GOCE DELCEV UNIVERSITY, SHTIP, NORTH MACEDONIA

FACULTY OF ELECTRICAL ENGINEERING

ETIMA 2021

FIRST INTERNATIONAL CONFERENCE

19-21 OCTOBER, 2021

TECHNICAL SCIENCES APPLIED IN ECONOMY, EDUCATION AND INDUSTRY

УНИВЕРЗИТЕТ „ГОЦЕ ДЕЛЧЕВ” - ШТИП
ЕЛЕКТРОТЕХНИЧКИ ФАКУЛТЕТ

UNIVERSITY „GOCE DELCHEV” - SHTIP
FACULTY OF ELECTRICAL ENGINEERING

ПРВА МЕЃУНАРОДНА КОНФЕРЕНЦИЈА
FIRST INTERNATIONAL CONFERENCE

ЕТИМА / ETIMA 2021

ЗБОРНИК НА ТРУДОВИ
CONFERENCE PROCEEDINGS

19-21 Октомври 2021| 19-21 October 2021

Главен и одговорен уредник / Editor in Chief
Проф.д-р Сашо Гелев
Prof.d-r Saso Gelev

Јазично уредување / Language Editor
Весна Ристова (Македонски) / Vesna Ristova (Macedonian)

Техничко уредување / Technical Editing
Доц.д-р Далибор Серафимовски / d-r Dalibor Serafimovski

Издавач / Publisher
Универзитет „Гоце Делчев" - Штип / University Goce Delchev - Stip
Електротехнички факултет / Faculty of Electrical Engineering

Адреса на организационен комитет / Adress of the organizational committee
Универзитет „Гоце Делчев" – Штип / University Goce Delchev - Stip
Електротехнички факултет / Faculty of Electrical Engineering
Адреса: ул. „Крсте Мисирков" бр. 10-А / Adress: Krste Misirkov, 10 - A
Пош. фах 201, Штип - 2000, С.Македонија / PO BOX 201, Stip 2000, North Macedonia
E-mail: conf.etf@ugd.edu.mk

CIP - Каталогизација во публикација
Национална и универзитетска библиотека "Св. Климент Охридски", Скопје

62-049.8(062)
004-049.8(062)

МЕЃУНАРОДНА конференција ЕТИМА (1 ; 2021)
Зборник на трудови [Електронски извор] / Прва меѓународна конференција ЕТИМА 2021, 19-21 Октомври 2021 = Conference proceedings / First international conferece ETIMA 2021, 19-21 October 2021 ; [главен и одговорен уредник Сашо Гелев]. - Штип: Универзитет "Гоце Делчев", Електротехнички факултет = Shtip: University "Goce Delchev", Faculty of Electrical Engineering, 2021

Начин на пристапување (URL): https://js.ugd.edu.mk/index.php/etima. - Текст во PDF формат, содржи 358 стр.илустр. - Наслов преземен од екранот. - Опис на изворот на ден 15.10.2021. - Трудови на мак. и англ. јазик. - Библиографија кон трудовите

ISBN 978-608-244-823-7

1. Напор. ств. насл.
а) Електротехника -- Примена -- Собири б) Машинство -- Примена -- Собири
в) Автоматика -- Примена -- Собири г) Информатика -- Примена -- Собири

COBISS.MK-ID 55209989

Прва меѓународна конференција ЕТИМА
19-21 Октомври 2021
First International Conference ETIMA
19-21 October 2021

ОРГАНИЗАЦИОНЕН ОДБОР
ORGANIZING COMMITTEE

Василија Шарац / Vasilija Sarac
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Сашо Гелев / Saso Gelev
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Тодор Чекеровски / Todor Cekerovski
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Далибор Серафимовски / Dalibor Serafimovski
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Маја Кукушева Панева / Maja Kukuseva Paneva
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Билјана Читкушева Димитровска / Biljana Citkuseva Dimitrovska
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Весна Конзулова / Vesna Konzulova
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Прва меѓународна конференција ЕТИМА
19-21 Октомври 2021
First International Conference ETIMA
19-21 October 2021

ПРОГРАМСКИ И НАУЧЕН ОДБОР
SCIENTIFIC COMMITTEE

Со Ногучи / So Noguchi
Висока школа за информатички науки и технологии
Универзитет Хокаидо, Јапонија
Graduate School of Information Science and Technology
Hokkaido University, Japan

Дионис Гашпаровски / Dionýz Gašparovský
Факултет за електротехника и информациони технологии,
Словачки Технички Универзитет во Братислава, Словачка
Faculty of Electrical Engineering and Information Technology
Slovak Technical University in Bratislava, Slovakia

Антон Белан / Anton Beláň
Факултет за електротехника и информациони технологии
Словачки Технички Универзитет во Братислава, Словачка
Faculty of Electrical Engineering and Information Technology
Slovak Technical University in Bratislava, Slovakia

Георги Иванов Георгиев / Georgi Ivanov Georgiev,
Технички Универзитет во Габрово, Бугарија
Technical University in Gabrovo, Bulgaria

Ивелина Стефанова Балабанова / Ivelina Stefanova Balabanova,
Технички Универзитет во Габрово, Бугарија
Technical University in Gabrovo, Bulgaria

Бојан Димитров Карапенев / Boyan Dimitrov Karapenev
Технички Универзитет во Габрово, Бугарија
Technical University in Gabrovo, Bulgaria

Сашо Гелев / Saso Gelev
Електротехнички факултет,
Универзитет „Гоце Делчев” - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Влатко Чингоски / Vlatko Cingoski
Електротехнички факултет,
Универзитет „Гоце Делчев” - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Божо Крстајиќ / Bozo Krstajic
Електротехнички факултет
Универзитет во Црна Гора, Црна Гора
Faculty of Electrical Engineering,
University in Montenegro, Montenegro

Милован Радуловиќ / Milovan Radulovic
Електротехнички факултет
Универзитет во Црна Гора, Црна Гора
Faculty of Electrical Engineering,
University in Montenegro, Montenegro

Гоце Стефанов / Goce Stefanov
Електротехнички факултет,
Универзитет „Гоце Делчев” - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Мирјана Периќ / Mirjana Peric
Електронски факултет
Универзитет во Ниш, Србија
Faculty of Electronic Engineerig,
University of Nis, Serbia

Ана Вучковиќ / Ana Vuckovic
Електронски факултет
Универзитет во Ниш, Србија
Faculty of Electronic Engineerig,
University of Nis, Serbia

Тодор Чекеровски / Todor Cekerovski
Електротехнички факултет,
Универзитет „Гоце Делчев” - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Далибор Серафимовски / Dalibor Serafimovski
Електротехнички факултет,
Универзитет „Гоце Делчев” - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Мирослава Фаркаш Смиткова / Miroslava Farkas Smitková
Факултет за електротехника и информациони технологии
Словачки Технички Универзитет во Братислава, Словачка
Faculty of Electrical Engineering and Information Technology
Slovak Technical University in Bratislava, Slovakia

Петер Јанига / Peter Janiga
Факултет за електротехника и информациони технологии
Словачки Технички Универзитет во Братислава, Словачка
Faculty of Electrical Engineering and Information Technology
Slovak Technical University in Bratislava, Slovakia

Јана Радичова / Jana Raditschová,
Факултет за електротехника и информациони технологии
Словачки Технички Универзитет во Братислава, Словачка
Faculty of Electrical Engineering and Information Technology
Slovak Technical University in Bratislava, Slovakia

Драган Миновски / Dragan Minovski
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Василија Шарац / Vasilija Sarac
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Александар Туџаров / Aleksandar Tudzarov
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

Владимир Талевски / Vladimir Talevski
Електротехнички факултет,
Универзитет „Гоце Делчев" - Штип, Северна Македонија
Faculty of Electrical Engineering,
Goce Delchev University - Stip, North Macedonia

PREFACE

The Faculty of Electrical Engineering at University Goce Delcev (UGD), has organized the International Conference ***Electrical Engineering, Informatics, Machinery and Automation - Technical Sciences applied in Economy, Education and Industry-ETIMA*.**
ETIMA has a goal to gather the scientists, professors, experts and professionals from the field of technical sciences in one place as a forum for exchange of ideas, to strengthen the multidisciplinary research and cooperation and to promote the achievements of technology and its impact on every aspect of living. We hope that this conference will continue to be a venue for presenting the latest research results and developments on the field of technology.
Conference ETIMA was held as online conference where contributed more than sixty colleagues, from six different countries with forty papers.
We would like to express our gratitude to all the colleagues, who contributed to the success of ETIMA'21 by presenting the results of their current research activities and by launching the new ideas through many fruitful discussions.
We invite you and your colleagues also to attend ETIMA Conference in the future. One should believe that next time we will have opportunity to meet each other and exchange ideas, scientific knowledge and useful information in direct contact, as well as to enjoy the social events together.

The Organizing Committee of the Conference

ПРЕДГОВОР

Меѓународната конференција ***Електротехника, Технологија, Информатика, Машинство и Автоматика-технички науки во служба на економија, образование и индустрија-ЕТИМА*** е организирана од страна на Електротехничкиот факултет при Универзитетот Гоце Делчев.
ЕТИМА има за цел да ги собере на едно место научниците, професорите, експертите и професионалците од полето на техничките науки и да представува форум за размена на идеи, да го зајканува мултидисциплинарното истражување и соработка и да ги промовира технолошките достигнувања и нивното влијание врз секој аспект од живеењето. Се надеваме дека оваа конференција ќе продолжи да биде настан на кој ќе се презентираат најновите резултати од истражувањата и развојот на полето на технологијата.
Конференцијата ЕТИМА се одржа online и на неа дадоа свој допринос повеќе од шеесет автори од шест различни земји со четириесет труда.
Сакаме да ја искажеме нашата благодарност до сите колеги кои допринесоа за успехот на ЕТИМА'21 со презентирање на резултати од нивните тековни истражувања и со лансирање на нови идеи преку многу плодни дискусии.

Ве покануваме Вие и Вашите колеги да земете учество на ЕТИМА и во иднина. Веруваме дека следниот пат ќе имаме можност да се сретнеме, да разменime идеи, знаење и корисни информации во директен контакт, но исто така да уживаме заедно и во друштвените настани.

Организационен одбор на конференцијата

Содржина / Table of Contents

UDC: 615.2:620.3

NANOTECHNOLOGY–BASED BIOSENSORS IN DRUG DELIVERY SYSTEMS: A REVIEW

Mihail Aleksandrov[1], Maja Kukuseva Paneva[2]

[1]Faculty of Medical Sciences, Goce Delcev University of Stip, Krste Misirkov, No. 10-A, 2000 Stip, Republic of North Macedonia; e-mail: aleksandrovmihail32@gmail.com
[2]Faculty of Electrical Engineering, Goce Delcev University of Stip, Krste Misirkov, No. 10-A, 2000 Stip, Republic of North Macedonia; e-mail: maja.kukuseva@ugd.edu.mk

Abstract

Going nano means not only the size of a matter will be reduced but also the matter can be manipulated on the molecular and atomic levels. As a result, it will bring many benefits. In the case of a nanoparticle or a quantum dot, for example, reducing the size will increase the surface activity and induce unique quantum effects (e.g., confinement of electrons or photons by controlling the densities of electron states or photon states). This in turn will lead to unprecedented electronic, optical, and magnetic properties of the nanoparticle and quantum dot. Furthermore, the ability to arrange and rearrange atoms and molecules at will in a material will help render novel physical and chemical properties for the material. In today's definition, biosensors are analytical devices that combine a biological-sensitive element with a physical transducer to selectively and quantitatively detect the presence of specific compounds in a given biological environment. The biological-sensitive element consists of biological receptors (as probes) made of molecular species such as antibodies, enzymes, or nucleic acids for binding the target analytes, and the physical transducer is for converting the biological recognition or binding event into an electrical or optical signal. Thus, from a material's viewpoint, today's biosensors consist of two major components: an organic part as the sensitive element and an inorganic part as the transducer element. Many progresses have been made in the development of lab-on-a-chip microscale devices, and surely these devices will become more compact and more functional with higher sensitivity, specificity, and reliability in terms of sensing and with higher controllability in terms of drug delivery as the field of nanobiotechnology advances, but full-fledged autonomous systems of biosensors for drug delivery applications may still be years away. Currently, the development of biosensors for drug delivery takes a slightly different route. As discussed in the Introduction, drug delivery systems have been evolving from the totally passive drug-carrying vehicles of the first-generation systems, the environmental-sensitive drug-carrying vehicles of the second-generation system, to the target-specific and bioactive drug-carrying vehicles of the third-generation systems. Following this route, one can see that by adding sensitive components to the drug delivery systems, integrated capabilities of biosensing and drug delivery can be realized. Thus, it is conceivable that the next-generation drug delivery systems could be biologically sensitive drug-carrying vehicles incorporated with an underlying transducer (e.g., optical or image based) for signal detection and communication. This route may eventually converge with the lab-on-a-chip route, leading to an autonomous system with both the diagnostic and therapeutic functionalities. But for now, one of the challenges in developing biosensitive drug delivery vehicles is to devise drug carriers that are biocompatible, resistive to biodegradation, resistive to host inflammatory and immunologic responses, and sensitive to specific targets, among other things. In addition, the drug carrier constructs should be highly effective in prolonged drug retention, especially for water-soluble drugs. Biological constructs such as liposomes are potentially good drug carrier materials due to their abilities to protect drugs from degradation and to target the specific site for action.

Key words: analytical devices, biosensors, drug delivery, nano-biotechnology, nanoparticle, physicochemical properties, transducer.

1. Introduction

Nanotechnology is not a single technology or discipline but it encompasses various technologies that crosses sectors, such as nanomaterials, medicine, devices, fabrication, electronics, communication and energy. It is the ability to measure and to control matter at the nanometer scale. Nanotechnology deals with the generation and alteration of materials to nanosize (10^{-9} m) [1]. Nanomaterials based biosensors which represents the integration of material science, molecular and electrical engineering, chemistry and biotechnology can markedly improve the sensitivity and specificity of biomolecule detection, hold the capability of detecting or manipulating atoms and molecules, and have great potential in application such as biomolecular recognition, pathogen diagnosis and environment monitoring.

As per IUPAC, biosensor is defined as "A self-contained integrated device which is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element which is in direct spatial contact with a transducer element". Biosensor is a device that combines a biological recognition element with a physical or chemical transducer detects a biological product [2]. It is a probe that integrates a biological component with an electronic component to yield a measurable signal. These biosensors consists of five components: (1) bioreceptors that bind the specific form to the sample; (2) an electrochemical interface where specific biological processes occurs giving rise to a signal; (3) a transducer that converts the specific biochemical reaction in an electrical signal; (4) a signal processor for converting the electronic signal into a meaningful physical parameter and finally and (5) a proper interface to display the results to the operator [3].

Going "Nano" means not only the size of a matter will be reduced but also the matter can be manipulated on the molecular and atomic levels. As a result, it will bring many benefits. In the case of a nanoparticle or a quantum dot, for example, reducing the size will increase the surface activity and induce unique quantum effects (e.g., confinement of electrons or photons by controlling the densities of electron states or photon states). This in turn will lead to unprecedented electronic, optical, and magnetic properties of the nanoparticle and quantum dot. Furthermore, the ability to arrange and rearrange atoms and molecules at will in a material will help render novel physical and chemical properties for the material [4]. In the case of biosensing, at the component level going "Nano" means that the capability to sense and detect the state of biological systems and living organisms will be radically transformed by the emerging ability to control the patterns of matter on the nanometer scale. Such a radical transformation is expected to enable sensing at the single-molecular level and with parallel detection of multiple signals in living cells. At the systems level, going nano will help decrease the size of the active sensing element to the scale of the target species (to increase the sensitivity and decrease the lower detection limit), reduce the required volumes of the analyte reagent, and minimize the detection time [5]. Reducing the size of biosensors can also result in tiny devices which maybe deployable to any desired location in the body.

Biosensors can provide feedback control by recognizing changes in its surrounding physiological or biological fluid and then taking "action", either in terms of simple movement of a device component or release of one or more drugs. In recent years we have seen an explosion in the field of such novel sensors and microfabricated devices for drug delivery [6]. Such devices provide a platform for well-controlled functions in the micro- or nano-level. They include nanoparticulate systems, recognitive molecular systems, biosensing devices, and

microfabricated and microelectronic devices. The synthesis and characterization of biomimetic gels for drug and protein delivery systems is a significant focus of recent research. There are numerous techniques for microfabrication of patterned polymer surfaces and microchips for medical devices [7]. While silicon has been the choice material for much of the research done, the methacrylates and acrylates could provide an inexpensive base for future work. Several applications have already been suggested including patterned surfaces for cell adhesion, biosensors, microfluidic devices, and arrays for chemical screening.

The physicochemical understanding of such hydrogels under the conditions of application is neither simple not well developed. Considering that all these carriers are ionic hydrogels, and that several ionic and macromolecular components are involved, with associated thermodynamically non-ideal interactions, it is evident that analysis and prediction of their swelling and response behavior is rather complex [8].

Environmentally responsive hydrogels lend themselves naturally to utilization in microfabricated devices. Polymerization of the required monomers and crosslinking agents can be done by free-radical polymerization using UV light, thus enabling photolithographic techniques to be adjusted to pattern these materials on the microscale. When hydrogels are immobilized within microstructures, the ability of the hydrogel to function is improved. There are many advantages of utilizing hydrogels in this way. First, hydrogels can be deposited permanently in specific locations of a substrate where they can exhibit their unique physiologically responsive characteristics repeatedly. Second, the hydrogels mechanical failure is less of an issue when the primary action is swelling against a well-defined structure. While biosensors and sensing devices are usually made of nonbiodegradable sensing materials and substrates, environmentally sensitive hydrogel networks whose crosslinks are degradable by hydrolysis can have a significant advantage over their nondegradable counterparts [9].

2. Hydrogel-based biosensing

Several decades of research have contributed to our understanding of stimuli-responsive hydrogels so that they can now be utilized in an abundance of sensing applications. A comprehensive knowledge of their physical and chemical properties exists along with how the materials interact with living systems [10]. Alongside, theory has evolved to explain the unique interaction of these systems with their environment and other external stimuli. Engineers are now poised to develop and utilize novel sensing systems that allow the biological processes of life to be monitored like never before.

Hydrogels are water-swollen hydrophilic crosslinked polymers, that do not dissolve in water or biological fluids because of chemical or physical crosslinks [11]. Certain hydrogels can sense changes in their environment on a molecular level, which lead to changes in their swollen volume. These are commonly referred to as environmentally responsive hydrogels. Large changes in the swelling ratio of these hydrogels can be observed with changes in the pH, temperature, ionic strength, nature of the swelling agent, and electromagnetic radiation [12]. Biomolecules are commonly immobilized within environmentally responsive hydrogels to yield biosensing materials. The most common of these is the immobilization of glucose oxidase within pH-responsive hydrogels to make glucose-sensitive materials.

pH-Responsive hydrogels are anionic, cationic, or amphiphilic. Anionic hydrogels exist in a collapsed state at low pH. When the pH of the external environment is raised above the pKa of the gel, they begin to swell. This is due to ionization of the side groups and repulsion of the like-charged chains. The charge repulsion is more powerful than other forces such as hydrogen bonding which exist between the chains in the collapsed state. At the molecular level and if the swelling is isotopic, this increase in volume corresponds to an increase in the network

mesh size. The reduced size of these hydrogel microstructures leads to faster mass transfer and chemomechanical response [13]. To better understand the kinetic response of hydrogel-based sensors, we must understand the kinetic response of the hydrogel itself. The swelling and shrinking of hydrogels requires transport of the stimulus into the network followed by water transport into or out of the network [14]. An interesting complexity in this system is that shrinking of the gel can generally occur more rapidly than its swelling. The characteristic response time in a hydrogel sensor is dependent on the square of the distance, so the hydrogel thickness should be as small as possible [15]. This is why microfabrication techniques are actively investigated with hydrogels. It is interesting to note that the type of transducer can further slow the kinetics of the sensor. If the method of transduction is based on measurement of the changes of the optical transparency or conductivity of the material, then free swelling kinetics can apply. If the volume change of the gel must be transduced mechanically, such as by the use of microcantilevers, then the sensor will be inherently slower. The external force required slows the sensor performance versus our free swelling models [15].

2.1. Application of hydrogels in biosensing – Hydrogels as immobilizing scaffold for biomolecules

The first examples of hydrogels in biosensing employed hydrogels for the immobilization of biomolecules to measure biospecific interactions. In one such example, *Fagerstam et al.* [16] covalently attached biomolecules to thin hydrogel films atop surface plasmon resonance chips to measure biomolecular interaction kinetics and concentration. Solutions containing biomolecules of interest were flowed over the hydrogel and small mass changes were measured with a sensitivity of 10 pg/mm^2. Some advantages of this early biosensor include that it did not require any biomolecular labeling and the sensor chip could be used repeatedly.

Immobilization of nucleic acids on solid supports has been widely used in the detection of DNA and other biomolecules in sensor technology. Because three dimensional hydrogel matrices offer significant advantages for capturing probes over more conventional two dimensional rigid substrates and the ability to provide a solution-mimicking environment, they are becoming increasingly attractive as desired supports for bio-analysis [17]. The use of hydrogels to immobilize enzymes for improved and sustained activity of biomolecules is not limited to the microscale. While commonly employed in lab-on-a-chip technologies, these materials also perform favorably in large-scale bioreactors as well. Hydrogel microspheres containing immobilized enzymes were used to monitor packed-bed bioreactor by *Guiseppi-Elie et al.* [18]. Enzyme activity was tested after the materials were stored in buffer at 4°C for one year. The materials retained 80% of their initial activity. This high stability shows promise towards the utilization of hydrogel-based biosensing materials on a variety of scales. Since scale-up is of common concern in the practice of chemical engineering, it is important to note that hydrogel-based biosensing elements have shown desirable performance at a variety of scales.

3. Drug Delivery Systems

Drug delivery system platform is a rapidly expanding market for pharmaceutical and biomedical engineering. In terms of pharmaceuticals, the need for drug carriers that will offer targeted drug delivery is of vital importance. This is of great value as it reduces the side effect profile by allowing usage of low dosage drugs, site specific activity and increased bioavailability. Non-targeted systemic drug administration leads to the bio-distribution of pharmaceuticals across the entire body [19]. This distribution causes toxicity effects on non-target tissues and wastage of pharmaceutical compounds since they are used by non-target

tissues. For biomedical engineering, design of devices that will offer better diagnosis and therapeutics is required to ensure better illness management. Biomedical engineering will aid in targeted drug delivery, selective targeting of imaging contrast agents, delivery of nucleic acid and genetic therapies, and prediction of pharmacokinetics and pharmacodynamics patterns of the drug [20].

Biomaterials are needed to design a stable and biocompatible drug delivery system. These can vary from natural polymers, metals compound, modified and synthetic polymers. Biocompatibility and biodegradation of these play a vital role in the toxicity effect of the system and its mode of action. A beneficial drug delivery system must have an effect on drug absorption, distribution, and metabolism levels [21]. This can be achieved by controlling drug delivery system. Controlled drug delivery systems function by means of controlling where and when the therapeutic agent will be released. The major features of controlled drug delivery system include the rate of drug release and mode of activation. Drug release may be rapid or may occur over a prolonged period of time depending on the required action and the location of the device in the body.

The mode of release and the rate is related to the biomaterial constituting the major part of the system. Depending on the location where the system is directed to release the drug, the biomaterial that make up the system play a role in terms of reacting with the physiochemical compounds to protect the therapeutics, sense the activator and also allow binding to the target site for localized drug release.

Targeted drug delivery can be done by means of using natural organic compounds. These natural compounds interact with surface of the synthetic/modified polymers and peptides. The use of sugar molecules which can be mucoadhesive allows targeting of the intestine. These will be stimulated by temperature (e.g., poly (N-isopropylacrylamide)) and pH level (polyacrylic acid and chitosan) for drug release. There are different kinds of polymers that can be used for this purpose; anionic (polyacrylic acid), cationic (chitosan), non-ionic (polyethylene glycols) and thiolated polymers (cysteine conjugates) [22].

Depending on the mode of action required for the drug delivery system, these biomaterials can be modeled into different forms such as spheres for carrying therapeutics and film/hydrogels layers for physiochemical response. For therapeutic implication, nanoparticles and liposomes are primarily used to adsorb and absorb drugs of interest and even for encapsulating the sensitive therapeutics. Targeted drug delivery requires binding of biochemical molecules which offer directed control of therapeutic action. For continuous and responsive drug delivery system, thin films and even nanoparticles may be used as they can respond to the physiochemical changes that may occur in the body. Hydrogels form a three-dimensional structure consisting of cross-linked networks of water-soluble polymers, which can undergo conformational changes once they interact with water [23]. They can further be modified to react at a certain temperature, detection of analyte based on interaction with functional groups or pH in relation to their mode of action and target site. Upon reaching a certain site of action, the swelling dynamics will change, allowing for the diffusion of a therapeutic from the network matrix. The fabrication of these systems relates to their chemical properties. If a system is designed for targeting the gastric intestinal tract, it must withstand physiochemical changes such as pH and temperature before it reaches its required site of action.

Polymers such as chitosan, polyvinyl alcohol and ethylene glycol, can be used for both targeted and responsive action. Chitosan as a drug carrier has been used for various administration routes such as oral, bucal, nasal, transdermal, parenteral, vaginal, cervical, intrauterine and rectal [24]. As a responsive or targeted drug delivery vehicle, these biomaterials can be cross-linked or conjugated to other compounds to offer a responsive and

improved targeting. Synthesis can be conducted by means of modifying temperature, ionic strength and pH during formulation. Physiochemical interactions such as hydrophobic/hydrophilic interactions, charge condensation, and hydrogen bonding have effects on the physiological interactions of the device.

4. Integration of Biosensors with Drug Delivery Systems

Biosensors are the tools that can shape illness treatment by increasing accuracy of diagnosis, illness monitoring and prognosis. The advantages of biosensors are that they are easy to use, inexpensive, rapid, robust and can allow analysis of different biomarkers simultaneously [25]. The other main advantage is that there is no sample preparation since the biosensor can detect the biomarker within a pool of other bimolecular substances and this makes the integration of biosensors with current drug delivery systems feasible. Microneedles are painless minimally invasive drug delivery systems that do not contact with blood thereby reducing infection and risk of device contamination. In drug delivery, these microneedles are used to inject a therapeutic transdermally whilst for biomedical sensing they aid in fluid extraction for analysis. Utilizing such and many other tools the current research in illness management focuses one of its aspects on integration of biosensors with drug delivery systems. Many such systems that have been studied and published are based on responsive drug release, biocompatibility, biofouling, self-regulatory implants and refillable reservoirs [26, 27].

4.1.Bio-Micro-Electro-Mechanical Systems (Bio-MEMS)

The development of Micro-Electro-Mechanical Systems (MEMS) devices is accomplished the process of micro-fabrication, where silicon, glass and plastic are used. The initial stage for designing MEMS device is patterning technique where photolithographic process is used to design desired patterns on the wafer surface. The wafer is photoresist and then exposed to radiation through a mask which contains the pattern of interest. Once a pattern has been formed the photoresist is removed. The next step is deposition process were a thin film of material (bioelectrics, polymers (polydimethylsiloxane (PDMS) and polymethylmethacrylate (PMMA)), silicon dioxide, silicon nitride, metals (electrodes) or biomolecules is deposited on the surface of the wafer [28]. This is followed by the process of etching which can be either wet where etching is due to liquid chemicals or dry where gas-phase chemistry is used. In both the phases etching processing can occur in all directions equally leading to mask undercutting and a rounded etch profile (isotropic) or be directional (anisotropic) due to either chemical or physical induction [29]. The final step is boding where the two substrates are bound together by anodic or fusion bonding [30]. The use of MEMS has led to the development of microfluidics which is a field of the design and development of miniature devices that can sense, pump, mix, monitor and control flow of small volumes of fluids [31].

BioMEMS technology has allowed fabrication of both disposable (external application) and implantable drug delivery systems and diagnostic tools. Solid durable, solid degradable and hollow microneedles can be used for delivery of insulin (JewelPump, Debiotech) and for vaccination (Intaza, Sanofi Pasteur) [32]. Implantable drug delivery microdevices designed by means of BioMEMS technology can reduce conventional implantable drug delivery devices disadvantages. Most implantable drug delivery devices have unintended drug dumping events which cause side effects and reduce patient compliance as this causes health risk to patients [33]. Implant lifetime also affects compliance as this increases cost of implant replacement. These implants have further problems such that the implant drug release rate and drug contents cannot be changed without invasive procedure.

Conventional pumps are usually osmotically, electrolytic or peristaltic driven [34]. By means of BioMEMS, a piezoelectric pump controlled drug delivery system was made for transdermal delivery of insulin by means of using microneedle, which improved precision and accuracy in relation to mechanical controlled pumps [35]. For longer lifetime and improved biocompatibility, the BioMEMS device will require use of biodegradable polymers or compounds that mitigate tissue response to the implant such as antibiotics or anti-inflammatory agents [36].

4.2.Smart Polymers

Smart polymers represent a group of polymers that function in the same manner as biological systems. Stimuli responsive hydrogels can undergo structural changes when exposed to external stimuli such as pH, temperature and ionic changes. The polymers are divided into three groups based on their physical form. Linear free chains in solutions are when the polymer undergoes a reversible collapse after a stimulus is applied, covalently cross-linked reversible gels are when swelling/shrinking are triggered by environmental changes and chain adsorbed/surface-grafted form represent polymers that have reversible swelling/collapse on the surface once a trigger is changed [37, 38]. Similar to affinity biosensors a hydrogel has been designed by grafting an antigen-antibody complex onto polymer network that will lead to competitive binding of the free antigen triggering a change in the network structure of the hydrogel [39]. Such behavior allows long term use of the system unlike affinity biosensors that get saturated over time as reversible binding is not favored. In another approach the entrapment of glucose oxidase within a pH responsive hydrogel (gluconic acid increase due to oxidation of glucose) and attachment of insulin allowed the smart polymers to act as both drug delivery vehicles for insulin in addition to being a biosensor of glucose concentration [40].

Other reversible systems include desthiobion/biotin and concanavalin in immobilized systems. Desthiobion/biotin-binding protein complex can be dissociated under physiological conditions by either biotin or desthiobiotin (analogue of biotin) [41]. Since biotin can be used to label a variety of proteins, this can be conjugated to either antibodies or antigens to serve as a reversible biosensor. Immobilization of Con A has shown to lead to a reversible sol-gel phase in the presence of free glucose again due to competitive binding with insulin conjugated to glucose [42].

4.3.Microfabricated Devices

Most of the microfabricated devices are in the form of biosensors. There is a time limitation to the use of microfabricated implantable biosensors due to their short time of functionality. Designing an implantable biosensor that has long term functionality can be a critical component of the ideal closed-loop drug delivery or monitoring system, without considering issue of implant biocompatibility and biofouling which must be addressed in order to achieve long-term in vivo sensing [43]. By use of a thermal, pH, ionic strength or biomolecular sensitive hydrogel as a transducer this can be implied in integration of drug delivery system and biosensor technology with better biocompatibility and reduced biofouling.

A cantilever can be employed as a lid on a reservoir whereby a sensing molecule embedded in a responsive hydrogel can stimulate the opening and closing of the lid in relation to analyte quantity. Furthermore the electrically responsive hydrogel can be used as components of MEMS-based sensors or drug delivery devices whereby the external electrical current can be applied on an implant to stimulate drug release intramuscularly. For drug delivery MEMS technology has been applied to formulate microparticles and micro-reservoirs.

Microparticles have been formed by means of generating a pattern of wells ranging in size from 25 to 100μm inside silicon squares ranging from 80 to 150μm in size [44]. These

wells are then filled with a drug of interest and then sealed with a dissolvable cap that has bioadhesive properties for targeted delivery. These microparticles can be further improved by use of smart polymers that can shrink when an analyte is detected as caps to facilitate responsive drug release, thus integrating with biosensor. Instead of voltage, smart polymers can be used to collapse in response to analyte concentration or by means of generating conductive polymers that can be stimulated during redox reactions. Microfabricated devices have led to the development of controlled release microchips [45].

5. Conclusions

In this paper a potentialities of various novel nanotechnologies- based sensors in drug delivery systems have been represented. Nanotechnology is new emerging technology that is assumed to take an essential role in drug delivery systems since it would change the treatment of diseases. The latest development in nanomaterial production techniques as well as the development of analytical technologies have led to establishing more effective methods for drug delivery of various therapeutic treatments.

References

[1] Suravi, Pandit / Debaprotim, Dasgupta / Nazneen, Dewan / Prince Ahmed: „Nanotechnology based biosensors and its application". *The Pharma Innovation Journal* 5(6), 2016, pp. 18-25.

[2] Akifumi, Kawamura / Takashi, Miyata:„4.2 – Biosensors". In *Biomaterials Nanoarchitectonics*. 2016, pp. 157-176.

[3] Chen, Jianrong / Miao, Yuqing / He, Nongyue / Wu, Xiaohua / Li, Sijiao: „Nanotechnology and biosensors". *Biotechnology Advances* 22, 2004, pp. 505–518.

[4] Sandeep, Kumar, Vashist / Konstantinos, Mitsakakis / Gregor, Czilwik / Günter, Roth / Felix, von Stetten / Roland, Zengerle: „Nanotechnology-Based Biosensors and Diagnostics: Technology Push versus Industrial/Healthcare Requirements". *BioNanoSci*. 2, 2012, pp. 115–126.

[5] Venkataramani, Anandan / Yeswanth, L., Rao / Guigen, Zhang: „Nanopillar array structures for enhancing biosensing performance". *International Journal of Nanomedicine* 1(1), 2006, pp. 73-79.

[6] Bayer, C.L. / Peppas, N.A.: „Advances in recognitive, conductive and responsive delivery systems". *J Controlled Release* 132, 2008, pp. 216-221.

[7] Heller, A.: „Integrated Medical Feedback Systems for Drug Delivery". *AIChE Journal* 51, 2005, pp. 1054-1066.

[8] Kryscio, D.R. / Peppas, N.A.: „Critical Review and Perpective of Macromolecularly Imprinted Polymers". *Acta Biomaterialia* 8, 2012, pp. 461-477.

[9] Doyle, F.J. / Dorski, C. / Harting, J.E. / Peppas, N.A.: „Control and modeling of drug delivery devices for the treatment of diabetes". Proceed. Amer. Control Confer., 1996, pp. 776-780.

[10] Hilt, J.Z. / Gupta, A.K. / Bashir, R. / Peppas, N.A.: „Ultrasensitive BioMEMS sensors based on microcantilevers patterned with environmentally responsive hydrogels". *Biomed Microdev* 5, 2003, pp. 177-184.

[11] Lowman, A.M. / Peppas, N.A.: „Solute transport analysis in pH-responsive, complexing hydrogels of poly(methacrylic acid-g-ethylene glycol)". *J Biomat Sci-Polym E* 10(9), 1999, pp. 999-1009.

[12] Peppas, N.A. / Hilt J.Z. / Khademhosseini A. / Langer R.: „Hydrogels in biology and medicine: From molecular principles to bionanotechnology". *Adv Mater* 18(11), 2006, pp. 1345-1360.

[13] Lei, M. / Ziaie B. / Nuxoll, E. / Kristof I. / Noszticius Z. / Siegel, R.A.: „Integration of hydrogels with hard and soft microstructures". *J Nanosc Nanotechn* 7(3), 2007, pp. 780-789.

[14] Dicker, M.P.M. / Bond, I.P. / Rossiter J.M. / Faul C.F. / Weaver P.M.: „Modelling and Analysis of pH-Responsive Hydrogels MRS". *Proceedings*, 2015, published on line, DOI: http://dx.doi.org/10.1557/opi.2015.20

[15] Richter, A. / Paschew, G. / Klatt, S. / Liening, J. / Arndt, K.F. / Adler H.J.: „Review on hydrogel-based pH sensors and microsensors". *Sensors* 8, 2008, pp. 561-581.

[16] Fagerstam, L.G. / Frostell-Karlsson, A. / Karlsson, R. / Persson, B. / Ronnberg, I.: „Biospecific interaction analysis using surface-plasmon resonance detection applied to kinetic binding-site and concentration analysis". *J Chromatogr* 597, 1992, pp. 397-410.

[17] Tang, J. / Xiao, P.F.: „Polymerizing immobilization of acrylamide-modified nucleic acids and its applications". *Biosens Bioelectron* 24(7), 2009, pp. 1817-1824.
[18] Guiseppi-Elie, A. / Sheppard, Jr. N.F. / Brahim, S. / Narinesingh, D.: „Enzyme microgels in packed-bed bioreactors with downstream amperometric detection using microfabricated interdigitated microsensor electrode arrays". *Biotechno Bioeng.* 75(4), 2001, pp. 475-484.
[19] Sijja, H.K. / East, M.P. / Mao, H. / Wang, Y.H. / Nie, S. / Yang, L.: „Development of multifunctional nanoparticles for targeted drug delivery invasive imaging of therapeutic effect". *Curr. Drug Discov. Technol.* 6, 2009, pp. 43–51.
[20] Pierige, F. / Rossi, S.S. / Magnani, M.: „Cell based drug delivery". *Adv. Drug Deliv. Rev*. 60, 2008, pp. 286–295.
[21] Deo, S.P. / Moschou, E.A. / Peteu, S.F. / Bachas, L.G. / Daunert, S.: „Responsive drug delivery system". *Anal. Chem*. 75, 2003, pp. 207–213.
[22] Inzelt, G. / Pineri, M. / Scheltze, J.W. / Vorotyntsev, M.A.: „Electron and proton conducting polymers: Recent developments and prospects". *Electrochim. Acta* 45, 2000, pp. 2403–2421.
[23] Deligkaris, K. / Tadele, T.S. / Olthuis, W. / Berg van den, A.: „Hydrogel-based devices for biomedical applications". *Sens. Actuators B Chem*. 147, 2010, pp. 765–775.
[24] Denkbas, E.B. / Odabasi, M.: „Chitosan microspheres and sponges: Preparation and characterization". *J. Appl. Polym. Sci*. 76, 2000, pp. 1637–1643.
[25] Tothill, I.E.: „Biosensor for cancer diagnosis". *Semin. Cell Dev. Biol*. 20, 2009, pp. 55–62.
[26] Anderson, J.M. / Langone, J.J.: „Issues and perspectives on the biocompatibility and immunotoxicity evaluation of implanted controlled release systems". *J. Control Release* 27, 1999, pp. 107–103.
[27] Maloney, J.M.: „An implantable microfabricated drug delivery system". *Am. Soc. Mech. Eng.* 70, 2003, pp. 115–116.
[28] James, T. / Mannoor, M.S. / Ivanov, D.V.: „BioMEMS-Advancing the frontiers of medicine". *Sensors* 8, 2008, pp. 6077–7107.
[29] Voldman, J. / Gray, M.L. / Schmidt, M.A.: „Microfabrication in biology and medicine". *Annu. Rev. Biomed. Eng*. 1, 1999, pp. 401–425.
[30] Roberts, H.Q. / Steyn, J.L. / Turner, K.T. / Carretero, J.A. / Yaglioglu, O. / Saggere, Y. / Su. Y. / Hagood, N.W. / Spearing, S.M. / Schmidt, M.A.: „A piezoelectric microvalve for compact highfrequency, hug-differential pressure hydraulic micropumping system". *J. Microelectromecha Syst.* 12, 2003, pp. 81–92.
[31] Nisar, A. / Afzulpurkar, N. / Mahaisavariya, B. / Tuantranont, A.: „MEMS-based micropumps in drug delivery and biochemical applications". *Sens. Actuators B* 130, 2008, pp. 917–942.
[32] Zhou, C. / Liu, Y. / Wang, H. / Zhang, P. / Zhang, J.: „Transdermal delivery of insulin using microneedle rollers in vivo". *Int. J. Pharma*. 392, 2010, pp. 127–133.
[33] Nuxoll, E.E. / Siegel, R.A.: „BioMEMS devices for drug delivery". *IEEE Eng. Med. Biol. Mag*. 28, 2009, pp. 31–39.
[34] Meng, E. / Hoang, T.: „MEMS-enable implantable drug infusion pumps for laboratory research, preclinical, and clinical applications". *Adv. Drug Deliv. Rev*. 64, 2012, pp. 1628–1638.
[35] Ma, B. / Liu, S. / Gan, Z. / Liu, G. / Cai, X. / Zhang, H. / Yang, Z.: „A PZT insulin pump with a silicon microneedle array for transdermal delivery". *Elec. Comp. C*. 56, 2006, pp. 677–681
[36] Cheung, K.C. / Renaud, P.: „BioMEMS for medicine: On-chip cell characterization and implantable microelectrodes". *Solid-State Electron*. 50, 2006, pp. 551–557.
[37] Tomar, L. / Tyagi, C. / Lahiri, S.S. / Singh, H.: „Poly(PEGDMA-MAA) copolymeric micro and nanoparticles for oral insulin delivery". *Polym. Adv. Technol*. 22, 2011, http://onlinelibrary.wiley.com/doi/10.1002/pat.v22.12/issuetoc22 , pp. 1760–1767.
[38] Kumar, A. / Srivastave, A. / Galaev, I.Y. / Mattiasson, B.: „Smart polymers: Physical forms and bioengineering applications". *Prog. Polym. Sci*. 32, 2007, pp. 1205–1237.
[39] De, S.K. / Aluru, N.R. / Johnson, B. / Crone, W.C. / Beebe, D.J. / Moore, J.: „Equilibrium swelling and kinetics of pH responsive hydrogels: Models, experiments and simulations". *J. Microelectromech. Syst.* 11, 2002, pp. 544–555.
[40] Traitel, T. / Cohen, Y. / Kost, J.: „Characterization of glucose-sensitive insulin release systems in simulated in vivo conditions". *Biomaterials* 21, 2000, pp. 1679–1687.
[41] Hirsch, J.D. / Eslamizar, L. / Filanoski, B.J. / Malekzadeh, N. / Haugland, R.P. / Bechem, J.M. / Haugland, R.P.: „Easily reversible desthiobiotin binding to streptavidin, avidin, and other biotin-binding proteins: Uses for protein labeling, detection and isolation". *Anal. Biochem.* 308, 2002, pp. 343–357.
[42] Qiu, Y. / Park, K.: „Environment-sensitive hydrogels for drug delivery". *Adv. Drug Del. Rev.* 53, 2001, pp. 321–339.

[43] Grayson, A.C. / Shawgo, R.S. / Johnson, A.M. / Flynn, N.T. / Li, Y. / Cima, M.J. / Langer, R.: „A BioMEMS review: MEMS technology for physiologically integrated devices". *Proc. IEEE* 92, 2004, pp. 6–21.
[44] Ahmed, A. / Bonner, C. / Desai, T.A.: „Bioadhesive microdevices for drug delivery: A feasibility study". *Biomed. Microdevices* 3, 2001, pp. 89–95.
[45] Tsai, A.H. / Moschou, E.A. / Daunert, S. / Madou, M. / Kulinsky, L.: „Integrating biosensors and drug delivery; a step closer toward scalable responsive drug-delivery systems". *Adv. Mater*. 21, 2009, pp. 656–660.