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{Review Article}

Nanolithography: A key Enabler of Advanced Drug Delivery System.

*[1]Mr. Harshal D. Borse**

[1] *Department of Pharmacology, Vaishalitai Jondhale College of Pharmacy, Dombivali, Mumbai, India.*

Abstract-

The present review article discusses recent advances in nanolithography and associated methodologies. In a word, nanolithography is the process of creating tiny shapes or patterns. These methods, which no longer require masking, aid in the development of nanomanufacturing--the same need-based processes that are now recognized as one of the most important aspects of practically all scientific research and development. In addition to the current knowledge, this review article discusses micro-contact printing, nano-imprint lithography, and scanning probe lithography. Each approach has also been discussed in terms of its merits, limitations, applications, and contemporary breakthroughs. The remaining scanning probe lithography and nano-imprint lithography subtypes are distinct. Alternative nanolithography technologies offer high- resolution pictures while being simpler and less expensive than UV and X-ray lithography. Recent developments in nanolithography are discussed in this article, with special attention paid to patented inventions, clinical trial validation, and new clinical uses.

Keywords- Nanolithography, Photolithography, Electron beam lithography ,X-ray lithography, Extreme UV lithography.

Introduction-

Lithography is essentially the process of transferring an image from a template onto a substrate, and it really took off in the printing world back in the 1700s. Now, when we talk about nanolithography, we're diving into the realm of manipulating structures at the atomic or molecular level. The name comes from "nano," which means one-billionth of a meter, and "lithography," which refers to writing or engraving. In simple terms, nanolithography is all about creating or replicating tiny patterns on materials or substrates. This technique plays a crucial role in fields like material science, electronics, and nanotechnology, allowing us to generate patterns on surfaces at an incredibly small scale. Nanolithography has a wide range of applications, from fabricating semiconductor integrated circuits to working with nanoelectromechanical systems (NEMS) and conducting research in nanoscience. It's an exciting and rapidly evolving area that involves constructing nanoscale structures on different materials using methods like etching, depositing, writing, and printing. When we refer to nanolithography today, we're talking about creating structures that measure anywhere from one billionth to one millionth of a meter.

In the world of nanolithography, there are three main ways to modify the sample surface:

- The setpoint mode of force-assisted lithography,
- The bias mode of bias-assisted lithography,
- The constant height lithography, also known as the Z scanner mode.

Nanolithography also has a significant role in studying domain switching in ferroelectric materials. In the pharmaceutical field, it's particularly valuable for developing drug delivery systems. By creating nanoscale carriers, like nanoparticles or nanostructured surfaces, we can deliver medications more accurately to specific areas in the body, which can enhance their effectiveness while minimizing side effects. When it comes to patterning at the nanoscale, there are several

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lithography methods available, and here are just a few of them:

- ✓ Photolithography
- ✓ Electron beam lithography (EBL)
- ✓ X-ray lithography
- ✓ Extreme ultraviolet lithography (EUVL)
- ✓ Light coupling nanolithography (LCM)
- ✓ Scanning probe microscope lithography (SPM)
- ✓ Nanoimprint lithography
- ✓ Dip-Pen nanolithography

- **Photolithography-**

Photolithography has its roots in Greek, with "photo" meaning light, "litho" referring to stone, and "graphy" translating to writing. When it comes to printing and image output, the techniques used in photolithography for nanolithography are quite similar to those found in traditional lithography. One of the most prevalent applications of photolithography is in the production of computer chips. The journey of photolithography began in the 1820s when Niepce developed a method using naturally occurring Syrian asphalt. You might also hear photolithography referred to as UV lithography or optical lithography. This process can create features as tiny as 50 nanometers. Essentially, photolithography is a light-driven technique that transfers patterns onto surfaces like silicon wafers or copper films, making it essential for producing integrated circuits and printed circuit boards.

Procedure-

1. Wafer Cleaning - The first step in the process is cleaning the wafer to get rid of any impurities and contaminants. This is done by treating the surface with a mix of isopropyl alcohol and distilled water.
2. Deposition of SiO_2 Barrier Layer - Next, a silicon dioxide (SiO_2) layer is applied to the wafer. This layer acts as a protective barrier for the wafer during the following steps.
3. Photo-Resist Coating Application - The wafer is then coated with a light-sensitive material known as photo-resist. This photo-resist is made up of polymers, solvents, sensitizers, and additives. The coating is applied using a technique called spin coating, which creates a uniform thin layer as the wafer spins rapidly.
4. Soft Baking, or Pre-Baking - To remove any leftover solvent from the photo-resist layer, the wafer is heated to 120°C for a set amount of time.
5. UV Exposure and Mask Alignment - UV light is directed through a photomask that has the desired pattern, which is aligned with the wafer. In the case of positive resist, the exposed areas become more soluble, while the negative resist is less soluble in those areas. There are three main methods for UV exposure:
   - Contact: The mask touches the wafer directly.
   - Closeness: There's a small gap between the mask and the wafer.
   - Projection: Lenses are used to project the pattern onto the wafer.
6. Progress - After the UV exposure, the wafer is placed in a developer solution. Depending on the type of resist used, either the exposed (for positive resist) or unexposed (for negative resist) areas will dissolve, creating the desired pattern on the wafer.
7. Hard Baking (Post-Baking) - To strengthen the remaining photo-resist and ensure it adheres

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

better to the wafer, the wafer is heated up.

8. Etching - The design from the photo-resist is transferred onto the SiO_2 layer or the wafer surface through a process called etching. This involves dipping the wafer into a solution that selectively damages only the exposed areas of the substrate, leaving the photo-resist-covered parts intact. Wet chemical etching is one way to achieve this, while plasma etching is another method that oxidizes and removes the exposed sections.
9. Photo-Resist - After etching, the remaining photo-resist is stripped away using plasma oxidation or a liquid resist stripper, revealing the intricate micro- or nanometer-sized patterns on the wafer.
10. The Final Exam - The finished wafer undergoes a thorough inspection to ensure the patterns are accurate and to check for any defects.

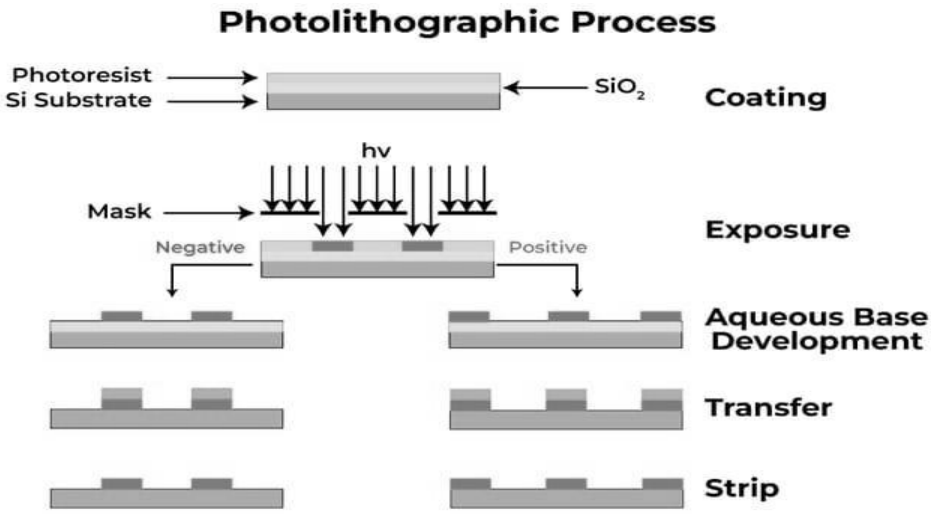


Figure-1

Lithography technique	Minimum feature size	Throughput	Applications
Photolithography (contact and proximity printings)	2-3 µm	Very high	common patterning at the lab level and the creation of different MEMS apparatus
Photolithography (projection printing)	Few tens of nanometers (37 nm)	High-Very high	commercial goods and cutting-edge technology, such as CPU chips and sophisticated integrated circuits

There are three exposure methods of photolithography i.e,

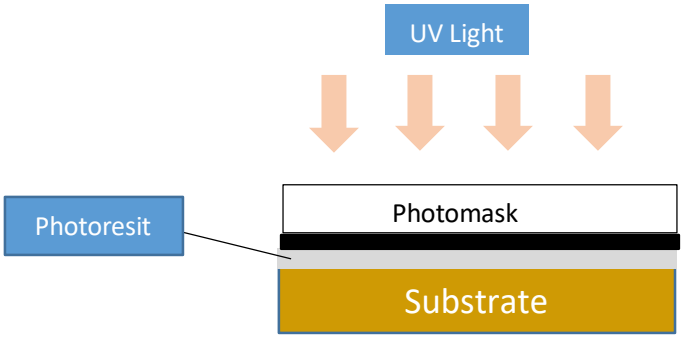
- Contact printing
- Proximity printing
- Projection printing

Contact printing - Contact printing - In this technique, the photomask is put in direct contact with the

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

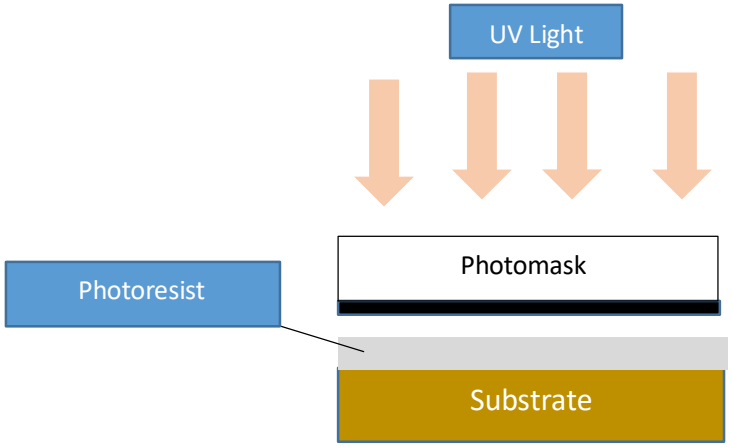
substrate. The light source is used to transfer the image from the photomask onto the substrate. This technique offers high resolution but can be prone to alignment problems.

Figure-1.1



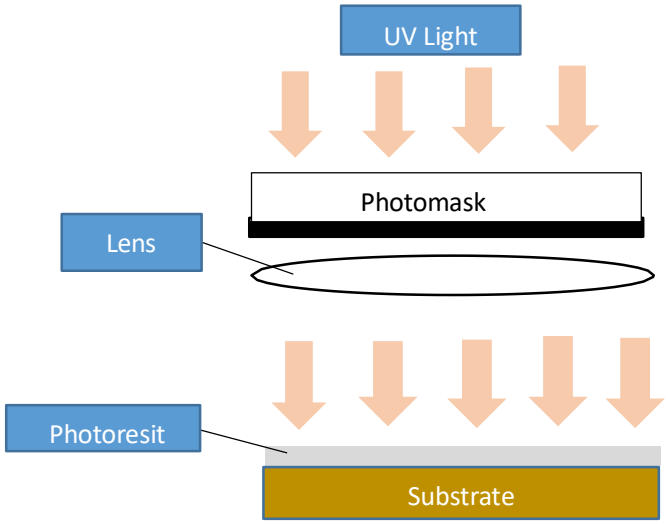
Proximity printing - In this technique, there is a limited distance between the substrate and the photomask. The light transfer the image from the mask to the substrate, but becomes distorted. Nonetheless, this technique provides improved alignment than contact printing.

Figure-1.2



Projection priniting - Here, the photomask image is projected onto the substrate with a lens. It permits size adjustment of the image and has high resolution. It provides flexibility and good resolution.

Figure-1.3



Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

The advantages of photolithography include:

1. High Resolution: The creation of very small and intricate features is enabled by the very high resolution of photolithography.
2. Precision: This method offers excellent alignment, which enables the creation of complex patterns with high accuracy.
3. Scalability: Photolithography is suitable for bulk production as it can be employed to microelectronics.
4. Versatility: It works with a range of materials, including polymers, silicon, and glass.
5. Cost-Effectiveness: It is ideal for mass production as it becomes cost-effective to create in large volumes when the initial setup is complete.[9]

The disadvantages of* photolithography *include:

1. Complex Process: It is challenging to install and sustain the photolithography process because it is complex.
2. Material Limitations: Some materials, like certain types of polymers, are not suitable for this technique.
3. Equipment Price: The upfront investment in good-quality photolithography equipment is high due to its high price.
4. Environmental Issues: Recycling and waste disposal come with additional challenges, and chemicals utilized in the process can prove harmful.
5. Precision limits: Even though photolithography is a very precise method, there are precision limits, which may prove to be issues at the nanoscale.[3]

There are numerous significant uses for photolithography in a variety of fields:

1. Microelectronics: It is primarily used in the manufacturing of integrated circuits, semiconductors, and microchips. Circuits with high density, which are required for modern electronics, can be manufactured due to this use.
2. MEMS (Micro-Electro-Mechanical Systems): By using photolithography, MEMS devices are required for sensors and actuators across a range of technologies.
3. Nanotechnology: Recent advances in photolithography make the fabrication of nanostructures feasible, significantly enhancing the field of nanotechnology.
4. 3D Photolithography: Intricate 3D structures for various applications can now be fabricated owing to novel methods such as two-photon polymerization.
5. Biotechnology: Technologies that involve lab-on-a-chip, microfluidics, and biomedical devices are all producede mploying photolithography.

- **Electron beam lithography (EBL)**

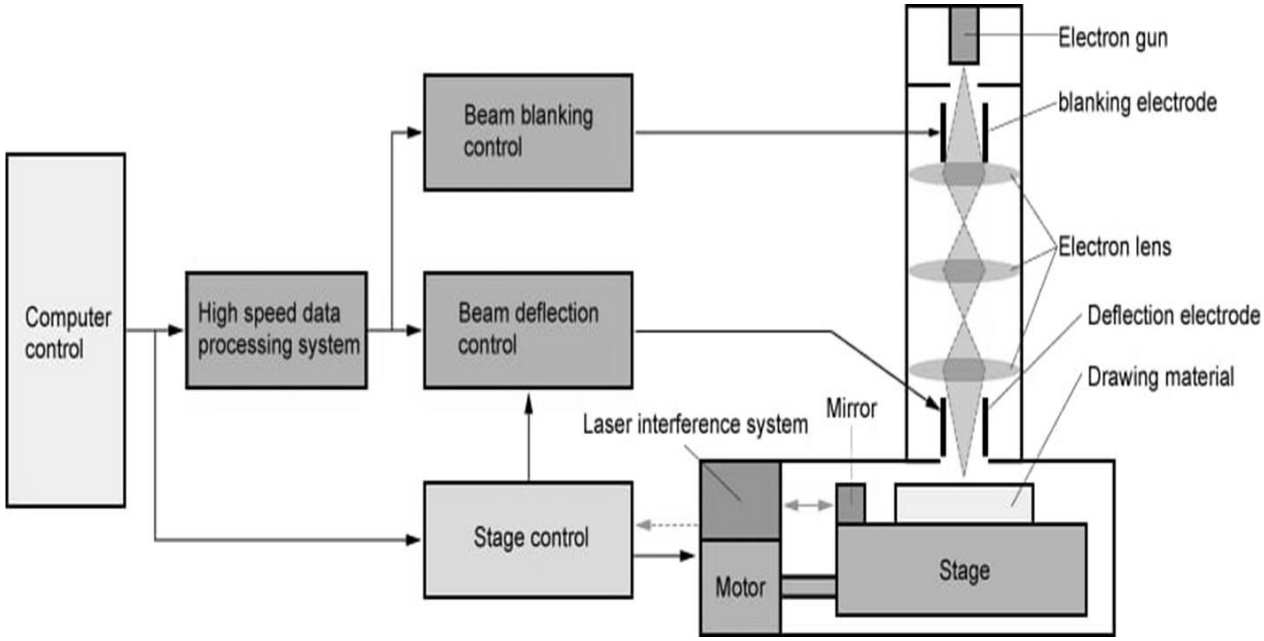
Electron beam lithography (EBL) is a fascinating technique that employs a finely focused electron beam to create incredibly tiny patterns. It's particularly valuable in high-resolution fields like semiconductor manufacturing, nanotechnology, and MEMS. The ultra-high-resolution (UHR) version of EBL takes a top-down approach, allowing for the translation of nanostructures onto substrates or the step-by-step construction of devices. Since the 1970s, this flexible, mask-less lithography method has gained traction for producing nanometric designs that are tough to achieve with traditional techniques. EBL operates with a concentrated electron beam that boasts a precision of 10 nm, free from diffraction, to imprint patterns onto a substrate. This pattern is

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

transferred onto an electron-sensitive film or resist, such as polymethylmethacrylate (PMMA), which is applied to the sample through a process called spin coating, where the coating is formed by spinning at speeds between 1000 and 6000 rpm.

Lithography technique	Minimum feature size	Throughput	Application
Electrom beam lithography.	< 5 nm	very low	Masks and ICs production, patterning in R & D including photonic crystals, channels for nanofluidics.

Figure-2



Procedure-

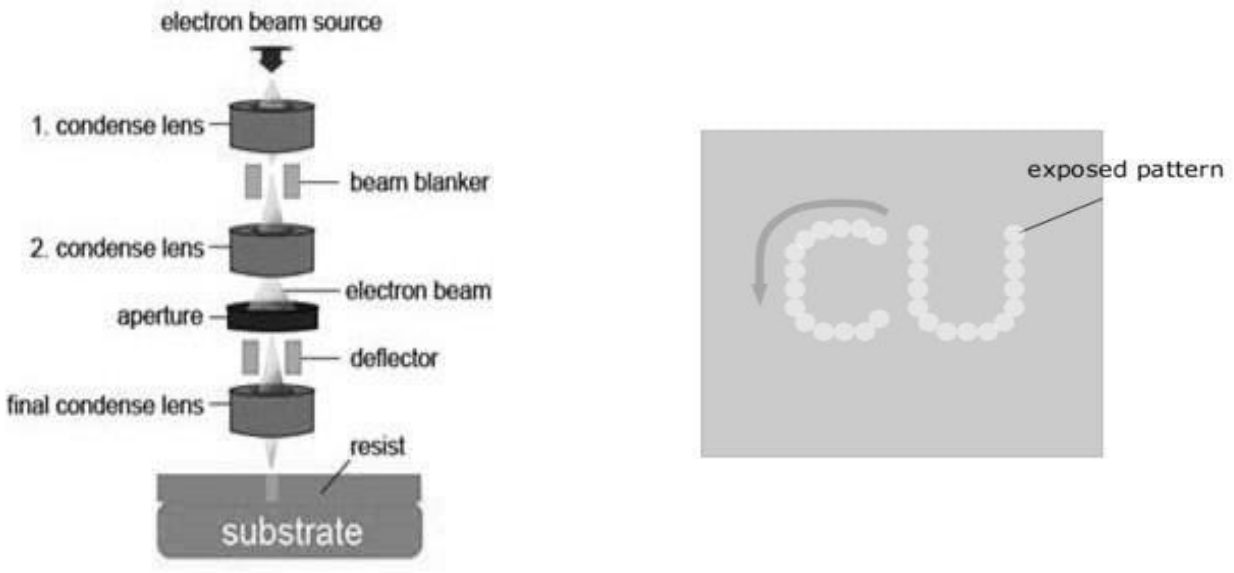
1. Substrate Preparation - First off, we need to clean the substrate and apply a thin layer of electron- sensitive resist. This could be PMMA if we're using a positive resist or SU-8 for a negative resist. Typically, the substrate is made of silicon, glass, or another suitable material.
2. Loading into the EBL System - Once the substrate is coated, it gets loaded into the EBL system. This machine operates in a vacuum to keep air molecules from scattering the electrons.
3. Electron Beam Generation - To create the electron beam, we use an electron gun, which is often a tungsten filament or a field emission source. The electrons are accelerated to really high energies, usually between 10 and 100 keV.
4. Beam Focusing and Scanning - We employ electromagnetic lenses to focus the electron beam into an incredibly thin spot, just a few nanometers wide. Then, with the help of

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

computer control, the beam scans across the substrate in a specific pattern.

5. Pattern Writing - As the beam scans, it exposes certain areas of the resist. This exposure alters the chemical structure of the resist, affecting how soluble it becomes in the developer solution.
6. Development - After exposure, we apply a developer solution to the substrate. Depending on whether we used positive or negative resist, the exposed areas will either dissolve or stay intact, revealing the pattern.
7. Pattern Transfer - The resist pattern acts as a mask for the next steps, like deposition, where we add material onto the substrate, or etching, where we remove material from it.
8. Resist Removal - Finally, we scrape off any leftover resist, leaving behind the desired nanostructures on the substrate.

Figure-3



The advantages of Electron beam lithography include:

1. Nanoscale Drug Delivery System Fabrication- For drug targeting, EBL can create accurate nanostructures (e.g., nanoparticles, nanocarriers, or nanochannels). By ensuring that the drug reaches specific cells or tissues and minimizing side effects, these structures can enhance the efficacy of drug delivery. highly sensitive biosensors. These biosensors improve early diagnosis and treatment monitoring by identifying biomarkers, infections, or drug interactions at very low concentrations
2. Biosensors and Diagnostic Tools- EBL enables the creation of nanoscale, highly sensitive biosensors. These biosensors facilitate early diagnosis and monitoring of treatment by identifying biomarkers, infections, or drug interactions at very low concentrations.
3. Surface Patterning for Cell Investigations- EBL is able to investigate cell growth, adhesion,

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

and behavior through patterning of surface nanocharacteristics. This aids in the development of new medicines through the understanding of how drugs interact with tissues and cells.

4. Vaccine Development- For better stimulation of immune responses while developing vaccines, EBL can be used for the assembly of nanostructures with virus particle-like structures.

The disadvantages of Electron beam lithography include:

1. High Cost- EBL systems are extremely expensive to purchase, keep, and deploy. Smaller research labs and pharmaceutical companies struggle to utilize the technology due to this.
2. Slow Process- EBL creates patterns point by point since it is a sequential process. This renders it slow, especially for high-throughput applications such as drug screening or mass production.
3. Complexity- In order to run the equipment and also maximize parameters such as beam energy, dose, and resist development, specialized expertise is required. This increases the overall cost and time.
4. Limited Scalability- Due to its slow writing speed, EBL is not suited for mass production. It is more suitable for small-scale research purposes or prototyping

Electron beam lithography (EBL) is significant for several reasons:

1. High Resolution: EBL is ideal for the fabrication of nanoscale drug delivery systems and biomaterials since it can fabricate structures at very small dimensions.
2. Improved drug Formulation: EBL is used to create accurate structures in drug formulations that have the potential to enhance bioavailability and release profiles.
3. Interfacing with Other Technologies: It is possible to fabricate intricate structures and devices by integrating EBL with other production techniques such as microfabrication and nanofabrication.
4. High Throughput: EBL is suitable for mass production as it can create many pieces simultaneously.

- **X-Ray Lithography-**

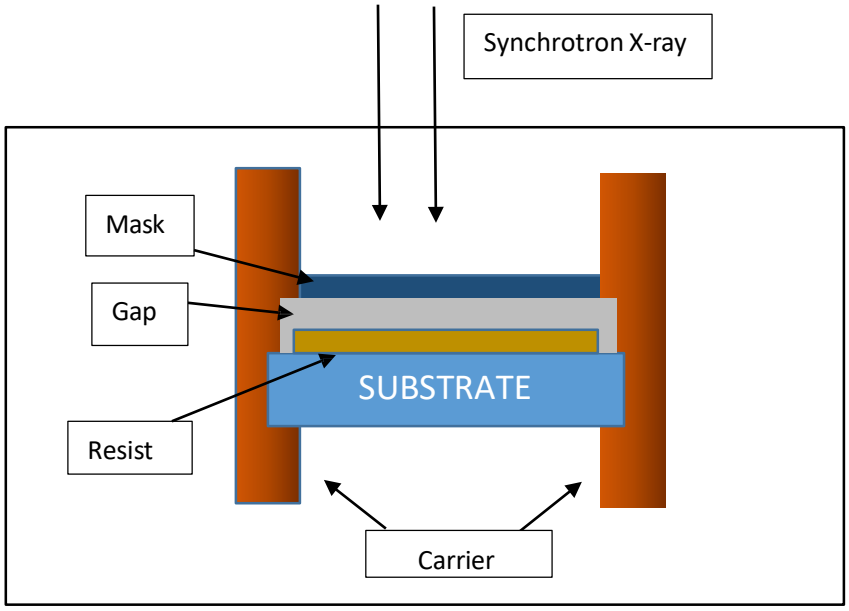
Just like photolithography, X-Ray lithography employs X-rays to transfer patterns from a mask onto a resist layer on a substrate surface. This technique was pioneered by Smith and Spears at MIT back in 1973. Since then, various organizations, including Hewlett Packard, Hughes Aircraft, and IBM, have contributed to its development. The main sources of X-rays in this process are synchrotron X-ray sources and electron impact. The patterned mask absorber plays a crucial role by selectively allowing or blocking synchrotron X-ray photons, which then pass through the photo-resist and deposit energy to expose it. Often, a gold absorber is used in this procedure. To create nanopatterns or nanostructures on a substrate, the etching and development processes are quite similar to those in photolithography. The image is enhanced to achieve an optical resolution of 15 nm by using brief illumination at a wavelength of 1 nm. The distance between the mask and the wafer is influenced by the wavelength and the size of the transparent features on the mask. Just like extreme ultraviolet and electron beam lithography, X-rays typically generate secondary electrons. Auger electrons, which have short path lengths, offer precise pattern definition, but the initial electrons can increase the resist's sensitivity over a wider area than X-rays.

- Sources of X-Rays -

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

1. Electron Impact X-Ray Sources: Here, electrons are accelerated at high energy by a metal anode. When these electrons strike the target, X-rays are emitted.
2. High-energy electrons are accelerated by a synchrotron, a powerful X-ray source, which periodically changes their direction.

Figure-4



Procedure-

1. Mask Preparation: A clear X-ray membrane (e.g., silicon nitride) is coated with a pattern of X-ray- absorbing material (e.g., gold) to create a mask.
2. Substrate Coating: A photosensitive resist material is deposited onto the substrate, e.g., a silicon wafer.
3. Exposure: X-rays are projected onto the mask when it is set over the substrate. The resist pattern within the mask is indicated by X-rays.
4. Development: Depending on the use of a positive or negative resist, the exposed resist is developed by removing the exposed or unexposed areas.
5. Pattern Transfer: Pattern is transferred to the substrate using the patterned resist as a mask for subsequent processing steps such as etching or depositing.

The advantages of X-Ray lithography include:

1. The ability to build tall buildings with aspect ratios of up to 100:1
2. X-ray's short wavelength (0.4–4 nm). Diffraction limits zero as a result.
3. Quicker than electron beam lithography and simple to use.
4. The submicrometer range has regular refraction pattern and correctness of structure.

The Disadvantages of X-Ray lithography include:

1. Traditional resist takes a long time to expose and is insensitive.
2. It is a slow process that accommodates a thin lens.

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

3. Manufacturing masks is costly.
4. Deformations and tremors during the operation

Significance of X-ray lithography i.e,

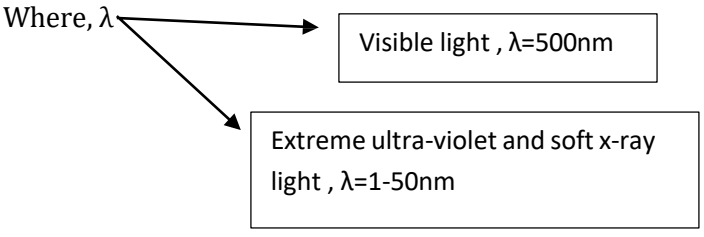
In the pharmaceutical industry, X-ray lithography has enormous potential, particularly for the production of drug delivery and diagnostic devices. Some of the potential applications include:

1. Drug Delivery Systems at the Micro and Nanoscale: X-ray lithography can be employed to design micro- and nanostructures to hold and deliver drugs in a controlled manner.
2. Lab-on-a-Chip Devices: X-ray lithography is capable of fabricating sophisticated patterns for drug screening and diagnostic microfluidic devices.
3. Implantable Devices: For enhancing the functionality and biocompatibility of implantable devices, such as stents or sensors, X-ray lithography can be utilized to create high-resolution patterns.

- **Extreme ultraviolet lithography (EUVL)-**

Extreme Ultraviolet Lithography (EUVL) is an innovative lithography method that's making waves in semiconductor manufacturing and advanced nanofabrication. By harnessing extreme ultraviolet (EUV) light with a wavelength of just 13.5 nm, it's possible to create features that are smaller than 10 nm. This technique is essential for the development of next-generation microchips and is also finding exciting new applications in nanotechnology, particularly in the biomedical and pharmaceutical fields. EUVL has the potential to craft intricate nanoscale structures that could lead to the creation of improved microfluidic devices for targeted drug delivery. These devices could enable precise delivery to specific cells or tissues and allow for exact control over how drugs are released. Plus, they might pave the way for nanoscale drug carriers, enhancing the effectiveness and bioavailability of medications.

Spatial resolution = $k \lambda / NA$.



Because all materials, including air, are absorbers of EUV light, EUVL relies on reflective optics and multilayer mirrors to concentrate the light. The process involves:

1. Utilizing plasma sources (e.g., tin plasma) to generate EUV light.

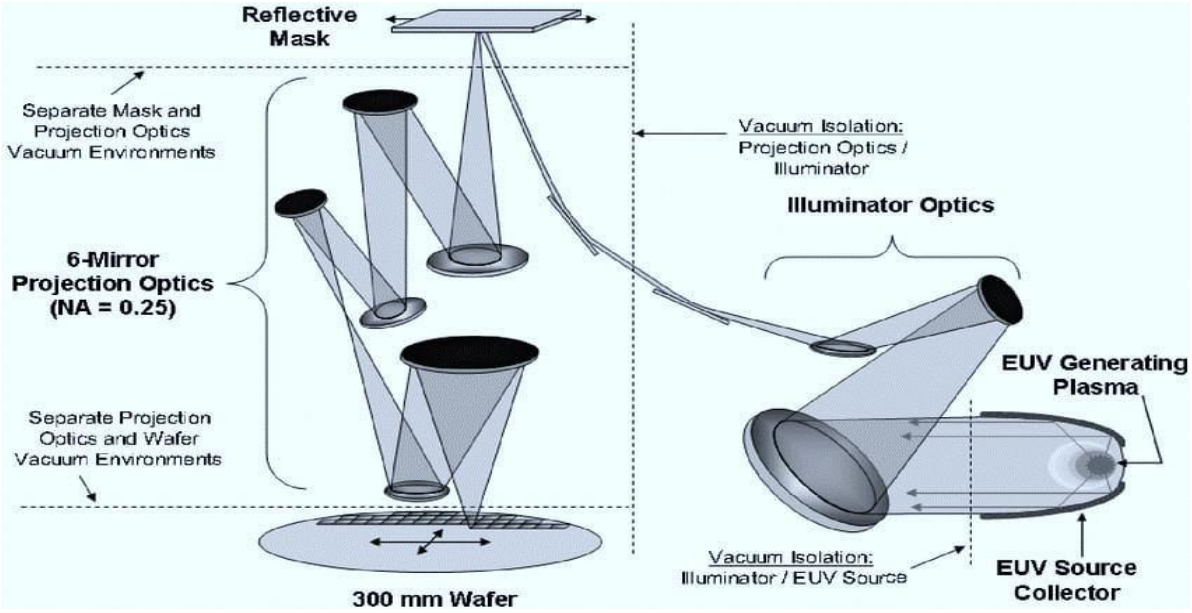
Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

2. Patterning the EUV light with a reflective mask with absorber materials (e.g., tantalum nitride).
3. In an effort to induce chemical alterations in the resist, the patterned light is directed onto a photoresist-coated substrate.

Procedure-

1. Mask Fabrication: - Mask Fabrication is a process of using multilayer mirrors, like Mo/Si layers, to create a reflective mask patterned with absorber materials.
2. EUV Light Generation: Tin droplets are ionized using a high-power laser to generate plasma that radiates EUV light.
3. Exposure: EUV light is projected onto a silicon wafer that has been coated with a chemically amplified resist (CAR) after being reflected off the mask.
4. Development: The resist that has been exposed is developed to reproduce the mask pattern by removing soluble regions.
5. Pattern Transfer: The resist pattern is used for deposition processes or etched into the substrate.

Figure-5



The advantages of Extreme ultraviolet lithography include-

1. Ultra-High Resolution: Critical for advanced semiconductor nodes, this capability is able to pattern dimensions below 10 nm.
2. Scalability: Facilitates the large-scale manufacturing of nanoscale devices.[20]
3. Precision: There are less optical aberrations compared to deep ultraviolet (DUV) lithography.
4. New Biomedical Applications: Potential to develop biochips and drug delivery devices at the nanoscale.

The disadvantages of Extreme ultraviolet lithography include-

1. Cost: Due to their complex optics and plasma sources, EUV systems cost anywhere from $150 to $200 million.

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

2. Mask Flaws: Contamination and defects are usual with reflective masks.
3. Throughput Limitations: Slow process due to low EUV light intensity.
4. Material Challenges: Few materials are wavelength-compatible with EUV.

Significance of Extreme Ultraviolet Lithography Includes-

Extreme ultraviolet lithography (EUVL) is a key technology in the semiconductor industry today, The following are some of the major include i.e

1. EUVL has a critical function in advancing Moore's Law, which forecasted the doubling of the density of transistors on a microchip about every two years.
2. EUVL creates intricate patterns on silicon wafers with the aid of light with a very short wavelength (13.5 nanometers). This is much more fine than those of previous lithography techniques.
3. The advancement of advanced technology such as artificial intelligence (AI), high-performance computing, and advanced mobile devices relies on EUVL.

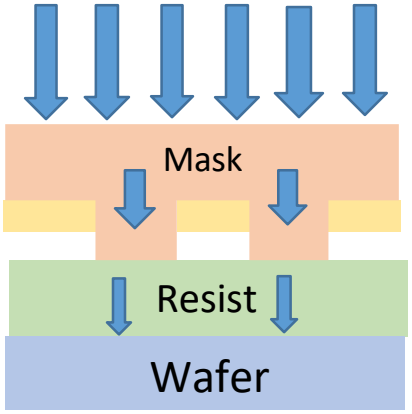
- **Light Coupling Nanolithography (LCM)-**

Light Coupling Nanolithography (LCN) is an innovative nanofabrication technique that achieves sub-wavelength resolution (less than 100 nm) by utilizing plasmonic coupling or near-field optics. This method allows for the direct coupling of electromagnetic energy into nanoscale features, effectively bypassing the diffraction limit of light, which is a common hurdle in traditional photolithography. It's particularly essential for creating high-resolution patterns in biomedical devices, such as drug delivery systems, electronics, and photonics.

In LCN, the photoresist comes into contact with a polymer mask. The transparent areas of the mask allow exposure where it's needed, and a very thin layer of gold can be added to enhance the contrast of the masked regions. To focus light energy beyond the diffraction limit, LCN makes use of surface plasmon polaritons (SPPs) or optical near-field coupling. The main mechanisms involved include:

- Near-Field Effects: The photoresist interacts with the evanescent waves produced by a sub- wavelength aperture or nanostructure.
- Plasmonic Enhancement: Metal nanostructures, like gold or silver, harness surface plasmons to concentrate light into tiny hotspots.
- Interference Patterns: Controlled light coupling in periodic nanostructures generates interference patterns.

Figure-6



Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

Procedure-

1. Mask/Probe Preparation: - A plasmonic mask (e.g., a nanoaperture array) or near-field optical probe (e.g., a tapered fiber tip) is fabricated.
2. Substrate Coating: The substrate (silicon, glass, or polymer) is coated with a photosensitive resist (e.g., SU-8 or PMMA).
3. Exposure: Sub-wavelength patterns are created on the resist by coupling visible or UV light through the mask/probe.
4. Development: In order to remove exposed and unexposed regions, the resist is developed chemically.
5. Pattern Transfer: Etching or deposition are employed to transfer the resist pattern onto the substrate.

The advantages of Light Coupling Nanolithography include-

1. The capacity to obtain features of the order 10–50 nm is referred to as sub-diffraction resolution.
2. Low Cost: There is no expensive EUV mask or source needed.
3. Flexible: Can handle a wide range of materials, such as biocompatible polymers.
4. Pharmaceutical Potential: Ideal for the development of biofunctional surfaces or drug carriers with nanoporous content.

The Disadvantages of Light Coupling Nanolithography include-

1. Throughput Limitations: Parallel lithography takes less time than serial writing.
2. Probe/Mask Wear: With time, physical contact or proximity leads to degradation.
3. Complex Alignment: Needs exact control over the distance between the probe and the substrate.
4. Shallow Patterning: Near-field degradation limits depth.

Significance of Light Coupling Nanolithography Includes-

1. Targeted Drug Delivery: Creation of nanopores or nanocavities for regulated drug release is made possible by LCN's accuracy.
2. Biosensors: Pathogen detection via high-resolution patterning of plasmonic sensors.
3. Nanostructured scaffolds for cell growth and adhesion: tissue engineering.
4. Lab-on-a-Chip: Nanoscale diagnostic characteristics in microfluidic channels.

- **Scanning Probe Microscope Lithography (SPML)-**

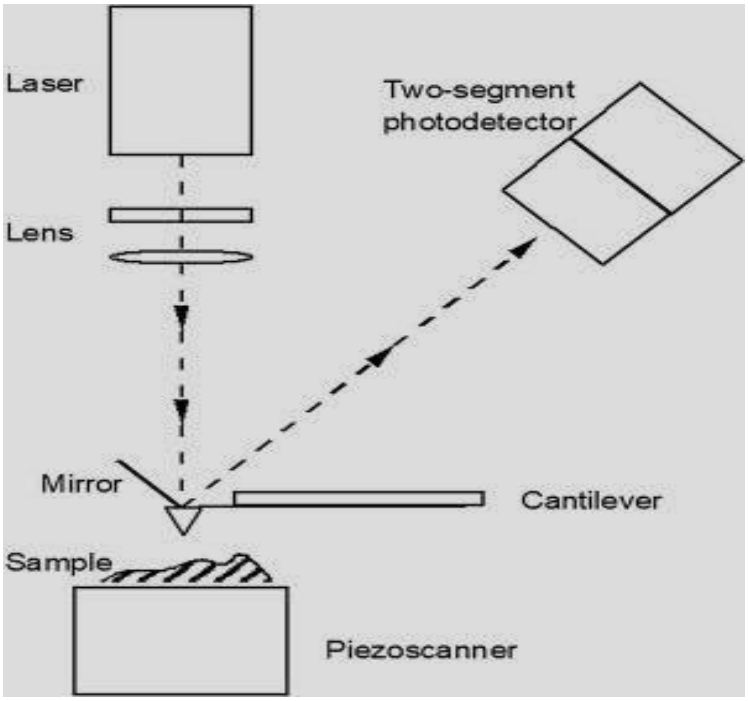
Probe Microscope Scanning Lithography (SPML) is a cutting-edge nanofabrication technique that crafts tiny patterns on a substrate using the tip of a scanning probe microscope (SPM), such as an atomic force microscope (AFM) or a scanning tunneling microscope (STM). This method is a go-to in the research and development of nanostructures for electronics, photonics, and even medical applications like drug delivery systems, thanks to its atomic-level precision. The technique gained significant recognition after the groundbreaking pattern studies at NST in 1989 and is primarily used in research settings. Unlike other methods, SPML is non-damaging and can achieve resolutions as fine as 10 nm. The equipment employs a probe to create the necessary indentations on the substrate. SPML operates by leveraging mechanical, electrical, or thermal interactions between a sharp probe tip and the substrate to modify the surface.
Here are some key components of the system:
- The scanning probe is the heart of the setup. It features a very sharp tip that interacts with the sample surface, typically made from metal or silicon. The type of tip used can vary depending on the

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

lithography method—like heated tips for thermal lithography or conductive tips for current-based lithography.

- Cantilever (in AFM-based systems): In atomic force microscopy-based lithography, the probe is attached to a flexible beam known as a cantilever. The deflection of this cantilever is measured to determine the force between the tip and the sample.
- Feedback Control System: This system keeps an eye on the interaction between the probe and the sample, adjusting the probe's position to maintain a specific setpoint. It's essential for achieving precise control during the lithography process.

Figure-7



Procedure-

1. Probe Preparation: An SPM is furnished with a very sharp tip (e.g., silicon, diamond, or metal- coated).
2. Substrate Coating: A resist or functional material is coated on the substrate, which may be silicon, glass, or polymer.
3. Patterning is done by scanning the probe tip over the surface and modifying it with chemical, mechanical, or electrical interactions.
4. Development: In resist-based SPML, material is dissolved by chemically developing the exposed areas.
5. Pattern Transfer: The pattern is transferred to the substrate through etching or deposition via the patterned resist.

The advantages of Scanning probe microscope lithography include-

1. The capability of obtaining features as fine as 1–10 nm is referred to as atomic-level precision.
2. Versatility: Able to work with a variety of materials, such as biomolecules, metals, semiconductors, and polymers.
3. Low Cost: No expense for expensive light sources or masks.
4. Pharmaceutical Potential: Ideal for creating biosensors, biofunctional surfaces, and nanoscale drug delivery systems.

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

The disadvantages of Scanning probe microscope lithography include-

1. Low Throughput: Serial writing processes take longer compared to parallel lithography methods.
2. Tip Wear: After a while, the pointed tip can wear away, reducing pattern quality.
3. Limited Area: Owing to its moderate scanning speeds, it is well suited for small-area patterning.
4. Complex Setup: Requires precise control over the interaction between the tip and substrate.

Significance of Scanning probe microscope lithography include-

The following applications benefit from SPML's accuracy and adaptability:

1. Drug Delivery Systems: creating nanoporous membranes or nanocarriers for regulated drug release.
2. Biosensors: Biomolecules (such as proteins and DNA) can be detected by patterning biofunctional surfaces.
3. Tissue engineering is the process of developing nanostructured scaffolds for the proliferation and differentiation of cells.
4. Lab-on-a-Chip Devices: Using nanoscale characteristics to pattern microfluidic channels for diagnostic purposes.

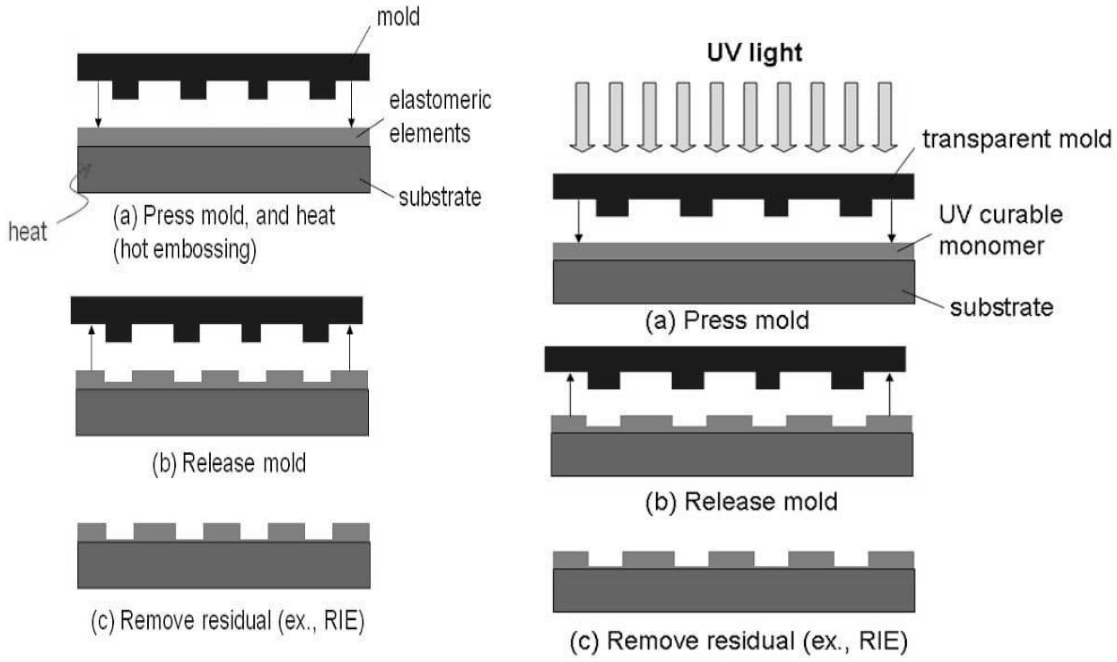
- **Nanoimprint lithography-**

S.Y. Chou was the first to introduce nanoimprint lithography, describing it as a "hot embossing technique" that allows for the creation of features with lateral diameters as tiny as sub-10 nm [27]. This high-resolution nanofabrication process, known as Nano Imprint Lithography (NIL), uses a physical mold to pattern a substrate. It's one of the most accurate lithography methods out there, capable of producing features as small as 5 nm. NIL is widely utilized in the manufacturing of semiconductors, optics, and even in biomedical applications, such as developing advanced drug delivery systems and biosensors. The process involves creating patterns by mechanically deforming the impression resist through additional techniques. During the imprinting, UV light or heat is used to cure the impression resist, which is usually a polymer or monomer formulation. To ensure that the mold releases properly, the adhesion between the template and the resist is carefully managed. Essentially, NIL works by pressing a nanostructured mold onto a substrate made of a malleable material, typically a resist or polymer. This material takes on the design from the mold and is then hardened to form a lasting pattern. The technique cleverly bypasses the light diffraction limit by using mechanical deformation instead of relying on optical or chemical changes. In 1996, to make the embossed material more fluid, a low-viscosity UV-curable monomer was introduced as a compliant polymer layer, leading to the evolution of what we now call UV-nanoimprint.

Lithography Technique	Minimum feature size	Throughput	Applications
Nano-imprint lithography	6-40 nm	High (>5 wafers/hr)	Biosensores, Bioelectronics, LOCs: nano cahannels, nano wires.

Figure-8*- Schematic illustrations of hot-embossing imprint nanolithography (left) and UV-imprint nanolithography (right).*

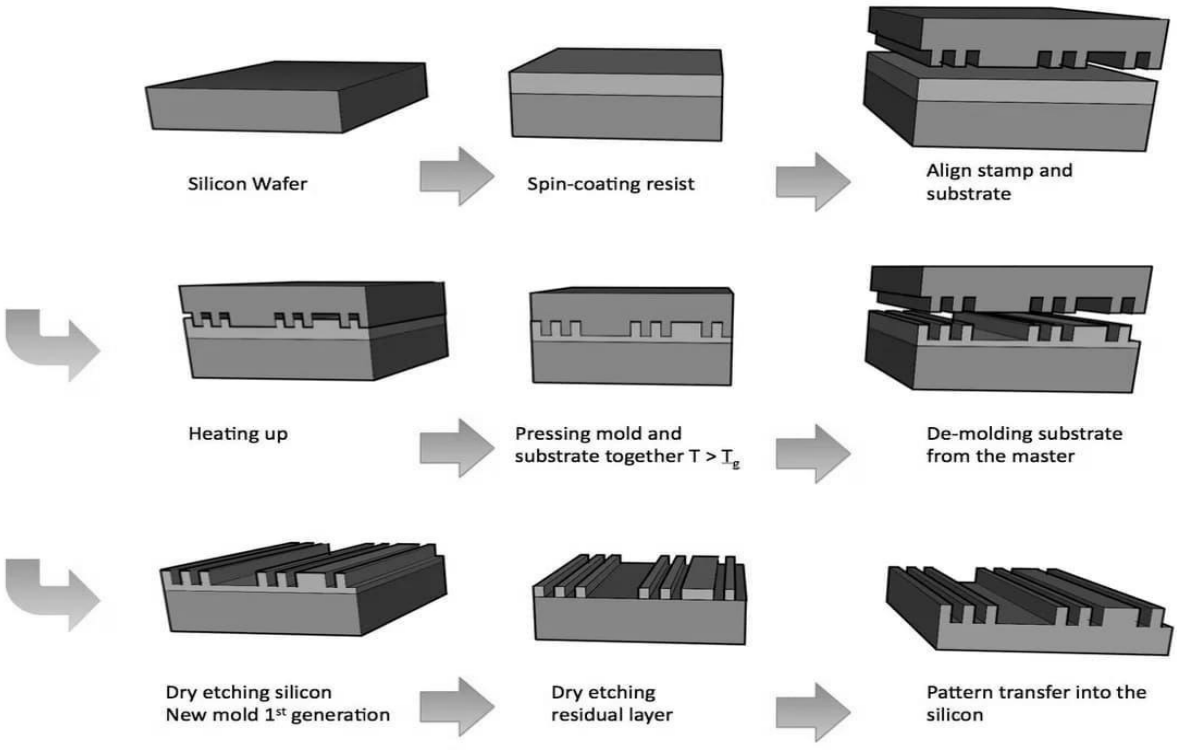
Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025



Procedure-

1. Mold Fabrication: Using techniques like focused ion beam milling or electron-beam lithography, a mold with the desired nanoscale pattern is produced. Silicon, quartz, or nickel are some typical materials.[20]
2. Substrate Preparation: - A resist material (e.g., PMMA, SU-8, or thermal/UV-curable polymers) is deposited on the substrate (e.g., silicon wafer, glass, or polymer).
3. Imprinting: - The mold is pressed against the resist under conditions of either UV light (for UV- NIL) or temperature and pressure control (for thermal NIL).
4. Demolding: The resist pattern stays on the substrate once the mold is removed.
5. Pattern Transfer: - Etching or deposition methods are employed to transfer the resist pattern to the substrate.

Figure-8.1



The advantages of Nano Imprint lithography include-

1. High Resolution: The smallest feature sizes of 5 nm are possible.
2. Cost-effective: No elaborate optics or expensive light sources are needed.
3. High Throughput: Due to its ability to perform parallel processing, it is suitable for bulk production.
4. Material Versatility: Capable of working with various materials, including metals, biomaterials, and polymers.
5. Scalability: Appropriate for large-scale production as well as small-scale research.

The disadvantages of Nano Imprint lithography include-

1. Mold Wear: Degradation and loss of pattern fidelity can occur due to repeated use of the mold.
2. Defects: The completed pattern might have defects owing to mold or resist flaws.
3. Alignment Challenges: Multi-layer patterning demands accurate alignment.
4. Limited Depth: The resistance and mold design limit the depth of patterned elements

Significance of Nanoimprint Lithography-

Because NIL can produce exact nanostructures, it has a lot of potential in the pharmaceutical sector. Important uses consist of:

1. Drug Delivery Systems: Synthesis of nanocarriers and nanoporous membranes for controlled release of drugs.
2. Biosensors: Developing nanoscale sensors to detect biomolecules (like proteins and DNA) in medical devices.
3. Tissue Engineering: Designing nanostructured scaffolds to enhance tissue regeneration and cell proliferation.
4. Anti-Counterfeiting: Drug packaging with nanoscale patterns to prevent counterfeiting.

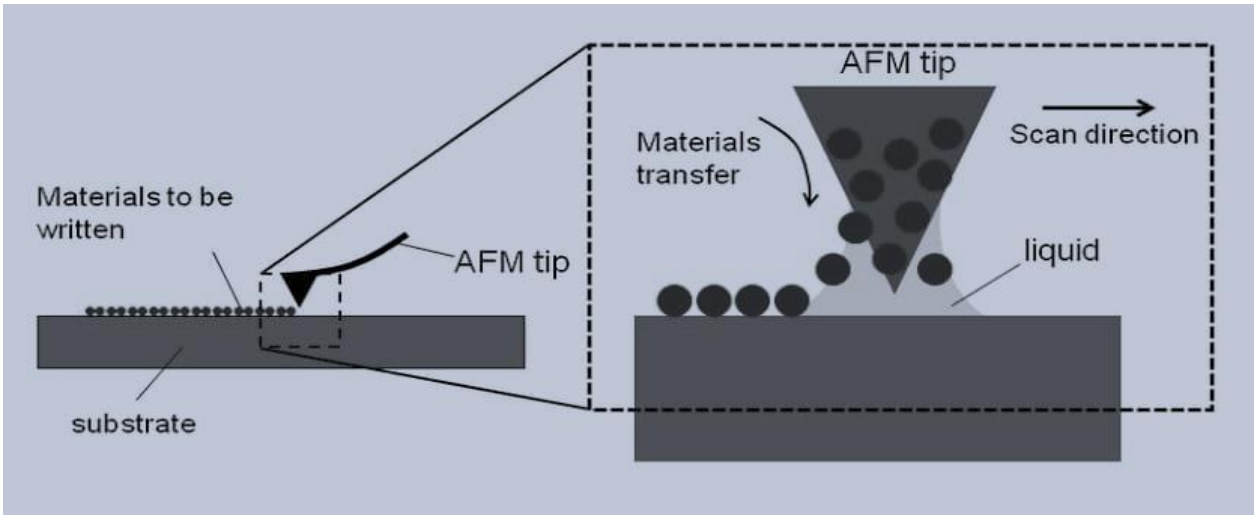
- **Dip-Pen Nanolithography-**

Dip Pen Nanolithography (DPN) is referred to as a soft-lithography method.[17]
Dip Pen An atomic force microscope tip is utilized in the direct-write nanofabrication technique called nanolithography (DPN) to deposit molecules with nanoscale precision onto a substrate. Patterns with feature sizes as low as 10–20 nm are possible due to DPN, which was created in the late 1990s. It is widely utilized in biosensing, nanotechnology, and pharmaceutical applications, such as the creation of drug delivery systems and biofunctional surfaces.[33]
Professor Chad Mirkin at Northwestern University's Nanotechnology Institute first developed this technique for printing thin organic films in patterns of feature sizes on the order of 10 nm, which is about 20 times more precise than the best optical lithography (Mirkin, 1999).[20]
DPN operates by employing an AFM tip as a "pen" to print molecules (e.g., polymers, biomolecules, or nanoparticles) onto a substrate.

Lithography Technique	**Minimum Feature Size**	**Throughput**	**Applications**
Dip-pen lithography	A few tens of nanometers	Very low-low, Possibly medium	Bioelectronics, Biosensors, gas sensors

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

Figure-9



Procedure-

1. Tip Preparation: The target molecules, e.g., proteins, polymers, or DNA, are deposited on the AFM tip.
2. Substrate Preparation: In order to ensure proper molecule adhesion, the substrate (e.g., silicon, glass, or gold) is cleaned and functionalized.
3. Patterning: - The top is pressed to the substrate, and as it travels over the surface, molecules are laid down.
4. Post-Processing: To enhance the applicability of the pattern, the patterned substrate can be subjected to additional processes like chemical etching or functionalization.

The advantages of Dip-Pen Nanolithography include-

1. Features of dimensions as small as 10–20 nm can be produced with high resolution.
2. Versatility: Capable of depositing a wide variety of materials, including nanoparticles, polymers, and biomolecules.
3. Direct Writing: Rapid prototyping and tailoring are facilitated by the absence of masks or resists.
4. The capacity to pattern biomolecules (like proteins and DNA) for biomedical applications is referred to as biocompatibility.
5. Low Cost: In comparison to other high-resolution lithography techniques, it is affordable.

The Disadvantages of Dip-Pen Nanolithography include-

1. Low Throughput: The serial writing process is slower compared to parallel lithography processes.
2. Tip Wear: Over time, the AFM tip will degrade, which will jeopardize the quality of the pattern.
3. Environmental Sensitivity: Temperature and humidity can affect the water meniscus, allowing it to alter the consistency of deposition.
4. Limited Area: Owing to its slow writing rates, it is suitable for small-area patterning.

Significance of Dip-Pen Nanolithography i.e,

Because DPN can produce precise, biofunctional patterns, it has a lot of potential in the

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

pharmaceutical sector. Important uses consist of:

1. Biosensors: Applying biomolecules (e.g., DNA or antibodies) to template them into ultra-sensitive diagnostic tools.
2. Drug Delivery Systems: Designing accurate surface functionalization on drug carriers at the nanoscale to allow targeted delivery.
3. Tissue Engineering: Creating nanostructured surfaces to control the development and attachment of cells.
4. Lab-on-a-Chip Devices: Nanoscale diagnostic characteristics are imprinted onto microfluidic channels.

- **Patents related to nanolithography techniques-**

The evolution of nanolithography techniques has been significantly supported by a variety of patents. These patents include breakthroughs in pattern transfer, improvements in resolution, and adjustments made for specific applications. Below are some notable patents related to the methods discussed in this article:

Sr No.	Patent Name	Inventor/Patent Number	Summary
1.	Nanoimprint Lithography	Inventor- Stephen Y. Chou. Patent- US5772905A	A method that creates tiny patterns by mechanically shaping a thermoplastic polymer, enabling production of features smaller than 100 nm at low cost and with high efficiency.
2.	Electron Beam Lithography	Patent- US4234791A	Describe a method for writing patterns on a resist-coated substrate using a focused electron beam. It offers excellent resolution, although it does have a slower speed limit.
3.	Dip-Pen Nanolithography	Patent- US6551614B1	Process that employs an AFM tip as a pen to apply molecular ink onto a surface, facilitating nanoscale patterning with chemical precision.
4.	Extreme Ultraviolet Lithography	Patent- US6949601B2	Describe an EUV lithography system using 13.5 nm wavelength light, essential for manufacturing of next-generation semiconductors.

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

- **Clinical Trails and Clinical Applications Involving Nanolithography-based Devices –** Clinical trials that focus specifically on medical devices made with nanolithography are somewhat scarce. This is mainly because nanolithography is more of a fabrication technique than a direct method for therapy or diagnosis. Nevertheless, we're starting to see more devices created through nanolithographic processes making their way into clinical evaluations, particularly in fields such as wound healing, implantable devices, and drug delivery systems.

-*Clinical Evaluations of Nanolithography-Enabled Devices*

1. Nanofibrous Scaffolds for Chronic Wound Healing- To tackle chronic wounds like diabetic ulcers and pressure sores, researchers are exploring nanofibrous scaffolds created through a nanolithographic process as potential skin substitutes. Clinical evaluations focus on their stability, biocompatibility, and effectiveness in restoring skin integrity.

2. Nanocoated Implantable Medical Devices- Nanocoatings are being applied to implanted devices, such as pacemakers and stents, to enhance biocompatibility and reduce the risks of thrombosis and restenosis. These coatings, which are applied using nanolithographic techniques, are currently

   undergoing clinical evaluations to determine their safety and effectiveness in improving device performance.

3. NEMS-Based Drug Delivery Systems - NEMS (Nanoelectromechanical systems) developed through nanolithography are being designed for targeted drug delivery applications. Devices like programmable micropumps and microneedle arrays are in clinical trials to assess their capability to deliver medications, such as insulin, in a controlled manner based on physiological signals.

-Clinical Applications

Nanolithography has an amazing ability to create super precise nanostructures that can engage with biological systems in unique and beneficial ways, which is what makes it so valuable in clinical settings. settings. While it's primarily a fabrication technique, the things it produces are used in a variety of cutting- cutting-edge clinical and biological applications:

- Diagnostic Devices and Biosensors
  - Lab-on-a-chip platforms: Thanks to nanolithography, these microfluidic devices can use tiny samples of blood or saliva to perform rapid diagnostic tests, like those for COVID-19 or cancer markers.
  - Nanoscale biosensors: These sensors, featuring nanopatterned surfaces, can detect low-abundance biomarkers such as proteins, DNA, or viruses with greater sensitivity.
  - For instance, nanosensor arrays can be used for monitoring glucose levels or for early cancer detection.

- Medical Implants
  - Surfaces with nanotextures: These surfaces help improve tissue

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

integration and reduce the chances of immune rejection.
- Implant coatings: These are applied to orthopedic or cardiovascular devices, like stents, to enhance cell adherence and minimize bacterial growth.
- A good example would be titanium implants that have nanopatterned surfaces to encourage bone growth.

❖ Systems for Drug Delivery
- Nano-carriers: These are nanoparticles or membranes that release medications in response to specific triggers, such as changes in pH, temperature, or the presence of certain enzymes.
- Microneedle arrays: Created using precise nano/microfabrication techniques, these devices allow for painless transdermal delivery of medications.
- For example, microneedles can be used to deliver insulin or vaccines without discomfort.

❖ Regenerative medicine and tissue engineering
- Scaffold design: Nanopatterned scaffolds can effectively guide the movement and development of stem cells.
- Bioactive surfaces: We can create topographies that mimic the extracellular matrix (ECM) using lithography techniques.
- One practical application is regenerative templates that aid in the healing of skin, bone, or nerves.

❖ Eye Instruments
- Contact lenses featuring nanopatterns can improve wettability or control the release of medication.
- Intraocular lenses (IOLs): These are surface-modified lenses designed to reduce inflammation and enhance compatibility.

- **Conclusion-**

Nanolithography stands out as one of the most crucial technologies in the realm of nanotechnology, enabling the creation of incredibly fine and precise patterns essential for a variety of applications, particularly in the pharmaceutical field. Each method, whether it's photolithography, electron beam lithography (EBL), or X-ray lithography, has its own advantages, making them suitable for different tasks based on the required size and level of detail. This technology is truly transforming the pharmaceutical industry by facilitating the development of advanced drug delivery systems that can target specific areas of the body, which not only boosts treatment effectiveness but also minimizes side effects. Additionally, it plays a key role in crafting highly sensitive biosensors, paving the way for personalized therapies by detecting diseases at their earliest stages. However, despite the remarkable precision and ability to create intricate structures that nanolithography offers, it does have its drawbacks. Some methods can be slow and reliant on expensive equipment, while others require

Date of Submission: 02/11/2025 Date of Acceptance: 09/11/2025 Date of Publish: 16/11/2025

specialized expertise to operate effectively. There are also potential issues regarding material compatibility and safety. Overall, nanolithography is reshaping the pharmaceutical landscape and opening up exciting avenues for innovation. Yet, to fully realize its potential and make it more accessible, it must address these challenges. With the backing of patented inventions and successful clinical trials, the advancements in nanolithography hold great promise for significant clinical applications.

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