

with a photosensitive material. By photolithographic imaging, a master pattern is transferred to the substrate. A thin film is deposited on the substrate surface, and this film is then selectively etched (wet or dry etching) to achieve the desired three-dimensional structure [22].

39.2.2 METALS

Metals have been employed for the manufacture of medicinal products for many years. Stainless steel, which is the most common metal used for hypodermic needles, has been used successfully in MN production. Titanium, palladium, palladium-cobalt alloys, and nickel have also been reported [23]. These metals have not only been extensively characterized in terms of their biocompatibility, an important aspect for commercial and regulatory approval, but they also provide good mechanical properties (higher fracture toughness and similar yield strength compared to silicon) [24]. The simplest way of manufacturing metal MN arrays is to assemble an array of stainless-steel hypodermic needles of a desired length on supporting material [25]. Alternatively, metallic MNs can be fabricated by electroplating (e.g., palladium), photochemical etching (e.g., titanium) or laser cutting (e.g., stainless steel) [24].

39.2.3 CERAMICS

The main ceramic used for MNs is alumina (Al_2O_3), a porous material that can be coated with therapeutic agents for controlled release [26]. Despite its high resistance against corrosion and mechanical compression, alumina is brittle and has lower strength compared to metals [27]. Other ceramics for fabricating MNs are gypsum ($\text{CaSO}_4 \cdot 2 \text{H}_2\text{O}$), brushite ($\text{CaHPO}_4 \cdot 2 \text{H}_2\text{O}$) [28], and the organic-ceramic hybrid Ormocer (three-dimensional network of organically modified silicon alkoxides and organic monomers) [29]. The biocompatibility depends on the type of ceramic, but they have been used as replacement parts for the musculoskeletal system for years and are considered safe, especially in the short-term application that is needed for MNs [30]. Micromolding is the main technique for manufacturing ceramic MNs, a low-cost approach that is also used for e.g., polymeric MNs and can be easily scaled up. MNs of different designs can be fabricated by using different mold designs, and the process involves the casting of a ceramic slurry into a mold followed by a sintering process [26].

39.2.4 GLASS

Silica and borosilicate glass can be used for manufacture of MNs in various geometries. Brittleness and fracture toughness of glass are comparable to silicon. Its biocompatibility is not fully understood, as it is physiologically inert, but it might cause granulomas [21, 31]. Hollow glass MNs are manufactured by manually pulling glass pipettes using a micropipette puller and beveling the tips. Even though this can be done quickly in laboratory scale, scale-up to commercial use is not realistically feasible [9].

39.2.5 SIMPLE CARBOHYDRATES

Carbohydrate MNs are mainly prepared from maltose, but the use of trehalose, sucrose, mannitol, xylitol, and galactose has also been described [24]. The main advantages of carbohydrates are their low cost and the high biocompatibility. They are naturally present in food and have been used extensively in approved parenterals. However, mechanical properties have not been well studied, and they come with many limitations during their manufacture (thermal treatment), storage (disintegration), and use (sealing of created holes during dissolution). Carbohydrate MNs can be easily produced by micromolding of hot melts or solutions. The therapeutic agents are mixed with the carbohydrates before casting and are delivered upon in-skin dissolution of the prepared MNs [32].