Smart nanofibres for specific and ultrasensitive nanobiosensors and drug delivery systems

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Abstract

Biosensors are dynamically developing analytical devices for the detection of substrates or other bioactive substances. They can be used for quick gas or liquid analyses and the construction of sensitive detection systems. This review highlights the advances and development of biosensors suitable for human and veterinary medicine and, namely, a novel contribution of nanotechnology for ultrasensitive diagnosis and personalized medicine. The synergic effect of nanotechnology and biosensors opens a new dimension for effective treatment and disease detection at their early stages.

Nanotechnology, detection, disease diagnosis, drug delivery

In recent years, much medical research has been focused on molecular diagnosis, regenerative medicine, and tissue engineering. In this respect, the application of nanotechnology seems to be very promising. Recent decades have been characterized by a massive transfer of nanotechnologies from basic and applied research to medicine and industrial application. Smart nanofibres seem to have an extremely high potential in medicine due to their unique biomimetic properties. Nanofibres can be functionalized both on their surface and in their core. The surface modification can be highly selective, which opens the door for advanced medical diagnostics as specific bionanosensors or controlled and targeted drug delivery. Our review was focused on the application of nanotechnology in novel diagnostic and delivery systems.

Advantages of nanofibres

Classical laboratory analytical methods are time-consuming with rather low sensitivity, and, thus, they seem to be obsolete nowadays. This naturally leads to new diagnostic and detection methods (Rodríguez-Lázaro et al. 2017; Cailing et al. 2021) and the application of sensors, more precisely, biosensors, which are fast, sensitive, selective, and potentially suitable for rapid detection of various substances such as proteins, saccharides, nucleic acids, and pathogens (Yoon 2016). Nanofibres are widely used for the construction of bionanosensors for their unique properties.

The large ratio between the surface and the volume of nanofibres and tiny pores in the nanofibre network gives them an advantage when used as a highly efficient filter unit. In addition, a specific modification of the surface of nanofibres, e.g., with a specific miRNA, rocket them up to a superior system that can filter a large volume of liquid, not only with

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high efficiency but also with high selectivity. As a result, when a relatively large amount of fluid is filtered through a specific filter, even a tiny amount of protein or other bioactive substance can be detected without the use of any complicated concentration processes. This is undoubtedly the most significant advantage of this proposal. The application of smart nanofibres has ambitions to open the door to new directions in personalized medicine. Smart nanofibre filters with anchored specific antibodies, aptamers, or miRNAs for selective Resource Description Framework (RDF) binding, possibly with electrical or optical detection, would mark an innovative breakthrough in methodology and application in practical medicine. Simple filtration of selected body fluids would be a straightforward method directly applicable in medical offices. Such an approach would allow immediate control and adjustment of medical treatment and dosage of drugs.

Polymeric nanofibres

The application of nanofibres is very wide, starting from regenerative medicine, tissue engineering or drug delivery, to using filtering and membrane functions to create biosensors (Manea et al. 2016). The biomedical use of nanofibres includes creating dressings or scaffolds for various fields of medicine: dentistry, traumatology and orthopaedics, abdominal surgery, vascular surgery, ophthalmology, neurology, and others (Vocetkova et al. 2016; Beznoska et al. 2019; Bellu et al. 2021; Kralovic et al. 2019). Nanofibres are also used to create structures with controlled release of drugs and drug delivery systems; widespread use is possible in cosmetology, skin regeneration, and rejuvenation haemostatic use (Vocetkova et al. 2016; Esmaeil 2016 Esmaeil 2017; East et al. 2018; Bellu et al. 2021, Kralovic et al. 2019) The use of polymer nanofibres as part of the bioreceptor of biosensor is discussed in the next section.

Application of nanofibres for biosensing

Development of personalized medicine is highly dependent on highly sensitive biosensors (Banerjee et al. 2021). Biosensors have several advantages: selectivity, sensitivity, linearity, short response time, reproducibility, and stability (Turner 2013; Dincer et al. 2019; Naresh and Lee 2021). The degree of sensitivity of a biosensor is an important indicator, and the idea of Quantum Dots and biosensors based on them is very promising (Banerjee et al. 2021). An alternative to this technology could be a biosensor, which includes polymer nanofibres as immobilization surface for the bioreceptor part.This technology would provide a huge interaction area between the analyte and the bioreceptor while retaining the basic principles (Teepoo et al. 2017). Early-stage identification of disease markers and their rapid detection plays an essential role in modern personalized medicine. The preparation of nanofibre-based detectors, functionalized on the surface of nanofibres with relevant antibodies, is critical in preparing highly sensitive and specific biosensors; recent studies show progress in this area (Zhang and Rojas 2017; Chauhan et al. 2018; Wongkaew 2019). The biosensor may include several components that can achieve more current diagnostics.

Specific detection of substrates in air and liquids

The detection of specific substrates from the air and liquids can be performed using biosensors. The bioreceptor of such a biosensor may be sensitive to various biological substances such as saccharides, peptides, proteins, nucleic acids (Yoon 2016).

One of the most detected substances is glucose. Today, glucose sensors make more than 85% of commercially used biosensors in medical applications (Yoon 2016). Glucose detection works on the catalytic reaction between the glucose molecule and enzyme (glucose oxidase). The measurement is performed from saliva, tear, interstitial fluid, sweat, and especially blood. Due to the ever-increasing number of diabetic patients, glucose biosensors are being modified, increasing their linearity and sensitivity (Mohamed et al. 2021, Roxana-Mihaela and Pinar 2020; Nese et al. 2021). The functionalization of the biosensing matrices may provide an increase in linearity and sensitivity. This was achieved, e.g., in the study by Roxana-Mihaela and Pinar (2020) in which the glucose biosensor based on the montmorillonite/polyacrylonitrile (PAN) nanofibre composite was modified by functionalizing the montmorillonite with dioctadecyl dimethyl ammonium chloride and methylene blue. In the study by Nese et al. (2021), another glucose biosensor based on PAN nanofibres was loaded with carbon nanotubes and ferrocene, increasing linearity and sensitivity.

Like glucose, β-amyloid (1-42) can also be detected in blood, or more precisely in blood plasma (Supraja et al. 2021) Aggregates of the β-amyloid (1-42) (AB42) can be considered one of the most viable biomarkers of Alzheimer's disease. This disease is incurable, but thanks to an early diagnosis combined with supportive treatment, its course can be alleviated and slowed down. To rapidly detect the AB42 peptide, the sensitive electrochemical biosensor was created by using SO_2 nanofibres with the immobilized antibody. This newly created sensor shows stability (over 126 days), selectivity, and repeatability (Supraja et al. 2021).

Analysis of the composition of the synovial fluid looks promising for the fields of orthopaedics and rheumatology. The fluid can contain all proteins that are found in plasma. Since it is an ultrafiltrate of blood plasma and a product of the metabolism of chondrocytes and synovial cells, this fluid plays a crucial role in joint metabolism. The synovial fluid composition will differ with common pathologies, an important diagnostic indicator for making an appropriate diagnosis (Rodovalho et al. 2018).

In addition to diagnosing diseases and controlling the disease status of individuals, it is also possible to use biosensors to control public health, for example, from wastewater and the air. However, the substances we want to detect within public health are present at very low concentrations. That is the reason for developing very sensitive and specific methods for detection (Markosian and Mirzoyan 2019; Gaviria-Arroyave et al. 2020; Kang et al. 2021).

Wastewater-based epidemiology (WBE) is low-cost, effective biomonitoring with an almost real-time response. Heavy metals, drugs, and various peptides, which can cause poisoning and various diseases, are often detected in wastewater. The so-called online detection of all these substances is performed by using biosensors. The most common are electrochemical sensors which use aptamers, highly specific nucleic acid sequences, as a bioreceptor (Markosian and Mirzoyan 2019; Gaviria-Arroyave et al. 2020; Kang et al. 2021).

In addition to the substances mentioned above, pathogens can also be detected inwastewater and air. Rapidly spreading pathogens can cause major and, above all, global problems. Early detection and warning of infectious diseases caused by these pathogens play an essential role these days (Kang et al. 2021).

In connection with the Covid-19 pandemic, paper-based biosensors for pathogen detection from the wastewater were tested. This biosensor with different functional areas printed with a wax printer integrates various processes, such as extraction, purification, elution, etc., suitable for nucleic acid testing into the low-cost paper material (Rodovalho et al. 2018; Kang et al. 2020).

In addition to the wastewater, the air is also a great source of substances for public health control. The 2020 research detects *Campylobacter* bacteria in air samples by using integrated laboratory-on-a-chip (ILOC) technology. The chip with a chamber volume of 10–15 μl and flow capacity of 120 ml of air per min was used for the detection. The ILOC technology enabled an easy sampling and convenient and fast evaluation of bacterial colonization in the air (Olsen et al. 2020). Another bacterium that has been detected directly from the air is *Staphylococcus aureus*. The original research used the specific bionanosensor produced of PAN nanofibres with immobilized antibodies (Varvařovská et al. 2021). An air sample with bacteria was filtered through the pure and functionalized nanofibre membrane, and the efficacies of these membranes were compared. Although pure nanofibres could capture many bacteria in their specific structure, the functionalization of the nanofibre membrane still contributed to increasing its effectiveness (Varvařovská et al. 2021).

Application of biosensors in veterinary practice

The use of biosensors has broad application prospects in the veterinary field. Many studies have already been published exploring the use of biosensors in diagnosing diseases of livestock and poultry.

Veterinary medicine is considering different strategies for applying biosensors, such as feeding and assessing the conditions of the place of livestock. It could analyse the influence of atmospheric pressure, sense the acoustics and, based on the obtained monitoring data, allow us to assess livestock confinement conditions comprehensively (Neethirajan et al. 2017).

Another wide area of application of biosensors in veterinary medicine is the analysis of the state of animals. Analysis of the stress level is possible based on the study of the composition of various animal fluids. Such analyses can be performed using different fluids, such as determining the level of cortisol in saliva (Kim et al. 2011; Oh et al. 2015, Du and Zhou 2018). The determination of cortisol also found response in human medicine in the saliva of obstructive sleep apnoea patients (Fernandez et al. 2017). The level of alpha-amylase in saliva can also indicate the presence of stress (Fuentes et al. 2011).

Combining these indicators would provide an opportunity to comprehensively assess the stress response, both from the hypothalamic-pituitary-adrenal axis and the assessment from the autonomic nervous system. (Strahler et al. 2017)

A separate area of application of biosensors in veterinary medicine is diagnosing pathological conditions. Research is being carried out to diagnose common diseases such as: bovine viral diarrhoea, foot-and-mouth disease, bovine respiratory disease and influenza (Neethirajan et al. 2017; Ayyar and Arora 2013). Biosensors are widely used for the detection of biomarkers showing the functioning of organ systems. Uric acid is an indicator of physical stress and a marker of renal metabolism (Kim et al. 2015).

Implantable biosensors can be more widely used for monitoring various disease states, both in human medicine (Gray et al. 2018) and veterinary medicine, especially in studies of *in vitro* models (Koschwanez and Reichert 2007; Joung 2013). Biosensors have even entered the field of beekeeping, where they are used for bee health assessment and environmental friendliness analysis (Bromenshenk et al. 2015).

When combining biosensor technology with nanotechnology, it is possible to achieve completely new results, and for this, veterinary medicine is the most fruitful and rapidly developing area.

Preparation of nanobiosensors based on nanofibres

The biosensor devices consist of several interconnected blocks. The first is the bioreceptor, which interacts with the analyte and specifically recognizes the substrate. After recognizing the desired substrate, the transducer reads the result of the bio-recognition reaction and converts it into a signal, depending on the type of receptor; this can be a final or intermediate stage (Bhalla et al. 2016)

The sensor elements can be different depending on the substance to be determined and could be categorized by a method of determining the substance (quantitative or quantitative). Transducers can be of various types, for example, electrochemical, optical, thermal, electronic, gravimetric, and acoustic (Ensafi 2019; Naresh and Lee 2021; Nagraik et al. 2021). Nanofibres appear to be a promising direction for their application in sensing systems (Bellan et al. 2011). The use of polymer nanofibres is possible as an immobilization surface of the bioreceptor. The result of applying the technology can be sensors of increased sensitivity, which would open possibilities for detecting the smallest substances.

Delivery of drugs

The applications of electrospinning in drug delivery are almost limitless. Electrospun nanofibres are promising drug delivery systems as their huge surface can serve for physical absorption or chemical conjugation. Drugs as antibiotics, antitumour agents, proteins, DNA, RNA, miRNA etc., can be encapsulated into conventional liposomes and, subsequently, encored on the nanofibre surface or be encapsulated into nanofibre core (Sill et al. 2008). Conventional liposomes are covered artificial vesicles where a hydrophobic membrane can encapsulate lipid-soluble substances and at the same time contain an aqueous interior hydrophilic molecule inside. They have many promising properties such as low toxicity, good biocompatibility, targeted delivery of bioactive compounds to the required site of action, incorporation of hydrophobic/hydrophilic drugs, etc. (Mickova et al. 2012; Akbarzadeh et al. 2013; Vocetkova et al. 2014). Their disadvantages, like low stability, short half-life, and insufficient ability to control long-term drug release, can be significantly improved by their adhesion to a nanofibre surface or their encapsulation into a nanofibre core (Sharma and Sharma 1997; Akbarzadeh et al. 2013). This system is mainly interesting when produced as a multi-release system from biodegradable nanofibres (Son et al. 2014). These systems were used as drug carriers and involved cell adhesion, proliferation, migration, and differentiation (Khil et al. 2011).

Nanofibre-based systems provide a suitable environment for cells in new tissue formation. The biggest advantages of using nanofibres are mainly due to their topographic properties (surface roughness, size of gaps between nanofibres, thickness, and orientation of nanofibres), which can be easily adjusted to suit specific applications in tissue engineering (e.g., abdominal hernia) (Bhardwaj and Kundu 2010; Grafahrend et al. 2011) where highly porous supports with interconnected pores are preferred (Plencner et al. 2014). As a post-production modification, surface bonding is the simplest method for functionalizing the substrate. However, the filling efficiency and release rate can be very variable and difficult to optimize. In addition, adsorbed molecules can be released quickly, and such systems are more suitable for short-term delivery. Several types of bioactive molecules can be adsorbed on the surface of nanofibres, such as growth factors to accelerate tissue regeneration after hernioplasty (Plencner et al. 2014), antibiotics to prevent postoperative adhesions, or liposomes containing growth factors to accelerate cell proliferation (Staffa et al. 2017; Rampichova et al. 2017). Another study tested a simple drug delivery system consisting of native platelets immobilized on the surface of fibrous carriers. Nanofibres here were made from polyethylene caprolactone using two different technologies: electrostatic and centrifugal spinning (Vocetkova et al. 2020). Target therapy also seems promising, especially therapy aimed at treating cancer (Barani et al. 2020). Research using nanoparticles is being carried out to treat prostate cancer, and it appears rather encouraging to use nanoparticles for intratumoral drug delivery (Borghese et al. 2017).

Conclusion

Development of biosensors and drug delivery systems are interdisciplinary and dependent on progress in many areas of medicine, starting from a theoretical basis and ending with the technical execution and possibilities of use, considering the available methods.

Today, technology is developing rapidly. This also brings new, cheaper, and more efficient devices such as various types of biosensors. These devices are very sensitive, and they allow specific detection of biological and chemical substances. The evolution of such sensors also matches with more efficient and faster diagnostics and control of diseases, such as diabetes mellitus or Alzheimer's disease, and the possibility of easy control of public health. In addition to reducing the time required for detection and lowering costs, there is also an effort to reduce the size of used devices. This is possible in consequence of reducing the size of the electronic components and nanostructures such as nanoparticles and nanofibres.

Molecular diagnosis and target therapy of diseases require deep knowledge of the normal and pathological forms of the condition. It is also necessary to determine the exact indices in which the determination of the desired marker would be useful and could help with the diagnosis, determining the effectiveness of treatment, or assessing the progression of the disease. This is a very promising field of future research.

However, the main unresolved problem hindering a more extensive application of these technologies on the market seems to be a production up-scaling beyond the laboratory scale. The currently used direct-current nanofibre spinning technology is characterized by a very low effectivity of production and, moreover, provides only 2D-like membranes which are unable or extremely difficult to be further processed by knitting or other textile technologies. The alternative-current technology is characterized with at least two orders higher production effectivity and, in addition, enables also the manufacturing of yarns (1D-like structures).

Conflict of Interest

The authors declare no conflict of interest.

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