ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
HUMAN

Human Journals
Review article
July 2020 Vol.:18, Issue:4

Nanosensor and Its Application in Pharmaceutical Industry

ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
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Submission: 23 June 2020
Accepted: 29 June 2020
Published: 30 July 2020

HUMAN JOURNALS

www.ijppr.humanjournals.com

Keywords: Nanosensors; Nanotechnology; Types; Pharmaceutical application

ABSTRACT

Nanotechnology is considered as a growing field with versatile applications. Nanosensor is a promising part of this technology. Nanosensors are highly sensitive and it can sense even very minute changes in its surrounding environment. Along with sensitivity, its smaller size makes it a better option than the existing sensors. In the current pharma field, it is widely used in drug discovery, protein & DNA identification, pH measurement, etc. It has shown the future potential of being widely used in cancer diagnosis, glucose monitoring, prediction of an asthma attack, etc. Thus, it is very useful in research fields. With proper research and development, it can overcome certain existing problems related to real-time analysis, sensitivity, selectivity, time for analysis in the pharmaceutical industry. Overall it can be a beneficial asset for the pharma field as well as can increase patient safety, patient compliance, and can be fruitful for the global population.

INTRODUCTION:

Nanotechnology is an integrative & multifaceted field of science, which is growing rapidly at present [4]. Nanotechnology has shown a very promising future in the field of the pharmaceutical industry. With the help of Nanotechnology, we can design, create, or synthesize & apply substances having at least one dimension in the nano range.

Nanosensor is one of the many advancements that nanotechnology has achieved, which can be very useful in the pharmaceutical industry. A nanosensor is a type of sensor which has its functional units made in nanoscale. It can detect any small physical or chemical changes or in other words, can obtain data on the atomic scale [3] and convert that into an analyzable signal, which can be then quantified by Data Acquisition System (DAQ) [1].

The concept of nanosensors should not be misunderstood by its name, nanosensors can be of any size. It is not necessary to reduce the size of the nanosensor into the nanoscale. It should have at least one functional unit in nanoscale & should use the unique property of nanomaterials for the detection of nanoscale events to be called as a Nanosensor.

Construction:

Nanosensors generally have one bio-sensitive layer containing biological recognition elements or it can even be made up of a biological recognition element [Figure No. 1]. For example, these biological recognition elements can be an antibody, a protein, an enzyme, a protein, whole-cells, tissues, or even whole organisms, etc. in the case of a biological nanosensor [14]. This layer is then covalently attached to a transducer element [3].

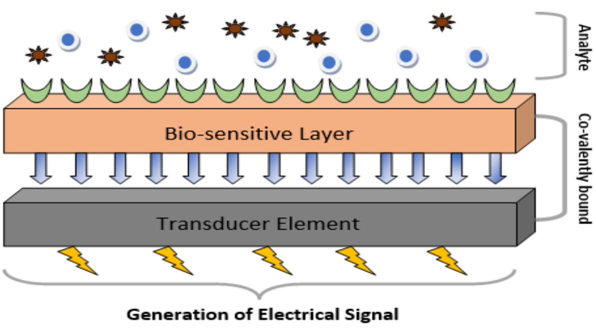

Figure No. 1: Basic construction of a nanosensor (adapted and recreated from Petolsky and Charles 2005) [9]

Nanosensors consist of two different types of receptor molecules:

A. **Affinity-Based:** They are used to bind the molecule of interest non-catalytically & irreversibly. Example- nucleic acid, antibodies, etc.

B. **Catalytic based:** These are microbe cells or enzymes. It finds & binds with the molecule of interest & then there is a chemical conversion of the molecule to a product that occurs which is detectable.

It works by the charge transfer that occurs between the analyte molecule and the sensitive material, resulting in an electrical or optical signal depending upon molecule number and type.

Existing methods available for the production of Nanosensor:

i. Top-down: It starts with taking a larger section of the material, which is then designed accordingly to manufacture the nanosensor.

ii. Bottom-up: It is technically the opposite approach to the top-down technique. Here the molecules are assembled in a specific order using certain sophisticated instruments to make the nanosensor. This method is very slow and costly.

iii. Self-assembly: It is the most popular & used method these days. In this technique the molecular component auto-assemble themselves to form the nanosensor. It is a very rapid & economically beneficial method [5].

Advantages of Nanosensor:

i. The nanosensors are useful to reduce the size of the sensing element in an instrument or system.

ii. The nanosensors are highly sensitive for particular analytes. Therefore, the use of nanosensors can help in increasing the sensitivity.

iii. Nanosensors are also capable of detecting a very minute presence of an analyte or even extremely minute changes in the concentration level of the analyte.

Types & Mechanism of Action (MOA) of the nanosensors: There are mainly three types of nanosensors available.

A. **Optical nanosensors:** This works through the calorimetric principles. Here due to the presence of the analyte, a chemical or morphological alteration occurs resulting in a visible color change. The properties measured include polarization, energy, amplitude, decay time, etc. It is very useful for intracellular measurements and live-cell imaging [13]. Apart from that, it is further useful in the detection of heavy metals through gold nanoparticles, measurement of cytochrome C, pH, ions like K+, Ca^{2+}, Cl^{-}, Na^{+}, etc.

It can be subcategorized into;

1. **Fiber optics or optical-fiber based nanosensors:** Depending upon the environment and application purpose, fiber optics with different tip diameter, taper angle and different fiber smoothness is required. The most common way to prepare an optical Nanosensor is by using a pulling instrument such as micropipette puller. This instrument uses a CO_2 laser to heat the fiber which passes via a scanning and a retro mirror and then the fiber is pulled along its major axis by a tension device. By varying the heating and pulling strength required factors like tip diameter etc. can be changed. Another method of fabrication of nanotips on the optical fiber is done by chemical echoing [13].

2. **Spherical optical nanosensors or PEBBLEs (Probes Encapsulated By Biologically Localized Embedding):** These are sub-micron sized (20-200nm) sensors specifically designed for minimally invasive analyte monitoring in viable, single cells which are designed to analyze drug, toxin, and environmental effects on cell function in real-time[16] and the response time of these sensors is less than 1 millisecond [6]. Apart from the usual uses of optical nanosensors it can be used for glucose and dissolved O_2 measurement [1]. Optical nanosensors are fabricated in microemulsion using polymerization methods. They contain fluorescent indicators entrapped in the polyacrylamide matrix. PEBBLEs can work by either direct or ion correlation method [6].

B. **Electromagnetic nanosensors:** It works by measuring either the enhancement in current or decrease in current as a result of a change in resistance of the nanomaterial due to the binding of the analyte. It also works under the same principle by measuring the change in magnetism. The use of nanowires like conductive nanotubes, carbon nanowires can be seen in electromagnetic nanosensors. These nanosensors are useful for the measurement of peroxidase, dehydrogenase, catalase, H_2O_2, Organophosphate substances, DNAs, ATP, Molecular interaction, enzymatic activity, Viral particles, etc.

C. **Mechanical nanosensors:** It works by measuring the changes in mechanical forces at molecular levels. They are very sensitive to mass & that makes them versatile. The sensitivity of a detecting instrument depends upon the mass of that instrument. Therefore, mechanical nanosensors having a mass of nanoscale gives very high sensitivity [7].

But, in the case of fluid, it faces a huge obstacle due to viscous damping. It is the phenomenon when a particle in a vibrating system obstructed by a constant force in the opposite direction to the velocity of the particle. It is useful in measuring pressure, resonance, frequency, etc.

Application in the pharmaceutical industry:

1. **Drug discovery:** Literature shows a very wide application of nanosensors in drug discovery. The organic molecules that can bind specifically to proteins are the focus of drug discovery and development in the pharmaceutical industry. Therefore, considered as the main target for nanosensors. For example- The identification of molecular inhibitors binds to tyrosine kinases. These are the enzymatic proteins that mediate signal transduction in mammalian cells by phosphorylating a tyrosine residue of a substrate protein using ATP (Adenosine triphosphate). It has been found that the deregulation of this process is linked with a large number of diseases which even includes cancer. For the screening of these small inhibiting molecules usually, the nanowire sensors are modified by linking the kinase Abl to the surface of the nanowire sensor. After that binding of ATP and competitive inhibition of the binding of ATP by any organic molecule is observed. In this configuration, the binding or competitive inhibition of the ATP is detected as an increase or decrease of the conductance of the nanowire device. Time-dependent data is obtained from the Abl-modified nanowire devices. Upon introduction of the solution with more concentration of ATP, it exhibits a reversible, concentration-dependent increase in conductance. Now using this technique plots of the normalized conductance are recorded using different small molecules by inhibiting the binding of ATP. It is found that the conductance decreases at constant small molecule concentration, which demonstrates that the degree of inhibition depends strongly on molecular structure. So, this explains the advantages of nanowire sensors over existing methods in terms of rapid, direct, and high sensitivity readout using a minimal amount of protein receptor. Therefore, it has great potential in the field of drug discovery [9].

2. **Testing drug strength:** It is found that nanosensors like carbon-nanotubes which are 50000 times thinner than a human hair can detect an extremely minute quantity of substances. They can even bind to proteins that can recognize specific target molecules. In the presence of a target, it alters the signal produced by the nanotubes in a detectable way. Large arrays of nanosensors have already been utilized where each of them is customized for different drug molecules so that it can identify various targets at once. It has been revealed by experimentation that an array of nanosensors shows unique properties. The first property discovered is distribution in binding strength of complex protein like antibodies in measurable by then. To be effective, the antibody-drug should strongly bind to the target. But as the manufacturing process is done by engineered non-human cells so it does not give batches of uniform binding ability. Using nanosensors arrays is for this purpose is much cheaper & less time consuming than the current technology used by the industries for this purpose.

3. **Detection of protein & DNA:** Biological macromolecules, such as proteins & nucleic acids are typically changed in aqueous solutions & they are readily detectable by nanowire sensors. For that purpose, it is necessary to fix the appropriate receptor to it.

As an example of the detection of protein, molecule biotin was lined with the oxide surface of the p-type Si-nanosensors. They are prepared by simple physical vapor deposition of ZnO nanowire fabrication on p-Si (100) substrates in a vacuum furnace [15]. Protein streptavidin is highly specific for biotin. When the solution of streptavidin is introduced to this modified nanowire sensors the conductance rapidly increases then maintains a certain level. To support that it has also seen that unmodified sensors do not show this conductance. Thus, it shows that this biotin modified nanowires are highly specific for the specific protein, it has also shown high sensitivity & can work in very low concentration. Most recently the field-effect device for p-type Si-nanowire is used for the detection of single-stranded DNA [9]. In this, the binding of negatively charged macromolecule leads to an increase in conductance. Peptide nucleic acid or PNA is used as a receptor of DNA. This estimation can be done to as low as 10 FM or 10 femtomolar concentration (1fM=10^{-15} mol/L). This technique also showed high reproducibility & less device to device variability.

4. **Cancer diagnosis:** For the identification of biological specimens, currently the widely used technique is Raman spectroscopy (RS). Improved version of RS or Surface Enhanced Raman Spectroscopy (SERS) is the latest addition to it. It has more accuracy for

identification. The methods that are used these days for the detection of cancer are ELISA, PCR, etc.

But these days the technology is bending towards nano-mechanical biosensors, derived from atomic force microscopy cantilevers [10]. It has the potential to surpass all the current technologies such as microarrays, Quartz crystal microbalance & surface plasmon resonance. This technology has the benefit of the detection of level free biomarkers without the requirement for target amplification in total cell background, such as BRAF (a human gene that encodes B-Raf protein) mutation analysis in malignant melanoma. They also govern the membrane protein & analyze their conformational dynamics related to surface stress change.

They have also been used for early cancer detection in blood vessels using mobile nanosensors (MNS) [11]. Generally, some special cells are produced & emitted by cancer cells known as cancer biomarkers. It indicates the chances of cancer in CVS. The concentration being very low in the early stages it becomes hard to detect by taking blood samples. However, near the cancer cell, the concentration of biomarkers is high. So, the MNSs are injected into the bloodstream & they freely circulate throughout the CVS. The MNSs can be activated by the biomarkers easily. Later by Fusion center MNSs are collected & the level of activation is measured.

5. **Detection of single viruses:** It can be demonstrated as a capability of nanosensors to detect chemical and biological specimens. Studies on the detection of viruses have been done already. It is very important as it is the main cause of disease in humans.

When a virus particle binds to the antibody receptor of a nanosensor, it creates a change in the conductance value. When the virus again unbinds, the conductance returns to bassline value [9].

Research had been done on the Influenza virus, where very dilute solution of Influenza A virus i.e. around 80 aM or 50 viruses/µL is introduced to p-type Si-RNA nanosensors which are modified by monoclonal antibodies for Influenza A virus. Definitive proof of conductance change that occurred resembles single virus binding/unbinding are obtained by simultaneous optical & electrical data using fluorescence level influenza virus [Figure No. 2 and 3].

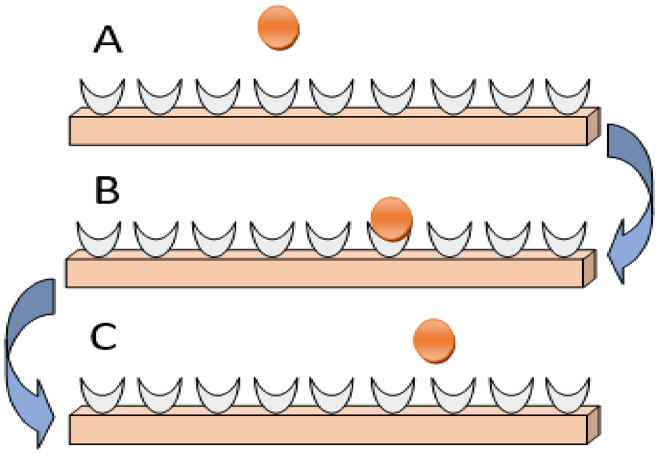

Figure No. 2: Diagram of a single virus binding and unbinding to the surface of the a-Si nanowire device modified with an antibody receptor (adapted and recreated from Petolsky and Charles 2005) [9]

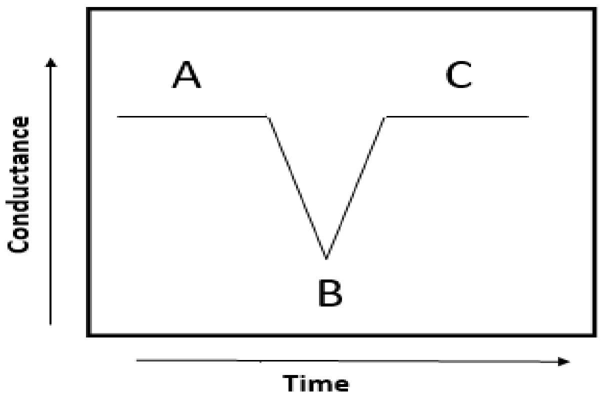

Figure No. 3: Diagram showing the change in conductance while binding and unbinding events of figure 2. Where A and C are normal conductance and B represents the decrease in conductance due to binding (adapted and recreated from Petolsky and Charles 2005) [9]

6. **Glucose monitoring:** In vivo glucose sensors have already been developed to detect hypoglycemia in type-1 diabetes patients. It is possible to make fluorescent nanosensors for this purpose. The dermal release of nanoparticles may allow transdermal monitoring of glucose change. So, being a non-invasive technique, it has a high patient acceptance & it will be free from biocompatibility problems.

Nearly a decade ago single-walled carbon nanotube optical nanosensors have been started to use as a glucose sensor. It modulates emission in the response to the adsorption of specific molecules. It can work on two different mechanisms, fluorescence quenching & charge transfer.

Generally, glucose oxidase is coated on it for its activity. Glucose oxidase breaks the glucose molecules. After that an electron-deficient molecule, Ferricyanide is sprinkled on the carbon nanotube surface. Ferricyanide moves electron from the nanotubes, quenching their capacity to glow when excited by IR light. If glucose is present it produces hydrogen peroxide by reacting with oxidase. This peroxide reacts with ferricyanide to satisfy the molecule's electron deficiency. So, higher glucose level gives higher fluorescence.

Another technique has been reported where detection for biologically relevant glucose has been possible. This glucose oxidase is immobilized into a microcantilever surface and when the glucose reacts with this glucose oxidase that enzyme-functionalized microcantilever receives stress on its surface and it undergoes bending[3].

7. **Detection of asthma:** Nanosensors can be used for the detection of chances of asthma attacks. A simple handheld device can be useful for this purpose. Usually in asthma patients especially before any asthma attack the nitric oxide level increases in their breath. Regular monitoring of these nitric oxide levels in breath can be lifesaving. They can be warned about it and required measured can be taken if the presence of high nitric oxide level is there or increase in the level is observed.

The base of this sensor is made of Nano Tube Field Effect Transistor (NTFET) coated with a polymer. It contains a random network of single-walled carbon nanotubes between source and drains gold electrode on a silicon oxide substrate [7].

8. **Organophosphorus compound detection:** There is three basic sensing mechanism available for this: immunoassays, inhibition of cholinesterase, and organophosphorus hydrolase (OPH).

AChE-based nanosensors have a drawback as organophosphorus, heavy metal, etc. are strong and specific inhibitors of AChE. So, the use of it is restricted. In comparison to that immunosensors are specific, cheap, selective, and sensitive and it works based on anti-pesticide antibodies. Direct immunosensors based on Quartz Crystal Microbalance (QCM) &

Surface Plasma Resonance (SPM) & impedimetric devices have already been reported for this purpose [3].

9. **Detection of gases:** In the cases of detection of various gases earlier technology that was being used is Mass spectrometry. But having some certain drawbacks like transportation of gas, size and power requirement for that instrument, long transportation lines, etc. nanosensors are coming up as the alternative method. Being very sensitive and small can be distributed over a large area, so, the results will be precise, and it can be regularly monitored. One more advantage is that we can easily place it in the area of interest and small leakage can be detected.

They are often used for *Astronaut's Diagnosis* [3], as the space shuttles often use very hazardous gases like hydrazine or some similar gases. These gases can be very dangerous even in very small concentrations also. So, it becomes necessary to detect, identify as well as to measure these gases. The nanosensors are being optimized to detect and quantify the presence of various gases in real-time.

10. **Detection of radiation:** These biosensors can pass through the membrane and reach White blood cells to detect damage of cells due to radiation or infections by observing some chemical changes. These sensors are formed layer-by-layer from dendrimers in spherical shape having a diameter of less than 5 nm. Due to this, they can easily be administered trans-dermally. The purpose is useful for people working in areas where there are chances of being exposed to radiations, astronauts, labs where experiments are going on radioactive devices. In the future aspect, it will reduce the requirement of taking injections or IVs during space missions, the requirement of drawing and testing of blood samples.

11. **pH measurement:** The first experiment performed demonstrating the pH sensing ability of nanowire field-effect devices was back in 2001. A Basic P-type Si nanowire semiconductor can be used as a sensor. This is modified with the 3-aminopropyltriethoxysilane, which yields amino groups on the outer surface along with naturally occurring silanol groups.

The amino and silanol groups work as hydrogen ion receptors. They usually go protonation and deprotonation reactions and due to this the net surface charge of nanowire changes. Significantly a stepwise increment in the conductance is observer when the pH is increased stepwise from 2-9. From a mechanistic point, the increase in conductance with the pH is consistent with either a decrease of the surface positive or increase in the surface negative charge, which turns on the p-type FET via the accumulation of carriers [9].

It is also found that without modification the silanol groups show a low change in conductance in pH 2-6 but a large change in 6-9 pH. So, it is evident that this modification is essential for the purpose.

SUMMARY:

Advancement in the field of nanotechnology is leading the path for the advancement of nanosensors. Nanosensors are very sensitive and can even detect a single biological molecule from a single cell, which serves as a major advantage of it.

In the future, the devices made using nanosensors for diagnosis purposes will be smaller than conventional and also, we will get a real-time result from them and this will probably be the biggest use of nanosensors in pharma industries. It is better from current technology available for these purposes due to its very high selectivity, ultra-high sensitivity, direct and level free usage. Shortly they should be produced in commercial levels especially for pharmaceutical applications for the benefit of mankind.

ACKNOWLEDGMENT: I would like to express my gratitude to Dr. Gautham G. Shenoy for suggesting this review topic.

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