



## An Overview: Detection and Management of Diabetes (Type1 & Type2) Using Sweat Sample by Wearable Device

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### ABSTRACT

In the 21st century, human health and life are accelerating, and to survive in this situation, we must lead a rapidly growing healthy lifestyle. Scientists and researchers are constantly working to make human life more convenient and healthy. Diabetes is the most common and easily detected disease affecting all age groups. Until the 21st century, when science can provide a definitive cure for diabetes. Recent advances in biotechnology, microelectronics, and biomedical engineering have led to the development of many electrochemical sensors and devices that fit in one's pocket and can be used at an individual level. There are two types of diabetes: type 1 diabetes and type 2 diabetes. This article describes a wearable device that uses biological fluids (e.g., sweat) to continuously monitor blood sugar levels. The device is designed as a system that can detect the levels of glucose and lactate found in human sweat samples. Here we will use sweat as the main analyte. The device is useful for both types of diabetes (type 1 and type 2) and can be used on both blood and sweat samples containing lactic acid. It is one of the non-invasive sweat glucose measurement devices that works by using the natural biological fluid of sweat. Scientists and researchers must develop these into wearable and cost-effective devices. So even the average person can use it and it helps determine blood sugar levels. Conventional blood glucose meters that use blood as the main analyte work on the principle of signal transmission. Signal Transduction: Changing energy from one form to another to produce a product. This device was invented at BITS, Pilani, Hyderabad. Blood sugar and lactate levels are analyzed using sweat as the primary analyte. The device is based on 3D printing technology. It can be used to detect both types of diabetes. Key advantage: "Can be used on both blood and sweat samples."

The basic principle behind this invention is electrochemiluminescence.

Electrochemiluminescence: It triggers electric signal as receiving sweat as input and initiate chemical reaction and generate light as output.

This device is combination of

3D printing tech.

Co2 LASER

Graphene Based Electrode

**Keyword:** - Diabetes, Sweat Sensors, Non-Invasive, Pilocarpine, Raman Spectroscopy, Electrochemiluminescence, 3D printing technology, Co2 LASER.

### 1. Introduction

Human sweat is a biofluid that will take on a whole new meaning for people with diabetes. Recent research suggests that you can measure your blood sugar levels through your own sweat. Researchers at the University of Pennsylvania have developed a prototype of a wearable, non-invasive glucose sensor that can measure glucose levels in a person's sweat with just the touch of a fingertip.

The touch test means far fewer finger pricks, which are often quite painful. Exploratory sensory testing uses a special algorithm to measure blood sugar levels in sweat and correlate this with blood sugar levels. According to a recent validation study, the accuracy of predicting blood sugar levels before and after meals is over 95%. In this paper work introduces, "The wearable device which (biosensor) helps in detection and management of blood glucose level using the sweat as primary analyte". In the Diabetic conditions the increase in the blood glucose level also result in effective change in glucose level in sweat.

The glucose level in blood correlates with the glucose level in sweat. But it seems to be most challenging and risky way to detect blood glucose level. It made up of a system introduces to analyze glucose and lactate level found in sweat sample, using 3D printing technology. Here we use sweat as primary analyte, so it is useful in both the types of Diabetes.

The device is combination of

- 3D Printing Technology
- Co2 LASER
- Graphene Based Electrode

The key advantage of these device is that , it works well and good with both the blood and sweat sample excreted by sweat gland and the level of glucose present in biofluid .

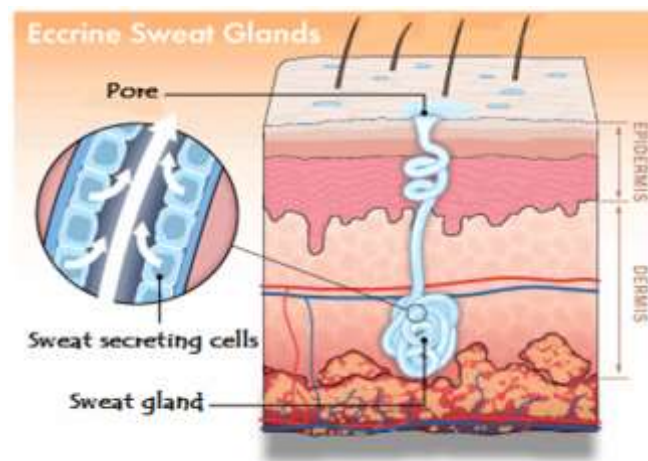
Biofluids : The fluids founds in the human body , like sweat , blood , plasma etc .

Body odor seems to be occur when sweat is metabolized by bacteria present on the skin. Other medical and nutritional medications can also cause odor. Some conditions, such as kidney failure and diabetic ketoacidosis, can affect sweat odor.

#### Sweat As The Primary Analyte :-

A new wearable non-invasive monitoring device has been developed that shows a strong correlation between sweat and blood sugar levels. According to the Birla Institute of Technical Research, “the concentration of glucose in human sweat is about 100 times lower than that in blood.” The team's prototype device uses a personalized algorithm to accurately measure glucose levels in sweat and is sensitive enough to reflect concentrations in the blood.

But there are many problems. Because sugar levels are much lower than blood sugar levels and can vary depending on the rate at which a person sweats and the characteristics of their skin, glucose levels in sweat generally do not accurately reflect blood sugar levels. The good news is that some newly developed devices can do the job simply by using sweat from diabetics or even attaching them to the user's skin.



**Fig.1 Eccrine Sweat Glands**

Every portion of the sweat gland have specific function such as

- Secretory Gland : Responsible for sweat production
- Ductal Gland : Desalination of sweat by the lining of duct

Salty elements like sodium and chloride are reabsorbed are significantly a hypotonic solution

- Acrosyringium : Least active part of sweat gland . It conduct the final flow of sweat to skin surface . The most active glands in the body are sweat glands in fluid secretion .

Sweat provides non-invasive, continuous, simple and convenient sample collection. Sweat can be produced in several sensitive areas of the body as needed.

For example, the forehead, chest, palms or soles of the feet.

Wearable sensors can also measure sweat on the skin. Collect and test without disrupting natural behavior of user. Wearable sweat sensor enables continuous use, Collecting samples over long periods of time is useful for the discovery of a variety of biomarkers. Health comparison of sweat and other biological fluids .Monitoring serum assays are considered the gold standard for measuring analyte concentrations.

A majority of medical tests in clinical study are primarily use urine and blood which are not practical for active and continuous monitoring . As such, significant interest has shifted in developing technologies to accurately monitor and characterize changes in saliva, tears, sweat ,and interstitial fluid. Each biofluid has its own set of challenges for sensing applications. Tears are difficult for continuous or on-demand monitoring applications because existing sample collection protocols cause eye irritation and produce reflex tears that interfere with the data readout.

Reliable monitoring of saliva in the day time is challenging as chemical composition of samples is dependent on the most recent meal or drink consumed by the person . furthermore, Saliva may contain bacteria from plaque and food particles.This can contaminate the sensor surface and compromise data reliability. Examining interstitial fluid requires the use of a fine microneedle. Alternatively, samples can be collected using subcutaneous excitation current. It causes irritation and discomfort in skin tissue. [Reference ]

Sweating is a physiological function of the body that helps in removal of toxic compounds from the body and regulates body temperature. Sweat is a liquid secreted by sweat glands. Sweating areas are widespread across the skin of the body. The average person evaporates 500 to 700 ml of water per day. During strenuous physical activity, the rate of sweating can reach 2-4 l/h.

Therefore, Sweat is a common and easily accessible biological fluid. Human sweat is rich in chemicals and can reflect physiological condition of the human body. In general, sweat contains metabolites (lactic acid, 2 glucose, 3 etc.), electrolytes, trace elements and small substances and macromolecular components. These biomarkers can be used toNon-invasive detection of physiological health conditions as well as diseases Diagnosis and Treatment. Blood during health checkup Painting is often unavoidable and many people shy away from it.

Blood is drawn because of the pain caused by the needle. furthermore, Blood tests are unlikely to provide consistent information. Levels of chemical molecules in blood and sweat, such as glucose,4 lactate,5 ethanol,6 ammonia, and urea, have been reported to be correlated7.Sweat tests can replace blood tests to some extent. But the chemical composition of sweat samples is complex and the collected The amount is usually small.

**Table 1 :- List Of Biofluids and their analyte [1]**

Biofluids	Analytes
Urine	Calcium (Ca),Potasium(k),Sodium(Na),Urea.
Blood	Calcium(Ca),Potasium(k),Sodium(Na) Haemoglobin , Glucose .
Saliva	PH and lactate
Sweat	Potasium(k),Sodium(Na),Oxygen(O),Zinc (Zn),Copper(Cu),Iron(Fe),Cortisol.

### History Of Word – Diabetes :-

The word diabetes originates from the Greek word diabetes (siphon, to pass) and the Latin mellitus (to sweeten). A review of history reveals that the term diabetes was first used by Apollonius of Memphis around 250-300 BC. B.C. Ancient Greek, Indian and Egyptian civilizations discovered the sweet properties of urine in this condition, which gave rise to the word diabetes.

In 1889, Mering and Minkowski discovered the role of the pancreas in the development of diabetes. In 1922, Banting, Best, and Collip isolated the hormone insulin from the bovine pancreas at the University of Toronto and developed an effective treatment for diabetes in 1922. Over years ,work has been done and many discoveries and management strategies have been made to address this growing problem.

Unfortunately, even today, diabetes is the most common chronic diseases around the world. It remains the seventh leading cause of death in the United States.

### Diabetes :-

It is also known as Diabetes mellitus . Diabetes mellitus (DM) is a disease associated with improper regulation of blood sugar levels. It has many subcategories, including

1. Type 1,
2. Type 2,
3. Adult-onset diabetes (MODY),
4. Gestational diabetes,
5. Neonatal diabetes, and

#### 6. Steroid-induced diabetes.

Type 1 diabetes and type 2 diabetes are the main subtypes, each with different pathophysiology, symptoms, and treatment, but both have the potential to cause hyperglycemia.

##### ■ Diabetes Type 1 :

In type 1 diabetes, autoimmune destruction of pancreatic islet beta cells occurs over months or years, resulting in an absolute deficiency of insulin. The exact etiology of T1DM is still unknown, but researchers believe there is a genetic predisposition closely related to specific HLA alleles (DR and DQ). This association is more pronounced in T1DM in adolescents compared to T1DM in adults. Many other genes also contribute to heredity.

It is generally believed that in at-risk individuals,

- Environmental factors,
- Including viruses,
- Dietary factors, and

Other stressors may trigger autoimmune destruction of beta cells. Some researches have shown an increase in development of T1D by exposing person to infection with

- Coxsackie virus,
- Rubella virus,
- Influenza B,
- Mumps virus,
- SARS-CoV-2 (COVID-19)

The Environmental Determinants of Diabetes in the Young (TEDDY) study were conducted. However, a systematic review and meta-analysis concluded that the breastfeeding and the later introduction of gluten, fruit, and cow's milk are associated with the lowering the risk of developing T1D. Research helps to better understand the etiology of T1D is ongoing. The presence of circulating pancreatic islet autoantibodies indicates the risk of developing the T1D in person.

The antibodies included in T1D are islet cell cytoplasmic antibodies (ICA), antibodies to insulin (IAA), glutamic acid decarboxylase isoform 65 (GAD65), insulinoma antigen 2/islet tyrosine phosphatase 2 (IA-2) and zinc transporter isoform 8 (ZnT8). IAAs are primarily found in children. GAD65 is the most known autoantibody found in adults. ICA is no longer routinely recommended because it is an inaccurate test. The greater the number of antibodies detected and the higher the titer, the higher the risk of developing T1DM. [5]

##### ■ Diabetes Type 2 :

90% of all diabetes cases from the diabetes are of T2DM. In T2DM, there is a decreased response to insulin, which is defined as insulin resistance. In this condition, insulin is ineffective and the patient initially responds by increasing insulin production to maintain glucose homeostasis, but over time, insulin production decreases, leading to type 2 diabetes. T2DM occurs most commonly in people over 45 years of age. However, it is occurring increasingly in children, adolescents, and young adults due to the rise in obesity, physical inactivity, and high-energy diets. [6]

This review article provides an update on the current status and commercial prospects of continuous sweat glucose monitoring. Let us take a closer look at the different mechanisms that sense glucose from sweat, including sweat collection mechanisms and sweat recognition and transformation. Higher sensitivity is needed because glucose levels in sweat are very low. We also remember that probing is fraught with the possibility of infection and many other problems. All issues related to sweat collection, sweat sample digestion, inter-individual differences, glucose sensitivity and commercial viability are addressed. In the electrochemical sensing analytical methods, have been used in BG sensors, show greater potential to be commercialized in future of health sector. The recent breakthroughs in the development of skin-worn, non-invasive electrochemical Glucose Biosensors, and their prospects and limitations for enhanced glycemic management, are highlighted.

It also focuses on the usefulness of the sweat glucose biomarker and provides a historical perspective of sweat glucose sensors; and explains why sweat is the main useful reliable analyte which can be used for several biomarkers and an alternative bioanalyte source of glucose monitoring.

It looks into measurement methods used so far for the analysis of sweat, including sensor materials and sensors based on different sweat collection techniques. These discuss the challenges associated with non-invasive glucose monitoring. And looks into various efforts that are underway for commercializing sweat glucose monitoring.

Finally, it gives concluding remarks and future perspectives that may increase forecast accuracy, according to the collected data in this research article.

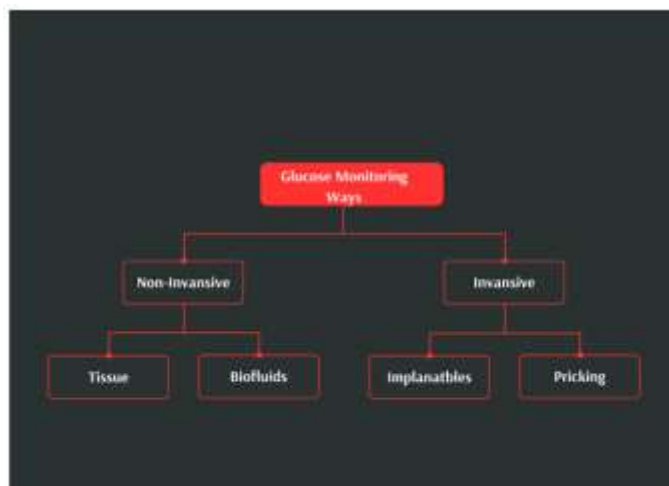


Fig 2. Glucose Monitoring Ways

**Biosensors :**

The first biosensor was invented by American biochemist L.L. Clark in 1950. This biosensor is used to measure the amount of oxygen in the blood, and the electrode used in this sensor is called the Clark Electrode or Oxygen Electrode.

Biosensors are the analytical device which are used to change biological stimulus into electrical signal. These are the sensors which work by the detection of concentration of substance and resulted concentration of light.

The elements of

- Analytes / Sample Matrix
- Biorecognition Elements
- Transducers
- Amplifier
- Display

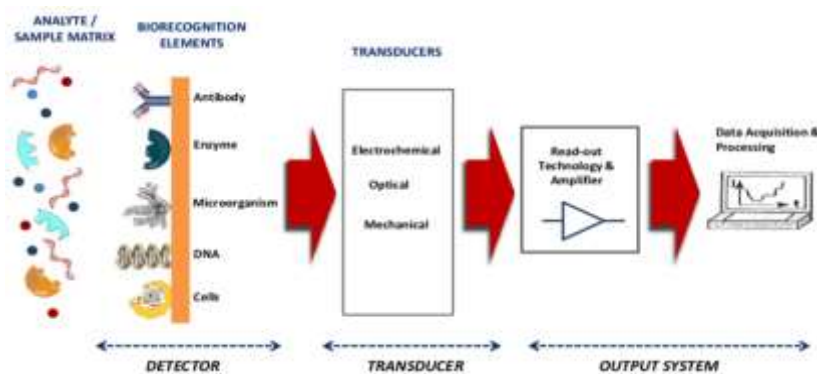


Fig 3 . Schematic Representation of Biosensors

**Working And Principle Of Biosensors :**

The biological material needed is usually in the form of enzymes. Through a process called electroenzyme, which is a chemical process that converts enzymes into electrical products (usually electric current) with the help of sensors.

Modern blood glucose meters use three main enzyme reactions: glucose oxidase, glucose dehydrogenase, and hexokinase.

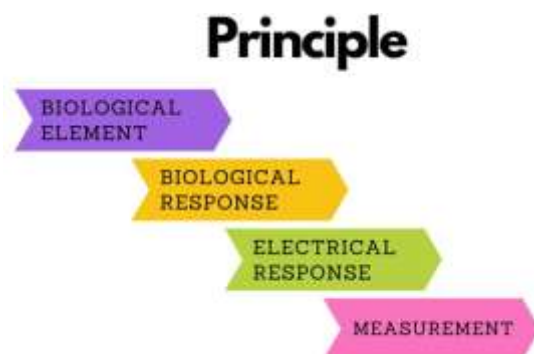
One of the most commonly used enzymes is the oxidase enzyme. Oxidation acts as a catalyst and changes the pH of biological products. Changes in pH will directly affect the available transport capacity of the enzyme, which in turn will be directly affected by the enzyme being tested.

The output of the sensor is now a direct representation of the enzyme being tested. Current is usually converted to voltage so that it can be analyzed and displayed accurately.

All meters are sensitive to heat and cold because enzymes are proteins that can be denatured and inactivated at extreme temperatures.

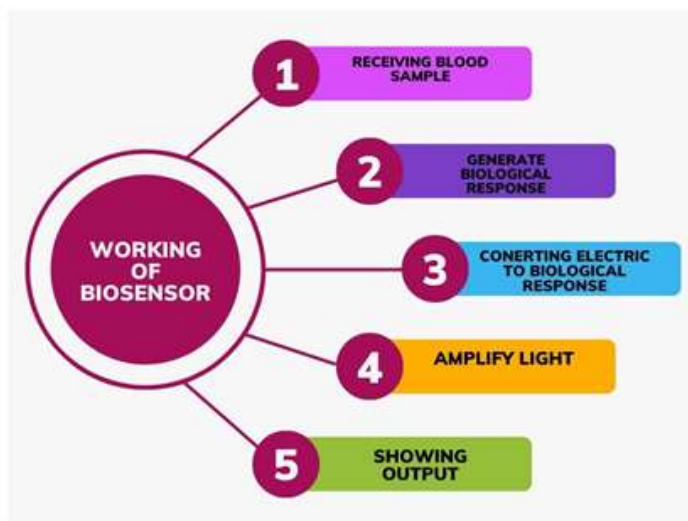
Although enzymes are packaged dry, exposure to moisture can cause premature rehydration of the proteins, limiting their reactivity when used for patient testing.

Therefore, disposable glucose meter reagents must be protected from temperature and humidity extremes.(7)



**Table 2 : Principle Of Biosensors**

> 180 mg/dl	Unhealthy/ Hypertensive
80 - 130 mg/dl	Good/Average
< 70 mg/dl	Unhealthy/ Hypotensive



**Table 3 : Working Of Biosensor**

### Why Sweat ?

There have been several attempts to estimate blood glucose levels by measuring fluid secretion from different surfaces of the skin, including applying negative pressure to the skin and glucose iontophoresis.

Chemical analysis of sweat is highly attractive; however, conventional electrochemical clinical analyzers are not applicable for this aim because sweat components inactivate platinum used as the transducer in the corresponding biosensors.

Human sweat has already attracted special interest in the noninvasive method of diagnosis of hypoxia. Attempts to monitor sweat lactate using biosensors and non-enzymatic sensors have been reported.

Apparently, sweat has also been considered for non-invasive diabetes monitoring. Recently, a variety of devices have emerged that combine sweat analysis, transduction and signal transduction, including blood glucose detection. However, because the change in sweat glucose concentration is almost threefold and much higher than the blood glucose level, it is not possible to determine the threshold level of sweat glucose that distinguishes normal patients from hypoglycemia or hyperglycemia. We attempt to find a relationship between sweat and blood glucose levels based on reliable sweat sampling using a clinically relevant pilocarpine stimulation procedure. However, data predicting blood sugar levels based on sweat glucose concentration is still lacking.

Regarding the diagnostic value of sweat, there was a positive correlation between the rate of blood glucose increase and sweat, which is a sufficient requirement for noninvasive monitoring of diabetes.(8)

### Mechanism of sweating :

Sweating helps to body to regulate temperature. Sweating is controlled by specialized areas of the brain called the preoptic area and the anterior hypothalamic area, which contains temperature-sensitive neurons. Additionally, the thermal control function of the hypothalamus is affected by skin temperature receptors. When skin temperature rises, the hypothalamus adjusts the sweat point and activates the response to the change in core temperature. However, in general, sweat's response to an increase in body temperature is greater than its response to an increase in average skin temperature. Sweating helps reduce core temperature by evaporative cooling of the skin surface. When large energy molecules evaporate from the skin, they release energy absorbed by the body, causing the skin and blood vessels in the face to cool. The cold venous blood then returns to the body, preventing the temperature from rising. Nerves stimulate sweat glands, causing sweating, which occurs in two periods: body temperature and emotional state. While sweating caused by emotion is generally limited to the palms, feet, arms and sometimes the forehead, sweating caused by body heat spreads to the whole body. The average number of sweat glands in a human is approximately two to four million, but the amount of sweat produced by each gland is affected by many factors, including gender, genetics, environment, age and fitness level. Condition level and weight are two important factors that affect sweating. Heavier people may sweat more because their bodies need more energy to function and have more body space to cool. In contrast, healthy people tend to sweat sooner and more easily. As fitness improves, the body does a better job of regulating temperature and sweat glands change along with the rest of the body.

### Composition :

Microfluidic modeling of eccrine sweat glands provides detailed information about the fluids contained in sweat, how they are distributed and transported to the skin. Sweat consists mostly of water with bacteria, lactic acid and urea dissolved in it. Minerals in sweat can vary, but some common indicators include sodium, potassium, calcium and magnesium. The concentration of sodium ions in sweat is lower compared to blood plasma and other fluids. Sweat, initially produced in the eccrine glands, contains high amounts of sodium ions. However, as sweat passes through the sweat ducts, sodium ions are reabsorbed into the tissue via epithelial sodium channels. In addition to food, sweat also contains many harmful substances such as zinc, copper, iron, chromium, nickel and lead. These elements are released through sweat, although their concentrations vary. Other lower cavities can be drained through sweat, but to a lesser extent. Sweat also contains organic compounds found in some types of mushrooms that create a "maple syrup"-flavored perfume. H sweat is hypotonic compared to plasma, that is, it has low pressure. It usually occurs in the moderately acidic to moderate pH range of 4.5 to 7.0. Various glycoproteins are also found in sweat.

### Other Biofluids to detect blood glucose level :

- blood,
- interstitial fluid,
- urine,
- cerebrospinal fluid,
- pleural fluid and
- ascitic fluid i

### Inventions :

- Glucose sensor :

1962 - First Enzymatic Electrode

Invented by : Clark & Lyons

It uses an amperometric electrode for determination of blood glucose level by enzymatic method, using glucose oxidase (GOX or GOD). (9)

Reaction :

Glucose + O<sub>2</sub> → Gluconic Acid + H<sub>2</sub>O<sub>2</sub>

- **Glucose Biosensor :**

1973 - Enzymatic catalysis

Invented by : Guilbault et al.

It based on amperometric monitoring of hydrogen peroxide produced by enzyme. (9)

- **Glucose sensor :**

1975 - First sensor for direct glucose monitoring

invented by : Clark & Lyons

It exploits oxygen electrode act as substrate and produces hydrogen peroxide. (9)

In 1962, Clark and Lyons provided the initial description of a biosensor, marking a significant milestone in the field. Five years later, Updike and Hicks developed the first practical enzyme electrode, which further advanced the capabilities of biosensors.

In 1973, a glucose enzyme electrode was introduced, utilizing the detection of hydrogen peroxide. This development paved the way for the detection of glucose levels in various applications.

The first commercial biosensor, known as the YSI analyzer, was relaunched in 1975, making biosensor technology more accessible to the public.

In 1976, the first bedside artificial pancreas was introduced by Miles, revolutionizing the management of diabetes.

Shichiri made a breakthrough in 1982 with the development of the first needle-type enzyme electrode for subcutaneous implantation, enhancing the convenience and accuracy of glucose monitoring.

In 1984, Cass introduced the first ferrocene mediated amperometric glucose biosensor, which further improved the performance of glucose detection.

The year 1987 witnessed the launch of the MediSense ExacTech blood glucose biosensor, expanding the range of available biosensors for glucose monitoring.

In 1999, MiniMed introduced a commercial in vivo glucose sensor, providing a more convenient and continuous monitoring option for individuals with diabetes.

Finally, in 2000, the GlucoWatch was introduced as a wearable noninvasive glucose monitor, offering a novel approach to glucose monitoring. These milestones highlight the continuous advancements in biosensor technology, enabling improved healthcare and quality of life for individuals with diabetes and other medical conditions.

**Table No 3 : History Of Inventions(10)**

Year	Affairs
1962	Idea proposing by Clark & Lyons
1967	Enzyme electrode 1 <sup>st</sup> practical by Hicks
1973	Glucose enzyme electrode
1975	first commercial biosensor, known as the YSI analyzer,
1976	first bedside artificial pancreas was introduced by Miles
1982	first needle-type enzyme electrode



1984	first ferrocene mediated amperometric glucose biosensor
1987	MediSense ExacTech blood glucose biosensor
1999	MiniMed introduced a commercial in vivo glucose sensor
2000	GlucoWatch

### **Methods and Experimental Work :**

#### **❖ Raman Spectroscopy (11) :**

Raman spectroscopy, including spontaneous Raman spectroscopy, coherent anti-stokes Raman spectroscopy, and stimulated Raman gain spectroscopy, is extensively utilized in the fields of physics, chemistry, and biology to investigate vibrational modes. However, its application in medical diagnostics for in-vitro and in-vivo patient analysis is limited due to the challenges posed by low signal levels and significant background interference. The conventional Raman techniques employed for detecting constituents within the human body typically require long exposure times (several tens of minutes) and high power laser pump fluency, which surpass the safety limits for laser illumination in medical applications. Additionally, these techniques are hindered by strong noise background. Consequently, conventional Raman spectroscopy is not sufficiently sensitive to accurately determine the level of analytes, such as glucose, in humans due to the overwhelming background noise.

In order to accurately measure low concentrations of analyte molecules in the presence of a strong background, such as measuring the glucose level in the body, we propose the utilization of the "difference Raman spectroscopy" method. This method allows for more efficient measurement of the Raman spectra of glucose and other blood analytes by modulating the quantity of blood in a specific region of the body where blood flow can be manipulated.

To improve the detection of Raman spectra from blood analytes, the following steps are involved:

1. Initially, the Raman spectrum of an examining area on a finger, ear, arm, leg, or any other body part is measured under normal blood flowing conditions. This measured Raman spectrum includes contributions from both tissue components and blood analytes. However, accurately determining the Raman lines of the blood analytes within the body tissues is challenging due to the strong Raman line intensities from tissue components and structures.
2. The blood quantity in the same examining area is then modulated by either decreasing or increasing the blood flowing in that area. For instance, pulling the examining area of a finger, ear, arm, leg, or any other body part can reduce the blood flowing and blood quantity in that specific area.
3. Subsequently, the Raman spectrum of the same examining area is measured under the condition of reduced blood quantity. This measured Raman spectrum contains the same contributions from tissue components but significantly less contribution from the blood constituents.
4. The Raman spectrum obtained under the condition of reduced blood quantity is subtracted from the Raman spectrum obtained under normal blood flowing conditions. This subtraction yields a resulting spectrum known as the difference Raman spectrum. The signal-to-noise ratio of the difference Raman spectrum is improved because the contribution of tissue components and structures to the Raman spectrum is reduced through the subtraction process. Consequently, the Raman modes of the blood analytes can be clearly determined from the difference Raman spectrum.
5. Finally, the intensities of one or more Raman modes for blood analytes from the difference Raman spectrum are compared to appropriate standards in order to determine the levels of glucose.

By employing the difference Raman spectroscopy method and following these steps, it becomes possible to accurately measure low concentrations of analyte molecules, such as glucose, in the presence of a strong background.

The patent provides a description of the initial experimental findings, which demonstrate the enhancement in detecting Raman spectra from blood analytes through the utilization of "difference Raman spectroscopy." These results are presented in their non-optimized form, highlighting the potential for further improvement in the future.

It present NiGARA, a new method that uses Raman spectroscopy analysis for non-invasive blood glucose measurement. Our approach involves an optical system that efficiently delivers Raman scattered light into the optical system and customized computer algorithms that leverage the power of Raman spectroscopy. In this paper, we demonstrate the advantages of our method, especially the data processing and analysis method for non-invasive blood glucose measurement. Previous studies have investigated the use of Raman spectroscopy in noninvasive blood sugar measurements. But our approach is different in many ways.

First of all, our optical correction method is very user-friendly because it does not require any focusing or search functions.

Second, we have made significant improvements in measurement and data processing problems, such as improving the measurement device, increasing laser power and power, using state-of-the-art methods for background removal, adaptive filtering, and predictive modeling.

These advances have greatly increased the efficiency of Raman spectroscopy. Also, unlike traditional Raman spectroscopy, our technique does not require additional preparation or subcutaneous equipment. It also does not rely on laser techniques such as coherent anti-Stokes Raman spectroscopy.

#### **Experimental work :**

Raman spectra were obtained by utilizing a specialized NiGARA measurement head developed by TNO in Zeist, Netherlands. This measurement head was optimized for skin measurements at a depth of 100-200  $\mu\text{m}$  and had a measurement spot diameter of approximately 8 mm. It was connected to a Shamrock SR-163 spectrograph manufactured by Andor Technology in Belfast, UK.

The spectrograph was equipped with a 1200 lines/mm grating, and detection was carried out using an iDus DU-401A BR-DD CCD detector cooled to  $-90^\circ\text{C}$ , also manufactured by Andor. Excitation was achieved using a LASER-785-LAB-ADJ-S laser system from Ocean Optics in Duiven, Netherlands, which had the capability to deliver continuous laser radiation at 785 nm with a power of up to 400 mW. Calibration was performed using the on-spectrograph micrometer, and a cuvette containing cyclohexane (>99.5% purity, Biosolve, Valkenswaard, Netherlands) was used to verify the calibration before each set of measurements. All spectra were recorded using SOLIS software, version 4.14 from Andor, with a range interval of 541 to 1818  $\text{cm}^{-1}$ . Automatic background subtraction was applied to all experiments, and each spectrum was recorded as the accumulation of 10 seconds exposure repeated 10 times(12)

#### **❖ ARDUINO :**

The advantage of this method is that it does not penetrate and does not enter the body.

#### **Experimental work :**

Blood sugar measurement is done with a measuring device. The conductivity of a sweat sample is a measure of its ability to conduct electricity. Sodium content in sweat is measured as voltage. It is related to the sugar voltage range with the help of the interpolation equation. The conductivity of electrolyte solution is monitored by determining the solution of two plate electrodes placed which is placed at a certain distance.

1. Copper electrode: Copper has greater strength than silver but is less resistant to oxidation. Copper is a common base metal used in electrical contacts and electrodes. It is also used in alloys with graphite, tellurium, and tungsten, and to make brass and bronze. Copper electrodes are used for conductivity measurements because they have a high tensile strength against electricity.
2. ArduinoUNO: Arduino UNO is a microcontroller board based on ATmega 328. It has 14 digital I/O pins, 6 analog inputs, a 16 MHz ceramic resonator, a USB header, a power header, an ICSP header, and a reset button. Here Arduino is used as a controller. It receives analog signals from electrodes and converts them into digital format.
3. LCD: Liquid crystal display (LCD) is a technology used in the displays of laptops and other small computers. An LCD is a flat panel display or other electronic visual display that uses the light modulation properties of liquid crystals. Liquid crystals emits zero amount of light directly. (13)

#### **❖ Wearable Glucose sensor on cotton fabric :**

The objective of this research is to elucidate the development of a flexible electrochemical sensor that can be attached to the skin. This sensor utilizes nanomaterials and exhibits exceptional proficiency in detecting glucose levels in human sweat. The manufacturing process of this electrode was carried out at room temperature using a straightforward immersion technique, eliminating the need for complex and time-consuming procedures such as photolithography and chemical vapor deposition (CVD).

#### **Experimental work :**

1. First, create conductive cotton by following the necessary steps.
2. Next, apply a layer of Cu-Mn onto the conductive cotton fabric through deposition.

#### **Instrumentation :**

- ❖ To perform electrochemical experiments, you need to set up a three-cell configuration on your electrochemical workstation. This requires using an Ag/AgCl reference electrode, a platinum counter electrode, and a modified cotton/PPY/Cu/Mn electrode as working electrodes. The electrochemical responses of both unmodified and modified electrodes were studied using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques. All electrochemical studies were performed at a scan rate of 0.05 V/s using 0.1 M PBS buffer containing 5 mM  $[\text{Fe}(\text{CN})_6]^{3-/4-}$ .
- ❖ **Wearable Device for continuous glucose detection using sweat :**



Scientists at BITS have created a portable system that utilizes 3D printing technology to analyze glucose and lactate levels in sweat samples. This innovative device can be connected to smartphones, eliminating the need for blood samples to assess glucose levels. Additionally, it has the capability to detect lactate concentration using sweat samples. Currently, the researchers are focused on developing a wearable version of this device.

According to Professor Sanket Goel, the utilization of 3D printing, CO<sub>2</sub> laser, and graphene-based electrodes has led to the development of this device. It is worth mentioning that the researchers were responsible for extracting the graphene. The remarkable aspect of this system is its non-invasive nature, eliminating the requirement of blood samples for glucose level assessment. Although it can also operate with blood samples, the true breakthrough lies in its capability to detect lactate concentration through sweat samples, as highlighted by Sanket Goel.

A unique procedure is employed to detect lactate concentration, involving a novel mechanism. Professor Goel elucidated that this mechanism relies on Electrochemiluminescence (ECL). When sweat is provided as input, the device activates an electrical signal, which in turn initiates a chemical reaction resulting in the production of light as an output. By assessing the intensity of this light, the lactate concentration can be precisely determined.

The group has effectively created a compact gadget that can establish a connection with mobile phones, enabling individuals to retrieve human metabolite information via a specialized application. Their current efforts are focused on designing a wearable variant of the gadget to facilitate uninterrupted monitoring.

The basic principle behind this invention is electrochemiluminescence.

Electrochemiluminescence : It triggers electric signal as receiving sweat as input and initiate chemical reaction and generate light as output .

This device is combination of

- ◆ 3D printing tech.
- ◆ Co<sub>2</sub> LASER
- ◆ Graphene Based Electrode

#### Electrochemiluminescence :

Electrochemiluminescence (ECL) is a phenomenon which is caused by the high-energy conversion of electromagnetic radiation, causing atoms to be in an excited state and resulting in photon emissions. As a powerful research tool in the field of bioassays, ECL is attracting increasing attention from academia and industry. In fact, it has many advantages, such as high sensitivity, low background signal, and the ECL intensity being proportional to the concentration of the luminescent species of interest. Finally, the low cost of the required equipment in addition to the above features makes it popular.

ECL occurs via two different mechanisms :

- i) ion destruction and
- ii) co-reactive ECL.

ECL has proven to be a useful, excellent and selective method in clinical applications. [7] It offers the advantages of chemiluminescence analysis (no background signal) and the advantage of easy reaction control using electronic devices. As an analytical method, it has the best of other analytical methods because it is versatile, easy to tune optical light compared to photoluminescence (PL), and has physical and spatial control compared to chemiluminescence (CL). The choice of ECL analysis is improved by varying the potential to control the products oxidized/reduced on the electrode and involved in the ECL reaction [8] (see Electrochemical Analysis). It often uses ruthenium complexes, especially  $[\text{Ru}(\text{bpy})_3]^{2+}$  ( $\text{bpy} = 2,2'$ -bipyridyl tripropylamine) which emit photons at  $\sim 620$  nm and react in the liquid phase or regenerate with TPrA at the liquid-liquid interface. It can be used as a monolayer fixed to the electrode surface (e.g. made of nafion or a special film made by Langmuir-Blodgett technology or self-assembly) or as a co-reactant or as more than a label and can be used in HPLC. Ru-labeled antibodies based on immunoassays, PCR, etc. Ru-labeled DNA probes for biosensors based on NADH or  $\text{H}_2\text{O}_2$  production, oxalate and organic amine detection, and many other applications can be detected with picomolar sensitivity to more than six orders of magnitude Dynamics. Photon detection is done by photomultiplier tubes (PMTs) or silicon photodiodes or gold-plated fiber optic sensors. The importance of ECL detection technology for biologically useful applications is well known. [9] ECL is used commercially in large quantities for various diagnostic applications.(16)

### 1. 3D Printing Technology :

In recent years, the utilization of three-dimensional (3D) printing technology, also known as additive manufacturing technology, has become increasingly sophisticated in the pharmaceutical field. This technology enables the creation of personalized 3D-printed drugs through computer-aided model design. Notably, Triastek's 3D-printed drug applications have received investigational new drug (IND) approval from the Food and Drug Administration (FDA), following the successful commercialization of Spritam® in 2015. Compared to traditional drug preparation methods, 3D printing technology offers significant advantages in personalized drug manufacturing. It facilitates the production of preparations with complex structures or drug release behaviors, as well as the rapid manufacturing of small batches of drugs. This comprehensive review aims to summarize the mechanisms of the most commonly used 3D printing technologies, delineate their characteristics, advantages, disadvantages, and applications in the pharmaceutical industry. Furthermore, it analyzes the progress of global commercialization of 3D printed drugs, identifies associated problems and challenges, and provides insights into the development trends of the 3D printed drug industry. Ultimately, this review serves as a valuable resource for researchers involved in the field of 3D printed drugs.

The utilization of three-dimensional printing technology is widespread across various industries, including automotive, construction, aerospace, medical, and more. The pharmaceutical sector is currently experiencing a global surge in research into 3D printing technology [5,6]. In comparison to traditional preparation methods, 3D printing provides flexibility in designing intricate 3D structures within drugs, adjusting drug doses and combinations, and rapid manufacturing and prototyping. This enables precise control of drug release to meet a wide range of clinical needs, a high degree of flexibility and creativity in personalizing pharmaceuticals, and a significant reduction in preparation development time. As a result, 3D printing technology is driving a breakthrough in drug manufacturing and transforming the way we design, manufacture, and use drugs [7,8,9]. Medicinal products such as immediate-release tablets, controlled-release tablets, dispersible films, microneedles, implants, and transdermal patches have been manufactured using three-dimensional printing technologies [10]. The primary 3D printing technologies utilized in pharmaceuticals are BJ-3DP, FDM, SSE, and MED in material extrusion, and SLA.(17)

#### Advantages :

The versatility of three-dimensional printing technology allows for the production of targeted medicines by adjusting various model parameters, including size, shape, and fill rate .

This technology has proven particularly useful in the production of low-dose personalized medicines for pediatric patients, as well as in improving the appearance and taste of medicines to increase compliance among this patient population .

For elderly patients who have difficulty swallowing, 3D printing technology can prepare loose and porous preparations, making it easier for them to take medication.

Additionally, for patients who take multiple drugs simultaneously, different drugs can be partitioned and combined into a single tablet to avoid errors or missed doses, thereby increasing the safety and effectiveness of medication.

Furthermore, specially shaped preparations or symbols can be printed on the surface of the medication to provide convenience for patients with visual impairments .

The benefits of 3D printing technology for personalized drug delivery provide technical support for the realization of personalized medicine.

Some companies, such as FabRx in the UK, are already moving towards this goal by preparing personalized drugs for children with maple diabetes and conducting clinical trials using SSE printers in the pharmacy of a Spanish hospital.(18)

3D printing, a new technology in the pharmaceutical industry, offers many benefits. The 3D pharmaceutical printing field is advancing toward the development of cutting-edge customized medicines thanks to the innovative efforts of companies and the active support of government agencies such as the Pharmaceutical Review Center.

The world witnessed an important milestone in 2013 when Spritam®, the first 3D printed drug, received IND approval from the FDA. Recognizing the need to encourage and facilitate the successful approval of new technology products in the pharmaceutical industry, the FDA established the Emerging Technologies Panel (ETT) in 2014. ETT's participation directly contributed to the successful approval of Spritam® in 2015.

In January 2017, the FDA published a review highlighting the emergence of 3D printing as a technology with immense potential in pharmaceutical manufacturing. This publication emphasized the future prospects of 3D printing. Subsequently, in July of the same year, the FDA issued an industry guidance document that focused on the advancement of emerging technology applications for pharmaceutical innovation and modernization. This guidance specifically highlighted the importance of 3D-printing technology and continuous manufacturing as strategic directions for the industry.

In 2019, the China Center for Drug Evaluation (CDE) also published a review, expressing recognition and concern for the 3D-printed drug industry. CDE anticipates the advent of 3D printing, which will usher in an era of personalized and intelligent drug delivery.

Triastek's 3D MED printing technology was approved to join the FDA Emerging Technologies program in 2020, signifying regulatory approval for the technology. In January 2021, T19, the world's second 3D printing mechanism, received FDA IND approval. Triastek also actively participated in Q13, a continuous manufacturing conference hosted by CDE in China in the same year to promote pharmaceutical technology innovation.

In 2021, the National Academies of Sciences, Engineering, and Medicine commissioned the Center for Drug Evaluation and Research to produce a report on drug manufacturing innovations. The report concluded that 3D printing has the potential to revolutionize pharmaceutical manufacturing.(18)

## 2. Co2 LASER :

A laser is a tool that emits a concentrated beam of light through stimulated emission, a process that amplifies the light's intensity. Due to its narrow beam, the laser can be focused on a small area, making it highly directional. This ability to concentrate its energy in a small space results in a more intense light than regular light.

The wavelengths of lasers used in photosurgery vary depending on their intended use and come in different types. Among these lasers, the CO<sub>2</sub> laser is widely utilized in the field of dermatology. With a wavelength of 10,600 nm in the mid-infrared range, the CO<sub>2</sub> laser is highly absorbed by water. Since the skin has a high water content, the CO<sub>2</sub> laser is particularly suitable for precise and safe removal of tissue, while also ensuring effective control of bleeding. Apart from its effectiveness in removing benign raised lesions, the CO<sub>2</sub> laser has also shown promising results in esthetic dermatology, specifically in treating acne scars and achieving photorejuvenation. By fractionating the energy beam into numerous microbeams, the fractional CO<sub>2</sub> laser has bridged the gap between fully ablative procedures and nonablative skin rejuvenation systems of the 2000s. This advancement has allowed for the rejuvenation of photoaged skin on both the face and other areas of the body.(19)

The CO<sub>2</sub> laser, invented by Kumar Patel of Bell Labs in 1964, was among the earliest gas lasers to be developed and remains one of the most valuable. It is currently the highest-power continuous wave laser available and boasts impressive efficiency, with output power to pump power ratios reaching up to 20%. The CO<sub>2</sub> laser emits infrared light with primary wavelength bands centered around 9.4 and 10.6 micrometers, and its laser action is achieved through transitions between vibrational and rotational levels of molecules. The construction of this laser is straightforward, and its output is continuous. In the CO<sub>2</sub> molecular gas laser, transitions occur between the vibrational states of carbon dioxide molecules.

### Principle :

The active medium comprises a gas blend consisting of CO<sub>2</sub>, N<sub>2</sub>, and He. The laser transition occurs within the vibrational states of CO<sub>2</sub> molecules. The active medium comprises a gas blend consisting of CO<sub>2</sub>, N<sub>2</sub>, and He. The laser transition occurs within the vibrational states of CO<sub>2</sub> molecules.(21)

## 3. Graphene Based Electrode :

Graphene has a relatively low specific capacitance since it only stores the charge on the electrode's surface in the EDL. A single electrode material in a supercapacitor cannot provide enough energy and power density. It is reasonable to create a composite electrode using two different materials to combine their advantages and reduce their disadvantages. Graphene displays a relatively low specific capacitance due to its ability to only store the charge on the electrode's surface in the EDL. A single electrode material in a supercapacitor is insufficient in providing the necessary amount of energy and power density. It is a logical approach to produce a composite electrode by utilizing two different materials to merge their benefits and mitigate the drawbacks of the materials.(22)

The potential of graphene and its composites as electrodes has been widely recognized due to their impressive electrical conductivity and large surface area. These electrodes can be categorized into various types, including graphene, graphene composites with metal oxides, conductive polymers, ferrites, and other advanced materials. Among all carbon-based electrodes, graphene-based electrodes have garnered significant attention due to their exceptional conductivity, ideal power density, and remarkable mechanical properties. However, it is important to note that graphene does have some limitations, such as poor capacitance and lower energy density, as it solely stores energy through electrostatic adsorption and desorption processes.

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In the current Li-ion battery (LIB) technology, graphite is commonly used as an anode material due to its safety and low cost. However, graphite's tightly stacked layered structure limits its theoretical capacity (372 mAhg<sup>-1</sup>) and rate performance, making it unable to meet the high energy and power density requirements of modern electronic devices. The emergence of graphene presents an opportunity to utilize carbon materials in constructing a nanostructure with superior electrochemical performance compared to bulk graphite. In defect-free graphene sheets, LiC<sub>3</sub> structures can be formed, allowing lithium to be stored on both sides of the graphene sheet and resulting in a theoretical capacity of 744 mAhg<sup>-1</sup>. Graphene has already surpassed many carbon materials in the field of energy storage due to its large surface area and high conductivity. However, challenges still exist. Specifically, the full utilization of graphene's potential is hindered by the tendency of graphene nanosheets (GNS) to aggregate during preparation and application processes. This aggregation leads to the loss of individual GNS properties and the formation of discontinuous channels that impede fast ion transport.

Furthermore, graphene's high surface area and conductivity make it an ideal candidate for supercapacitor electrodes. The electric double-layer capacitance (EDLC) of a material is directly proportional to its surface area, making graphene well-suited for this application. The use of graphene as a supercapacitor electrode was initially explored by Ruoff and colleagues, who discovered that chemically derived graphene powder exhibits specific capacitances of 135 and 99 Fg<sup>-1</sup> in aqueous and organic electrolytes, respectively. Subsequent reports have highlighted different forms of graphene with improved performance. The variations in capacitance values obtained with different forms of graphene primarily depend on the stacking and surfaces of the graphene nanosheets.

#### **Conflicts of interest :**

**None Of Declared .**

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## **II. Conclusion :**

Sweating is a bodily function that regulates body temperature through evaporation, but it is also an important autonomic function in hypoglycemia. Sweat is primarily composed of water, but also contains sodium, chloride, potassium, lactic acid, and urea. A chemical study found that combining sweat measurements with electrocardiogram signals could predict the development of hypoglycemia in patients with type 1 diabetes.

Although sweat contains lower concentrations of glucose than blood (10–200 µM), harvesting glucose from the skin must be done carefully to avoid contamination. Wearable sensors can use sweat without affecting human health. There is interest in developing sweat-based sensors and systems designed to monitor health to help manage diabetes. One study developed a microfluidic device that used cotton threads and filter paper in conjunction with a smartphone to detect sweat glucose. The device exhibits distinct lines in the range of 50–250 µM with a detection limit of 35 µM, and the nature of the sensor structure makes it flexible, easy to integrate, and inexpensive to build. Another study developed a biosensor based on graphene oxide nanostructured composites embedded with gold and platinum nanoparticles for the detection of diabetes in human sweat. The device exhibits short response time and high linearity when testing using sweat samples. A 3D printed electrochemical sweat sensor has been shown to be able to monitor sweat glucose levels ranging from 12.5 to 400 µmol/ring. You can read it on your smartphone.

However, the experimental model was limited to one healthy volunteer. Similarly, Semionatto et al. (2021) developed a sweat sensor to estimate blood sugar levels. The electronic sensor consists of a sweat mechanism, a glucose biosensor and a non-sweat substrate. The sensor achieved good correlation (i.e. 0.95) with all points in regions A and B of the blood glucose and Clark error tables. In another study, a tandem catalytic system was developed for the detection of glucose in sweat based on chemiluminescence. This system demonstrated high sensitivity and a detection limit of 0.1 µM compared to solutions containing glucose. Smart wearable devices worn on the wrist have become an important part of fitness and exercise. Health care. The convenience of wearing a watch on your wrist further expands the range of applications of portable devices. Various wristband sensors have been developed to detect glucose in sweat. One study demonstrated an anaerobic wearable sensor that can detect glucose in sweat.

The sensor is made of silver electrodes coated with a fluorocarbon material. The sensor-embedded bracelet continuously monitors your sweat levels and displays the results via a smartphone app. Their solution was shown to be able to detect glucose in the range of 30 to 1100 µM. However, the tool was developed solely to test samples collected by participants and has nothing to do with diabetes.

Another research group has developed a combination that allows continuous monitoring of glucose levels in sweat. The device has a flexible battery and a photovoltaic array that is used to harness solar energy to power the device (e.g. for signal processing and imaging). Sweat analysis is based on an electrochemical sensor connected to a control module. A small monitor is used to provide immediate intervention. This wearable device demonstrates the ability to detect changes in sweat glucose levels in the range of 50 to 200 µM during activities such as running and cycling.

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