procedures and suggestions for routine inspections and calibration have been put out by pipette manufacturers. In order to obtain laboratory certification in clinical, industrial, and regulatory settings, conditions must be met for accuracy and precision, and guidelines are in place to guarantee that the equipment is maintained and satisfies these requirements.<sup>[10]</sup> Although the hardware is covered by these standards, other possible causes of variation include the operations, consumables, technique, and environment. All of these need to be closely watched in order to guarantee good manufacturing practice (GMP) and good laboratory practice (GLP). Assessments of pipetting precision are, in fact, frequently carried out in industrial settings to guarantee operator proficiency. Academic laboratories, on the other hand, have different laboratory procedures and less strict criteria. However, scholarly research has made a substantial contribution to the fields of medicine development and diagnostics as well as non-healthcare industries including food, gasoline, and other consumer goods. The development of research skills, such as pipetting, begins in the classroom, and comprehension of the method and the need for accuracy and precision should start early as well.<sup>[10]</sup>

**2. Dilutions-** Dilution is the process of lowering the concentration of another solution by combining it with a solvent. Laboratory techniques include manual dilution. Achieving the appropriate concentrations in stock solutions and preparing samples for numerous tests and investigations are two uses for this liquid handling technique. A few of the many vital purposes of dilution include putting target analytes into the linear assay detection range, lowering sample matrix effects, and mixing samples with particular reagents at particular dilution ratios. Pipetting, either automated or manual, is used to process samples in traditional laboratory settings.

The availability of high-quality diagnostic tests is constrained when dealing with low resources since there is a lack of appropriately educated individuals and laboratory equipment. Manual pipetting and other manual dilution techniques use portable pipettes to measure and move the liquids. To perform accurately, this calls for staff who are trained and skilled. Manual dilution increases the likelihood of inaccuracies in the results. We need qualified staff and labs with the right tools for a high-quality diagnosis, but in locations

across the world without these resources, the diagnosis is more likely to be inaccurate and prone to mistakes. Manual pipetting and other dilution techniques are preferable in locations without well furnished labs. These techniques are used manually to measure and dilute liquids.<sup>[11]</sup>

**3. Mixing**-Mixing is a very important step in liquid handling to make sure that all of the components are evenly distributed throughout the sample or solution. For the preparation of samples, tests, and reactions, homogeneous liquid mixing is crucial. The three techniques of mixing are automatic mixing, vortexing, and manual stirring. Manual mixing procedures aren't the best when quality assurance is taken into consideration because they raise the possibility of errors.<sup>[11]</sup>

### VOLUMETRIC INSTRUMENTS GLASS/PLASTICS

A common procedure in the laboratory is the volumetric measuring of liquids. Volumetric instruments, including bulb pipettes, graduated pipettes, graduated cylinders, burettes, and volumetric flasks, are hence common equipment. They might be composed of plastic or glass. Volumetric instruments come in a variety of quality levels from suppliers. Volumetric instruments do not include graduated beakers, Erlenmeyer flasks, dropping funnels, and similar devices. The scale simply acts as an approximate guide, and they are not exactly calibrated. Here are some examples of BRAND's volumetric instruments.<sup>[12]</sup>

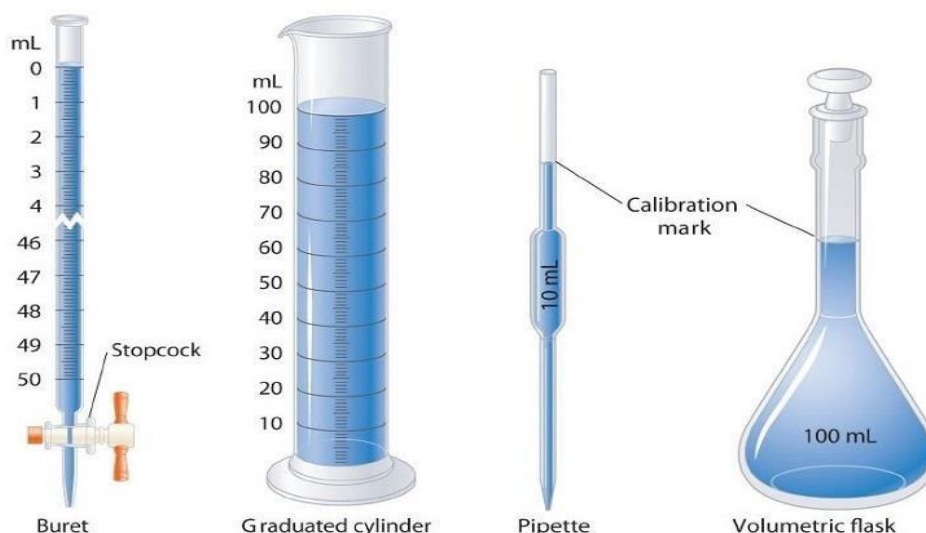


Fig. No.1.

### LIQUID HANDLING INSTRUMENTS

New tools are continuously being created, such as those for dispensing, pipetting, and

titrating, to suit the ever-increasing demands on volumetric measuring in the lab, such as testing in series. Typically, the functional principles of instruments created by many manufacturers for a given purpose are rather similar. However, when building details and design are the main focus, significant variances become obvious. This assortment of BRAND's liquid handling equipment demonstrates the variety of instruments that are available.<sup>[12]</sup>



1. Bottle top burette    2. Bottle top dispenser    3. Micro pipette

**Fig. No.2**

## **LIQUID PROPERTIES**

The range of liquids examined in laboratories is as diverse as the industries in which they are used, ranging from petroleum that flows quickly to sticky honey. Hand pipettors or Hamilton automated liquid handlers can be used to move these different liquid kinds, depending on what the lab needs to test. The type of liquid and how it behaves in a specific environment must be understood for liquid transfers to be successful. To choose the best course of action for each liquid, a lab tech can rely on expertise and intuition. In order to ensure that the liquid dispenses fully, the lab technician learns how to keep the tip in the proper position to avoid contamination between samples, where to place the tip to ensure that there are no bubbles, and how long to hold the tip.

A liquid handler that is automated needs to be fully informed about the liquid beforehand, whereas humans may easily evaluate its characteristics and adjust accordingly. The automated liquid handler receives information about liquid handling from the attributes in this area, and this information is crucial to a successful transfer. Environmental factors including temperature, humidity, and atmospheric pressure all have an impact on the characteristics of liquids to some extent. In the sections that follow, these conditions and their effects are explained.<sup>[13]</sup>

1. Viscosity

2. Density
3. Adhesion / Cohesion
4. Capillary Action
5. Surface Tension
6. Contact Angle
7. Vapor Pressure
8. Environmental Influences

### 1. Viscosity

Liquids with a high viscosity flow thicker and are less fluid. Glycerin and honey are two examples of liquids with a high viscosity.

Liquids with low viscosity flow more easily and are more fluid. Water and petroleum are two examples of liquids with low viscosity.

#### ✓ Elevated Viscosity Fluid

Lower the flow rate. Inaccurate volumes can arise from aspirating too quickly because suction in the tip keeps the fluid from getting there.

Switch to the surface dispense mode. High viscosity liquids are less effective when dispensed by jet.

#### ✓ Minimal Viscosity Fluid

Employ a greater flow rate. The objective is to move the liquid as quickly and efficiently as possible into the tip. Since low viscosity liquids don't struggle to get to the tip, the flow rate can be increased.

### 2. Density

The amount of space that a substance can fill is measured by its density. The density of a material creates the appearance of either lightness or weight. Temperature and atmospheric pressure have an impact on density.

Ranges of Densities -To illustrate the range, the densities of several liquids and solids are displayed below(in g/cm<sup>3</sup>).

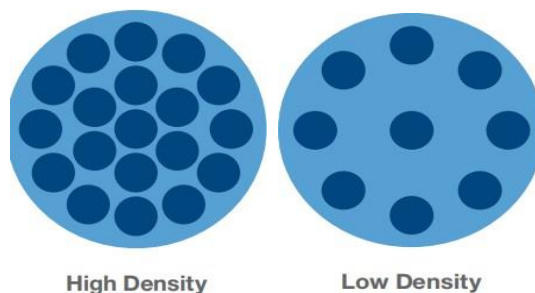


Fig No. 3.

### 3. Cohesion and adhesion

- There are two ways to characterize a liquid's stickiness: adhesion and cohesion. High concentrations of one or both can have distinct effects on the transport of liquids.

Why It's Vital ?

Cohesion and adhesion have quite distinct effects on how a liquid moves. Two sample liquids and instructions for communicating their properties to an automated liquid handler are displayed in the spectrum below.

- Liquid with High Adhesion

Raise the blowout volume. To remove a sticky substance off the tip, more force is required.

- Liquid with Low Adhesion

Reduce the volume of the blowout. Less force is required to remove the liquid from the tip because it doesn't fight being taken out.

- Liquid with Low Cohesion

To prevent drips, increase the air transfer volume. The liquid has a larger air buffer inside the tip during transport thanks to the higher air transport capacity.

- Liquid with High Cohesion

Reduce the volume being transported by air. It takes less force to keep the liquid in the tip because it wants to adhere to itself.

Perhaps the blowout volume needs to be increased.

### 4. Capillary action

Capillary action is a liquid's propensity to defy atmospheric pressure and gravity. It is actually possible for small amounts of liquids with high capillary action to climb the tip. Capillary action happens when a liquid's cohesiveness and adhesion combine to push the liquid higher. Vapor pressure and other environmental factors are among the other characteristics that can affect capillary action.

Larger amounts of any liquid, including those with little capillary action, are often pulled downward by atmospheric pressure and gravity.

The reason It's crucial

Capillary action has extremely particular effects on how a liquid is transported. The spectrum that follows provides two liquid examples along with instructions on how to communicate the properties to the automated liquid handler.

➤ A liquid with high capillary action

Take cautious when using low volumes. The impact of capillary action can be greater, particularly when using 10 or 50  $\mu\text{L}$  tips. One may aspirate more fluids than desired.

➤ A liquid with low capillary action

There is nothing to alter. There is no need to account for this element further because the liquid has no tendency to climb the tip.

## 5. Surface Tension

The elastic property of liquids known as surface tension causes them to gain the least amount of surface area. Surface tension has an impact on how well the molecules at the liquid's surface adhere to one another and to the tip walls when handling liquids.

A higher value indicates a higher surface tension and a greater likelihood of a strong cohesive layer forming at the liquid's surface.

Surface tension affects a liquid's transport in very particular ways. The spectrum that follows provides two liquid examples along with instructions on how to communicate the properties to an automated liquid handler.

➤ High Tension at the Surface A liquid

Reduce the air transport volume. A significant air buffer is not necessary to hold liquids with high surface tension in place; instead, the liquid remains in the tip.

Break the connection between the liquid in the tube or well and the tip by using a high exchange speed.

The liquid can be extracted from the tip more readily if you use side touch or reduce the distance between the tip's end and the labware.

➤ Low Liquid Surface Tension

Expand the volume of air transportation. Increasing the transport capacity creates a larger air buffer in the tip since the liquid wants to exit it.

Reduce the settling time to avoid droplet formation and to reduce the amount of time the tip is in contact with the liquid.

## 6. Contact Angle

The angle that the liquid creates with the labware's surface is known as the contact angle. Low volumes are more difficult to transfer at low contact angles, such as  $0^\circ$ , since the liquid spreads out very thinly. Although a high contact angle, such as  $180^\circ$ , makes the liquid stand taller in smaller volumes, it can also make aspiration and dispense challenging since the cohesiveness may be repellent. The kind of surface on which the liquid rests has an impact on the contact angle as well. The following describes the various surfaces.

- The contact angle will be small ( $0^\circ$ ) on a hydrophilic surface.
- The contact angle will be high ( $90^\circ$ ) on a hydrophobic surface.
- A contact angle greater than  $160^\circ$  will occur on a very hydrophobic surface. A range of contact angles, from  $0^\circ$  to  $180^\circ$ , are depicted in the picture below.

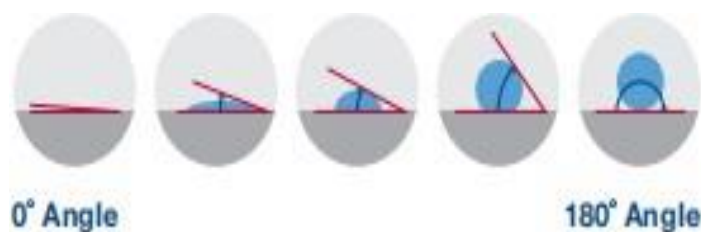


Fig.No. 4.

➤ Elevated Angle of Contact

Verify that the tip is correctly inserted into the liquid.

The liquid may distort around the tip and result in volume problems if the contact angle is large.

➤ Minimal Angle of Contact

Take cautious when using low volumes. Since the liquid's height is so small, a low contact angle liquid could be challenging to aspirate in small volumes.

To get to the bottom of the well or tube, use bottom touch off during aspiration and dispense.

## 7. Vapour Pressure

- The pressure that vapor creates above the surface of a liquid is known as vapor pressure. The vapor pressure of the liquid is pushing upward while the air pressure is pushing downward.
- High vapor pressure liquids also have a propensity to evaporate rapidly. A volatile material is one that has a high vapor pressure at room temperature. Ethers and alcohols are examples of liquids with high vapor pressure.
- A comparison of three liquids' temperatures and pressures is displayed in the chart below. Keep in mind that atmospheric pressure is 760 mmHg.
- Vapor pressure can be significantly impacted by the lab's environmental characteristics. When the liquid starts to off-gas, variations in elevation might cause changes in the air pressure.
- Elevated- Pressure Vaporized Fluid-  
Put Anti-Droplet Control to use. Dripping is more likely to occur in liquids with high vapor pressure.

Wet the tip first. The pre-wetting method entails aspirating a sufficient volume for the liquid transfer after quickly dispensing some liquid to allow the tip's vapor pressure to adapt.

Increase the blowout volume to make space for the vapor.

- Low-Pressure Vaporized Fluid-  
There is nothing to alter. Since off-gassing indicates that the liquid is unlikely to leak, this attribute doesn't require any more considerations.

## 8. Environmental Factors

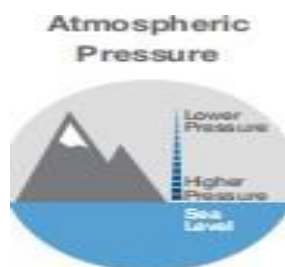
### Impacts of the Environment

The characteristics of the surroundings that affect the liquid's behavior are known as environmental factors.

Some significant environmental factors to take into account, along with how they affect liquids, are as follows.

**Fig. No.5.**

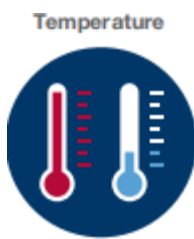
1. Low humidity causes less liquid in the air, which raises the rate of evaporation. Additionally, there might be more static electricity occurrences, which might affect low volume pipetting.
2. High humidity causes the air to become saturated, which lowers the rate of evaporation.

**Fig.No.6.**

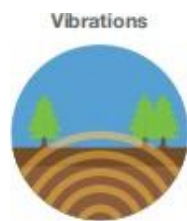
- Vapor pressure is closely related to the rate of evaporation, which increases as pressure decreases.
- Elevation causes a shift in atmospheric pressure. For instance, test a liquid class once more at sea level before utilizing it in a lab at 6,000 feet above sea level.

**Fig.No.7.**

- Alters a substance's chemical characteristics.

**Fig.No.8.**

- Any liquid's density, viscosity, atmospheric pressure, and vapor pressure can all alter in response to temperature changes, even if they are only a few degrees.
- Temperature management in the laboratory is advised.
- Create liquid courses at standard lab temperatures at all times. Take note of the temperature while it is developing.

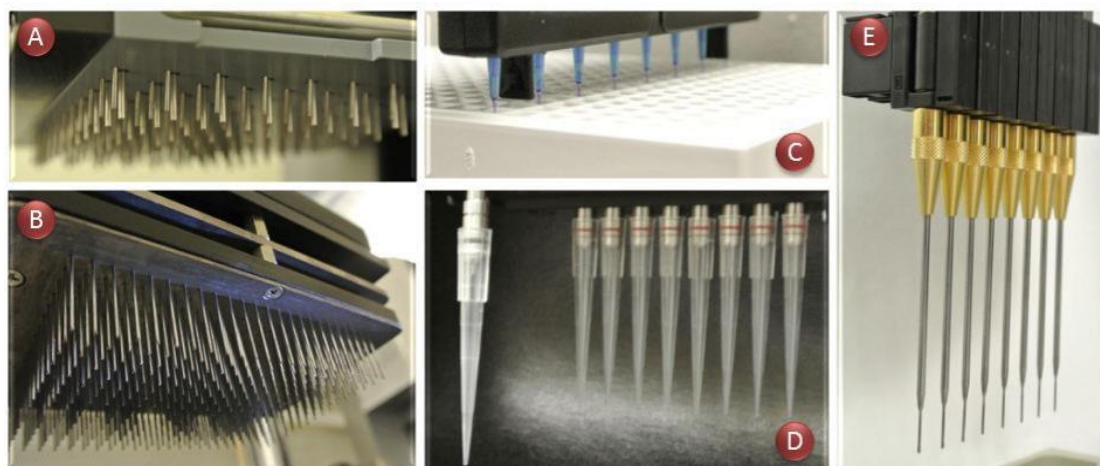
**Fig.No.9.**

- ❖ ■ Drops may occur as a result of vibration. It is ideal to avoid vibrations, particularly when doing gravimetric measurements.

#### ❖ **TYPES OF LIQUID HANDLING DEVICES**

Every fact of drug discovery has led to the development of a wide variety of liquid handlers. These tools use various technology to achieve different goals. Regarding their use, they can be roughly categorized as plate washers, transfer devices, and bulk liquid dispensers.

These devices can use either contact or non-contact dispensing modes, depending on how the reagent is being transferred (Kong et al. 2012). A reliable and easy substitute for sub-microliter fluid handling, contact-based devices enable the fluid to be transported to touch the surface of the destination container or solution. Because gravity alone is insufficient to effectively dispense small volumes, non-contact devices use additional force in addition to gravity to eject liquids (Kong et al. 2012). The procedure is quicker than using permanent tips or pins (Fig. 1) since there isn't a washing step in between deliveries, and it also reduces evaporation and cross-contamination (Dunn in 2000).



**Figure 10: Various types of liquid handling tips, pins and heads from A) washer B) pintool C) peristaltic pump-based bulk dispenser D) liquid handler with single and 8-channel pipettors E) pipettor with 8-independent channels.**

### 1. Peristaltic-based devices

Together with a flexible tubing cartridge and a nozzle head (Fig. 1C), the peristaltic pump is utilized for the bulk reagent dispensing process. A motor-connected set of rollers is encircled by the tubings. The rollers compress the tubings while the motor rotates, resulting in a continuous fluid motion because of positive displacement.

For 96-, 384-, and 1536-well plate layouts, this kind of dispenser can usually handle amounts as small as 5  $\mu\text{L}$  and provide a quick dispensing option. It is possible to autoclave the entire liquid path and the disposable tubing cartridge is already sterile. Variable rolling speed settings, customizable dispensing volume, and discrete column-wise dispensing are all typically included in these devices' programming capabilities. The pump may perform priming and emptying operations by rolling both forward and backward. One significant drawback is the inability to dispense into separate wells.

### 2. Fixed-tip transfer devices

Fluid handlers that utilize fixed-tips (Fig.1E) are usually efficient at transferring relatively small volumes (100  $\mu\text{L}$  or above) and have been largely used for compound pipetting (“cherry picking”) and serial dilutions. They incorporate 2-/ 4-/ 8-channel expandable liquids.

Drug Discovery 178 uid handling arms in addition to 96 and 384 channel heads. This type of liquid handling device functions based on air displacement mechanism. The dilutor or syringe

plunger pulls system liquid from the pipette tubing to aspirate the sample, with an air gap separating both fluids. The plunger speed, syringe size and resolution are factors that affect pipetting flow rate.

### 3. Changeable-tip transfer devices

Disposable tips (Fig. 1D) are an easy way to get around the washing procedures needed for fixed-tip based systems while totally removing the possibility of cross-contamination.

The air displacement mechanism used by these instruments is standard. A vast range of commercially accessible tip sizes, materials, and molding properties provide the scientist with a great deal of versatility. Any standard pipettor can be equipped with customized tips that have the ability to convey data at the nanoliter scale (Murthy *et al.* 2011; Ramírez *et al.* 2008).

### 4. Pintool transfer devices

A popular contact-based dispensing technique for managing nanoliter quantities is Pintool (Cleveland and Koutz 2005). It is composed of a set of precisely made stainless steel pins with uniform size (Fig. 1B). To avoid non-specific binding, the bottom end of the pins may be solid, grooved, or slotted, and a hydrophobic coating may be applied (Dunn and Feygin 2000; Rudnicki and Johnston 2009). The volume is heavily dependent on the contact surfaces and solution characteristics, and solutions are transferred via a combination of surface tension and capillary action (Dunn and Feygin 2000). Typically, the pin array is put together in a floating pin cassette to prevent pin damage and guarantee that all of the pins are soaked in uneven surfaces.

### 5. Piezoelectric dispenser

The piezoelectric dispenser is a non-contact technology that delivers solutions as multiple tiny drops of a defined size (Niles and Coassin 2005). This technology has been used in modern inject printers and refined for use in biological sciences; tests of various biochemical solutions (DNA, RNA, proteins) and bacterial suspensions have shown no adverse effects (Schober *et al.* 1993). The system consists of a capillary tube made of steel or quartz, with one end attached to the reagent reservoir and the other end terminating in an orifice from which droplets are ejected (Niles and Coassin 2005). The solution-filled capillary is attached to a piezoelectric crystal collar. The application of voltage causes the piezoelectric element to contract, which puts pressure on the capillary and produces tiny droplets. Low nozzle

wetness and high acceleration characterize the ejection (Schober et al. 1993). According to Schober et al. (1993), several thousand droplets can be dispensed every second, with achievable drop sizes falling between picoliter and nanoliter. A number of variables, such as bore diameter, solution viscosity, and the voltage pulse's frequency and amplitude, affect droplet volume (James and Papen 1998; Kong et al. 2012).

## 6. Solenoid-based devices

Non-contact dispensers that employ a positive displacement mechanism are known as solenoid-based devices (Bateman et al. 1999). An electric current activates a solenoid valve, which blocks the passage of pressurized liquid but permits liquid to flow through it. The fluid pressure, orifice diameter, solution characteristics, and length of time the valve is open all affect the dispensed volume (Bateman et al. 1999; Niles and Coassin 2005). Depending on how long the valve is open, the device can either spew a continuous stream or droplets (Niles and Coassin 2005).

## 7. Acoustic droplet ejection

A new touchless technology that has gained a lot of traction recently is acoustic droplet ejection (ADE). It uses acoustic energy to precisely push droplets from a variety of liquids. To enable solution transfer from any well in the source plate to any well in the destination plate—the latter of which is inverted—the source plate stays fixed while the transducer and destination plate move (Olechno et al. 2006). In addition to requiring only microplates (Olechno et al. 2006), this approach expedites the procedure by eliminating the need for washing steps and enabling the preparation of assay-ready plates (Turmel et al. 2010).

## 8. Microplate washers

The purpose of microplate washers is to automate and speed up assay applications where a cleaning phase is crucial. In fields like enzyme-linked immunosorbent assays (ELISA) and high-content screening, they are crucial. Using easily accessible materials, Stobbs created the first multiple plate washer in 1990 as an affordable substitute for the commercially available plate washers of the time. Many capabilities have been added to completely programmed plate washers throughout the years. Automated plate washers have reduced the amount of time needed for the time-consuming washing procedures that are part of many screening tests and enhanced reproducibility by standardizing plate handling throughout several wash cycles.

## ADVANCEMENT IN LIQUID HANDLING SYSTEM

Automated liquid handling is made possible by robotic technologies that have long been used in factory automation, and laboratory automation has grown in popularity in recent years. There are always new application-based gadgets coming out for this use.<sup>[14]</sup> As molecular biology, human genetics, and functional genomics advance, there are more and more targets to investigate. Advanced detection and screening skills are now more important than ever. The development of experimental techniques in the biotechnology industry prioritizes less time and reduces errors. The ability to complete numerous laboratory protocols in a completely automated fashion has been transformed by high-throughput platforms, which is advantageous for particular operations and screens. A robotic platform called TECAN EVOware software guarantees optical pipetting performance, which is crucial for biopharmaceutical applications. Each pipetted liquid's pipetting parameters can be customized with its liquid glass editor module.<sup>[15]</sup> A TeVacS two-position vacuum filtering manifold, an eight-channel liquid handling arm with stainless steel tips, and an integrated capacitance function are all features of the Freedom EVO 200.<sup>[16]</sup> A workstation for completely automated sample preparation from sample tubes to the ready-to-inject 96-well plate is provided by this highly customized robotic equipment.<sup>[17]</sup> More advanced workstations and research instruments are now required due to recent developments. However, assembling that many devices by hand takes a lot of time, is expensive, and is prone to mistakes. This calls for an effective, repeatable method to support the construction of large, intricate, high-throughput devices. An innovative development platform focused on speed and flexibility is an automated robotic liquid handling system.

Large-scale experiments with discrete and continuous variables can be conducted using the hardware and software that make up the LFA system.<sup>[18]</sup>

Using a single piece of limited equipment that can be improved with add-on modules that may be connected to the primary worktable is another method of lowering equipment expenses.<sup>[19]</sup> Since these add-ons resemble those often found in the majority of cutting-edge technological gadgets, more users, particularly those with limited resources, may have easier access to automation; nevertheless, this could have the drawback of lacking robust and user-friendly software.<sup>[19]</sup> Every day, lab professionals mix, measure, and distribute liquids. A crucial component of scientific study in a variety of fields, including microbiology, food production, and cosmetics, is liquid handling. Single, 384-well, and bey-one microplates are

common sizes, although filling one by hand could take several minutes. Because of this, a lot of businesses have included an automated liquid handling workstation in their labs to lower minimum sample sizes, boost throughput, and minimize human error. Let's examine the uses and salient features of robots that handle liquids.

### **AUTOMATED LIQUID HANDLING-ASSISTED PK METHOD DEVELOPMENT**

Since it directly affects the creation of a correlation between exposure and toxicity/efficacy during nonclinical and clinical research, drug concentration measurement is a crucial part of pharmaceutical development. After years of preclinical and clinical development, PK findings are produced and analyzed across several investigations. This necessitates high-quality PK results, which calls for strong and highly reproducible PK techniques. The fabrication of standard calibrators and QC samples, the dilution of QC and research samples, and the additions and preparation of reagents are some of the variables that might directly affect the accuracy and precision of a PK method.<sup>[21]</sup>

A detailed description of establishing a modular strategy for employing LBAs (Ligand Binding Assay) for discovery is provided by Duo et al.<sup>[20]</sup> These phases can also involve the adoption of modular automated liquid handling devices to enhance the reliability of PK technique performance in a clinical context. Once storage and processing stability are proven in method validation, huge volumes of standard calibrators (>5 ml per calibrator) and QCs (>20 ml per QC level) can be reliably repeated on automation instruments to cover bioanalysis for large projects. Automation not only expedites method development but also increases intralaboratory and interlaboratory ruggedness by ensuring reproducible preparation of standard calibrators and QC samples. This also increases the likelihood of success in subsequent method validations and "laboratory to laboratory" method transfers, if necessary. Diluted test samples for QCs and study samples can also be prepared with the use of automated liquid handling. It is necessary to write and validate distinct automation scripts for various matrices, labware, and liquid handling settings (also known as "liquid class"). Since any slight variation in a dilution scheme can be amplified exponentially during serial dilutions with the same dilution scheme (e.g., performing consecutive 1:10 dilutions multiple times) or in combination with other dilution schemes, it is imperative that each dilution scheme be checked for accuracy. With more repeatable assay results due to increased pipetting precision from automated liquid handling and uniformity in mixing frequency/volumes.<sup>[22]</sup>

**Table No. 1: Applications using commercially available liquid handling devices reported in Pub Med between 2020 and 2022.**

Brand	Device employed	Purpose of research	Use of Device	Type of institution	Reference
Tecan	Freedom EVO	Develop an automated tube labeller for high- throughput purification	To manipulate the tubes that will be labelled using a Pick- and-Place (PnP) arm	Industry:Abb Vie	[23]
	Tecan Fluent and Perkin Elmer JANUS	Perform a contrast between both liquid handling devices to perform toxicological assays	Contrast between 2 devices highlighted the importance of consistent results, but also device bias	Industry: Arup Laboratories; Academia: University of Utah	[24]
	Freedom EVO	Perform a high-throughput process to test purification of viral antigens	Use of the device to expand the research space (samples and variables)applied to scale-down chromatography	Academia:UCL	[25]
	Tecan Fluent and Perkin Elmer JANUS	Identify difficulties and optimization of chromatographic purification in liquid handling devices	To perform scale-down chromatography to identify the bottlenecks and obstacles when trying to set up a new device	Industry: CSL Behring GmbH	[26]
	Fluent	Automate the cultivation of hiPSC and their differentiation into patient- specific retinal pigment epithelial cells for use in drugtesting	Functioned as the core of the automated protocol to improve reproducibility	Academia: University of Minnesota	[27]
	Freedom Evo	Demonstrate scheduling complications and solutions for an automated laboratory	Device for sample preparation for deep sequencing	Academia: Nara Institute of Science and Technology and University of T sukuba; Industry: Tecan Japan Co., Ltd.; Research institution: RIKEN Center for Biosystems DynamicsResearch	[28]

	Freedom EVO	Develop an automated cPass surrogate virus neutralisation test to determine surveillance of SARS-CoV-2 and blocking antibodies	To automate both objectives in order to develop a proof of concept for large-scale application	Industry:Genscript USA, INC., Cayman Chemical, Cure- Hub, FourthWall Testin LCC, DYNEX Technologies, KaiserPermanente	[29]
	Freedom EVO	Provide with a non-affinity purification method for SARS-CoV-2 spike ec to domain protein	Used along with robo columns to test multiple operation conditions without wasting time and larger resources	Government: National Institutes of Health	[30]
	Fluent	Set-up a fast and massive Covid-19 testing laboratory	To process all the sample and prepare them for RT-PCR(up to 14,000 per day)	Industry: InActive Blue, Biogazelle, Tecan Trading AG, Sanquin Diagnostics, Bodegro B.V., HiFiBio Therapeutics, Genmab B.V.; Research Institution:On code Institute, Hubrecht Institute, University Medical Centre Utrecht, StichtingPAMM,	[31]
	Freedom EVO	Determine antibody levels before and after in oculation with a pneumococcal vaccine (23vPPV)	To validate results obtained from another institution using another automated laboratory	Academia: The University of Melbourne; Research Insitutions: Royal Children's Hospital (Melbourne), Population Allergy Research Group &Melbourne Children's Trial Centre	[32]
	Freedom EVO	Validate an automated protocol for quantification of methyl malonic acid in clinical samples	To facilitate a multi-step protocol for sample preparation before using LC- MS/MS analysis	Research Institution: Drug AbuseLaboratory (Sweden)	[33]
Hamilton	Microlab ADAPSTA R (application-	Create an automated SARS-CoV-2 antibody detection by	To perform complete protocol from sample preparation to qPCR	Industry:Hamilton Company, Enable Bioscience; Research	[34]

	oriented variation)	agglutination-PCR (ADAP) to		Institutions: Nevada State Public Health Laboratory	
	Microlab STAR	Create an automated islet auto anti body detection by agglutination-PCR (ADAP) for type 1 diabetes	To perform complete protocol from sample preparation to qPCR	Academia: Stanford University; Industry: Hamilton Company, Enable Bioscience	[35]
	Microlab Genomic STARlet (application-oriented variation)	Perform concentration of forensic DNA samples	To incorporate monitored multi-flow, positive pressure, evaporative extraction to perform DNA concentration	Government: Centre of Forensic Sciences (Ministry of the Solicitor General, Canada)	[36]
Agilent	Bravo	Automate preparation of libraries for spatial transcriptomic analysis	To provide High accuracy, virtually non-existent technical variability automation for more samples and less processing times than other devices can offer: Complex protocol comprising Several steps	Academia: KTH Royal Institute of Technology, Karolinska Institute	[37]
	Bravo NGS (application-oriented variation)	Perform an automated preparation of single-strand DNA libraries for sequencing ancient biological remains and Other sources	To manipulate up to 96 simultaneous sensitive samples prone to degradation with minimal cross-contamination	Academia: Max Planck Institute for Evolutionary Anthropology	[38]

## DISCUSSION

The prototype technology that is being demonstrated makes it possible to dispense liquid aliquots from the nanoliter to the microliter range without the need for calibration. With the new technology, the advantages matches between a highly dynamic non contact dispenser and a highly accurate and precise positive displacement syringe pump. In addition to increasing specificity and reproducibility, automated liquid handlers can greatly increase the throughput of a laboratory, and free up researchers for scientific creativity instead of monotonous tasks.

## CONCLUSION

Because of the rise of research activities in life science and drug screening in recent years, there is a high demand for automated liquid-handling systems. The trend is in favor of those

that can dispense smaller volumes and operate in a high-throughput fashion. The purpose is to reduce the volume of biosamples used in the experiments as well as to increase the efficiency of the experiments as both biosamples and labor are expensive. In addition, accuracy and precision are two important attributes of an ideal system.

In the limited space of this article, we have reviewed the current state-of-the-art for automatic liquid handling, including fundamental technologies as well as new developments in the design of dispensing devices, robotic workstations, and various components used in the integration of the robotic workstations as being developed by both research and industrial organizations. Through this review, we can see that a large number of technologies and products are available for dispensing small-volume liquid in a high throughput fashion. Nevertheless, challenges for advancing the field continue to arise, which present opportunities to researchers and engineers in the field to further develop new technologies.

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