ISSN: 2976-7466

Journal of Biosensors and Bioelectronics Research

Mini Review

Open Access

Advances in Lactose Biosensors and Sensors: A Mini Review

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ABSTRACT

Quantitative determination of lactose in different dairy products is required to access their nutritional value and diagnosis of various diseases such as lactose intolerance, diarrhoea, nausea, abdominal bloating, vomiting and flatulence. Among the various methods available for lactose, bio-sensing, methods based on immobilized β-galactosidase and glucose oxidase are better, as these are more simple, sensitive, specific and rapid. The present mini review describes various bio-sensing and sensing methods for determination of lactose. The lactose biosensors work ideally in the pH range, 5.0 to 7.0, temperature 30-35^{0}C, response time 4-30s and linear concentration range 1μM to 100 mM, with LOD ranging from 1 μM to 4 mM. The lactose biosensors had storage stability between 10-20 days at 4^{0}C.The miniaturization of lactose biosensors is expected to make them portable and commercial individuals. Non enzymatic lactose sensors offer advantages over enzymatic biosensors byovercoming enzyme stability, simpler fabrication and providing higher sensitivity, broader working range(1fM to 3.47 mM) and lower detection limit 200aM to 26μM.However, non enzymatic biosensors are not specific like enzymatic biosensors.

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Received: April 02, 2025; **Accepted:** April 04, 2025; **Published:** April 16, 2025

Keywords: Lactose, Biosensors, Sensors, β-Galactosidase, Glucose Oxidase, Dairy Products

Introduction

Lactose, a disaccharide of glucose and galactose linked by beta - 1,4 glycosidic bond, is found in milk or other biological fluids. Determination of lactose is very important due to its relationship with nutritional value of milk, diagnosis and medical management of lactose intolerance, diarrhoea, nausea, abdominal bloating, vomiting and flatulence. The inability of adults and children to digest lactose is known as lactose malabsorption. The production of lactase declines mostly in the children of ages 2-5 years [1, 2]. The people in whom lactose is not metabolized, called lactose intolerant. It acts as substrate for gas-producing gut flora, which convert it into acetic acid, butyric acid, propionic and other short chain fatty acids, which can lead to diarrhoea, bloating, flatulence, and other gastrointestinal symptoms. A gassy and nauseous feeling is caused by CO2, methane and hydrogen as by-products [3, 4]. Compared to tedious, time consuming, expansive traditional methods such as spectrophotometry, infrared spectroscopy, titrimetry, and chromatography, biosensing methods are more simple, sensitive, specific and rapid for determination of lactose [5-9].

Concept of Biosensors/Sensors

A biosensor is an analytical device, used for the detection of an analyte that combines a biological component with a physico-chemical detector (Fig. 1). Biosensor represents an interesting alternative for the development of fast, efficient, user-friendly and low-cost diagnostic devices. Since the development of the first biosensor almost 50 years ago in 1962 by L.C. Clark, biosensors technology has experienced a considerable growth in terms of complexity of devices and suitable applications. Nowadays, this growth has been increased, due to the use of electrodes –modified with nanostructured materials, in order to increase the power detection of specific molecules. Sensors differ from biosensors, as these do not involve biological component and are also not much specific.

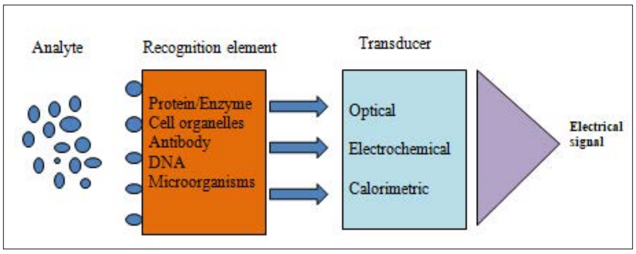

Figure 1: Elements of Biosensor

Enzyme, antibody, nucleic acid, lectin, hormone, cell structure or tissue can be used as bio- components. Its role is to interact specifically with the target analyte and to measurable signal. Transducer converts the biological signal into a measureable signal [10].

Classification of Biosensors/Sensors

Based on transducer, biosensors can be classified into following types (Fig. 2):

Electrochemical
The basic principle for this class of biosensors is that chemical reactions between immobilized biomolecule and target analyte produce or consume ions or electrons, which affects measurable electrical properties of the solution, such as electric current or potential [11]. These are of two types: Amperometric and potentiometric.

Amperometric
Amperometric biosensors measures the current generated by enzyme catalyzed reactions such as electroxidation/electroreduction/hydrolysis/phosphorylation [12].

Potentiometric
This class of biosensors quantifies the difference in potential that is generated across an ion-selective membrane separating two solutions at virtually zero current flow [13].

Conductometric (Impedimetric)
Conductometric biosensors sense the change in conductivity or resistivity of the reaction mixture as ions or electrons are produced during the course of biochemical reaction [14].

Ion-Sensitive
Biosensors based on ion-selective field-effect transistors (ISFETs), earlier considered as a category of potentiometric sensor [15].

Optical
The optical biosensors are based on fluorescence or optical diffraction. A fluorescence-based device detects the change in frequency of electromagnetic radiation emission, which is generated by either absorption of radiation or by generation of an excited state lasting for a very short time .Surface plasma resonance (SPR) biosensors are included under this class/category [16].

Piezoelectric (Mass-Sensitive)
These are based on the coupling of the bioelement with a piezoelectric component like quartz-crystal coated with gold electrodes. Different materials e.g. quartz, tourmaline, lithium niobate or tantalate, oriented zinc oxide or aluminium nitride exhibit the piezoelectric effect and can be used for fabrication of piezoelectric biosensors [17].

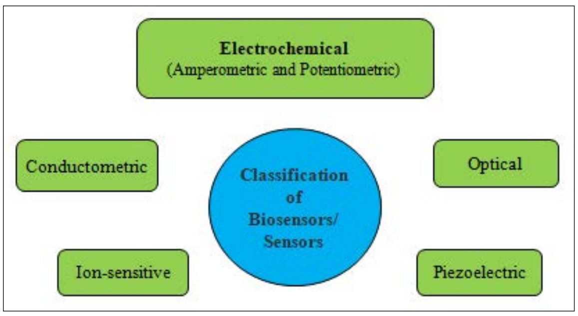

Figure 2: Classification of Biosensors/Sensors

This review describes the development of enzymatic sensors (Biosensors) and non-enzymatic sensors for lactose and their improvements in recent years.

Enzymatic Lactose Sensors or Lactose Biosensors
Working Principles of Lactose Biosensor
Lactose biosensing is based on enzymatic hydrolysis of lactose in solution into glucose and galactose by β-galactosidase (β-GaL), followed by measuring the decrease of the dissolved oxygen concentration in oxidation of glucose-by-glucose oxidase (GOx) or generation of H_2O_2 followed by its electrolytic oxidation into 2H+, ½ O_2, and 2e- (current) under high voltage, which is measured amperometrically (Fig 3). The resulting oxygen consumption rate or current generated, is directly related to the lactose concentration.

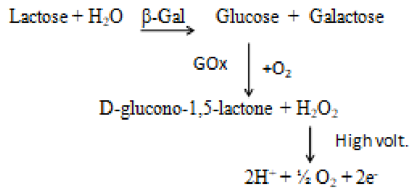

Figure 3: Chemical Reactions Involved in Biosensing of Lactose

Membrane Based Lactose Biosensors
Polyethersulphone Membrane Based Amperometric Lactose Biosensor
Lourenço et al., developed an amperometric biosensor for lactose determination in raw milk based on immobilization of β-galactosidase (β-Gal) and galactose oxidase on a derivatised polyethersulphone membrane. The sensitivity and the LOD of biosensor were 1.06uA/cm ^{2} /mM and 0.15mmol/L respectively. The storage stability in cold of biosensor was 20-days [18].

Langmuir-Blodgett (LB) Films-Based Biosensor
Similarly, Sharma et al., fabricated Langmuir-Blodgett (LB) films of poly (3-hexyl thiophene) (P3HT)/steric acid (SA) for estimation of lactose in milk. The enzyme immobilized LB film was used as working electrode and platinum as reference electrode. The enzyme electrode showed a linear range of 1-6g/dl of lactose, at pH 7.0 and 30^{0}C [19].

Polyvinyl Formal Membrane Based Lactose Biosensor
Sharma et al., developed lactose biosensor by immobilizing β-galactosidase and galactose oxidase in a polyvinyl formal membrane and attached it onto the oxygen electrode of a dissolved oxygen analyzer for determination of lactose in milk and milk products. The enzyme immobilized polyvinyl formal membrane was characterized by atomic force microscopy. The biosensor showed a linear range of 1-7g/dl of lactose and was reused for upto 20 measurements. The immobilized enzyme membrane was found stable up to 35^{0}C and pH 6.5 [20].

Nanosized Poly (Meta-Phenylenediamine) Film Based Biosensor
Pyeshkova et al., developed a new three-enzyme (β-galactosidase, mutarotase, glucose oxidase) based lactose amperometric biosensor modified by nanosized semipermeable poly (meta-phenylenediamine) film. Platinum disc electrode was used as a working electrode. The biosensor showed linear range from 0.01 mM to 1.25 mM of lactose, high signal reproducibility (RSD=1.16%), high sensitivity (LOD=0.005 mM) and high selectivity. The response time was 30s. Thus, the developed biosensor suited for rapid, inexpensive, sensitive, selective and simple determination of lactose in milk samples [21].

Enzyme Electrode Based Lactose Biosensors
These are classified further into following:

Indium Tin Oxide (ITO) Electrode Based Amperometric Biosensor
Campos et al., developed amperometric lactose biosensor using

β-galactosidase immobilized in layer-to-layer films with the polyelectrolyte poly (ethylene imine) (PEI) and poly (vinyl sufonate) on an indium tin oxide (ITO) electrode modified with a layer of purussian blue (PB). This biosensor showed a detection limit (LOD) of 1.13 mmol /L and was able to detect lactose in milk [22].

Platinum Electrode Based Electrochemical Biosensor
Nguyen et al., fabricated a lactose biosensor by co-immobilizing β-galactosidase (β-Gal) and glucose oxidase (GOx) onto surface of Pt/graphene/ polydiaminonaphthalene (P(1,5-DAN) for its use in dairy products. Graphene was synthesized by chemical vapor deposition on copper tape and manually transferred to the electrode surface. The characterization of modified electrode was studied by Raman spectra analysis, Field emission scanning electron microscopy (FE-SEM), Atomic Force Microscopy (AFM) and cyclic voltammetry. The observations revealed that deposited electrode surface induced considerable enhancement in current signal, over 20- times as high as the uncoated electrode surface. The developed sensor showed sensitivity (1.33 μA/(μgml^{-1}), correlation coefficient (R^2) (0.995) and a LOD of 1.3 μg/ml [23].

Gold Electrode Based Biosensor
Marrakchi et al., constructed a conductometric lactose biosensor based on glucose oxidase and beta galactosidase immobilized onto Au electrode for specific determination of lactose in milk. A linearity for lactose concentration between 60 and 800μM (0.03 to 0.3 g/l) was observed [24].

Nanomaterial Based Lactose Biosensor
Carbon Nanotubes (CNTs) Based Biosensor
Brito et al. in 2020, developed an amperometric biosensor based on lactase (LAC) and graphite (carbon) paste (CP) which were immobilized on carbon nanotubes (CNTs) for determination of lactose. The electrochemical cell of this biosensor was composed of three electrodes: reference electrode (Ag/AgCl), auxiliary electrode (platinum wire), and working electrode (CP/LAC/CNT). The composite was studied by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). The biosensor (CP/LAC/CNT) showed sensitivity as 5.67 μA cm^{-2}.mmol^{-1} L and detection limit of 100×10^{-6} mol L^{-1} (electrode area = 0.12 cm^2). An increase in the stability of the electrode was observed with the introduction of CNTs for 12 h, which caused no variation in the signal (current). These results indicated that the association between the CNTs and LAC favoured the electrochemical system [25].

Carbon Nanotube Matrix-Carbon Paste Based Biosensor
Recently, Brito et al. 2021, fabricated an electrochemical biosensor based on immobilization of lactase in the carbon nanotube matrix-carbon paste base for the quantitative detection of lactose in skimmed milk. The biosensor exhibited good sensitivity (1.06 μA cm^{-2} mmol^{-1} L), low detection limit (0.15 mmol L^{-1}) for lactose. The operational stability of electrode was observed for 10- days [26].

Gold Nanoclusters Based Biosensor
Guo et al. 2021, manufactured a fluorescence lactose sensor based on co-immobilization of β-galactosidase (β-Gal) and glucose oxidase (GOx) onto zeolite imidazole frameworks (ZIF) containing Au nanoclusters (AuNCs) for detection of lactose. The composite (AuNCs/β-Gal/GOx@ZIF-8) was prepared using co-precipitation methods at room temperature. AuNCs showed distinct advantages due to extremely small size (<1 nm), simple synthesis, excellent biocompatibility and high stability compared to other fluorescent nano-materials. Furthermore, the bovine serum albumin on their surfaces could promote the formation of ZIF-8 coating; thus, AuNCs were co-encapsulated in ZIF-8 with the enzymes together. Fluorescence microscope images, Fourier transform infrared (FTIR) spectra and energy dispersive X-ray spectroscopy indicated the presence of AuNCs in the composite. The introduction of the fluorescent probe and the quenching agent (Fe^{2+}) enhanced the quenching effects in AuNCs/β-Gal/GOx@ ZIF-8 system. Furthermore, quenching effects were enhanced by the ZIF-8 coating [27].

Hapin G et al. (2022) presented the development of lactose biosensors for rapid quantification of lactose in dairy samples like whey permeates and milk protein isolates (MPI). The biosensor involved a CS (chitosan) /enzyme/crosslinker configuration with enzymes, β-Gal and GOx at Pt and Glassy carbon (GC) electrode. The linear range was between 5.83mM -16.5mM with LOD of 1,38mM. The method showed good correlation (R^2 =0.92) with HPLC method [28].

Enzyme Nanoparticles Based Lactose Biosensor
We have prepared enzyme nanoparticles (ENPs) of β-galactosidase (β-Gal) and glucose oxidase (GOx) by desolvation method using ethanol as dehydrating agent and characterized them by Transmission electron microscopy (TEM) and Fouier Transform Infra-Red Spectroscopy (FTIR). These ENPs were then co-immobilized covalently onto polycrystalline Au lectrode to construct an improved amperometric lactose biosensor. The working electrode was studied by scanning electron microscopy (SEM) and cyclic voltammetry (CV) before and after immobilization of ENPs. The biosensor showed optimum activity within 5s at pH 6.5 and 25^{0}C, when polarized at 0.25V. The biosensor had a linearity in 1.0-10.0 mg/ml with a LOD of 1.0mg/ml. Within and between batch coefficient of variation (CV) were < 3.0 and <4.0 respectively. The biosensor was employed for detection of lactose in milk of human, cow, buffalo and goat. It retained 50% of its initial activity, when used regularly for120-times, with storage at 4^{0}for 3 months. The biosensor showed a good correlation (R^2=0.91) with standard enzymic colourimetric method [29].

Cellobiose Dehydrogenase (CDH) Based Lactose Biosensors
Stoica et al., constructed a third-generation lactose biosensor based on cellobiose dehydrogenase (CDH) immobilized on the electrode surface by physical adsorption. It showed a linear range from 1-100 μM, detection limit of 1 μM, sensitivity of 1100 μA·mM^{-1}·cm^{-2}, a response time of 4s and correlation coefficient 0.998. This sensor measured the content of lactose in pasteurized milk, buttermilk and low-lactose milk [30].

Yakovleva et al., developed thermometric and amperometric biosensor for determination of lactose based on immobilized CDH. The reactor was prepared by cross linking CDH onto aminopropyl-silanised controlled pore glass (CPG) beads using gluteraldehyde. The combined biosensor worked in flow injection analysis (FIA) mode. The linear response for lactose was obtained between 0.05 mM and 50mM [31].

Choi et al. in 2020, fabricated a lactose biosensor by immobilizing CDH onto Co-hemin metal organic frameworks (Co-hemin MOF)/chitosan composite. The biosensor exhibited outstanding electrochemical performance for lactose detection with high sensitivity (102.3 μA mM^{-1} cm^{-2}), fast response time (5 s), low detection limit (4 mM) and the broad linear range (10 to 100 mM) [32].

Nasiri H et al., utilized a nanohybrid of a graphite nitride($g-C_3N_4$) supported by magnetic chitosan (MNM/CS), CDH on Au thin layer to construct a Surface Plasma Resonance (SPR) lactose biosensor. CDH was immobilized covalently on this support. The finite difference time domain (FDTD) approach was used to mimic the sensor's SPR behavior. The method could be used in food industry, in the range 0.01-100 mM a with LOD of 5 µM, the biosensor was extremely sensitive demonstrating its accuracy in lactose determination [33].

Alternating Current Electrophoretic Deposition (AC-EPD) Based Biosensor

Ammam et al., immobilized β-galactosidase and glucose oxidase onto platinum electrode as working electrode using alternating current electrophoretic deposition (AC-EPD) to synthesize a lactose sensor. The sensor showed linearity up to 14mM lactose, fast response time (~8s) and reasonable stability without using any stabilizers outer polymer membrane. The biosensor was simple and easy to manufacture, highly reproducible and cheap, because low activity enzymes were used. The immobilized enzyme electrode was stable up to 30^0C and pH 4.9 [34].

Recently, Ding Y et al., reviewed the advanced lactate biosensors materials, methods and application in modern healthcare. The review described the concept and composition of electrochemical lactate biosensors, such as surface related materials and detection techniques. They also discussed implantable and non-implantable miniaturization. However other types of biosensors like CDH based and SPR based lactose biosensors and non-enzymic lactose sensors were not included in this review [35].

Non-Enzymatic Lactose Biosensors

Although the enzyme-based sensor showed high selectivity and excellent sensitivity, the activity of enzyme decreases with the use of the sensor and the enzyme is easily denatured during its immobilization procedure, due to the intrinsic nature of enzyme. In addition, the activity of enzyme is liable to be affected by temperature, pH, and toxic chemicals. Moreover, the reproducibility of enzyme-based biosensor is not very good and therefore requires to be improved further. These disadvantages restricted the application of lactose biosensor. In order to overcome the disadvantages of enzymatic lactose sensors, non-enzymatic lactose sensors have been designed and fabricated with high stability, reproducibility, low cost and freedom from oxygen limitations. Few lactose non enzymic sensors have been reported.

Copper (Cu) Foam Electrode Based Sensor

Jin et al., designed Cu foam electrode for non-enzyme quantitative and qualitative analysis of D-Glucose, D-Galactose, and D-Lactose. The electro-oxidation process occurring on Cu foam electrode was measured by cyclic voltammetry (CV). The results demonstrated that Cu foam electrode fast responded to D-glucose, D-galactose, and D-lactose in linearity between 0.18 mM and 3.47 mM, limit of detection (LOD) was 9.30 µM, 29.40 µM, and 26 µM respectively (S/N = 3) and sensitivity of 1.79 mA cm^{-2} mM^{-1}, 0.57 mA cm^{-2} mM^{-1}, and 0.64 mA cm^{-2} mM^{-1}, respectively which provided a promising way for sweetener non-enzyme quantitative and qualitative analysis of D-glucose, D-galactose, and D-lactose [36].

HPAEC-PAD Based Sensor

Scheppingen et al., constructed a new high performance anion exchange chromatography with PAD detection (HPAEC-PAD) analysis on a Carbo Pac PA100 column to separate lactose from other disaccharides. The sample was prepared by dilution, centrifugation and ultrafiltration to separate lactose from the sample matrix. The demand for low lactose dairy products is increasing and more different lactose free food is commercially available. The level of lactose in these products decreased during the last years and nowadays a concentration of <0.01% is generally accepted as "lactose free". Hence this method was employed for the determination of low concentrations of lactose in a wide range of dairy products [37].

Graphene Field-Effect Transistors (G-FET) Based Biosensor

Monti et al., fabricated field-effect transistor (FET) lactose biosensor based on graphene decorated with gold nanoparticles (AuNPs). The graphene was functionalized with a carbohydrate recognition domain (CRD) of the human galectin-3 (hGal-3) protein. This biosensor achieved lactose linearity ranging from 1 fM to 1 pM (10^{-15} to 10^{-12} mol L^{-1}), low detection limit (200 aM), which indicated the potential of a combined lectin and graphene FET (G-FET) sensor to detect lactose at high sensitivity and specificity for disease diagnosis [38].

Molecularly Imprinted (MIP) Sensor Based on Disposable Graphite Paper Electrode

Silva et al., developed an innovative disposable paper-based non-enzymatic voltammetric sensor for sensitive detection of lactose using electropolymerized pyrrole (Py) molecularly imprinted polymer (MIP) on graphite paper electrode (PE). MIP was used as a synthetic receptor for the recognition of lactose. The results showed that under optimized conditions, the electrode was highly sensitive and selective, with two dynamic linear ranges of concentration (1.0–10 nmol L^{-1} and 25–125 nmol L^{-1}) with a detection limit of 0.88 nmol L^{-1}. It was useful for detection of lactose in whole and lactose-free milks. The proposed MIP/PPy/PE sensor exhibited good stability, as well as excellent reproducibility and repeatability [39].

Conclusion

It is concluded that bio-sensing methods are comparatively better method than conventional methods as these are comparatively more simple, specific, sensitive and rapid. The lactose biosensors were optimally active in the pH range 5.0 to 7.0, temperature 30-35◦C, response time 4-30s and linear concentration range 1µM to 100 mM, with LOD ranging from 1 µM to 4 mM. However, the bio-interference and bio-recognition of lactose biosensors are still not fully understood. Future research can be focused on miniaturization of lactose biosensors to make them portable and their application in miniaturized form.

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