Design and Manufacturing of Microneedles Toward Sustainable Products

Museau M.

G-SCOP Laboratory, CNRS: UMR5272, Grenoble Institute of Technology, University Joseph Fourier, Grenoble, France

Butdee S.

IMSRC, Department of Production Engineering, Faculty of Engineering, KMUTNB, Bangkok, Thailand

Vignat F.

G-SCOP Laboratory, CNRS: UMR5272, Grenoble Institute of Technology, University Joseph Fourier, Grenoble, France

Abstract

Microneedles can be used for drugs delivery instead of conventional hypodermic needles with some advantages: they cause less pain and skin irritation, the risk of transmitting infection is less important and they can be more economical to manufacture. A presentation of different families of microneedles and their advantages compared to conventional needles can be found in the first part of this paper. Then, current manufacturing processes of microneedles are presented and discussed, followed by the proposition of an innovative manufacturing strategy to make a patch composed of hollow microneedles. This strategy combines micro machining processes to make an insert that will be use during injection moulding. At last, the concept of sustainability is presented with the aim to start discussion on the sustainable aspects of the designed microneedles, and then provide some answers.

Keywords*: Sustainable Design and Manufacturing, Microneedles, Micro Manufacturing Processes, EDM, Injection Moulding*

1 Introduction

Microneedles are medical devices that are getting more and more popular. These devices can be used for transdermal delivery of drugs, instead of conventional hypodermic needles, with some advantages. Microneedles cause less pain and skin irritation than conventional needles and the risk of transmitting infection is less important. Moreover, they can be more economical to manufacture, because mass manufacturing processes and relatively inexpensive materials can be used, in order to reduce the price of each device. A project is currently underway, with the objectives to design and produce a patch composed of hollow microneedles, made in polymer by injection moulding. This project is conducted in partnership between a Thai company, the IMSRC (Integrated Manufacturing System Research Center) of KMUTNB (King's Mongkut University of Technology North Bangkok) and the Thai German Institute (TGI). The concept of sustainability is based on three pillars, environmental, economic and social. Designing a product from a sustainable point of view should thus seek fair balance between these pillars, through the all product life-cycle. As there is a need today to design more sustainable products, we aimed to evaluate in which extend the microneedles, under development in the current project, can be considered sustainable. In the first part of this paper, we provide more information on microneedles, the different architectures of products and their advantages, in comparison to conventional needles. Then, the current materials and manufacturing processes of microneedles are presented and discussed. This leads us to propose an innovative manufacturing strategy to produce a patch composed of hollow microneedles. At last, the concept of sustainability is presented, followed by a discussion on the sustainable aspects of the designed microneedles.

2 Microneedles: presentation and advantages

Oral administration of drug is not always possible, due to poor absorption, enzymatic drug degradation in the gastrointestinal tract and liver, or low bioavailability. That is the case for some biopharmaceutical drugs or vaccines, which are currently delivered by the parenteral route using hypodermic needles. Injections using hypodermic needles are reliable and effective but present some disadvantages. First, they require expertise for delivery and it is therefore not possible to deliver drugs by this way without the help of a nurse. Then, they may cause pain, discomfort or generate needle phobia for certain categories of anxious people. Some patients prefer to avoid treatment instead of receiving it using hypodermic needles [1]. Last, they can lead to transmission of blood-borne infections, particularly in the case of unsafe injections, defined as the reuse of syringe or needle between patients without sterilization, and which are suspected to occur routinely in developing countries [2]. As most of the molecules that have to be injected in the human body have nanometer dimensions, the use of conventional hypodermic needles with millimetre scale is not necessary and other devices for the transdermal delivery of drugs were studied. An approach is the use of needles of micrometer dimensions, called microneedles. Currently, microneedles can be classified in four families with different architectures and different approach to deliver drug in the body [3-4]. First (Figure 1, a.) is the use of an array of solid microneedles to make holes in the skin, followed by the application of drugs using another device (a patch, for example). Second (Figure 1, b.) is the use of solid microneedles first coated with the drug that has to be delivered and then inserted into the skin for dissolution of the coated drug in the body. This approach is effective for rapid bolus delivery of molecules, even if due to the micro-size of the device, the coating process may be difficult to control, and some molecules cannot be coated on the needles [5]. Third (Figure 1, c.) is the use of microneedles made with biodegradable and mechanically robust material, which encapsulate drug. The device is inserted in the body and both the molecule and the needle dissolve in the body, for bolus delivery of medicine, without leaving behind sharp biohazardous waste [6]. The last approach (Figure 1, d.) is the use of hollow microneedles for drug injection. The main advantage is to increase and better control the quantity of drug distributed in the body, by combining the hollow microneedles with a microprocessor controlled pump. This can also permit to deliver drugs at specific time, over a prolonged period of time and modulate rates of medicine in real time [7]. Hollow microneedles could also be used to remove fluid from the body for analysis, and to then supply drug as required: diabetics' people could use it to monitor blood glucose and then take the right quantity of insulin [8].

Whatever the architecture of microneedles, they are able to overcome some disadvantages of conventional hypodermic needles. Due to their size, microneedles should not cause pain during an injection. Indeed, to deliver drugs, a needle has to penetrate the outermost skin barrier layer, the stratum corneum, to create pathway for molecules. Microneedles are strong enough to pierce the stratum corneum (which is a structure that contains no nerves), but thin enough to not require significant effort for their insertion, and short enough to not stimulate the pain receptors that are located deeper. Several studies have been conducted to verify this hypothesis. One of the first was made by [9], to measure pain response following the application of an array of 400 silicon microneedles, each one with a height of approximately 150μm, a base diameter of 80μm and a 1μm radius of curvature for the tip. The results of this study show that sensation caused by these microneedles was statistically indistinguishable from application of a smooth silicon surface, and statistically painless than the insertion of a conventional hypodermic needle. Other studies have been conducted to explore these results and provide more information on both pain sensation and microneedles functionalities trough the body perception. For example in the one presented by [10], twelve subjects received single-blinded insertions of a conventional hypodermic needle and two microneedles arrays (36 pyramidal needles of 180 and 280 μm height). The results confirm that the pain and discomfort sensations caused by the microneedles were less than the ones caused by the hypodermic needle. Micro channels were formed in the skin following the use of microneedles, but these channels were repaired and resealed 8-24 hours after the application. Microneedles therefore induce minor skin abrasion and irritation, which is an advantage for patients that need to receive injections in daily life.

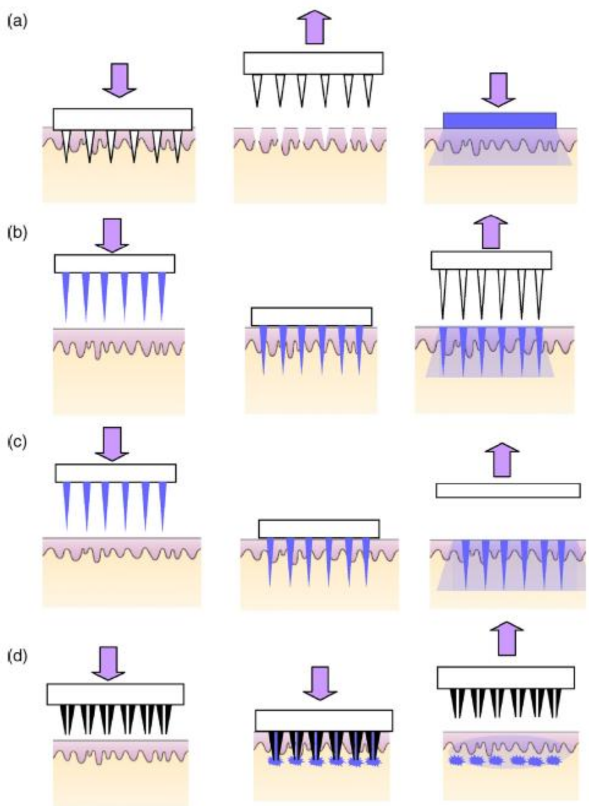

Figure 1 : Different design of microneedles for drug delivery [3]

The safety of microneedles must also be demonstrated. The microbial penetration trough holes induced by microneedles has been studied by [11]. The results show that although micro organisms can traverse the microholes in the stratum corneum, the infection risk associated with microneedles application is less important than the one associated with conventional needles, even if for the moment this has been studied in vitro and more studies are now required to demonstrate this in vivo. The authors also recommend the use of microneedles made with self-disabling materials, in order to prevent inappropriate or accidental reuse of needles and so increase the safety of the injections. Finally, microneedles can be more economical to manufacture and to use than conventional needles. Most of these products may be in the form of a patch that can be directly applied on the skin (for solid needles) or previously connected to an interface (for hollow needles). The patient may use this type of packaging alone, without the help of a nurse, in order to reduce treatment costs. The ability to use mass production manufacturing processes and relatively inexpensive material, to reduce the price of each device, will be discussed in the next part of the paper

3 Manufacturing processes of microneedles

3.1 *Materials and manufacturing processes currently used.*

Manufacturing processes of microproducts can be categorised in two main families: processes derived from VLSI (Very Large Scale Integration) technologies and miniaturisation of processes classically used in "macro" mechanical manufacturing (micro hot embossing, micro injection moulding, micro milling, micro EDM…) [12] This observation is also valid for the manufacturing processes of microneedles. VLSI technologies are traditionally used to produce IC component, and since the 90's, they are also used to produce microproducts. Consecutively deposing, patterning and etching materials, 3D structures are created on a substrate. This substrate is typically a silicon wafer, and the first microneedles created with VLSI technologies were silicon microneedles [13-14]. Silicon is attractive as a well-known material in the microelectronic industry, but it is also relatively expensive, fragile, and unproved as a biocompatible material [15]. Other materials are less expensive, mechanically strong enough to pierce the skin, and known to be biocompatible, since they are already used for medical application for many years, like polymers or glass. Polymer microneedles may provide advantages, compared to others. They can be made with biodegradable materials, such as Polylactic acid (PLA), polyglycolic acid (PGA), and their co-polymers (PLGA) [16]. That is a design requirement for certain needles that need to dissolve in the body to deliver encapsulated drugs, as presented in the previous part (Figure 1, c.) That is also useful for safety reasons, as if biodegradable microneedles accidentally broke in the skin, it would safely degrade and disappear. Moreover, a biodegradable material makes easier the safe disposal of the devices, and destruction of used needles in developing countries to prevent re-use has been defined as a priority by different international agencies [2]. VLSI technologies can also be used to produce polymer microneedles: for example, [17] presents PMMA (polymethylmethacrylate) hollow needles made with LIGA techniques. But one other interest of polymer devices is that they can be manufactured using replication processes (like hot embossing or injection moulding) that have been developed in recent years to manufacture non-silicon based microproducts with lower costs than VLSI technologies [18-19]. Replication processes have also been used to manufacture microneedles, but as the tooling used (i.e. the mould, the insert, the embossing matrix…) is also a microproduct, it is again possible to separate those processes in two families: replication processes using a tooling made by VLSI technologies or made by miniaturisation of "macro" machining. Both solid and hollow microneedles have been manufactured using replication processes whose tooling was made using VLSI technologies. Recently [20] has presented a novel fabrication method to make mass producible and inexpensive patch of solid microneedles made with biocompatible polymer. Two kinds of masters with different material (PMMA and nickel) and different shapes (quadrangular and triangular pyramids) are first made using Deep X-ray lithography process. One or other of these masters are then used to produce the tooling, a PDMS (polydimethylsiloxane) mould. A hot embossing process, using this PDMS mould, finally produces the microneedles patch. To make hollow microneedles, [21] present a method based on polymer investment moulding. Two different processes are used to make mould inserts with different geometries: reactive ion etching (RIE) and anisotropic etching using potassium hydoxide (KOH). To realise the hollow part, a sacrificial element (investment) is placed into the inserts. After the moulding process, the plastic part is removed from the mould and immersed in etchant that dissolves the investment, leaving a hollow plastic part. This method has successfully delivered hollow microneedles, with an inner diamater of 35 µm and different external shapes (according to the mould insert used). As an example, an microneedle with a length of 280 µm and a cross section of 160µm x 100µm can be seen on Figure 2. Nevertheless, some problems may occur with this process. Great care must be taken during the removal of the part from the mould to avoid bent tip and ensure a sharp needle point, or heating the mold during injection can be employed to improve the strength of weld lines. But the main difficulty is to control the positioning and the bonding of the investment to avoid misalignment during moulding process (see Figure 2, bottom). Currently, this step is not automated and it is hard to ensure the quality of final products. Finally, in this process, the sacrificial elements are placed in the mould joint, what makes possible to obtain array of hollow microneedles, but not a square patch of microneedles.

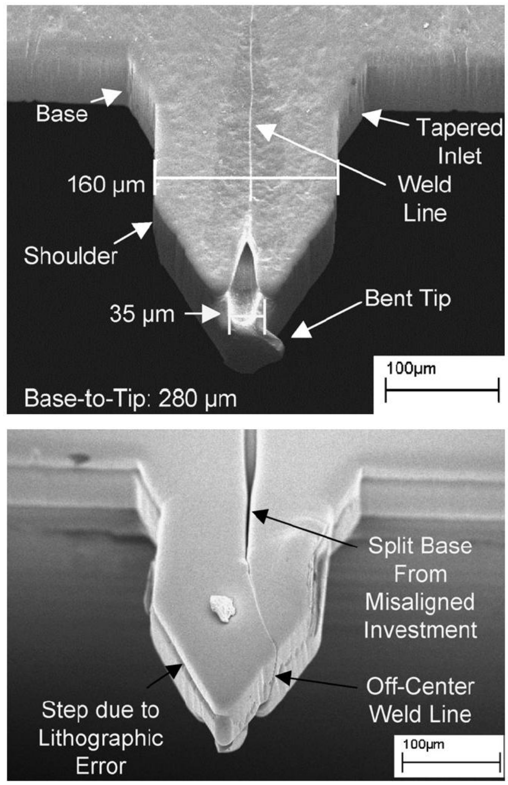

Figure 2 : Hollow microneedles made from RIE insert. Needle fully formed (top) and errors in investment molded (bottom) [21]

Miniaturised conventional machining processes have also been used to manufacture mould in order to produce polymer-injected microneedles. This can be found in [22], where a mould insert machined by using precision NC machining and a drill with a diameter of 250µm, is presented. Nevertheless, it can be seen on Figure 3 that the dimensions of the final product are much bigger than the ones of the microneedles previously presented. And microneedles with smaller dimensions, made with the same strategy (using a mould made with conventional machining processes) have not been found in the literature review. However, taking into account the current capabilities of miniaturised conventional machining processes, it would seem that some of them are able to manufacture mould inserts having dimensions comparable to those achieved by VLSI processes and then used to produce microneedles. For example, [23] have presented three processes to manufacture micro moulds: micro milling, micro EDM and laser beam machining. The possibilities, capabilities and restriction of each process have been pointed out, as well as samples of moulds made using these processes. Given the sizes of the features that it is possible to achieve, it seems possible to use miniaturised conventional machining processes to manufacture a mould for polymer-injected microneedles with smaller dimensions. That will be discussed in the next part of the paper.

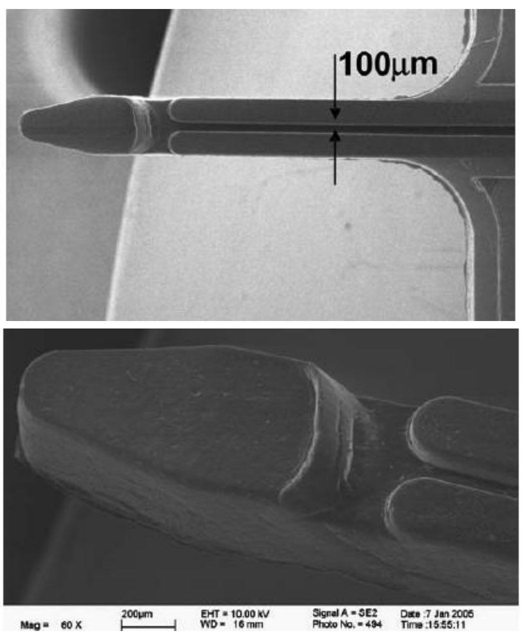

Figure 3: SEM micrograph of a moulded microneedle. The mould insert used to produce it is made with non-VLSI processes [22]

3.2 An innovative manufacturing strategy for microneedles

In the project that is underway, we aim to realise a patch of biodegradable microneedles made with polymer. The patch will have the form of a disk, containing 200 hollow microneedles, each spaced 0.4mm. The microneedles have a total length of 500µm, and an eccentric cylindrical hole of 50µm. The diameter at the base of the needles is 200µm, and it is reduced linearly until 100µm at the length of 400µm from the base, then forming a sharp tip, see Figure 4. To produce the polymer patch and for economical reasons a replication process is intended to manufacture the final product. Given the shape of the product, the need for hollow parts and the existing know-how in the Thai German Institute, a decision is taken, during the first meeting between the customer and the manufacturing experts: among the existing replication processes that could be able to produce the micro shapes, the choice is made to use injection moulding process to manufacture the patch.

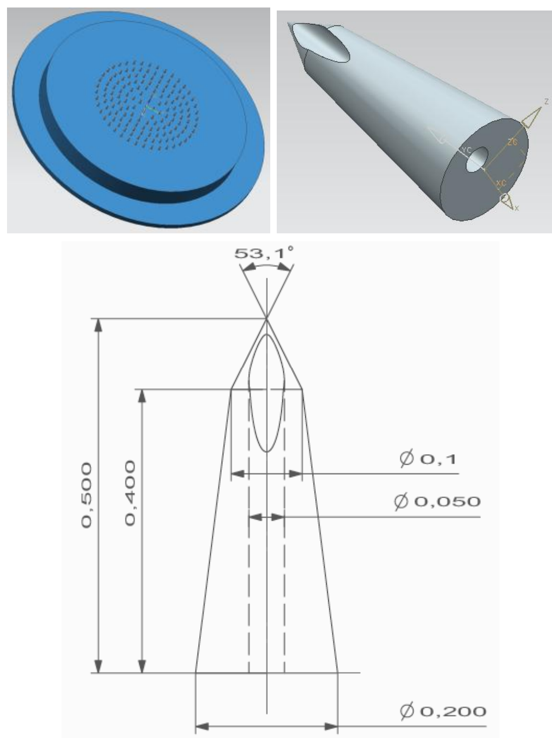

Figure 4 : Schematic of the patch (top, left) and one neelde (top, right and bottom)

In order to manufacture the mould insert, two micro machining processes are available at TGI. First is a micro EDM machine, which makes possible to combine micro EDM milling, drilling and sinking. It also has an integrated Wire Electro Discharge Grinding (WEDG) unit that can be used to form very thin rods, or electrodes with complex shapes. Second is a micro-milling machine, using tools with a minimum diameter of 50µm. These two micro manufacturing processes have been used for machining the mould insert and the moulding tests are in process. The manufacturing strategy is still under optimization and more details on process parameters will not be provided in this paper. Nevertheless, regarding to the first results, we can assert that the selected manufacturing processes (µEDM, µmilling and injection moulding) could achieve to produce the patch of microneedles. We will refer to the selected manufacturing process in the part 5 of this paper, in order to evaluate the sustainable aspects of microneedles. In the next part of the paper, the concept of sustainability is presented.

4 The concept of sustainability

The sustainable development has been defined for the first time in 1987 by the World Commission on Environment and Development, as a development that "meets the needs of the present without compromising the ability of future generations to meet their own needs" [24]. Sustainability is a concept based on three pillars: environmental, economic and social. Sustainable design of a product should thus seek fair balance between these pillars, what implies thinking how to meet the need for growth while at the same time reducing negative environmental and social impacts [25]. This has to be taken into account for all the product life cycle, not only during its manufacturing and use phases, but from the extraction of raw materials to the end-of-life (EOL) of the products and the waste management. Consideration of environmental and economical pillars of sustainability during the design of a product has started almost twenty years ago with the development of Design For Environment (DFE, also called ecodesign). DFE has been defined by [26] as "the systematic consideration of design performance with respect to environmental health & safety objectives over the full product or system and process life-cycle". In parallel, different ecodesign tools have been developed to permit an actual implementation of DFE in the industries, but nature and performances of these tools differ widely [27]. The most known of these tools is Life Cycle Analysis (LCA) which is normalised by the ISO 14040 series. LCA evaluate through impact indicators the potential environmental impacts and resources used throughout the all product's lifecycle [28]. This tool has already been implemented in various areas, as presented by [29]. But this recent review also shows some limitation of LCA: it is time consuming and data intensive. As a consequence, it is not easy to implement this tool during the design of a product, and the conclusion of a study may be biased due to the unavailability or inadequacy of some data. Other ecodesign tools have been developed, like the EcoDesign Pilot web tool helps designers to identify relevant ecodesign strategies for their product [30] or the quantitative and multicriteria recyclability indicators that can be used during design process of complex products [31]. These tools have the advantages to be less exhaustive and so more practical but however present some drawbacks. The web tool is mainly qualitative, and the recyclability indicators focus only on the end-of-life of the product. The concept of sustainability is based on three pillars, and it has been stated by [32] that sustainable industrial production has not only the dimensions of economic prosperity and environmental protection but also of social equity. There is a need to evaluate then reduce the social impact of a product during its all life cycle, but also to propose a product that can meets expectation of customers that are interested in orienting their consumption habits towards more sustainable solutions, by envisioning appropriate ecologically and socially responsible product alternatives [33]. In order to improve sustainable consumption and production patterns, the Design For Sustainability (D4S) concept has been defined by [34] as a "globally recognised way companies work to improve efficiencies, product quality and market opportunities (local and export) while simultaneously improving environmental performance". The D4S methodology, including tools like guidelines, checklists and worksheets package, has been developed in parallel in order to present the practical approaches to execute a D4S project in a company. It is a more simple and qualitative sustainability assessment method, based on a step-by-step approach, that mainly focuses to the redesign of existing products in small and medium enterprises. Nevertheless, some steps of this method may be used independently, during the design of a new product, in order to predict or evaluate the impact profile of the designed product. This will be presented and discussed in the next part of this paper.

5 Microneedles: sustainable products?

The aim of this part is to propose ways to evaluate whether the patch of microneedles that is currently designed can be considered as a sustainable product. Our first proposition is to discuss about social and environmental impacts as well as economical performances of this product, through its life cycle and using information and data that are available at this step of the design process. The product is still under design, however we already have information about its use, its materials or its manufacturing, as it has been presented in the previous parts of the paper. And although detailed quantitative data are not always available, it is still possible to evaluate the sustainable benefits of this product, by comparing it to conventional hypodermic needles fulfilling the same functions, or comparing to microneedles manufactured with other micro manufacturing processes (like VLSI technologies). To determine the D4S impacts of the product through each stages of its life cycle, we decide to use and fill the Impact Matrix, which is one of the steps of the D4S methods [34]. This matrix is a qualitative or semi-qualitative method that provides an overview of the environmental inputs and outputs, social aspects and profit flows at each stage of the product life-cycle. It also provides an idea of where additional information is needed. The columns of the matrix correspond to the different product life-cycle stages and the rows concentrate on the relevant D4S criteria. We focus on three life-cycle stages: manufacturing, use and end-of-life. Due to the evident single usage of microneedles, some life-cycle stages, such as "maintenance", have no place in this matrix. Other are not represented due to lack of data: although the material of the designed needles has already been chosen, more details from our supplier are required to evaluate the impacts of the "raw material" life-cycle stage. The impact assessment matrix can be seen on Figure 5.

Issue	Manufacturing	Use	E-O-L
Material	EDM: Worpiece, wire, rods, lubricant, Injection: polymer		Recycled parts and materials
Energy use	Electricity, compressed air	No	
Solid waste	Used wire and lubricant, polymer wastes from injection		Obsolete parts
Toxic emissions		No	
Social responsability	Disturbance of neighbors	Pain, skin irritation, transmission of infections	
HRM	Working condition (security, health)	Working condition (security, health)	
Cost	Material and manufacturing costs	Treatment costs	Recycling costs

Figure 5 : Impact assessment matrix of microneedles

Microneedles seems to present advantages in terms of impacts, particularly during the "use" and "E-O-L" stages. Regarding to the social pillar of sustainability and as it has been explained previously, an injection using microneedles causes less pain and less skin irritation than one made by conventional needles. The risk of transmitting infections is also less important, both for the patient and the medical staff. Concerning environmental impacts, this product does not consume energy during use. It is made using biodegradable polymers, in order to allow a self-elimination of any waste left in the human body in case of a rupture of needles during use. The choice of biodegradable polymer also facilitates the recycling process, when compared to needles made with glass, metal or silicon. The treatments costs are also reduced, when compared to conventional needles, because the patient should be able to use the patch alone, without the help of a nurse. During the "manufacturing" stage and at this current state of the design and manufacturing processes, more information is needed in order to conclude about the benefits of such a product in a sustainable point of view. Nevertheless, regarding to the economical pillar of sustainability, we consider manufacturing the product using a mass production process (plastic injection), which is less expensive than VLSI technologies, and should permit to reduce the price of each devices. And regarding to the environmental impacts, the common stereotypes in the field of micro manufacturing is that the small size induces less material, less production energy and less material to waste, hence being more environmentally friendly. This stereotype has been pointed out by [35] which also shown that it was not valid. Thus, there is a need to develop tools to verify the advantages of this kind of product compared to classical one. These tools can be based on simulation of product life cycle (from material extraction to E-O-L) and collection of relevant information such as amount of energy used, toxic emission and, what is more difficult, social impact such as user but also worker satisfaction and health

6 Conclusions

A presentation of different families of microneedles as well as the advantages to use these devices has been first presented in this paper, followed by an overview of the manufacturing processes used to make these products. The use of mass manufacturing process is obviously considered for economical reasons. Currently, replication processes like hot embossing or injection moulding has been used to produce microneedles, even if for making hollow devices, their usage is still marginal. The tooling is mainly manufactured using processes derived from silicon technologies, and several manufacturing steps are required to obtain the hollow parts. Given the current micro-machining process capabilities, we proposed a manufacturing strategy to make a mould insert that will be used for plastic injection of microneedles. This strategy is still under optimization, but nevertheless, we can assert that the combination of micro EDM, milling and injection moulding is able to produce the patch of microneedles. In parallel, and since there is a need to design more sustainable products, the concept of sustainability has been presented through its three pillars which are profit, planet and people. The aim was to start discussion on the sustainable aspects of the designed microneedles then provide some answers. The social and environmental impacts of microneedles seem to be reduced and the economical interest effective, especially during the "use" and "E-O-L" life cycle stages. During the "manufacturing" stage, further studies are required, in particularly to assess relevant environmental impacts of the selected processes, and more generally of micro manufacturing.

Acknowledgments

The authors would like to thank the Thai German Institute for its partnership in the project and involvement on micro machining, in particular Mr. Narong Varongkriengkrai, Director of TGI, Mr. Manop Thongsaeng, Director of Mould and Die Technology Center, Mr. Somchai Jakkareen, Advanced Machining Manager, Mould and Die Technology Center and Mr. Mongkhol Laebua, Ph.D. student.

References

[1] Nir Y., Paz A., Sabo E. and Potasman I., 2003. Fear of injections in young adults: prevalence and associations, Am J Trop Med Hyg, 68(3): 341-344.

[2] Simonsen L., Kane A., Lloyd J., Zaffran M. and Kane M., 1999. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review, Bulletin of the World Health Organization, 77(10): 789-800.

[3] Arora A., Prausnitz M.R. and Mitragotri S., 2008. Micro-scale devices for transdermal drug delivery, International Journal of Pharmaceutics, 364(2): 227-236.

[4] Prausnitz M.R., 2004. Microneedles for transdermal drug delivery, Advanced Drug Delivery Reviews, 56(5): 581-587.

[5] Gill H.S. and Prausnitz M.R., 2007. Coated microneedles for transdermal delivery, Journal of Controlled Release, 117(2): 227-237.

[6] Lee J.W., Park J. and Prausnitz M.R., 2008. Dissolving microneedles for transdermal drug delivery, Biomaterials, 29(13): 2113-2124.

[7] McAllister D.V., Wang P.M., Davis S.P., Park J., Canatella P.J., Allen M.G. and Prausnitz M.R., 2003. Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: fabrication methods and transport studies, Proceedings of the National Academy of Sciences of the United States of America, 100(24): 13755-13760.

[8] Toon J., 2003. Microneedles: report describes progress in developing new technology for painless drug and vaccine delivery, Georgia Tech Research News, available at gtresearchnews.gatech.edu/newsrelease/needlespnas.htm,

[9] Kaushik S., Hord A.H., Denson D.D., McAllister D.V., Smitra S., Allen M.G. and Prausnitz M.R., 2001. Lack of pain associated with microfabricated microneedles, Anesthesia and Analgesia, 92(2): 502-504.

[10] Haq M., Smith E., John D., Kalavala M., Edwards C., Anstey A., Morrissey A. and Birchall J., 2009. Clinical administration of microneedles: skin puncture, pain and sensation, Biomedical Microdevices, 11(1): 35-47.

[11] Donnelly R., Singh T., Tunney M., Morrow D., McCarron P., O'Mahony C. and Woolfson A., 2009. Microneedle Arrays Allow Lower Microbial Penetration Than Hypodermic Needles In Vitro, Pharmaceutical Research, 26(11): 2513-2522.

[12] Museau M., De Grave A., Masclet C. and Paris H., 2009. A product-model supporting coupling's management during microproduct design, International Journal of Design Engineering, 2(4): 398 - 413.

[13] Roxhed N., 2007. A fully integrated microneedle-based transdermal drug delivery system, Thesis, Submitted to the School of Electrical Engineering KTH—Royal Institute of Technology, Stockholm, Sweden.

[14] Stoeber B. and Liepmann D.Fluid injection through out-of-plane microneedles, in 1st Annual International IEEE-EMBS Special Topic Conference on Microtechnologies in Medicine and Biology. Proceedings (Cat. No.00EX451), Lyon, France, 224-228.

[15] Runyan W.R. and Bean K.E., 1990. Semiconductor Integrated Circuit Processing Technology, Addison-Wesley, Revised.

[16] Park J., Allen M.G. and Prausnitz M.R., 2005. Biodegradable polymer microneedles: Fabrication, mechanics and transdermal drug delivery, Journal of Controlled Release, 104(1): 51-66.

[17] Moon S.J. and Lee S.S., 2005. A novel fabrication method of a microneedle array using inclined deep x-ray exposure, Journal of Micromechanics and Microengineering, 15(5): 903-911.

[18] Alting L., Kimura F., Hansen H. and Bissacco G., 2003. Micro Engineering, CIRP Annals - Manufacturing Technology, 52(2): 635-657.

[19] Dimov S., 2005. 4M Network of Excellence: An Instrument for Integration of European Research in Multi-Material Micro Manufacture, in Proceedings of the 4M2005 - First International Conference on Multi-Material Micro Manufacture, Elsevier, UK,

[20] Jin C., Han M., Lee S. and Choi Y., 2009. Mass producible and biocompatible microneedle patch and functional verification of its usefulness for transdermal drug delivery, Biomedical Microdevices, 11(6): 1195-1203.

[21] Lippmann J.M., Geiger E.J. and Pisano A.P., 2007. Polymer investment molding: Method for fabricating hollow, microscale parts, Sensors and Actuators A: Physical, 134(1): 2-10.

[22] Sammoura F., Kang J., Heo Y., Jung T. and Lin L., 2007. Polymeric microneedle fabrication using a microinjection molding technique, Microsystem Technologies, 13(5): 517-522.

[23] Fleischer J. and Kotschenreuther J., 2007. The manufacturing of micro molds by conventional and energy-assisted processes, The International Journal of Advanced Manufacturing Technology, 33(1): 75-85.

[24] World Commission on Environment and Development, 1987. Our Common Future, Oxford Paperbacks,

[25] Clark G., Kosoris J., Hong L.N. and Crul M., 2009. Design for Sustainability: Current Trends in Sustainable Product Design and Development, Sustainability, 1(3): 409-424.

[26] Fiksel J., 1995. Design for Environment: Creating Eco-Efficient Products and Processes, McGraw-Hill Professional Publishing, 70th.

[27] Mathieux F., Rebitzer G., Ferrendier S., Simon M. and mFroelich D., 2001. Ecodesign in the European Electr(on)ics Industry – An analysis of the current practices based on cases studies, The Journal of Sustainable Product Design, 1(4): 233-245.

[28] International Organization for Standardization, 2006. Environmental management -- Life cycle assessment -- Principles and framework, ISO 14040:2006.

[29] Finnveden G., Hauschild M.Z., Ekvall T., Guinée J., Heijungs R., Hellweg S., Koehler A., Pennington D. and Suh S., 2009. Recent developments in Life Cycle Assessment, Journal of Environmental Management, 91(1): 1-21.

[30] EcoDesign Pilot 2009, available at www.ecodesign.at/pilot/ONLINE/ENGLISH/INDEX.HTM,

[31] Mathieux F., Froelich D. and Moszkowicz P., 2008. ReSICLED: a new recovery-conscious design method for complex products based on a multicriteria assessment of the recoverability, Journal of Cleaner Production, 16(3): 277-298.

[32] Grutter J.M. and Egler H., 2004. From cleaner production to sustainable industrial production modes, Journal of Cleaner Production, 12(3): 249-256.

[33] Marchand A. and Walker S., 2008. Product development and responsible consumption: designing alternatives for sustainable lifestyles, Journal of Cleaner Production, 16(11): 1163-1169.

[34] UNEP-DTU, 2006. Design for Sustainability - A practical Approach for Developing Economies, United Nations Environmental Program; Delft Technical University.

[35] De Grave A.D., Olsen S.I. and Hansen H.N., 2009. EcoDesign and LCA approach toward sustainable micro products development, in Proceedings of the MIT2009, 10th International conference on Management of Innovative Technologies, 2009, Fiesa, Slovenia,