Chapter 6

Nanoimprint lithography and transdermal drug-delivery devices

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1 INTRODUCTION

Imprinting lithography is the process of transferring structures from a patterned stamp to a substrate surface. Nanoimprint lithography (NIL) is a replication technology of structures on the micro- and nanoscales. NIL has been around for nearly two decayed. NIL was invented in the mid-1990s as demonstrated by Refs. [1] and [2], as an alternative to photolithography and E-beam lithography to those who seek high-resolution patterning in low-cost and high throughput. E-beam lithography is costly and optical lithography has limited resolution in the nanometer regime. NIL has now been introduced to many different types of imprinting technologies such as roll imprint process, laser-assisted direct imprint, substrate conformal imprint lithography, ultrasonic NIL, and so forth not only the hot embossing and UV-based nanoimprint lithography (UV-NIL) types.

NIL has the advantages of imprinting 3D pattern and large area of micro- and nanostructure scale in low cost and high throughput. This capability allows many applications in the areas of data storage, optical elements, NEMS, etc. Commercially speaking, NIL has been applied in the manufacturing of hard disk drives (HDD), biological devices, optical devices (e.g., light-emitting-diode (LED)), large-area display, and so on, are mentioned in Ref. [33].

Nowadays many vendors in the marketplace offer a range of NIL equipment and tools. The intention here is to give a basic introduction to NIL, the technology, equipment, tools, materials, and processes.

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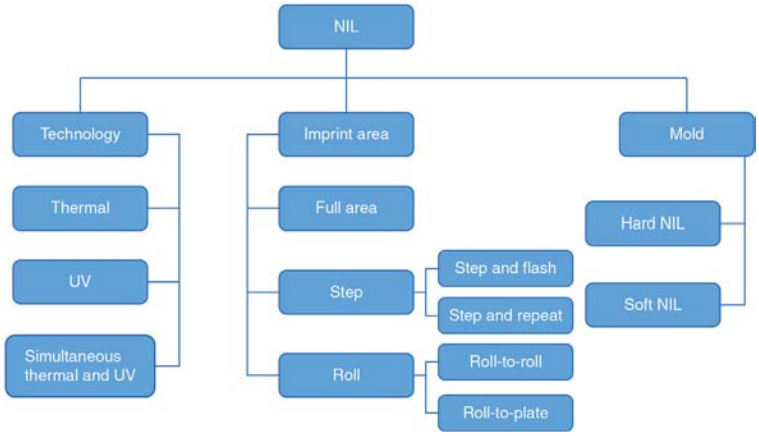


■ **FIGURE 6.1 Classification of nanoimprint lithography technology.**

Fig. 6.1 shows the NIL classifications and technologies.

Several companies worldwide are involved in nano- and microimprint lithography technologies. The following are the main companies classified according to their countries. Table 6.1 shows the key technology and applications of their products.

Later in the chapter, we will discuss the manufacturing of drug-delivery system and biosensors using NIL equipment and tools of this technology.

2 NANOIMPRINT LITHOGRAPHY TYPES

NIL is a replication technique that has high resolution compared to any other technique. Furthermore, it is a fast fabrication method for micro- and nanostructures with high throughput and low cost. These features are impossible in other methods. There are many types of lithography with practical resolution limits ranging 20–2500 nm.

The types of NIL are X-ray proximity, ion beam projection, electron beam, UV-proximity photolithography, deep-UV projection, extreme ultraviolet (EUV) interface lithography, EUV projection, UV nanoimprint, thermal nanoimprint, and soft lithography.

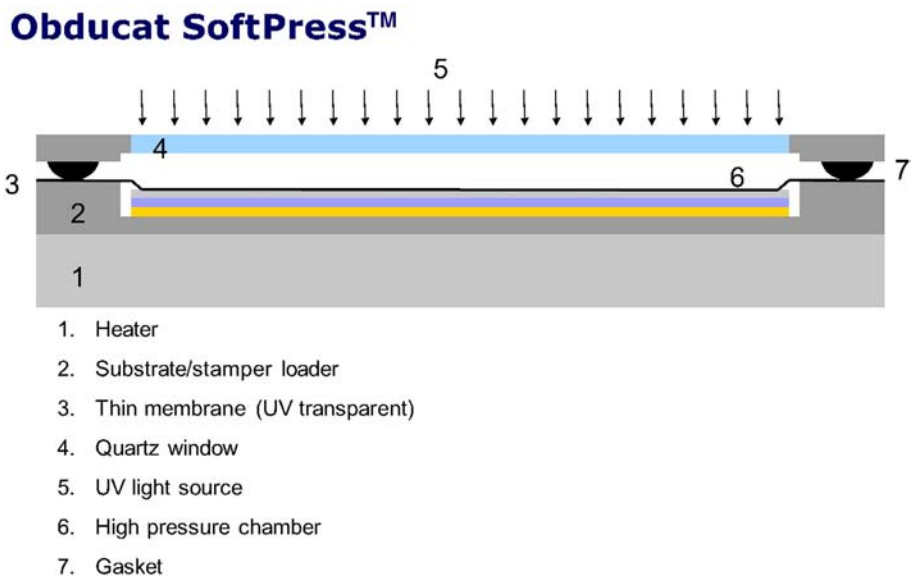
All the previously mentioned lithography techniques are for large and parallel methods. These methods will be discussed in more details in the following sections.

Table 6.1 Key Technology and Applications of Companies Worldwide

Country	United States	Sweden	Austria	Germany	
Company	***NANONEX***	***OBDUCAT***	***EVG***	***SUSS MicroTech***	***Heidelberg Instruments***
Key Technology	Thermal; UV; direct imprint; step-and-repeat	Thermal; UV; direct imprint; full area spin coaters; polymer coater; large area HVM equipment; STU; BDF-lasers; full-automatic equipment; microcluster	Single step; step-and- repeat; roll-to-roll; UV; hot embossing; auto hot embossing; large area	UV; soft stamp; large area; mask aligner; EBR system; direct writing	Direct exposure substrate; laser lithography
Applications	Displays; Opto; data storage; biotechnology; materials; microwave; semiconductors; and so on	Displays; Opto; data storage; biotechnology; materials; microwave; semiconductors; sensors; drug delivery; lenses; solar cell; MEMS; NEMS; LED; and so on	Microelectromechanical systems (MEMS); advanced packaging; compound semiconductors	Photomasks for: color filters; HB LED; touch panels; patterned media; sensors; other optical devices	Production of photomasks; MEMS; BIOMEMS; microoptics; microfluidics; sensors; other microstructure applications

Country	Denmark	China		Taiwan
Company	***NIL Technology***	***SVG Optics***	***Guang Doi Nano***	***Auro Tek***
Key Technology	Hot embossing; injection molding; roll-to-roll	Roll-to-roll; UV; hot embossing; pattern generation	Micro contact device; thermal; UV; soft mold UV alignment;	UV; auto loader; auto injection; direct press
Applications	Antireflection; Wire grid polarizer; Light difusers; Photonic band gap	Masks; Touch panels; Microfluidic; 3D Display; Antireflection for solar cell	Light diffusion film; LED	Large area nanosphere self-assembly; micro- and nanopatterned sapphire substrate; customized patterns

Country	Japan	
Company	**Toshiba Machinery**	**Cannon**
Key technology	Roll-to-roll; step-and-repeat; direct press thermal UV; XY-stage; vacuum chamber;	Roll-based jet and flash UV; Direct imprint; thermal; full area step-and-repeat
Applications	Electronic communication devices; biomedical equipment; solar cell	HDD; semiconductor industry



■ **FIGURE 6.2 Schematic diagram showing Obducat's Soft Press layout.**

3 NANOIMPRINT LITHOGRAPHY METHODS

3.1 Full area imprinting

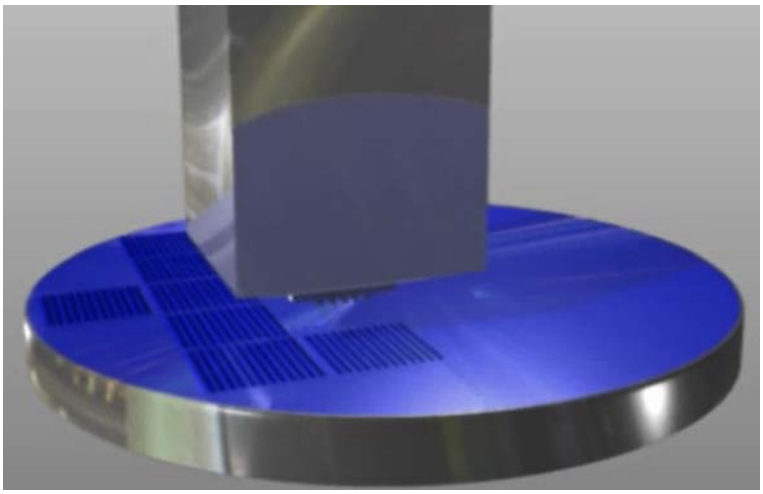
The tools of this technology imprint full and large area stamps in one go. It transfers the whole device from the stamp onto the target substrate, which increases the throughput of the tool. Obducat AB, a Swedish company, decided to focus on full and large area imprinting tools only. They have developed 3-inch-, 6-inch-, 8-inch- and recently 20-inch large-area imprinting tools. To make the full area imprint possible Obducat AB developed a *SoftPress*® technology to conform the surfaces for full contact, as shown in Fig. 6.2.

The SoftPress technology eliminates the roughness and wavy stamp or substrate effect on each other. It has been introduced by Obducat AB. The nanostructure transferred onto the target substrate uniformly.

The SoftPress technology applies gas pressure uniformly to the imprinting stack leading to auto-parallelization between the stamp and the substrate, which forces the material of both the stamp and the substrate to align with each other. This will compensate the irregularities to a certain degree depending on the stiffness of the stamp or the substrate, see Ref. [3] and [4].

3.2 Step and repeat imprinting

This technology uses small stamps (typically 1-inch × 1-inch) and replicates structures from a small stamp into a substrate and then steps the stamp to a



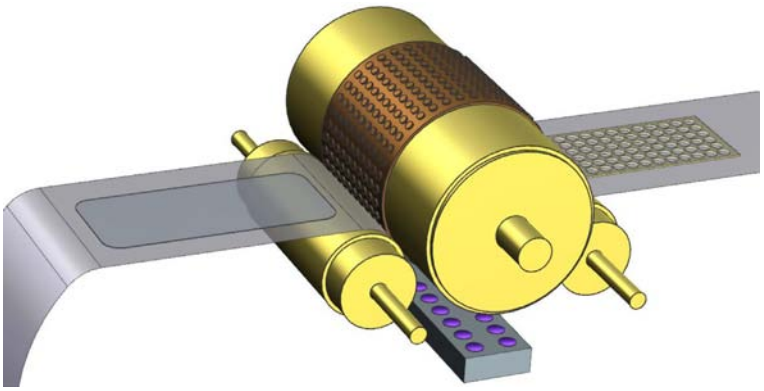
■ **FIGURE 6.3 Step-and-repeat nanoimprint.**

new area on the substrate to repeat the process again (Fig. 6.3). The technology has been introduced as Jet and Flash Imprint Lithography (J-FIL) by Molecular Imprints Inc., a US company. The advantage of this technology is that there is no need to large stamps and the alignment of the structure is more relax relative to the full area imprints. The disadvantage of this type of tools are, first, it leaves gaps without pattern between the printing steps, which affects the outcome especially when the desired device is larger than the stamp size; second, the throughput is slow; third, a small defect on the stamp will be replicated in all areas and cause larger defect level on the final substrate.

3.3 Roll-to-roll imprinting

Roll-to-roll (R2R) imprinting (Fig. 6.4) is a promising technology for very large area applications with high throughput production requirements, especially for applications such as flexible electronics and cosmetic patterning on films.

The stamps for this technology cannot be manufactured using conventional methods such as e-beam lithography because of the high cost; also the e-beam tools cannot accommodate such large substrates. Therefore, nanostructure patterns can be manufactured using laser interface lithography as in [5] or step-and-repeat methods as demonstrated by [6] for gratings and dot arrays and direct write laser lithography for other structures. These tools are available for both thermal and UV-based imprinting. For more information see Refs. [7] and [8].



■ FIGURE 6.4 Roll-to-roll imprinting from TNO the Netherlands.

3.4 Roll and imprinting

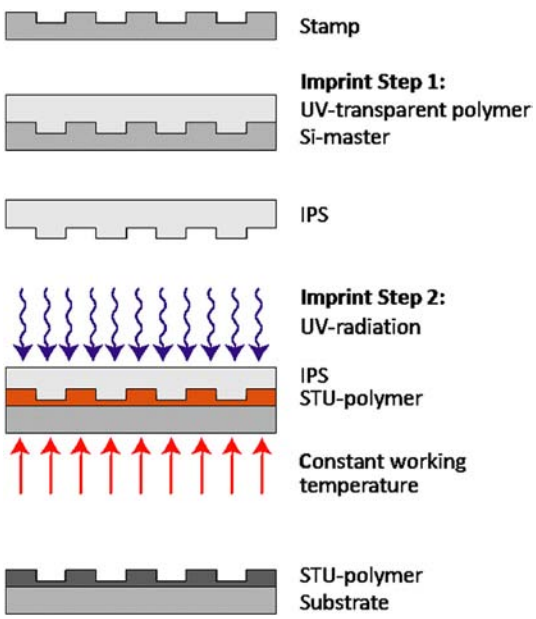
High volume manufacturing of Nanodevices using this technology has been realized by Obducat AB, a Swedish Company, using an intermediate polymer stamp (IPS)®. For full details see the two patents Refs. [9] and [34].

The process works as follows: a disposable polymer copy of the hard stamp (Si, quartz, Ni) is made by transferring the nanostructure pattern from the hard stamp onto the IPS. This copy is used to transfer the nanostructure onto the target substrate employing the SoftPress process. Fig. 6.5 shows how the IPS is used in the process. This process has been used for Industrial high volume production.

4 NANOIMPRINT STAMP CONSIDERATION

In this section, we will enlighten the resist materials and stamp materials that are used in NIL processes. The resists used for NIL are either as the intermediate layer for substrates or for specific applications as the functional layer. Below are some of the thermoplastic polymers materials for thermal NIL that have a range of glass transition temperature (T_g) between 95 and 190, the materials are: polycarbonate (PC), polystyrene (PS), polymethylmethacrylate (PMMA), mr-I T85, and mr-I 7000 to mr-I 9000.

The materials that are used for manufacturing a stamp for NIL purposes are nickel (Ni), TiN, diamond, PDMS, silicon (Si), quartz (fused silicon), fused silicon (SiO_2), silicon nitrite (Si_3N_4).



■ **FIGURE 6.5 Polymer stamp (IPS) roll and imprint on solid substrate/stamp.**

It is important when choosing the material for a stamp, to consider not only the mechanical properties but the chemical and optical properties as well, for example, the thermal stability, roughness, distortion during demolding, hardness, life time, and so forth.

4.1 Materials compatibility

The usability of the materials for stamps and substrates will be presented in the sections to follow. In general, there are two methods to transfer a pattern from the stamp. Different materials are used for each method—namely, hard/hard situation and one or both soft and flexible situation. Each of these methods has its consequences, which we must bear.

4.2 Hard/hard imprinting

When a small silicon stamp (1 cm^2) is printed onto a polymer layer deposited on a silicon substrate we may obtain a uniform replication. However, when the stamp becomes larger, other factors arise. The standard silicon wafers have surface waviness and variations of few microns according to SEMI M1-0323 (2002). This nonuniformity causes the surface of the stamp

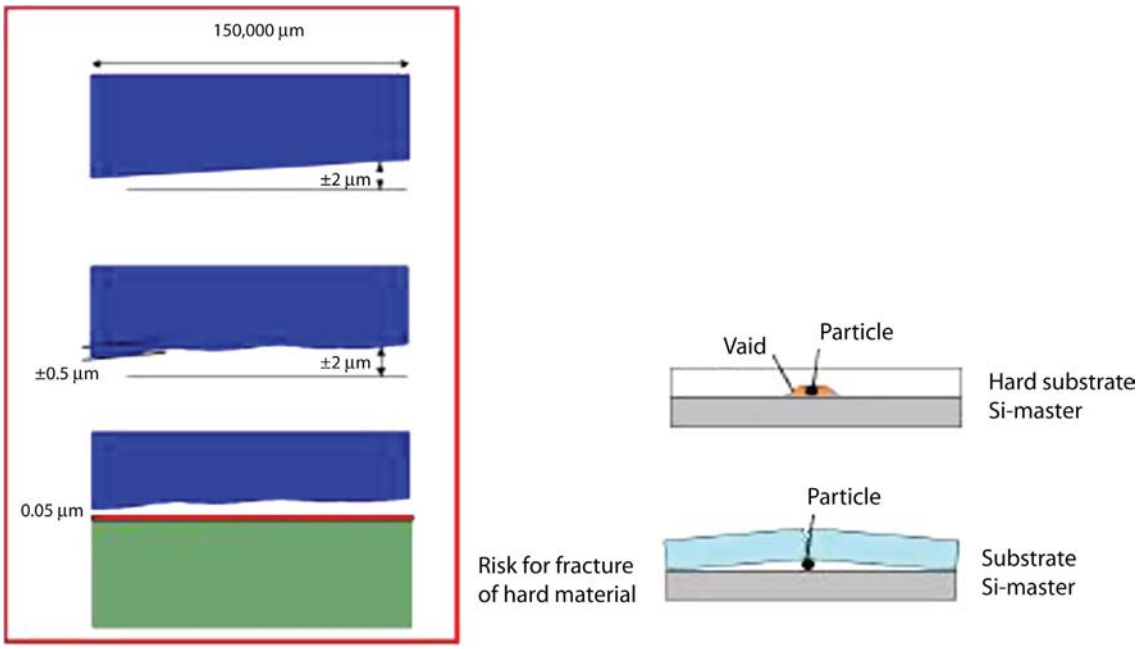
and the substrate to not come in contact uniformly. Therefore, we should expect larger defect areas with no pattern imprinted.

Imprinting is made when the two surfaces of the stamp and the target substrate are parallel. But irregularities in any of them will yield nonuniformity in transferring the nanostructure and defects will appear in the imprinting process. Manufacturing mechanical parts cannot be made with flatness greater than a few micrometers in accuracy, because +2 micrometer irregularity is a typical value in the very best case. There is also a high risk of breaking or destroy the stamp. These are the disadvantages of the hard-press equipment and tools, which is demonstrated in Fig. 6.6.

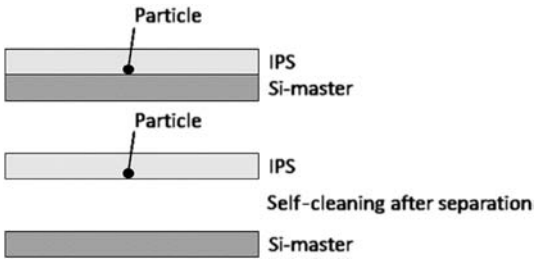
The other Issue with hard/hard imprinting is contamination (particles), which brings high risk that either the substrate or stamp will be permanently broken or damaged.

4.3 Hard/soft and soft/soft

Consider an imprint process of hard nickel stamp (Ni) and polymer sheet such as PC or PMMA. This process significantly reduces or completely eliminates the problem of the defected areas in the previous section (hard/hard imprinting), because the polymer substrate is flexible and the surface



■ FIGURE 6.6 Hard/hard imprinting .



■ **FIGURE 6.7 Hard/soft and soft/soft imprinting.**

allows for penetrating into the curvature and unevenness of the stamp. Furthermore, the polymer surface will absorb any hard particles on the stamp surface, if there are any. Fig. 6.7 shows the particle has been immersed in the IPS. The result will be no defects on the target substrate.

This implies that a suitable polymer layer will result in a uniform and defect-free imprint.

5 TYPES OF IMPRINT STAMPS

5.1 Silicon stamp

Silicon (Si) has been the most common material used for manufacturing of NIL stamps since most nanotechnology laboratories have an E-beam and reactive ion etching (RIE) tools as standard equipment in-house.

Resists for positive or negative stamp polarity are available, where the positive type resist shows higher resolution capacity than negative resists. Transferring patterns from the resist to the silicon stamp is done by the RIE using a patterned stamp directly as an etch mask.

Silicon stamps, Fig. 6.8, can be manufactured on pure silicon wafers or thermally grown silicon dioxide (SiO_2) on silicon as demonstrated by Refs. [10] and [36]. After etching the Si or SiO_2 on Si stamp, it needs to be coated with a thin layer of anti-adhesion material, which is a molecular monolayer of 1 nm thickness that is covalently bound to the stamp surface.

5.2 Quartz stamp

Silicon dioxide stamps are known as quartz (SiO_2) stamps, Fig. 6.9. They are usually made of fused Silica, which is available as a wafer material in different thicknesses and sizes. Quartz stamps are usually used in Hard/Hard UV-based imprinting processes.

The manufacturing of this type of stamp uses the same processes of manufacturing as the photolithography mask, adding the RIE etching step at the

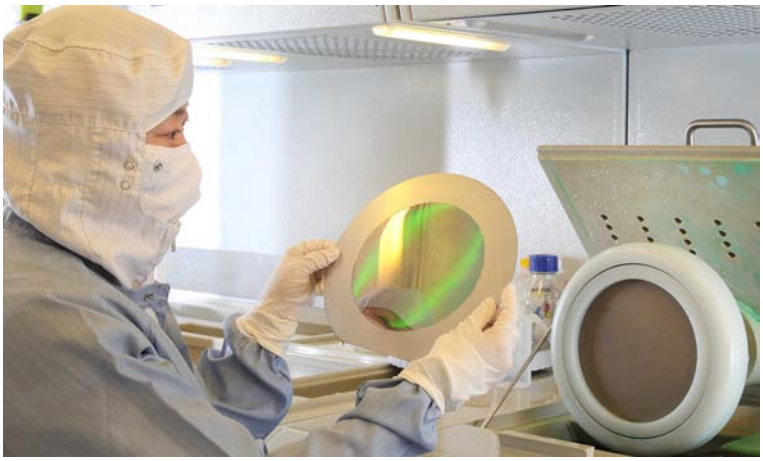
■ FIGURE 6.8 Silicon stamp.

■ FIGURE 6.9 Quartz stamp.

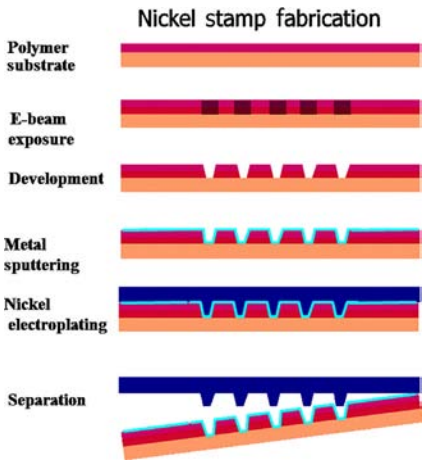
end. The same chemistry is used for depositioning an anti-adhesion layer as for Si stamp, which is demonstrated in Ref. [11].

5.3 Nickel stamp

Nickel stamps have been known for many decades. They have been used in injection molding for CDs and DVDs, and they are very popular due to the



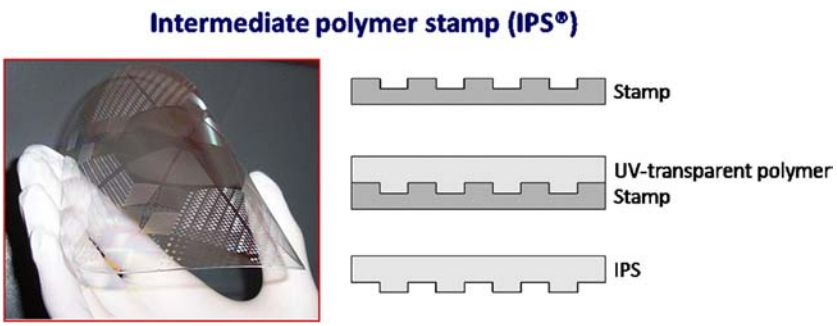
■ FIGURE 6.10 Nickel stamp.



■ FIGURE 6.11 Nickel stamp fabrication.

fact that metallic stamps are highly durable, not like the crystalline materials such as Silicon or Silica.

Nickel stamps are manufactured in any size or shape, and they are bendable into a cylindrical form to be used in R2R imprinting. An advantage is the possibility of making dozens of copies using soft imprint and electroplating method as demonstrated by Refs. [12] and [13], which decreases the cost of ownership of the manufacturing process for the stamp, as shown in Fig. 6.10 and the final product in Fig. 6.11 since the initial cost of the E-beam manufactured master stamp is very high. The smaller the structures, the higher the cost of the same area.



■ **FIGURE 6.12 Intermediate polymer stamp.**

The method for depositing an antiadhesion layer onto silicon or silica is not applicable for the Ni stamp. Obducat AB, a Swedish company, has developed its own proprietary molecules and plasma-depositing process for Ni stamps, which is a molecular monolayer of approximately 1 nm thick developed by Ref. [14].

5.4 Polymer stamps

Much attention has been made to the polymer stamps during recent years, because of the low cost and easy handling in the replication process, by casting or imprinting, from the costly master.

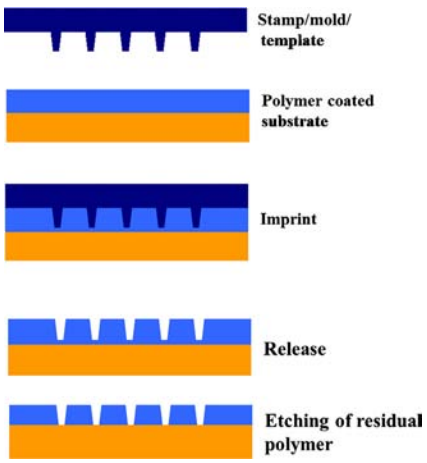
Manufacturing polymer stamps mainly uses UV-curable, as shown in Fig. 6.12, or thermoset polymer on a substrate. The substrates are typically Si or quartz. Thermal imprints or UV-based imprints are used for copying the master stamp onto the polymer layer ([15,16]). The polymer stamps can be of different sizes. Fig. 6.13 demonstrates the large-area polymer stamp.

Obducat AB developed polymer stamps materials that are used in imprinting. They do not need an antiadhesion layer deposition since the polymer used has the properties of anti-adhesion.

5.5 Imprint processes

This section introduces different imprint techniques and the advantages and disadvantages of the related materials. The user decides what stamp and imprint process should be chosen for the polymer material and its properties for the specific application. In general, the imprint process is a pattern transfer by mean of mechanical deformation of a polymer film, Fig. 6.14. The properties of the polymer film will define which specific method can be used to replicate the structure. In order to make the polymer layer printable one can use heat to decrease the viscosity of the material or, if the material

■ FIGURE 6.13 IPS can be made on different area sizes with the same process condition. This shows a large area.



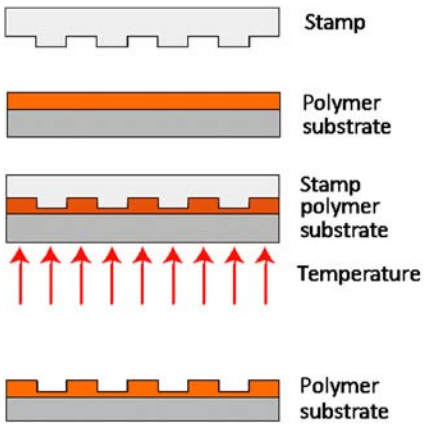
■ FIGURE 6.14 General nanoimprint process.

is liquid (monomers), a ray radiation—for example, UV-radiation can make the polymer solid, which makes the imprinted pattern registration solid.

5.6 Thermal NIL/hot embossing

Thermal NIL can be performed on any thermoplastic material that can be brought well above its glass transition temperature (T_g) without dissociation.

Thermal NIL differs from hot embossing. Thermal NIL imprints perform imprinting onto a thermoplastic material coated on a carrier material such



■ **FIGURE 6.15 Thermal imprint lithography.**

as silicon, quartz, or another polymer film, as shown in Fig. 6.15, whereas hot embossing performs imprinting onto thermoplastic polymer material without any additional substrate. Some thermoset polymers might be printable but are difficult to handle, as is demonstrated by Ref. [17], because the curing process starts during the heating process, which will influence the polymer flow properties significantly.

The thermal NIL equipment consists of heating and cooling units to raise the temperature to the required imprinting degree of the sample uniformly and cool it down to the demolding temperature after the imprint process is accomplished. The advanced equipment has a low thermal mass and enough heating power to allowing raising the temperature of the imprinting stack within a short time, as well as a water cooler to decrease the temperature to the demolding status within a reasonable time frame. Typical cycle time per thermal imprint for slow equipment is 30–60 min, while the advanced equipment (e.g., Obducat AB tools) can accomplish the thermal imprint cycle within 2–3 min.

The choice of the material is important for full-area imprints, because of the thermal expansion and contraction of the material during the process of heating and cooling. The best results can be obtained when the stamp and the substrate are of the same material, or at least of a material having similar or identical coefficients of thermal expansion (CTE). For example, imprinting a silicon stamp on a silicon substrate gives good results all over the wafer, whereas a thermal imprint of nickel stamp onto a polymer-coated silicon substrate leads to pattern distortion; in other words, everything looks fine at the center of the wafer and distortions are worse close to the wafer's edge.

The thermoplastic imprint polymer should have the following properties:

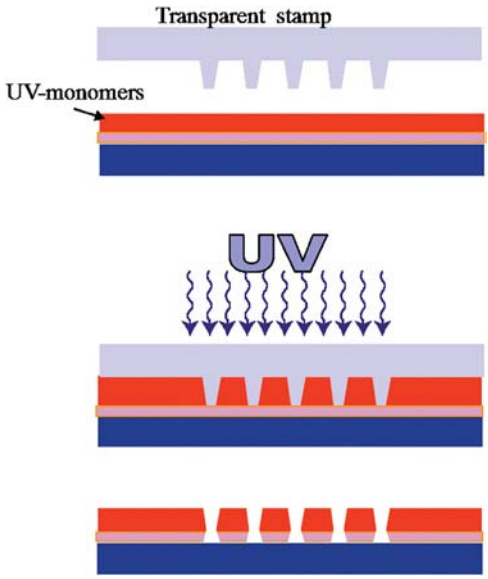
- The difference between imprinting and demolding temperatures should be small to minimize thermal expansion and contraction during the processes.
- The polymer should have low viscosity above T_g for good flow as Ref. [18] shows.
- The polymer should be printable without dissociation or out-gassing.
- The polymer should be easy to dissolve in organic solvent to allow simple cleaning of the stamp when the polymer residue sticks to it.
- Maintaining stability of the imprinted nanostructures after demolding depends on the glass transition (T_g) temperature of the polymer. Too low T_g results in relaxation or reflow of the pattern with time. The smaller the structures and the lower the T_g, the shorter the relaxation time.
- If the polymer is to be used in a lift-off process after imprint, there should be a compatibility with the underlying lift-off polymer. The underlayer should have higher RIE etch ratio than the imprint polymer layer to obtain the required undercut profile. Furthermore, the solvent of the imprint polymer should not attack the lift-off layer and dissolve it during spin coating.
- If the imprint polymer should be used as an etch mask for subsequent pattern transfer onto the substrate material, it should be able to withstand the RIE plasma as much as possible.
- Additional physical and/or chemical properties are required if the polymer is used as the functioning nanodevice itself.

In summary, it is not easy to design a polymer having properties that fit everybody's requirements. One has to choose the material carefully and according to the requirements of the imprint process, postimprint process conditions, and the application's specific parameters.

5.7 Ultraviolet NIL

Ultraviolet (UV) NIL processes are executed at ambient temperature into low- molecular-weight monomers. The photo-initiator with UV radiation of a certain wavelength will excite the monomer to undergo polymerization as shown in Fig. 6.16.

There are many tools available in the market for this technology, as mentioned earlier, for imprinting using UV. The most popular tools are the full area imprint and step and repeat tools. They both use either mercury-based arc lamps with a line spectrum over broadband xenon flash lamps or UV LED arrays with single or multiple wavelengths. Of course, the light source and the polymer should match—that is, if absorption peak of the photo-initiator does not match



■ **FIGURE 6.16 UV-based imprint lithography.**

the emission peaks of the UV light source it will not cure the polymer, which causes sticking problems and destruction of the imprinted structure.

There are varieties of UV-curable polymer materials in the market. For good processing performance the following points should be observed:

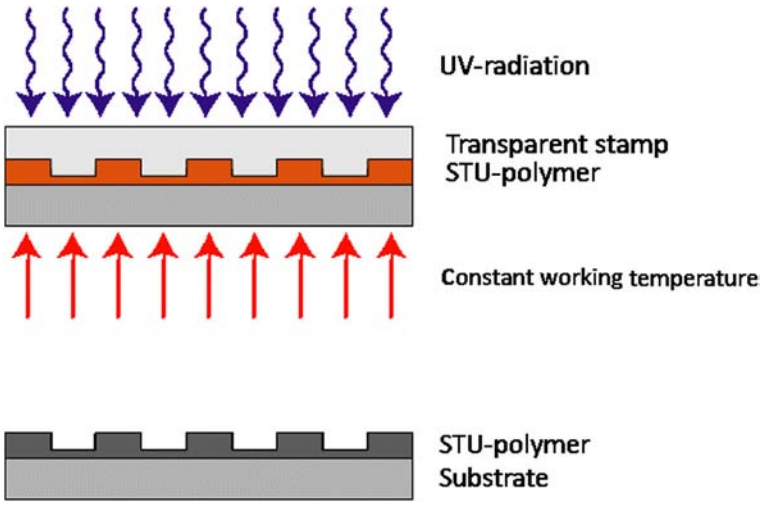
- The polymer should be spin-coatable with no droplets on the surface.
- The UV-curable polymer should cure fast to minimize the distortion and maintain the high throughput.
- The polymer may not be sensitive to polymer chain reaction interruption due to the presence of oxygen to eliminate the reasonable system design and operation.
- The polymer residue should be removable from stamps, if sticking occurs.

5.8 Simultaneous thermal and UV NIL

Simultaneous thermal and UV nanoimprint lithography (STU)® processes are executed at moderate elevated temperature into polymer/monomer layer. The photo-initiator with UV radiation of a certain wavelength will excite the monomer to undergo polymerization, which is demonstrated in Fig. 6.17.

5.9 Nanoimprint lithography application areas

NIL techniques have been carried out for pattern on metals, ceramics, plastics, mechanics, and biology for the fabrication of nanoelectronics devices, nanophotonic materials, and other micro- and nanostructures.



■ **FIGURE 6.17 Simultaneous thermal and UV imprint lithography**.

Applications in the electronics field include but are not limited to high-density data storage, back-end silicon processes, organic electronics, and localized growth of nanotubes. The photonic applications are diffraction and diffractive optics, one- and two-dimensional optic crystals, templates for self-assembly, nonlinear optics, organic light-emitting diodes (OLED), and photovoltaics (solar cells). The mechanics' applications consist of two- and three-dimensional NEMS; suspended patterned, variety of structures; and nanomotors. Applications in the field of biology include lab-on-a-chip modules, opto-microfluidics, biosensors, microneedles, templates for cells growth, chemical and biological assembly, and surface wetting.

Other examples of NIL technology devices such as polarization filters, anti-reflective surfaces, photonic band gap devices, polymer waveguides, optical encoder, photodetectors, and optical amplifiers in polymer films, and so on. Two applications will be discussed, which are within the scope of this chapter—namely, the microneedles for drug delivery devices and the biosensors using NIL technology.

The demand for the NIL lies in the need for nano structuring in many other applications rather than only within semiconductor industrial areas. There are many applications where nano structures add value to the devices that cannot be made with any other technology in comparison with NIL regarding low cost, precision, high resolution, and throughput.

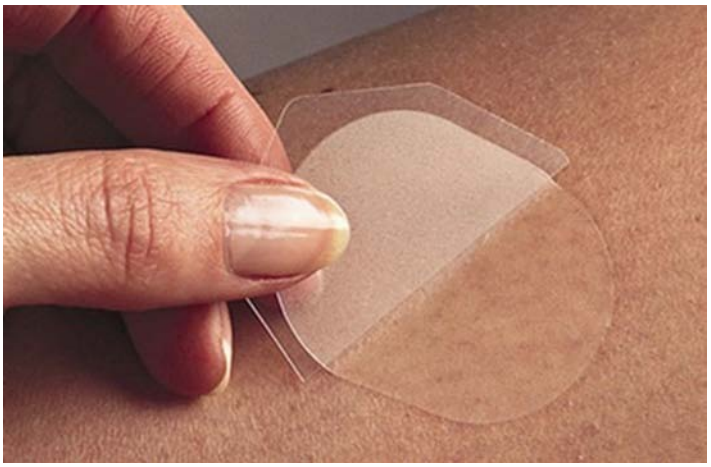
6 TRANSDERMAL DRUG DELIVERY SYSTEMS

Syringes and hypodermic needles have been used to deliver drugs to patients for more than 160 years. These syringes are painful when injected through the human skin to deliver the drug into the systemic circulation.

Transdermal patches are adhesive patches placed on the skin in order to deliver a specific amount of drug dose that will penetrate the skin to reach the blood stream. These patches were developed in the 1970s and first approved by the FDA in 1979. Nowadays, skin patches are used for motion sickness, quitting smoking, angina, to relieve the pain of shingles, and so forth, which has been discussed in Ref. [19].

The Transdermal Drug Delivery Patch is a method to deliver a liquid drug into the blood stream through the skin without pain. Some drugs are mixed with solutions to ease the penetration of the drug that is placed in the patches. These patches have limitations; it delivers only small drug molecules mixed with a solution such as alcohol to ease penetrating the skin, see Fig. 6.18.

Technology advancement in the field of micromechanics led to the invention and manufacturing of microneedles. Microneedles can deliver small and large drug molecules. The microneedles penetrate the hard skin surface (stratum layer), which was the barrier for not letting large drug molecules to pass through. The microneedles make holes big enough in the epidermis layer of the skin and the drug is delivered to the systemic circulation directly. The sizes of the holes made by the microneedles are in micrometers depending on the drug molecule size.



■ **FIGURE 6.18 Transdermal drug delivery patch applied to human skin.**

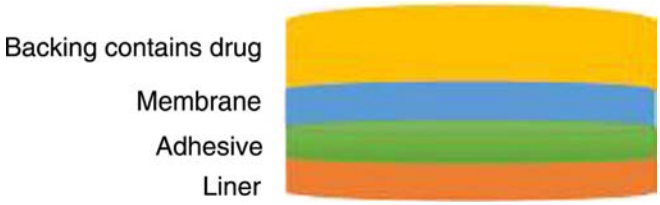
6.1 Types of the transdermal drug delivery patches

There are four types of patches,

- Single-layer drug in adhesive: This system characterized by having the drug within the adhesive layer. The release of the drug depends on the diffusion across the skin (Fig. 6.19).
- Multilayer drug adhesive: This system is similar to the single-layer system in that either two distinct or multiple drug layers separated by a membrane (Fig. 6.20).
- Drug reservoir in adhesive: The reservoir transdermal system is characterized by having a liquid compartment contains the drug solution separated by a semipermeable membrane from the release liner and adhesive (Fig. 6.21).

■ **FIGURE 6.19 Single layer drug patch.**

■ **FIGURE 6.20 Multilayer drug patch.**

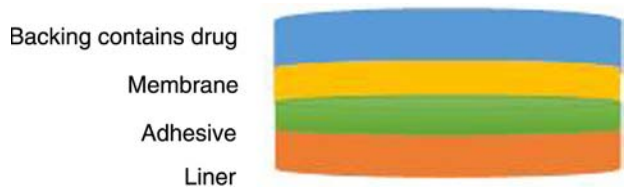


■ **FIGURE 6.21 Drug reservoir in adhesive.**

- Drug-matrix in adhesive: The design of the matrix system characterized by having semisolid matrix containing drug solution, which is in direct contact with the release liner. The skin adhesive part is surrounding the semisolid matrix (Fig. 6.22).

In all these types and the newly developed vapor patches, the drug molecules must be smaller than the pathway between the adjacent cells of the skin. For larger drug molecules a new method has been developed using microneedle patches (Fig. 6.23).

The main objective of the transdermal drug delivery system (TDDS) is to deliver drugs into systemic circulation of the human body through the skin at a predetermined rate with no human intervention. Also, it reduces the load from the digestive tract and liver and avoids pain of the hypodermic needles when injected into the skin. Many articles have been published describing how these types of TDDS manufactured and used, which will not be described here. We will describe briefly in the following section of this



■ FIGURE 6.22 Drug matrix in adhesive.

■ FIGURE 6.23 Microneedles transdermal drug delivery patch.

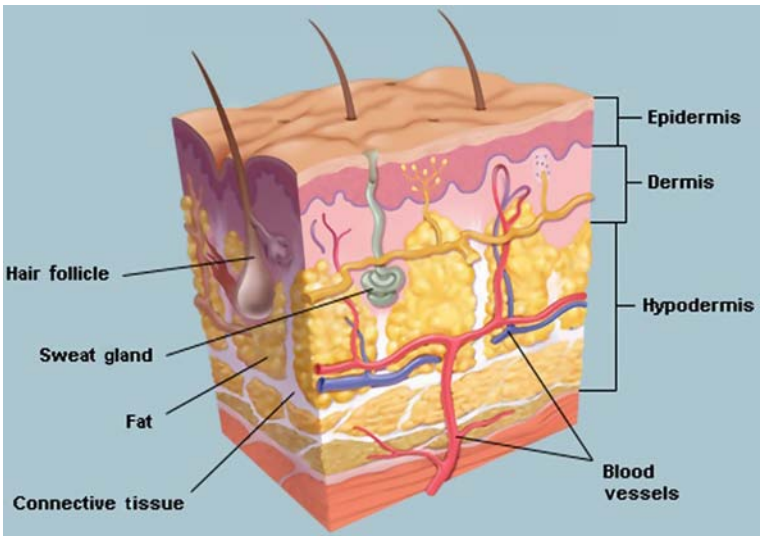
chapter the manufacturing of the advanced and more efficient microneedle TDDS using NIL technology.

Transdermal drug delivery device are sophisticated systems for delivering drugs via skin to the systemic circulation in the human body. Transdermal drug delivery device needs advanced technologies to manufacture at low costs in high volumes. The NIL system manufactures advanced transdermal drug delivery device using easy process in high volumes, fully automated, and cost effective.

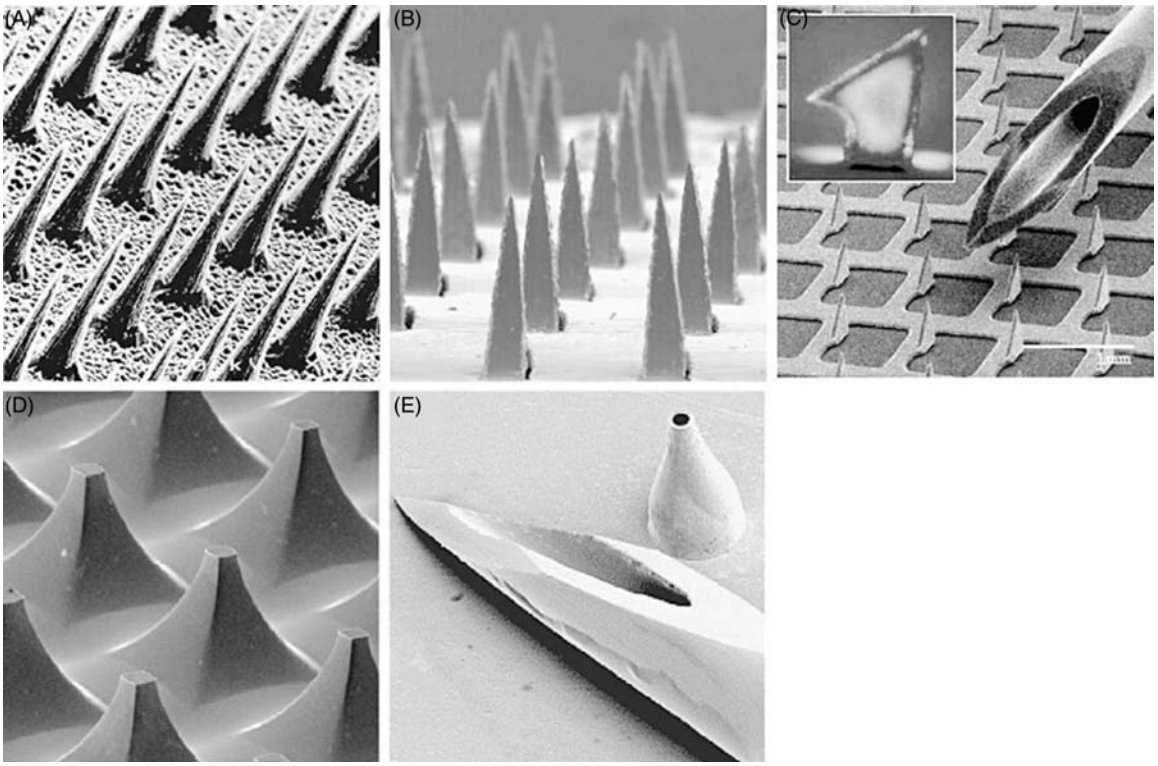
Microneedles TDDS is a sophisticated device from the manufacturing point of view. This type of TDDS has been developed to deliver large drug molecules as well as small drug molecules through the human skin continuously to the systemic circulation in the human body. Increasing the efficiency of the Transdermal Drug Delivery device needs advanced technology to manufacture at low cost in high volumes.

The microneedles physically disrupt painlessly the outer layer of the skin (stratum corneum), which is the greater barrier to delivering most drugs. Therefore, microneedles can deliver higher-molecular-weight and water-soluble drugs through the skin to reach the systemic circulation.

The largest organ in human body is the skin. The area of the skin in adults is about 1.5 m^2, which provides protection for all other internal organs as



■ **FIGURE 6.24 Skin detailed cross section.**



■ **FIGURE 6.25 Shapes of microneedles used for transdermal drug delivery.** *(Reproduced with permission from Elsevier.)*

demonstrated in Ref. [20]. The main layers of the skin are the pidermis, the dermis, and the hypodermis (subcutaneous). The epidermis layer encompasses the stratum corneum (the outer surface of the skin), and is 10–15 μm in thickness. The thickest part of the skin is the dermis at about 4 mm. It contains blood vessels, nerves, hair follicles, and oil glands ([21] and [22]). The third layer, the hypodermis (subcutaneous) is the adipose tissue (fat). Fig. 6.24 shows a detailed skin cross section of the human body.

The emergence of microfabrication manufacturing technology made it possible to utilize the microneedles for delivering small and large molecules through the stratum corneum of the skin to reach the dermis layer and deliver the appropriate drug.

The microneedles make micron-sized bores in the skin to deliver the drug across the dermis layer. This will help patients with needle phobia to apply the patch by themselves without pain as demonstrated by Ref. [23]. Fig. 6.25 shows the different shapes of the microneedles.

6.2 Microneedles types

Microneedles can be divided into four types: solid, coated, dissolving, and hollow as demonstrated by Refs. [21] and [22], and Fig. 6.26.

The solid microneedles are used to make bores (micro channels) in the skin; thereafter, a drug patch is applied on the created micro channels. Ref. [24] suggests that the drug patch should be applied instantly to prevent undesired infection by pathogenic microorganisms.

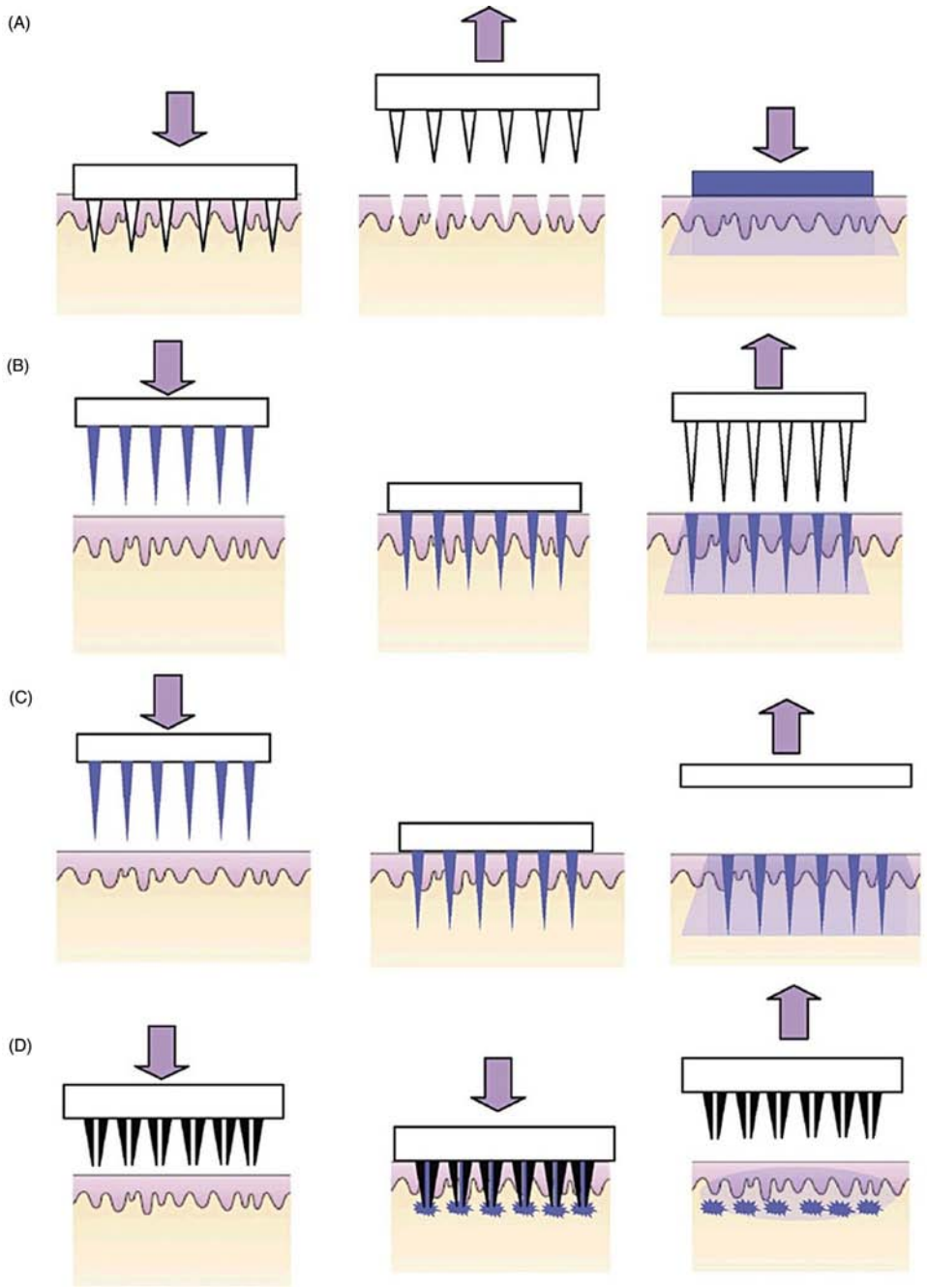
The coated microneedles are the solid microneedles coated with a drug. Many techniques for preparing coated microneedles have been suggested in the literature. One of these techniques is electrohydrodynamic atomization (EHDA) for preparing smart microneedles is demonstrated by Ref. [25]. This technique has been used to prepare nano- and micrometer-scaled pharmaceutical coating on stainless steel of 600–900 μm in height. Based on this technique by making some variants in the coating process, they manage to deposit particles 100 nm to 3 μm and fibers 400 nm to 1 μm directly on microneedles in a selected way.

Dissolving microneedles are convenient for patients, because it is a one-step application. They are fabricated from polymers using micromoulding method. It is fabricated by pouring polymer in its solution state into a structured female master for the microneedles array under vacuum or pressure to make the micro cavities of the microneedles array then filled with the solutions of the drugs and dried. The encapsulated drug will be released at the time the patch is attached to the skin. This method has been investigated by Ref. [26].

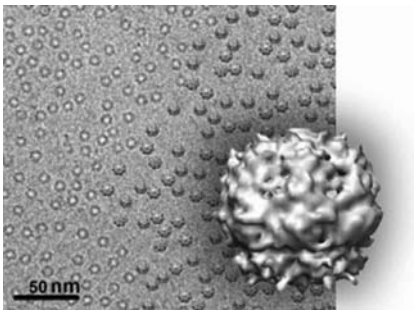
The hollow microneedles look like hydrodermic needles but much shorter. The drug liquid is infused through the bores in the microneedles into the skin.

6.3 Imprinting nanostructured foil

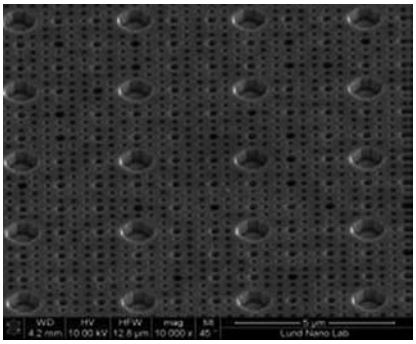
Ref. [27] disclosed a method to make the microneedles more efficient in delivering drugs and reducing the human body immune system response to the drug. A NIL system made this possible in advanced and more efficient manufacturing process. The first such device realized recently by the Swedish company, Obducat AB, and delivered to the customer, see Refs. [28] and [29]. The human cells structure is shown in Fig. 6.27. The developed NIL machine imprints a patterned thin foil with nanostructure similar to the human cell structure on the foil is shown in Fig. 6.28 and 6.29, which covers the microneedles, then followed by the laser cutting of the nanostructured foil to fit onto the microneedles device. This process ensures friendly reaction of the body cells to the external compound because the imprinted



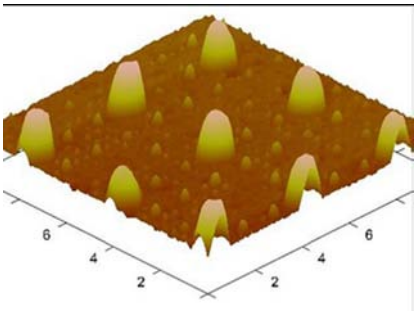
■ **FIGURE 6.26 Types of microneedles used for transdermal drug delivery.** (A) Solid microneedles ionically etched from silicon wafer, (B) solid microneedles laser cut from stainless steel, (C) solid microneedles acid etched from titanium sheet, (D) solid microneedles chemically etched from silicon wafers, and (E) hollow microneedles. *(Reproduced with permission from Elsevier.)*



■ FIGURE 6.27 Typical human cell physical structure.



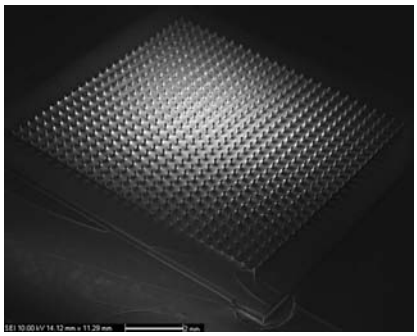
■ FIGURE 6.28 Scanning electron microscopy (SEM) image for the mold used for cell physical structure-like pattern.



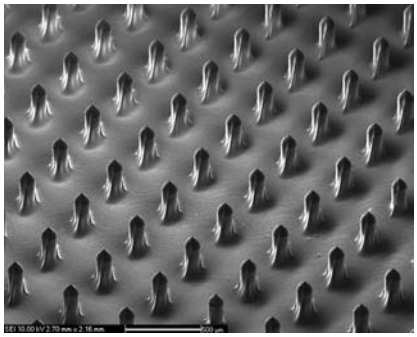
■ FIGURE 6.29 AFM (atomic force microscopy) image for the imprinted foil with replicated pattern using the mold.

structure that covers the surface of the microneedles mimics human cell structure. This technology has been described in the patents in Refs. [30] and [31].

Fig. 6.30 shows the microneedles array chip, and the enlarged microneedles array in Fig. 6.31.



■ FIGURE 6.30 Microneedles array chip.



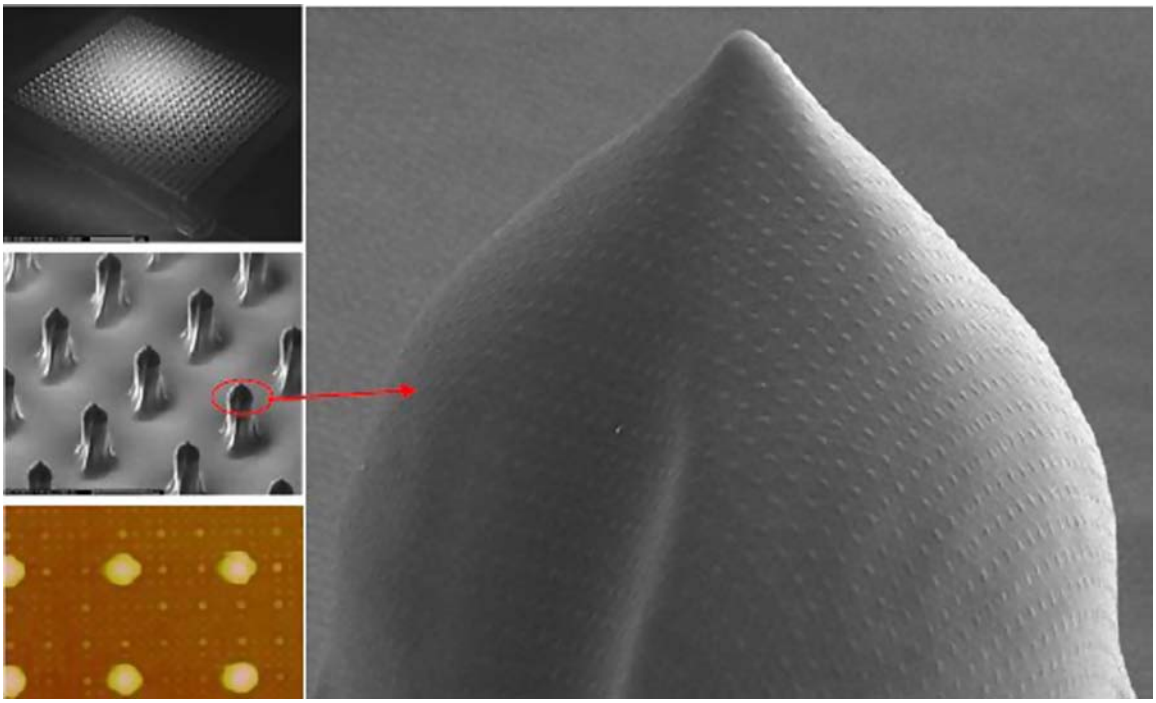
■ FIGURE 6.31 Microneedles array enlarged.

The replication of the nano structure using NIL technology that mimics cell structure is printed on a foil of a few microns' thick, accomplished by Soft-Press technology.

Fig. 6.32 shows the microneedles array chip (top left), microneedles array enlarged (middle left), the SEM image of the imprinted nanostructured foil (bottom left), and the tip of the one enlarged microneedle covered with the structured foil (right).

The manufactured TDDS in this process has the following advantages: the immune system does not respond to the TDDS, it is painless, the TDDS showed that the efficiency improved 200 times, and the system is sufficiently flexible and deformable, which permits the device to maintain agent-transmitting relationship on sensitive areas of skin.

The Fig. 6.33 bellow shows the imprinting section of the machine that imprints the nanostructured foil mimicking the body cells on the nanostructured foil, and it also shows a 6×6 chip tray holding the microneedles array chip.



■ **FIGURE 6.32 Microneedles covered with structured foil.**

Fig. 6.34 shows the foil imprinting and the laser cutting section of the machine where the foil is cut after it covers the microneedles array chip.

The nanoimprint machine looks like the Fig. 6.35. This machine houses the roller system of the foil, the nanostructures imprinting section, the laser cutting section of the foil to fit onto the microneedles array chip, and the robot section that handles the microneedles chips.

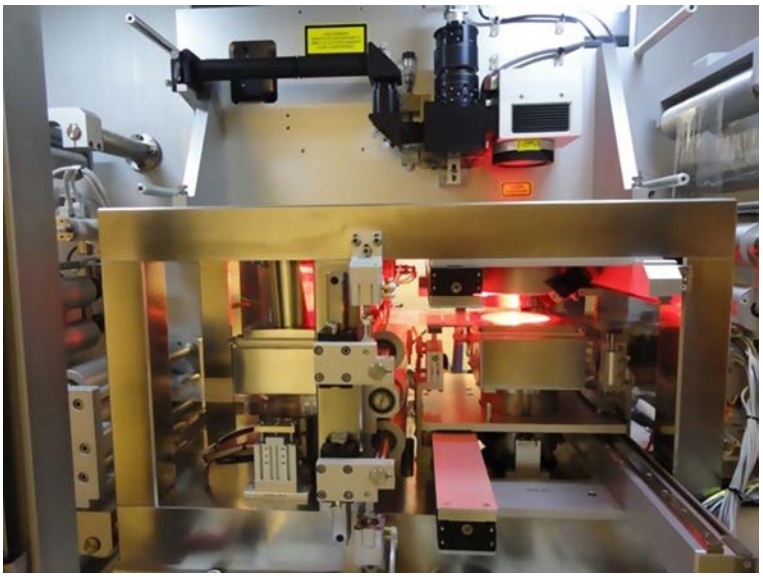
7 BIOSENSORS

A biosensor is defined, in general, as an analytical device to measure the biological response of a sample as an electrical signal. There are high numbers of patients—for example, diabetics—who can benefit from devices that rapidly measure the accurate glucose level in their blood.

Biosensors must have the following features among other things:

- Must be specific for the analyses purposes.
- Should be accurate, precise, and free from electrical noise.
- Must be easy to use by nonskilled persons.

■ FIGURE 6.33 The foil imprinting section and the microneedles tray on the right.



■ FIGURE 6.34 Laser cutting section.

- Must be stable under normal conditions.
- Must be affordable, portable, and small.

We will discuss a couple of examples of biosensors, which are manufactured using NIL technology.

■ FIGURE 6.35 The outer look of the nanoimprint lithography system manufactured by the Swedish company Obducat AB.

7.1 Interdigitized nanoelectrode sensors

Material science and nanotechnology have been useful to improve the electrode surface that acts as an electrochemical transducer. Point-of-care testing (POCT) is recognized as one of the most prominent of next-generation healthcare and requires rapid, automated, high throughput and accurate analytical systems. The market now is demanding new low-cost and user-friendly devices for quick diagnosis. Manufacturing biosensors and microfluidic technologies are key topics for the development of new point-of-care (POC) analysis system, which is stable, sensitive, selective, and cost effective to overcome the conventional problem such as metal collides immobilized on a substrate (high control process and density fluctuations), electron beam lithography (time-consuming and costly).

Obducat Technologies AB Lund, Sweden carried out a joint project with MicruX Technologies at Oviedo, Spain and Intrinsiq Materials Ltd. Hampshire, UK ([32]). The project focused on the development and modification of electrode surfaces based on new materials that can act as a transducer in microfluidic biosensors. More specifically:

- Development of new materials for the construction of electrodes based on thin- and thick-film technologies.
- Modification of the electrode surface with new nanomaterials, nanostructures, and polymer multilayers for improving the sensitivity and precision.
- Development of new immobilization strategies of biological elements for enhancing the selectivity, stability, device life-time and cost of (bio) sensors.

The project focused on the development of new electrode surfaces and recognition elements to get the next generation of sensitive and low-cost electrochemical biosensors integrated into a portable and user-friendly microfluidic platform.

In this sense, microelectrodes will be manufactured in different designs and materials by using thin- and thick-film technologies. Moreover, the electrode surface will be modified with different nanostructures (by using NIL), nanomaterials (such as metal nanoparticles), polymer layers, and so forth to enhance the sensitivity and selectivity of the sensors. The methodologies for the fabrication of the electrodes and carrying out the modifications should be the simplest possible, low cost, environmental-friendly and easily scalable to the industrial level. Hence, the production of the new materials for the electrodes must fulfill these requirements too.

The development of an electrochemical biosensor will also involve the immobilization of biological materials (such as enzymes, antibodies,

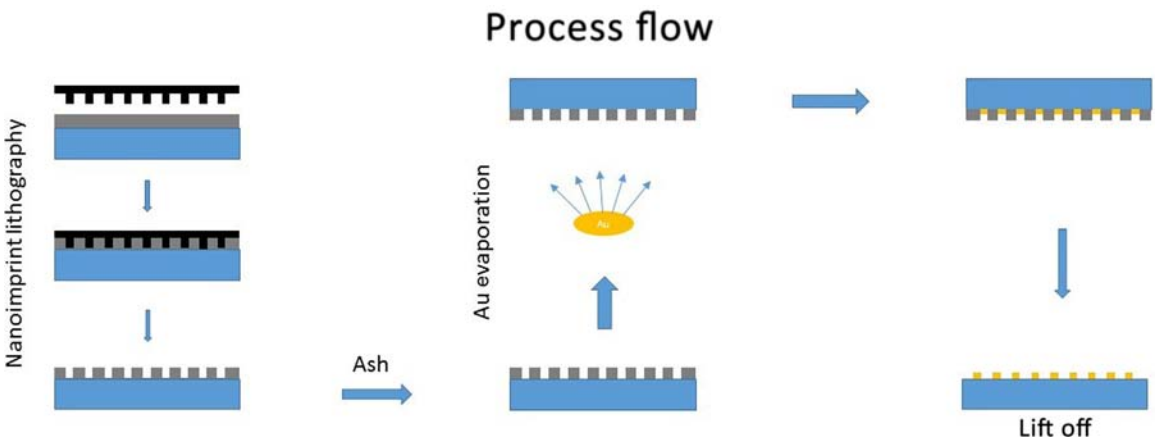
antigens) as recognition element in the surface of the electrodes. Different immobilization methodologies will be evaluated before the construction of the sensing element. Thus, the use of new materials and micro-/nanotechnologies is going to improve the immobilization of the biological elements enhancing the stability, device lifetime, sensitivity, and selectivity of the sensor.

Moreover, the biosensor will be integrated into a microfluidic platform to improve and make easy the use of the new device as a POC system. Microfluidic technologies will also enable the use of very small sample volume as well as the possibility of integrating multisensing elements on the same platform.

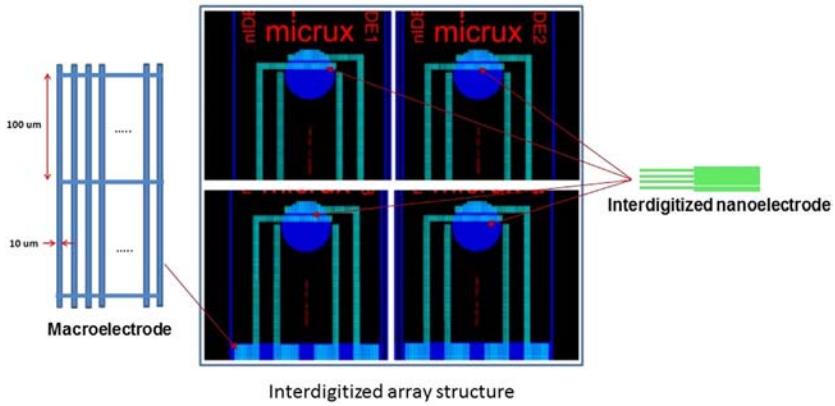
As a proof of concept, the new smart materials and methodologies will be evaluated in the construction of a microfluidic multibiosensor focused on the simultaneous determination of different cardiovascular blood metabolites such as total and free cholesterol, glucose, and lactate, which can open new market opportunities for the companies involved.

The electrodes were fabricated with NIL using Obducat's patented IPS and STU processes. After removing the residual layer, gold (Au) was sputtered on the exposed substrate. Finally, a lift-off process finally removed the remaining resist (Fig. 6.36).

PMMA or acrylic was chosen to serve as the lift-off layer, and a functional layer added on top to achieve good performance of NIL. A 20 nm gold (Au) layer successfully deposited on a silicon substrate demonstrating process viability.



■ **FIGURE 6.36 The NIL process flow.**



■ **FIGURE 6.37 Schematic diagram of the interdigitized array structure.**

NIL can provide a cheap option to mass produce components for POCT devices in nanoscale, see Fig. 6.37. These systems may be more efficient and compact than the microscale products of today. The development of electrochemical nanosensors based on interdigitated nanoelectrode arrays is very useful in POC systems. Thus, the miniaturization of electrochemical sensors at the nanolevel enhances the sensitivity and detection limits, keeping key features such as portability, as well as low power requirements and low cost.

7.2 Surface plasmon resonance sensors

Surface plasmon resonance (SPR) is defined in Reference. MD as:

> *A biosensing technique in which biomolecules capable of binding to specific analytes or ligands are first immobilized on one side of a metallic film. Light is then focused on the opposite side of the film to excite the surface plasmons, that is, the oscillations of free electrons propagating along the film's surface. The refractive index of light reflecting off this surface is measured. When the immobilized biomolecules are bound by their ligands, an alteration in surface plasmons on the opposite side of the film is created which is directly proportional to the change in bound, or adsorbed, mass. Binding is measured by changes in the refractive index. The technique is used to study biomolecular interactions, such as antigen-antibody binding. [37].*

SPR sensors do not need any labeling and enable sensing in real-time with high throughput. This type of sensor has received high attention and becomes more important since it achieves fast (on the order of minutes)

measurements in diagnosing diseases in medical care. SPR sensors have been applied widely to analyze samples in biomedical, environment, and food science.

Using NIL technology will reduce both cost and process time. The process of fabricating SPR sensors is as follows: A master mold is prepared using conventional methods such as E-beam lithography. To make a replica from the master mold, nanoimprint tools can make many polymer stamp copies from the master in a very safe process. This process transfers the nanopattern from the master mold to the polymer stamp. The next step in the process is to put a seed layer on top of the polymer stamp to get it ready for electroforming process. The last step in the process after the electroforming is peeling off the polymer stamp from the produced metal mold copy. This metal mold will be used to manufacture the required sensors.

Nowadays, there are nanoimprinting tools for areas as large as 500×500 mm^2 (manufactured by the Swedish Company Obducat AB). This means that the cost will be very low and the throughput very high for manufacturing the disposable usage biosensor devices.

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