# Applications Of Nanofabrication Methods In Nanotechnological Medical And Pharmaceutical Devices

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***Abstract*: Contributions in the world of nanotechnology have led to advancements in nanofabrication methods that yield useful devices for real-world applications in a plethora of fields including medicine. In this paper, we will be focusing on nanodevices and their pharmaceutical applications. Nanofabrication methods in recent years have revolutionized the development of medical devices such as nanotubes, nanowires, and nanoparticles (NP). Those medical devices can be categorized into drug delivery devices and implantable transdermal devices, which contain Nano-biosensing technologies, NPs, mechanical devices, and other systems. The nanodevices we will cover are quantum dots, gold NPs, and dendrimers. The greatest challenge and drawback of nanodevices is the cytotoxicity of said devices when given to patients. Another relevant challenge is oxidative stress, and how the effects of free radicals can damage tissues in the body as a result of an implanted NP oxidizing. Solutions to the previous challenge and the latter are discussed in the coming sections of this paper.**

***Key terms: Nanoparticle (NP), Nanodevice, Nano biosensor, Cytotoxicity, Oxidative stress.***

## I. INTRODUCTION:

The field of study "nanotechnology" and its application over the years has advanced to a great extent, but its advancement in the field of medicine and pharmacy has revolutionized the twentieth and present century. Nanotechnology is the arrangement of individual atoms, molecules, or compounds into structures to produce materials and devices with special properties [1]. Hence, nanotechnology is called the study of extremely small structures. Nanotechnology deals with material that have dimensions in the nanometer scale. This fits the description nanofabrication and thus provides the development of nanomaterials and nanodevices. Table 1 shows the periodical development in nanotechnology.

| Year | Development in nanotechnology |
|---|---|
| 1959 | R. Feynman initiated thought process |
| 1974 | The term nanotechnology was used by Taniguchi for the first time. |
| 1981 | IBM Scanning Tunneling Microscope |
| 1985 | "Bucky Ball" |
| 1986 | First book on nanotechnology Engines of Creation published by K. Eric Drexler, Atomic Force Microscope |
| 1989 | IBM logo was made with individual atoms |
| 1991 | S. Iijima discovered Carbon Nano tube for the first time. |
| 1999 | 1st nano medicine book by R. Freitas "Nano medicine" was published |
| 2000 | For the first time National Nanotechnology Initiative was launched |
| 2001 | For developing theory of nanometer-scale electronic devices and for synthesis and characterization of carbon nanotubes and nano wires, Feynman Prize in Nanotechnology was awarded |
| 2002 | Feynman Prize in Nanotechnology was awarded for using DNA to enable the self-assembly of new structures and for advancing our ability to model molecular machine systems. |
| 2003 | Feynman Prize in Nanotechnology was awarded for modeling the molecular and electronic structures of new materials and for integrating single molecule biological motors with nano-scale silicon devices. |
| 2004 | First policy conference on advanced nanotech was held. First center for nano mechanical systems was established, Feynman Prize in Nanotechnology was warded for designing stable protein structures and for constructing a novel enzyme with an altered function. |
| 2005-2010 | 3D Nano systems like robotics, 3D networking and active nano products that change their state during use were prepared. |
| 2011 | Era of molecular nano technology started |

**Table 1: Periodical development in nanotechnology** [1].

The Nanofabrication is a method of manufacturing devices with the nanometer as the dimension. There is no basic definition of nanofabrication, but we can say that it is an evolution of a device's size from micrometers to nanometers. As a result, microfabrication was rebranded as nanofabrication. The driver of nanofabrication technology was the manufacturing of Integrated Circuits (IC) [2]. The purpose of the nanofabrication is to produce nanoscale structures to form a system, device or component in large quantities at very low cost [3].

Nanofabrication can be categorized into two methods of approaches: the top-down method, and the bottom-up method. The top-down approach is not efficient as it is not feasible to remove extra material from bulk material to form Nano features. Hence, the bottom-up approach is the most efficient method. Nanofabrication has four techniques, which are lithography, deposition, dry etching and bottom-up wet chemical etching.

In this paper, the applications of nanofabrication in the medical field and pharmaceutical devices are the main concentration. nanofabrication helps bring revolution in the development of medical devices like nanotubes, nanowires, and nanoparticles [4]. Nanodevices have many advantages over their macroscale counterparts, and as a result of their minute size, these devices need less sample reagent for analysis or operation, saving money and time [5].

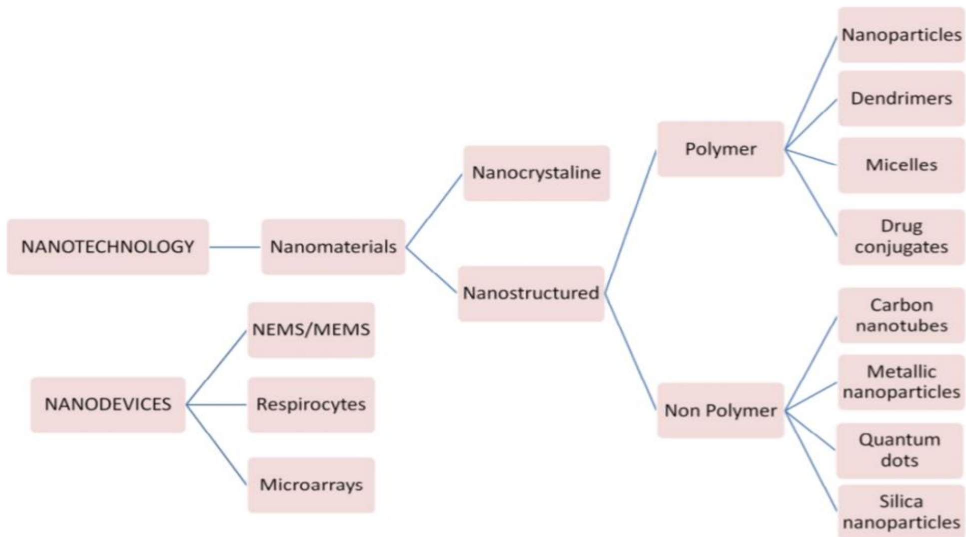


**Fig 1: Various types of pharmaceutical Nano systems [1].**

### A. Tools and techniques used Nanofabrication of Nanodevices [6]

1. Laser shock imprinting: Forms nanoscale metallic shapes for gears
2. Desktop nanofabrication tool: Uses beam-pen lithography arrays to build nanoscale structures.
3. Nanoscale diamond tips: Creation of longer-lasting AFM tips for etching or depositing material in nanomanufacturing processing

**B. New Processes that enable Nanomanufacturing** [6]

1. Chemical vapor deposition: Reacting chemicals produce pure, high-performance films.
2. Molecular beam epitaxy: Deposits highly controlled thin films
3. Atomic layer epitaxy: Deposits layers that are of one-atom thickness.
4. Dip pen lithography: Dipping the tip of an atomic-force microscope into a chemical fluid to "write" on a surface.
5. Nanoimprint lithography: "stamping" and "printing" nanoscale features onto a surface.
6. Roll-to-roll Processing: Producing nanoscale devices on ultrathin plastic or metal.
7. Self-assembling: Bringing a group of components together into an ordered structure without outside direction.

## II. APPLICATIONS OF NANOFABRICATION IN THE MEDICAL FIELD

The applications of nanotechnology are dispersed into various fields. The following are listed fields where nanotechnology is used.

1. Health and Medicine
2. Electronics
3. Transportation
4. Food
5. Fuel cells and Solar cells
6. Fuels
7. Batteries
8. Space
9. Better water and air quality
10. Chemical sensors
11. Sporting goods
12. Fabric

Concentrating on the health and medical fields of nanotechnology, nanomedicine is an application of nanotechnology that deals with health and medical aspects. Nanomedicine makes use of nanomaterials and nanoelectronics biosensors. There is speculation that nanomedicine will be of advantage for molecular nanotechnology. With the help of nanomedicine, early detection and prevention, improved diagnosis, proper treatment and follow-up of diseases are possible. These nanodevices have contributed immensely to the fields of biology, molecular biotechnology, and medicine. The following are applications of nanodevices in the medical and pharmaceutical fields [1] [5],

a. **Drug delivery devices**:

Nanofabrication techniques offer a range of possibilities for the preparation of peptide, protein, drug, or gene delivery devices. This is possible by controlling the size, architecture, topography, and functionality of drug delivery vehicles. Various drug delivery nanodevices are:

- Injectable nanodevices.
- Gene delivery with Nano-machined devices.
- Stents for drug delivery
- Microneedles for transdermal drug delivery
- Implantable microfabricated drug delivery chips
- Microfabricated and mucoadhesive systems
- Nanofabricated biosensors [7]
    - DNA sensors
    - Immunosensors
    - Cell-based sensors
    - Point of care sensors
    - Bacteria sensors
    - Enzyme sensors

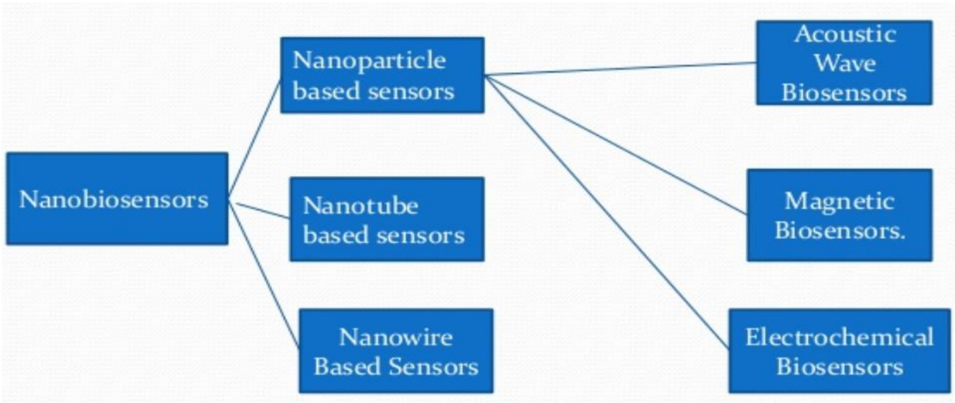


**Fig 1: Classification of Nano biosensors [8].**

**b. Implantable transdermal devices:**

Transdermal is a method of delivering drug into a body through a protective skin barrier. There are various transdermal methods. The purpose of transdermal devices that make use of nanotechnology is to conquer skin barriers [7].

- Implantable Biosensors
- Integration with monitoring systems
- Chronic disease monitoring
- Implantable cardioverter-Defibrillators
- Implantable drug delivery systems
- Pacemakers
- Cochlear implants
- Muscle stimulators
- Wireless-real-time monitors
- Implanted microelectrodes


**Fig 3: Implantable devices in nanotechnology in the medical field** [9]

### c. Applications of Nano systems in cancer therapy are:

- Carbon nanotubes - detection of DNA mutation and Disease protein biomarker.
- Dendrimers - Used for controlled release drug delivery and image contrast agents.
- Nanocrystals - Improved formulation for poorly-soluble drugs, labeling of breast cancer marker
- Nanoparticles - Used in MRI and Ultrasound image contrast agents, targeted drug delivery, permeation enhancers and reports of apoptosis, angiogenesis.
- Nano-shells - find application in tumor-specific imaging, deep tissue thermal ablation.
- Nanowires - used for disease protein biomarker detection, DNA mutation detection, and gene expression detection.

**d. Applications in ophthalmology:**

- ❖ Treatment of oxidative stress
- ❖ Measurement of intraocular pressure
- ❖ Theragnostic
- ❖ Treatment of choroidal new vessels
- ❖ Treatment of retinal degenerative diseases using gene therapy
- ❖ Prosthetics
- ❖ Regenerative nanomedicine
- ❖ Sight restoring therapy

**e. Surgery**

**f. Visualization**

**g. Tissue engineering**

**h. Antibiotic resistance**

**i. Application in medicated textiles:**

- ❖ Antibacterial cotton by nanotechnology used for antibacterial textiles

## III. FABRICATION METHODS

Many strategies for the fabrication of Nanodevices within medicine are taken from semiconductor manufacturing. Methods such as film deposition, photolithography, and soft lithography.

### A. Film Disposition

Film deposition put simply is the use of films in manufacturing as masks to either help grow or etch substrate into various shapes. These films can be made from silicon, plastic, or any other material that can be easily shaped into films [1].

### B. Photolithography

Photolithography is an already very well-known process of fabricating nanodevices as it is used to create very accurate micro to nanostructures using photosensitive material and light. Within this process, a thin film of photoreactive substance is placed over a substrate as a mask. Then using ultraviolet light, the undesired parts of the device are bound with the photo resistive material, making them soluble in a solution that can absorb the newly bonded photo resistive and substrate material as shown in Figure 1. [1]. The substrate is then left in a solution that will then dissolve the unwanted parts in a process known as “cleaning” [1]. This comes with the unfortunate downside of taking time to dissolve and is a major drawback of Photolithography.

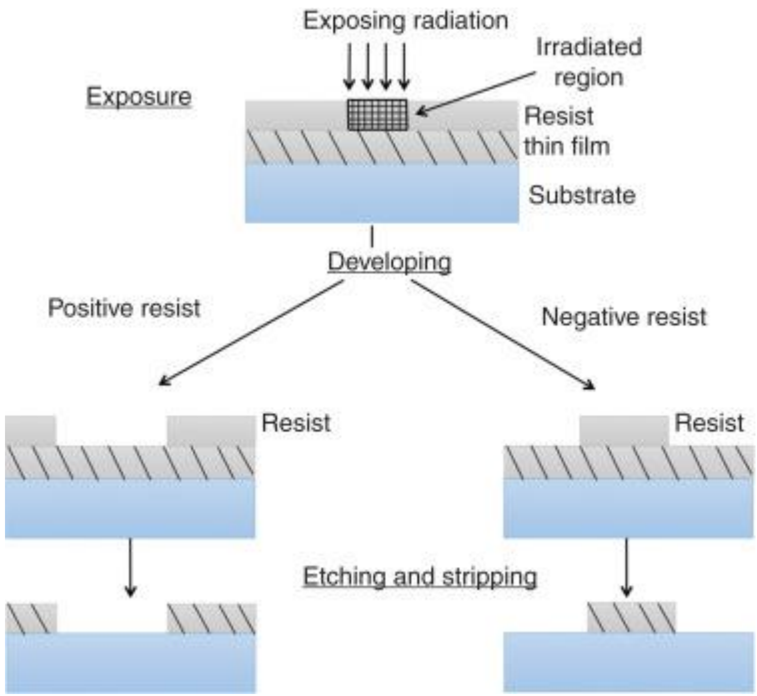


**Fig 3. Photolithography** [10]

### C. Soft Lithography

Soft lithography is another process that is like photolithography that it uses a thin photosensitive layer, is prevalent in microfabrication, and has the advantage of not requiring any kind of “cleaning” process, making it low cost compared to photolithography. Soft lithography encompasses many smaller techniques, the two being microstamping and microfluidic patterning [5].

Microstamping is a stamping method wherewith the photosensitive layer is pressed against a stamp and a substrate to form a self-assembled monolayer (SAM). Through this, polysaccharides, peptides, and proteins can be printed and protected during other processes [5].

Microfluidic Patterning is a process that uses the photosensitive material to create a channel for fluids. These channels are used for printing on cells within the field of tissue engineering [5]. These incredible devices are able to allow for separate fluid transfers within the same channel using Laminar flow [5].

## IV. NANODEVICE APPLICATIONS

Several Nanodevices are already within the development in medicine. Of these, a few practical and intriguing devices are Quantum Dots, Gold Nanoparticles, and Dendrimers. Few applications of nanoparticles are shown below in Table 2.

### A. Quantum Dots

Quantum Dots are one of the currently more famous nanodevices being used in medicine for their application in imaging cell organelles, DNA, and various other molecular organics. These devices are created out of a crystalline semiconductor material that are on the incredibly small scale of 2-10 nm and are able to fluoresce at different wavelengths of light [11]. These devices can be implanted to track bodily and cellular functions by observing light waves that are emitted after the device is hit with light [11]. The only downside to these devices is that a large majority of them are inherently cytotoxic [11].

### B. Gold Nanoparticles

Another device which Gold Nanoparticles is, or Gold NPs, are currently being explored for their ability to fight cancers and tumors in a very indirect way. Currently, advancements in medicine allow for specific cancer cell targeting using lasers. The main issue being the high-powered lasers are harmful and difficult to target only the cancer cells. To combat this, Gold NPs are being lasered instead of the cells and are using the imminent heat to kill the cancer cells and holds promise as a more effective way of fighting cancer cells in a less destructive method [12]. Past this, Maryland University researchers found that when using gold Nanoparticles within rats suffering from tumor growths the Gold NPs could be injected into the mice’s tumor and the blood flow could be disrupted [12]. In turn, this could stunt the tumor and prevent it from growing.

### C. Dendrimers

Lastly, Dendrimers have many exciting applications in delivering medicine to specific areas and even cells within the body. The Dendrimer anatomy consists of a core, branching dendrons with receptors at the end and an internal cavity that can be used for storing and administering medication in controlled areas as shown in Figure 2. [13].

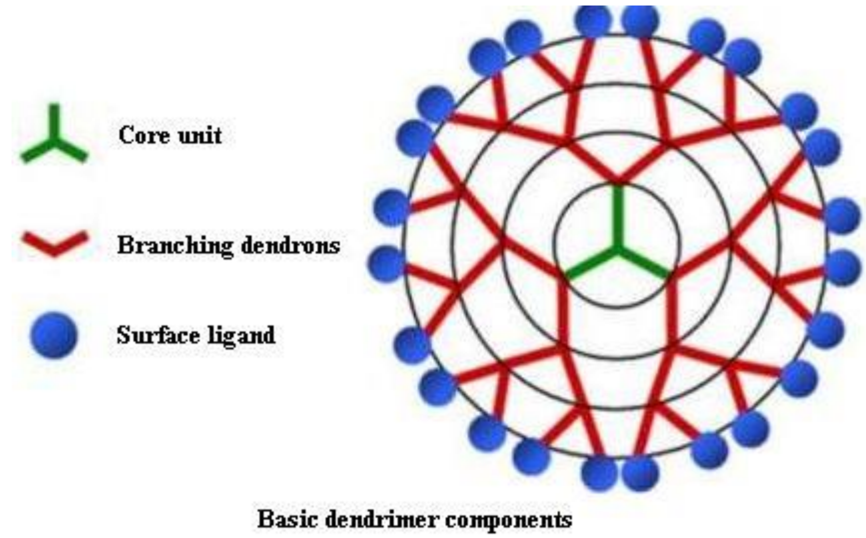


**Fig 4. Dendrimer Structure** [13]**.**

Specifically, the dendrimer can be designed in such a way that the drug stored will only be administered when in contact with a protein in various cancers [14]. This allows for normally harmful drugs in the body to be used within the body as the release of the drug is only triggered by the cancerous protein.

| | | |
|---|---|---|
| Liposomes | Doxil® | Liposomes provide both hydrophilic and hydrophobic environments, enhancing drug solubility<br>High carrying capacity – each liposome can entrap up to tens of thousands of drug molecules (11) |
| Nanoshells | Quantum dots<br>Nanospectra AuroShell® | Laser ablation<br>Quantum dots can be used as imaging agents with fluorescence energy proportional to size<br>Semiconductor properties<br>In vitro imaging |
| Metal colloids and metal oxides | Gold colloid<br>Iron oxide<br>Aurimune® | Biocompatible drug-delivery platform<br>Laser ablation<br>Imaging properties<br>Electron dense |
| Carbon structures | Carbon nanotubes<br>Fullerenes | Efficient heat conductors; high tensile strength and elastic modulus |
| Nanoemulsions | Propofol/Diprivan® | Both hydrophilic and hydrophobic environments |
| Nanocrystals | Rapamune® | Single crystalline<br>Electrical and thermal properties depend on size |
| Polymer- or protein-based | Abraxane®, Cyclosert®, Avidimer® | Provide both hydrophilic and hydrophobic environments, enhancing drug solubility |
| Viral vector | Rexin-G® | Commonly used tool of molecular biology to deliver genetic material into cells |

**Table 2: Major classes of nanoparticles used in clinical applications** [15]

## V. CHALLENGES AND CYTOTOXICITY

Of the many nanodevices manufactured for medical applications, several challenges within their design arise. The greatest challenge being the device's toxicity to the patient they are given to. In most other fields, the devices need only to complete a function while in Medical applications these devices must complete their function while being safe to their host or else run the risk of doing the opposite of their purpose: poisoning their host and making them worse off. These devices must be very carefully studied within their entire life spans from initial use to their degradation in order to observe their effects on patients.

Numerous factors such as surface chemistry, roughness, surface energy, level of degradation, the release of by-products, oxidative stress functions, crystallinity, and other parameters affect the toxicity of nanodevices used for biological applications [16].

### A. Surface Shape and Charge

Surface shape and surface charge are two interesting factors relative to their cytotoxicity and applications. As a result of this, even the shape must be carefully considered for the NP design. For example, gold has shown itself to be a very useful metal within biological applications for many years, with even larger implants such as teeth previously being made out of gold. As mentioned previously, gold still has its applications even on a molecular scale. Things such as both golden nanorod NPs and golden nanosphere NPs have been explored for various applications in biomedical applications. The main difference between the two is that gold nanorods have proven themselves to be toxic to much more undesired cells, while spherical shaped gold particles are far less cytotoxic [16].

Past this, spherical shapes are easier for cells to absorb within their cellular membrane, increasing their performance over their non-spherical designed counterparts.

Both the properties of increased cellular absorption and decreased cytotoxicity in spherical golden NPs hold true for most NPs and lead to most being fabricated in a spherical shape [17].

### B. Oxidative Stress

Unfortunately, many useful chemical compositions for cancer treatments are still toxic regardless of its shape such as manganese oxide ($Mn_3O_4$), iron oxide ($Fe_3O_4$), or zinc oxide ($ZnO$) [17]. This leads to one of the more important and toxic factors of Nano Medical Fabrication.

Oxidative Stress is brought about by the creation of so-called free radicals which are by-products of a NPs function. Free radicals are reactive molecules or particles that want to bond with other molecules. These can be anything from protons to Oxygen atoms to enzymes [18]. Free radicals bind through oxidation with various molecules within the body, targeting proteins, DNA, lipids, and various molecular structures within the body [19]. This leads to a very large complication within the design of NPs as many useful metals oxidize and can deliver Oxygen molecules to cells in the body. Aside from this, numerous other factors that create oxidative Stress can be introduced when using NPs like simply inflammation and response to foreign materials within the body [19].

Unfortunately, the design of a non-toxic NPs becomes much more unrealistic with Oxidative Stress being created from so many different by-products of NPs operating. So, the design of NPs is more focused on minimizing Oxidative Stress.

Researchers have shifted towards safer creation of NPs, including the use of polymers and other biodegradable substances that won't introduce as much Oxidative Stress as their metal counterparts, however currently, most of these are experimental and needs more testing before being reliably used.

## VI. CONCLUSION

In conclusion, our research has shown many promising nanodevices that have grown in popularity with the help of recent nanofabrication methods that are either commercially in use or currently researched in the pharmaceutical field. Of course, nothing is perfect, and these medical devices come with their drawbacks and challenges. Research is being conducted today to further reduce the negative and toxic effects of nanoparticles and other nanodevices for the purpose of alternate methods of drug delivery and implantable devices in hopes of a future where nanotechnology is the go-to method of combating notorious diseases around the world.

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## CONTRIBUTIONS

**LEVI -** Writer of

- Fabrication Methods
- Nanodevice Applications
- Challenges and Cytotoxicity

**JANANI -** Writer of

- Introduction
- Applications
- Advantages
- Also worked on citation and Formatting

**JAMES -** Writer of

- Abstract
- Conclusion