Thermoforming of Film-Based Biomedical Microdevices

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For roughly ten years now, a new class of polymer micromoulding processes comes more and more into the focus both of the microtechnology and the biomedical engineering community. These processes can be subsumed under the term "microthermoforming". In microthermoforming, thin polymer films are heated to a softened, but still solid state and formed to thin-walled microdevices by three-dimensional stretching. The high material coherence during forming is in contrast to common polymer microreplication processes where the material is processed in a liquid or flowing state. It enables the preservation of premodifications of the film material. In this progress report, we review the still young state of the art of microthermoforming technology as well as its first applications. So far, the applications are mainly in the biomedical field. They benefit from the fact that thermoformed microdevices have unique properties resulting from their special, unusual morphology. The focus of this paper is on the impact of the new class of micromoulding processes and the processed film materials on the characteristics of the moulded microdevices and on their applications.

1. Introduction

In the course of the nearly four decades long history of polymer micromoulding or -replication,[1–3] various moulding processes have been established. This includes micro injection moulding,[4–6] also in the form of reaction injection moulding, injection compression moulding, hot embossing[7,8] and casting of polydimethylsiloxane (PDMS).[9] In addition to the classical micromoulding processes, there are moulding processes as powerful alternatives for resist patterning by photon- or particle-radiation-based lithography. This comprises nanoimprint lithography[10,11] and most soft lithography processes.[12–16] There exist also processes for moulding of porous microdevices.[17–19] As this progress report reviews a moulding process which can be classified as a secondary forming process, see next paragraph, two other polymer micromoulding processes shall be mentioned which fall under this category, too. These are room temperature imprinting[20] or the similar micro cold forging,[21,22] and thermo flow forming.[23] Some of the above micromoulding processes have been completely new developments. Others have been further developments of the corresponding macroscopic processes, so, for example, micro injection moulding.

Besides the primary forming process injection moulding, in the macroscopic world, there are two other important moulding processes for the production of plastic mass products. These are the secondary forming processes thermoforming[24] and blow moulding.[25] While, in simple terms, blow moulding stands for stretch forming of hot thermoplastic (film) tubes, parisons or hollow preforms by means of compressed air, thermoforming stands for stretch forming of heated plastic films or plates by various means. Primary forming of plastics with the aid of heat occurs in a liquid or flowing, thermoplastic state of the heated thermoplastic polymer, that is with the polymer in the form of a melt. By contrast, plastics secondary forming occurs in a softened, but still solid, thermoelastic state of the thermoplastic. Unlike the primary forming processes, the secondary forming processes have not participated in the sustainable development of polymer microtechnology so far. This holds true at least for thermoforming.

For blow moulding, meanwhile, there exist quite some examples for miniature processes. Besides only a few examples for miniature blow moulding processes in an academic environment,[26,27] this includes mainly miniature blow moulding on an industrial scale. Examples are the blow moulding of all kinds of medical miniature balloons such as angioplasty,[28] kyphoplasty,[29] vessel occluding or artery perfusion balloons, or of miniature balloons for diagnostic purposes. Further examples are the blow

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DOI: 10.1002/adma.201003538

moulding of plastic transfer pipettes or unit-dose vials.[30] While the wall thicknesses of blow-moulded parts out of these processes are partly already in the ten-micrometres range, the other dimensions are still in the millimetre range. In contrast to the blow moulding of miniature parts, a potential blow moulding of real microdevices is not yet established. One reason for this might be that the tubes considered as semi-finished products for micro blow moulding have to have a smaller diameter than the blow-moulded microdevices themselves. Another reason might be that it is hardly possible to realise chip-type layouts, the dominant design in microtechnology, by blow moulding.

For roughly ten years now, initiated by the joint first authors of this paper, a new class of polymer micromoulding processes comes more and more into the focus of the microtechnology community. These processes can be subsumed under "microscale thermoforming" or just "microthermoforming", a term introduced by said authors. In this first progress report on thermoforming of microdevices, we review the different process variants of microthermoforming including the laboratory scale equipment and the polymer semi-finished products used so far. Processes for covering and sealing of thermoformed microfluidic structures as well as advanced processes for patterned modification of the thermoformed microdevices are presented, too. Furthermore, we review first applications of the microthermoforming technology. Finally, latest process developments and potential future trends in microthermoforming are discussed.

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2. Microscale Thermoforming Processes

2.1. Definition, Principles and Terminology of Thermoforming

Thermoforming means, as indicated before, shaping of a heated semi-finished product in the form of a thermoplastic polymer film (or plate) by three-dimensional stretching. For this, the film is clamped at its edges or around the forming zones, in contrast to deep drawing. The stretching results in thinning of the semi-finished product compared to its initial thickness.

The film is heated and consequently softened to such an extent that its stretching is enabled or eased without tearing it. This is the case when the film or its polymer is in the entropy- or rubber-elastic state, that is above its energy-elastic, glassy state and below its viscous state. The softening behaviour of the film strongly depends on the thermomechanical history of its manufacturing. In the film, this history is stored in the form of orientations, stress and crystallinity. In the course of heating up, the film's thermomechanical memory is only partially deleted due to the comparatively low temperatures over comparatively short periods of time. Films from amorphous thermoplastics are typically thermoformed somewhat above the glass transition temperature of their polymer. Films from semi-crystalline thermoplastics are formed between a temperature above the glass transition temperature of their amorphous matrix and a temperature slightly above the melting temperature of their crystalline domains. Heating up the film is performed by contact, convection or radiant heaters. The heated film is formed by vacuum or compressed air which is then called "vacuum forming" or "pressure forming", or mechanically via tools. Forming is often carried out as a two- or multistep process where in the first step or steps the film is prestretched and in the last step it is given its final shape. If in this process the film is formed over the protrusions of a "male" or "positive mould" so that the inner surface of the thermoformed part touches and thus replicates the mould, this is called "positive forming" (**Figure 1**a); in case it is formed into the cavities of a "female" or "negative mould" so that the outer surface of the part replicates the mould, this is called "negative forming" (Figure 1b).[24] Positive and negative thermoforming result in characteristic thickness distributions of the part's walls (Figure 1a and b). These wall thickness distributions are due to a hindering of the stretching of the film where it sticks and locally cools when contacting the mould surface. After forming, the film is cooled down below its softening range to freeze its three-dimensional shape. Cooling down of the formed film is normally performed by conduction via the mould surface. For this, the mould is kept at a constant temperature by cooling or heating. Then, the thermoformed part is demoulded. Finally, the part is cut out of the surrounding film or "trimmed" by various means, typically around the formed regions.

The macroscopic thermoforming process brings along some attributes making it very attractive to downscale the process into the microrange. So, provided an appropriate technical

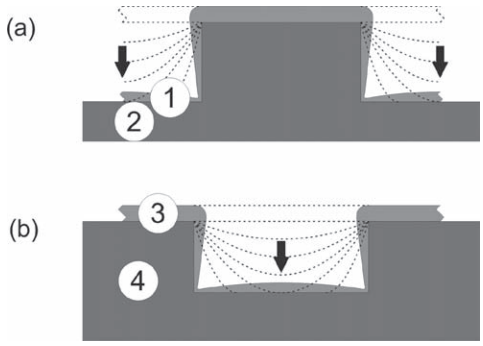

Figure 1. Two basic types of thermoforming processes: (a) Positive and (b) negative forming (simplified schemes with a single mould protrusion or cavity, moulds without draft angles and edge or corner roundings; (1, 3) formed thermoplastic film (or plate), (2) positive mould, (4) negative mould; dashed lines represent the contour of the film at different stages of its forming over or into the mould).

implementation, the process allows high to highest manufacturing throughput. However, due to comparatively low tooling costs and short lead times from design to production, it can be cost-efficient already at small numbers of pieces. Furthermore, the process allows the manufacturing of very thin-walled parts, and that even from polymers with high melt viscosities. Last but not least, it allows the processing of textured films, printed films or metallised or other multilayer or composite films with their structure and properties being preserved.

In the following section, different variants of the microscale thermoforming process are presented. The process variants differ from each other mainly in the way the heated film is forced to stretch into or over the mould to adapt the mould's three-dimensional shape. This in turn has an impact on the different aspects of the process performance (**Table 1**; see end of Section 2.2.). The presented microthermoforming processes are all one-step processes without prestretching and, with the exception of one process, discontinuous or batch processes. Among the microscale processes, there are positive as well as negative forming processes. The fact that a microscale thermoforming process is performed as a positive or negative forming process also impacts its performance (**Table 2**; see end of Section 2.2.). In contrast to macroscopic thermoforming, in the discontinuous microthermoforming processes, the films so far are not only cooled, but also directly or indirectly heated via the moulds. The moulds are cycled between moulding and demoulding temperature. Even though this "variotherm(al)" approach is comparatively slow concerning heating and cooling times, it is much simpler, faster and cheaper to implement. Therefore, it is attractive for research laboratories applying thermoformed microdevices or developing applications for such devices.

2.2. Process Variants

2.2.1. Forming with a Matching Counter Tool – Micro Matched-Die Moulding

Kurosawa et al. reported on forming of a heated thin plastic sheet by pressing it between an upper and a matching lower metal "emboss die" with a concave and a convex detail, respectively.[31] "Embossing" was performed first in a continuously heated press, then in a continuously cooled, adjacent press ("Fujikura method"). Compared to a single, thermally cycled press, working with two presses kept at constant temperatures, a hot and a cold press, can save cycle time. The sheet was pressed in a sandwich together with an additional "cushion sheet" to improve shape reproduction.

Forming of heated thin polymer films by pressing them between patterned upper tools and matching lower counter tools from metal was also reported by Dreuth and Heiden.[32] Thermoplastic structuring was performed in discontinuous processes between grooved stamps (**Figure 2**a; simplified scheme without the comparatively large draft angles typically required in matched-die moulding) or in continuous processes between grooved rollers. In the continuous processes, the transporting speed was up to 39 mm s^{-1}. Partly, the films were alternately transported approximately 50 µm forward and 20 µm backward. Heating of the films in each case was carried out via the upper tools. Cooling was carried out either via the unheated lower stamp or by a stream of air at room temperature applied at the film exit between the rollers. In this context, Dreuth and Heiden noted that the thermal time constant of a polymer film with a thickness in the order of 1 µm is in the order of 1 µs. Defined pressing of the films between the stamps or rollers was ensured by weights. In case of a very thin, fragile film in the roller process, it was partially sandwiched between two identical thicker films of a similar material as the thin film in between. Thus, the thin film was protected against damage resulting from sharp tool edges or film-transport-induced overstrain. Depending on the film thickness and the characteristic dimensions of the tool structures, Dreuth and Heiden distinguished two cases in thermoplastic structuring of thin polymer films which differ in the kind and extent of film deformation. (i) If the characteristic dimensions of the microstructures are of the same order as the film thickness, the heated and softened films are mainly (hot-)embossed. (ii) If the characteristic dimensions are of a larger order, the films are bended and folded in the main.

2.2.2. Forming with an Elastomeric Counter Tool – Rubber-Assisted Hot Embossing

Nagarajan and Yao reported on "rubber-assisted hot embossing" as forming of a heated polymer thin film by pressing it between a hard upper "embossing die" from metal, in this case with a wave pattern, and an unpatterned soft lower counter tool in the form of an elastomeric sheet on a metal plate (Figure 2b; because of the limited deformability of the elastomer sheet, rectangular cross sections of the thermoformed device as displayed in the simplified scheme are hardly feasible).[33,34] Heating and active cooling of the film were performed via the stamp in a "single-" or a "two-station embossing" approach.[33] The latter approach was also carried out in a single press station, but in two different positions, first in a continuously heated, then in a continuously cooled one. Two-station embossing resulted in reduced cycle times whereas the single-station approach led to better embossing results. Depending on the film thickness and the characteristic sizes of the microstructures, according

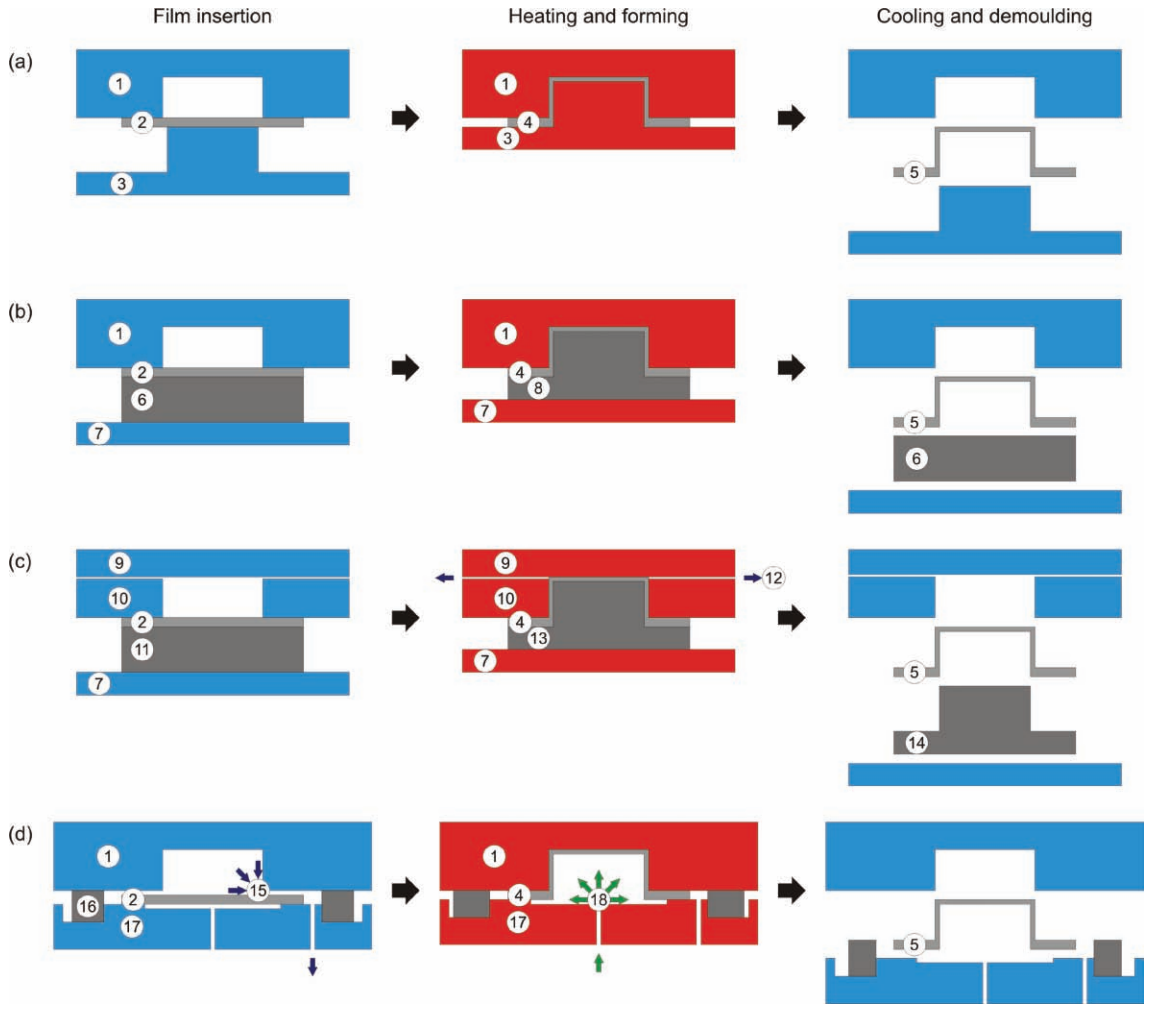

Figure 2. Variants of the microscale thermoforming process (using the example of negative forming versions): (a) Forming with a matching counter tool – micro matched-die moulding, (b) with an elastomeric counter tool, (c) with a softened polymer – micro back moulding, and (d) with compressed gas – micro pressure forming (simplified schemes; (1, 10) micromould/-tool/-stamp, (2) thin thermoplastic film to be thermoformed, (3) matching counter tool, (4) softened and formed film, (5) solidified thermoformed film microstructure, (6) elastomeric counter tool/sheet, (7) lower press plate, (8) compressed elastomeric sheet, (9) mould support (can coincide with upper press plate), (11) thicker thermoplastic film for providing the back moulding polymer, (12) displaced air, (13) compressed softened or flowing polymer, (14) solidified backing, (15) vacuum, (16) axial seal, (17) counter plate with openings for evacuation and gas pressurisation, (18) compressed nitrogen; for (1, 3, 7, 9, 10, 17): blue and red corresponds to cold and heated, respectively).

to Dreuth and Heiden,[32] Nagarajan and Yao distinguished between "surface microstructures" and "shell microstructures".

2.2.3. Forming with a Softened Second Polymer – Micro Back Moulding and MeME

Dreuth and Heiden reported on forming of heated thin polymer films by pressing them between a patterned hard upper tool from metal and an unpatterned lower counter tool in the form of a stack of thermoplastic sheets on a metal plate with the sheets also being softened at film forming temperature.[32] Forming was performed using grooved stamps. Heating and pressing were carried out as described in Section 2.2.1.

The "membrane micro emboss (MeME)" process as a process for positive forming of thermoplastic polymer membranes by pressing them between a duromeric master mould and a deformable plastic support substrate from paraffin was reported by Ikeuchi and Ikuta.[35–37] The MeME process includes sealing of the thermoformed or "embossed" microfluidic structures in the membrane with another, unformed membrane by heat sealing or other sealing methods such as solvent vapour fusion. Sealing was carried out after separating the membrane from the positive mould, but before removing it from the support substrate. Removing the substrate in turn was performed by detaching it, melting it, or dissolving it in a selective solvent. The forming as well as the sealing process were performed in an improvised tabletop apparatus. Ikeuchi and Ikuta also reported on the "membrane micro emboss following excimer laser ablation (MeME-X)" process as an extension of the MeME process.[38,39] In this process, before substrate removal, the thermoformed and sealed membrane microstructure was cut out in the sealed area around the formed region by laser. A lateral

opening in the hollow membrane structure was realised by cutting also through the formed region.

Negative forming of a thin polymer film into the microcavities of a metal mould by temporary back moulding was reported by Reinhardt et al. (Figure 2c).[40] During the microscale back moulding in a hot press, the thin film to be thermoformed was forced into the micro mould cavities by a pressurised, softened or flowing second polymer. This polymer was provided by another, thicker thermoplastic film or an appropriate film stack. Forming was performed using a perforated-sheet-like mould with hexagonal through holes. The air which was displaced by the film being formed into the through holes could escape through a very small, implicit gap between the mould sheet and a mould support. Heating and active cooling of the film were carried out both via the mould and the opposite press plate. After micro back moulding, the thermoformed film was just peeled off from its embossed backing film. In other cases, alternatively, the backing was selectively dissolved. Instead of removing the backing directly after moulding, it can also remain for some time on the thermoformed film as a temporary carrier substrate or protective layer. This can facilitate transport, intermediate storage, dicing, bonding or other postprocessing of the formed film.

2.2.4. Forming with Compressed Gas – Micro Pressure Forming

Truckenmüller et al., Giselbrecht et al. and other authors reported on negative forming of thin polymer films into the microcavities of a metal mould by compressed nitrogen at absolute pressures of up to 5 MPa (Figure 2d).[40–52] This microscale pressure or high-pressure forming process is an adaptation of macroscopic "trapped sheet forming".[24] The process was performed in a tool consisting of a plate-shaped mould, a counter plate with openings for evacuation and gas pressurisation, and an axial seal in between. The micro pressure forming tool was mounted into a modified hot embossing press. Before forming the film into the blind-hole-like mould cavities, they were evacuated. Heating and active cooling of the films were carried out both via the mould and the counter plate. A similar process at gas pressures of a few tenths of a megapascal was also reported by Choudhury et al.[28]

2.2.5. Combination of Miniature Pressure Forming and Gas-Assisted Hot Embossing

Focke et al. and Lutz et al. reported on miniaturised positive forming of comparatively thick polymer films over elastomeric moulds by compressed nitrogen at differential pressures of a few tenths of a megapascal.[53–55] The same forming process combined with gas-assisted micro hot embossing was reported by Disch et al.[56] In the latter case, a thick multilayer film and metal moulds were used. When in this case the film was formed over the miniature structures of the mould, it could bend around and stretch along the structures, and adapt their spatial shape, which means that the film was thermoformed. When at the same time formed over the adjacent microstructures of the identical mould, the thick film could not bend around the structures. These were instead pressed into the film which had a thickness greater than the height of the microstructures. This means the film was hot-embossed. In the microstructured regions of the mould, the thick film as a whole retained a more or less flat shape. As already the micro pressure forming process, the combined thermoforming and embossing process is also an adaptation of trapped sheet forming. The process was performed in a tool consisting of an upper and a heatable lower half-shell, and a mould insert mounted in the lower one. The tool for miniature pressure forming was mounted into a modified hot embossing press. The polymer film to be formed was clamped in between the two shells thus also sealing and separating the shells. The heated film was formed into the mould by loading the upper shell with compressed gas while the lower shell was already evacuated.

Table 1. Comparison between different variants of microscale thermoforming.

	Micro matched-die moulding	Rubber-assisted hot embossing	Micro back moulding	Micro pressure forming
Simplicity of process setup	•	•••	•••	••
Miniaturisation capability	•	•	•••	••
Replication fidelity	• … •••	•	••	••
Ability for processing thin films	•	•	•••	••
Compatibility with surface-modified films	•	•	••	•••
Ability for near-room-temperature processing	•••	•••	•	••
Efficiency of use of polymeric material	•••	••	•	•••
Extensibility towards high manufacturing throughput	•••	•	•••	••
Specific limitations	Mismatch between tool and counter tool can damage the film or the tools.	Sharp-edged mould structures can wear out the elastomeric counter tool to such an extent that it has to be replaced every cycle.	Parabolic pressure distribution[8] in the softened back moulding polymer can lead to a correspondingly non-uniform replication.	Forming of porous films requires special measures.

•, •• and ••• corresponds to relatively low, medium and high, respectively.

Table 2. Comparison between positive and negative thermoforming of microdevices.

	Positive forming	Negative forming
Simplicity of process setup	Lower	Higher
Replication fidelity at the inner/outer surface of the formed microdevice[a]	Higher/Lower	Lower/Higher
Miniaturisation capability concerning structure size/distance[b]	Higher/Lower	Lower/Higher
Maximum aspect ratio realised so far[b]	3[53,55]	~1.5
Possibility of using perforated-sheet-like moulds	No	Yes
Possibility of sealing the formed film without first demoulding it[c]	No	Yes
Geometric definition of the transition between the sidewalls of the formed film microstructure and the sealing film[c]	High	Low
Compatibility with surface-modified films[d]	Low	High[e]
Possibility of forming microstructures with spherical bottoms by free forming[f]	No	Yes
Independence of neighboring forming events, for instance of wells in microwell arrays[f]	No	High

[a], [b], [c], [d] and [f] See also Section 2.1., 2.4., 4., 5. and 6.5.1., respectively. [e] In case of forming by differential gas pressure.

2.3. Differentiation from Hot Embossing

While the differences between micro injection moulding and microthermoforming are obvious, this is not always the case for the differences between hot embossing and some variants of microthermoforming. So, the starting products mostly used in hot embossing are, similar to the ones used in microthermoforming, semi-finished products in the form of thermoplastic polymer films. Furthermore, the machines mainly applied in microthermoforming so far are, like in hot embossing, hot presses. However, besides these similarities in the outer appearance of both micromoulding processes, what happens to the films inside the moulding tools is totally different for microthermoforming and hot embossing. As a consequence, the characteristics of the outcomes of these processes, that is of the moulded microdevices, are different, too, see also Section 6.1. In the following, the major differences between microthermoforming and hot embossing are listed. (i) In microthermoforming, the film is forced to line the surfaces of the mould structures, for instance walls and bottoms of cavities. For this purpose, the film thickness has to be smaller than the characteristic lateral dimensions of the mould structures. Staying with the example of cavity-type structures, along with the lining of the mould cavities goes a stretching and consequently a thinning of the film which at the edges of the cavities is explicitly or implicitly hindered to slip into the cavities. In contrast, in hot embossing, the melt of the film is forced to completely fill the volumes of the mould cavities. For this, the initial film thickness normally has to be larger than the characteristic depths of the mould structures. From this difference, further differences can be derived. (ii) Lining the cavities' surfaces in microthermoforming is only possible if the film is in a softened, but still solid state enabling the film to be stretched into the cavities without tearing it. That is, the film has to be formed under conditions of high material coherence. By contrast, complete filling of the cavities' volumes in hot embossing is only possible if the film is in a liquid or flowing state. The film has to be formed under conditions of low material coherence. Therefore, while microthermoforming is a typical representative of a secondary forming process, standard hot embossing represents a primary forming process. (iii) Lining the cavities with a film fixed at the cavities' edges leads to a film which in the film plane is almost entirely under tensile stress. In contrast, filling the cavities with a molten polymer results in a polymer under compressive stress. (iv) Lining cavities finally leads to thin-walled hollow structures of the thermoformed microdevice. In contrast to that, filling up the same cavities results in solid, not hollow structures of the hot-embossed device.

2.4. Process Limits

Concerning the moulding of smallest structures and structures with high aspect ratios, micro injection moulding and particularly hot embossing are clearly more powerful than microscale thermoforming. When considering the walls of thermoformed cavities or protrusions as moulded structures, and not the cavities or hollow protrusions themselves, the situation often changes in favour of microthermoforming. For the strengths of microthermoforming concerning the geometrical properties of the formed microdevices, see Section 6.1.

Regarding the moulding of smallest structures, the limiting factor in microthermoforming is the thickness of the film to be formed as it has to bend around and stretch along the mould structures. For negative forming into mould cavities, the film has to "fit" into the cavities. Therefore, as already mentioned, the film thickness has to be smaller than the characteristic lateral dimensions of the mould cavities. To be able to handle a non-framed or -supported cut film, it should have a minimum thickness of a few micrometres. For a reasonable reproduction of groove-like mould cavities, for example, they should have a width of at least a small multiple of the film's thickness. Under these boundary conditions, the size of the smallest thermoformable structures can be estimated to be somewhere in the low ten-micrometres range. The distance between these structures can be considerably smaller. As regards positive forming,

the situation is reversed. Thermoforming microchannel-like test structures from 5 µm thin membranes, Ikeuchi and Ikuta found the lateral resolution of their MeME process, which they defined as the minimum mouldable distance between adjacent parallel structures, to be smaller than 15 µm.[35] The corresponding vertical resolution, defined as the minimum mouldable structure height, was found to be around 1 µm. The authors noted that with thinner membranes the resolutions can be much smaller.

Regarding the moulding of high aspect ratio structures, a limiting factor in microthermoforming is the finite ability of the film to be formed to stretch over high or into deep mould structures without tearing. In this context, the corresponding wall thickness distributions (compare Figure 1a and b) play an important role. Another limiting factor are restrictions in terms of a damage-free demoulding of the thermoformed film. In practice, without special measures, the aspect ratio of negative-formed microstructures is limited to values not much higher than 1. In case of a channel-like microstructure, for instance, an aspect ratio of 1 already corresponds to a mean uniaxial stretching of roughly 200%. Locally, this value can easily be a few hundred percent higher. For positive-formed microstructures, depending on the distance between the mould structures, the aspect ratio can be clearly higher than 1. Focke et al. reported on positive forming of miniature channels with aspect ratios of 3.[53,55] The stretching at the sidewalls of these channels reached more than 400%.

3. Machines, Moulds and Semi-Finished Products

3.1. Machines

First and foremost, the thermoforming machine or apparatus provides the forming process with heat and pressure. Moreover, it can provide the mould vacuum, active cooling, the film clamping force, and the opening and closing motion of the tool. Microscale thermoforming was so far applied to fabricate microdevices in academic environments, and that as laboratory models or in small quantities for the own use of researchers. For this, conventional hot (embossing) presses were used, or other, self-made lab scale equipment. The latter included an apparatus for continuous film structuring.[32] A converted hot embossing press provided with a corresponding tool for microthermoforming was also the basis for the first-ever technical implementation of microscale pressure forming, and that by the first authors of this paper (**Figure 3**a and b).[41,43] Besides keeping the upper and the lower half of the tool closed against the gas pressure by the force of the press, as in this case, or simply by weights, the tool halves can also just be screwed together or interlocked.

3.2. Moulds

The same materials and fabrication methods that are used for moulds in the other thermal micromoulding processes, for example in hot embossing, can also be used in microthermoforming. Dreuth and Heiden reported on the fabrication of nickel stamps by lift-off processes on polished metal substrates with the nickel being deposited by evaporation.[32] Dreuth and Heiden also reported on the fabrication of structuring rolls from brass by first micromilling into brass rings, then electrochemically polishing of the rings and finally soldering the rings onto heated rollers. The fabrication of moulds or a mould insert from brass by micromilling was reported by Truckenmüller et al., Giselbrecht et al. (**Figure 4**a) and Disch et al.[41–44,49,56] As generally valid in moulding, Giselbrecht and coworkers found that also in microthermoforming moulds with draft angles in the range of a few degrees can already decrease demoulding forces noticeably.[43] Disch et al. also reported on the fabrication of a nickel mould insert by a UV LIGA (acronym derived from the German words for lithography, electroplating and moulding) process.[56] The fabrication of an embossing die from stainless steel by micro wire electrical discharge machining was reported by Nagarajan and Yao.[33,34] For the micro-back-moulding-based thermoforming reported by Reinhardt et al.,[40] a perforated-sheet-like mould was used (Figure 4b). The mould was fabricated

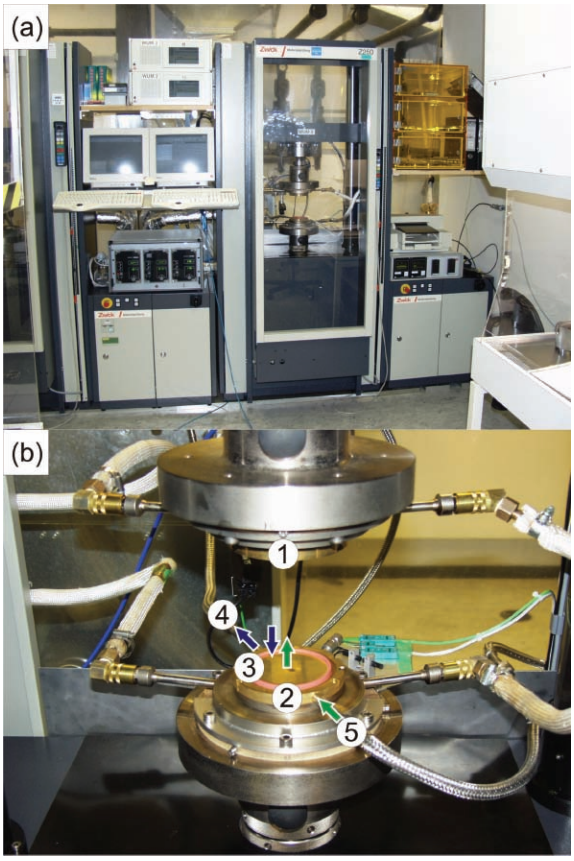

Figure 3. Thermoforming machine and tool: (a) Machine for micro pressure forming on a laboratory scale based on a converted hot embossing press (Jenoptik, Jena, Germany; type WUM) provided with (b) a corresponding microthermoforming tool ((1) micromould, (2) counter plate with evacuation and gas pressurisation openings, (3) seal, (4) vacuum, (5) compressed nitrogen). (b) Reproduced with permission;[49] Copyright 2008, The Royal Society of Chemistry.

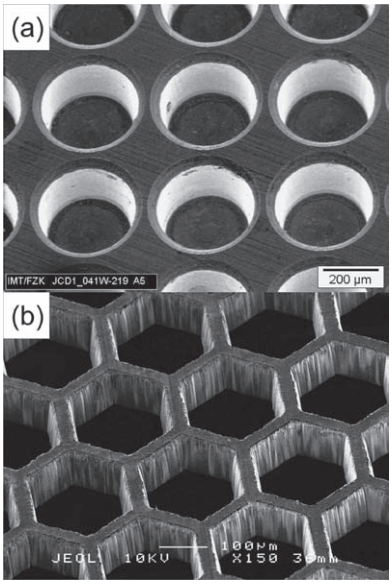

Figure 4. Microthermoforming moulds: (a) Mould from brass fabricated by micromilling (scanning electron microscope (SEM) image; mean diameter of blind-hole-like microcavities: 325 µm; grid of cavity array: 400 µm; cavity depth: 300 µm; draft angles: 5°; cavities additionally equipped with 20 µm wide 45°-bevels to further facilitate demoulding). (b) Perforated-sheet-like mould from stainless steel fabricated by laser micromachining (SEM image; mean incircle diameter of the hexagonal through holes or clearance of the honeycomb mesh: 190 µm; mean web width: 30 µm; thickness of the steel sheet: 100 µm; draft angles: 5°). (a) Reproduced with permission;[49] Copyright 2008, The Royal Society of Chemistry.

from high-grade steel by laser micromachining. In contrast to the blind-hole-like cavities of a conventional micromould, the through holes of such a sheet-like micromould do not require evacuation prior to each forming operation or allow eased evacuation via the gap between the mould and a mould support (compare Figure 2c). Moreover, compared to plate-shaped moulds, such a mould sheet has a considerably smaller thermal mass. This results in shorter heating and cooling periods of the variotherm microthermoforming process. Richter et al. reported on a similar perforated-sheet-like mould, and that as an insert for a micro pressure forming tool.[52] Such a mould concept easily allows to fix the film to be thermoformed on the mould sheet outside the forming tool, place a photomask on the film and align the mask to and via the through holes of the mould beneath the film. In this way, said authors fabricated photopatterned surface modifications aligned to the subsequently thermoformed structures.

When it comes to application of micromoulds, concerning break and wear resistance, metals as a mould material with their unique combination of strength, stiffness, ductility and hardness are the material of choice, especially in the area of large numbers of pieces. Particularly in the field of prototyping and small piece numbers, moulds fabricated from stiff, but also from flexible polymers can be an interesting alternative. Ikeuchi and Ikuta, and Ikuta and Hirowatari reported on the fabrication of a mould from a photocurable epoxy resin by microstereolithography.[35,38,39,57] The mould surface was coated with a fluorocarbon polymer to reduce the sticking and sliding friction between the mould and the embossed membrane during moulding and demoulding. The fabrication of a mould from PDMS by casting the elastomeric resin over a micromilled master from polymethyl methacrylate (PMMA) or cycloolefin copolymer (COC) was reported by Focke et al. and Lutz et al.[53–55] Focke and coworkers found that for the used mould material demoulding is uncritical even without draft angles. One reason is the flexibility of the elastomer material. Another reason is the thermal expansion coefficient of the polymeric mould material being close to the one of the polymer films to be thermoformed.

3.3. Semi-Finished Products

The semi-finished products used so far were monolayer films from various commodity, engineering, high-performance and biodegradable polymers, amorphous as well as semi-crystalline ones (**Table 3**; examples of films as they were used for forming the cell culture chips described in Section 6.5.1., first paragraph). A special case is the usage of films from crab-shell-derived chitosan by Fernandez et al.[58] To enable forming of these films, instead of softening the films by applying heat, they were reversibly shifted from a rigid state to a flexible state of an ionic polymer gel by hydration following a previous protonation. The thicknesses of the films used until now ranged from 1.5 to more than 100 µm. Compared to macroscopic thermoforming, in microthermoforming, the ratio of the film thickness to the characteristic dimensions of the mould structures

Table 3. Examples of films[a] used in microthermoforming and their forming[b] temperatures.

Polymer	Producer/type	Manufacture	Orientation	Thickness	Glass transition/melting temperature	Forming temperature[c]
High-impact PS	NSW/Norflex	Blown film[d]	Biaxial	50 µm	101 °C[e]	110–114 °C
PC	LOFO/Pokalon OG 461 GL	Cast film	None	50 µm	159 °C[e]	164–169 °C
COP	Zeon/Zeonor ZF14–50	Flat film[d]	None	50 µm	136 °C[e]	142–145 °C
PLA	Sidaplax/EarthFirst Packaging Film	Blown film[d]	Biaxial	25 µm	58 °C[f]/~160 °C[f]	60 °C

[a] Monolayer films with glossy finish. [b] Pressure forming at gas pressures between 1–5 MPa. [c] Not necessarily the same after a film premodification, for example as part of a SMART process, see Section 5. [d] Extruded film. [e] Measured by differential scanning calorimetry. [f] Manufacturer information.

is much larger. This is mainly due to availability and handling issues. In most cases, the used films were commercially available flat or blown films, the latter automatically biaxially oriented, or commercial cast films, which are typically unoriented. There were also films self-made by spin coating, and that in the form of dense[35,38,39] or porous films.[36,37] Another special case is the 300 μm thick multilayer laminate used by Focke et al. and Disch et al.[55,56] Its submillimetre thickness required a different strategy for film forming compared to microscale thermoforming of micrometre-thin films, see Section 2.2.5.

Oriented films need comparatively low thermoforming temperatures not to release too much the stress which was already stored in the films during stretching in film manufacturing. Comparatively low temperatures are also necessary to enable demoulding of the formed thin films from the thermocycled moulds in the variotherm microscale thermoforming processes. In combination with the relatively large ratios of film thickness to characteristic mould structure dimensions in microthermoforming, the forming pressures often have to be higher than in macroscopic thermoforming. Pressure forming in the microscale then has to be performed as high-pressure forming at pressures of at least a few megapascal.

A big advantage of microthermoforming as a film secondary forming process is that, in contrast to hot embossing as a film primary forming process, it can benefit from state-of-the-art plastic film or sheet technology[59] to a great extent. This is due to the fact that during thermoforming there is a permanent material coherence of the semi-finished products to a high degree. Modern multilayer films have polymer layers with thicknesses down to the micrometre range, or partly even below that, and inorganic layers from aluminium, aluminium oxide or silicon oxide, for example, with thicknesses typically in the ten-nanometres range. Film technology includes also pretreatments of the film surfaces such as plasma or corona discharge treatments. Thus, today's plastic films are true micro- and nanotechnology products, and that in the form of low-cost mass products.

4. Process Extension for Covering and Sealing of Thermoformed Microfluidic Structures

A key task in the manufacturing of fluidic microdevices is the liquid-tight covering of their microfluidic structures. Truckenmüller et al. reported on sealing of thermoformed fluidic microstructures by heat sealing in combination with the micro pressure forming process.[41,42,44] In the combined process, negative forming of a first film and heat sealing of a second, plane polymer film onto the formed first film were performed in two consecutive cycles of the same press, and in the same tool. Between the two press cycles, the formed film stayed in the mould and the second film was fed into the tool. Leaving the film microstructures in the cavities of the mould protected the microstructures against collapsing under the sealing pressure. Sealing the formed film without first demoulding it was possible because the functional inside of the microstructures in the film device was on the far side of the mould where during forming the pressure gas cushion was present. This is in contrast to positive thermoforming or primary forming of microdevices where the moulded devices have to be demoulded before they can be sealed in another tool or press. Sealing of thermoformed fluidic miniature or microstructures by using adhesive films or by lamination and subsequent to the processes described in Section 2.2.5. was reported by Focke et al., Lutz et al. and Disch et al.[53–56] In the latter case, in a microscale adaptation of macroscopic pharmaceutical "blister packaging", positive forming of the fluidic structures in a barrier laminate was combined with sealing of the structures using a plane aluminium-film-based laminate after demoulding the formed film. The positive-formed film structures show geometrically defined, sharp-edged transitions from their sidewalls to the plane of the initially unformed film (compare Figure 1a) or the later sealing plane.[55,56] This is comparable to primary-formed microstructures, but contrary to negative-formed microstructures. Here, the transitions from the sidewalls to the initial film plane show roundings with radii in the order of the film thickness (compare Figure 1b). Sealing of the thermoformed fluidic film or membrane microstructures is also an integral part of the MeME process.

5. Smart Technology for Patterned Modification of Thermoformed Microdevices

Giselbrecht, Truckenmüller and Welle initiated the "substrate modification and replication by thermoforming (SMART)" processes as processes for the fabrication of thermoformed film microdevices with micro- or nanopatterned modifications of the film surface or bulk.[40,45–52] The film modifications or functionalisations can be of a physical, chemical or biological nature. In a SMART process, still on the unformed, plane film, premodifications of the film material define the locations where later, then already on the spatially formed film, the final local (post)modifications are generated. The definition of the modification sites is normally performed by highly anisotropic, directed lithographic processes. Due to the ability of the flexible thin film to adapt to planar masks or substrates, lithography-based premodification can be performed with minimal influences from diffraction effects or effects of limited focus depth, and therefore with maximum resolution. The modification itself is usually performed by isotropic, undirected wet-chemical processes after film forming. The final isotropic modification provides access over the entire three-dimensional (3D) film microdevice. This modification however is site-specific because of the premodification. Due to the task sharing between the premodification before and the postmodification after thermoforming, one can obtain highly resolved patterns of even temperature- and stress-sensitive modifications also on or in hardly accessible side walls and behind undercuts of thermoformed microstructures.

On the basis of cell culture chips, see Section 6.5.1., as a kind of reference application for the SMART technology, the above authors showed that (spatially curved) bottoms and sidewalls of microthermoformed devices can be provided with micro- or nanopores (**Figure 5**a and **6**a), cell adhesion micropatterns (Figure 5b and 6b), thin film microelectrodes (Figure 5c and 6c),

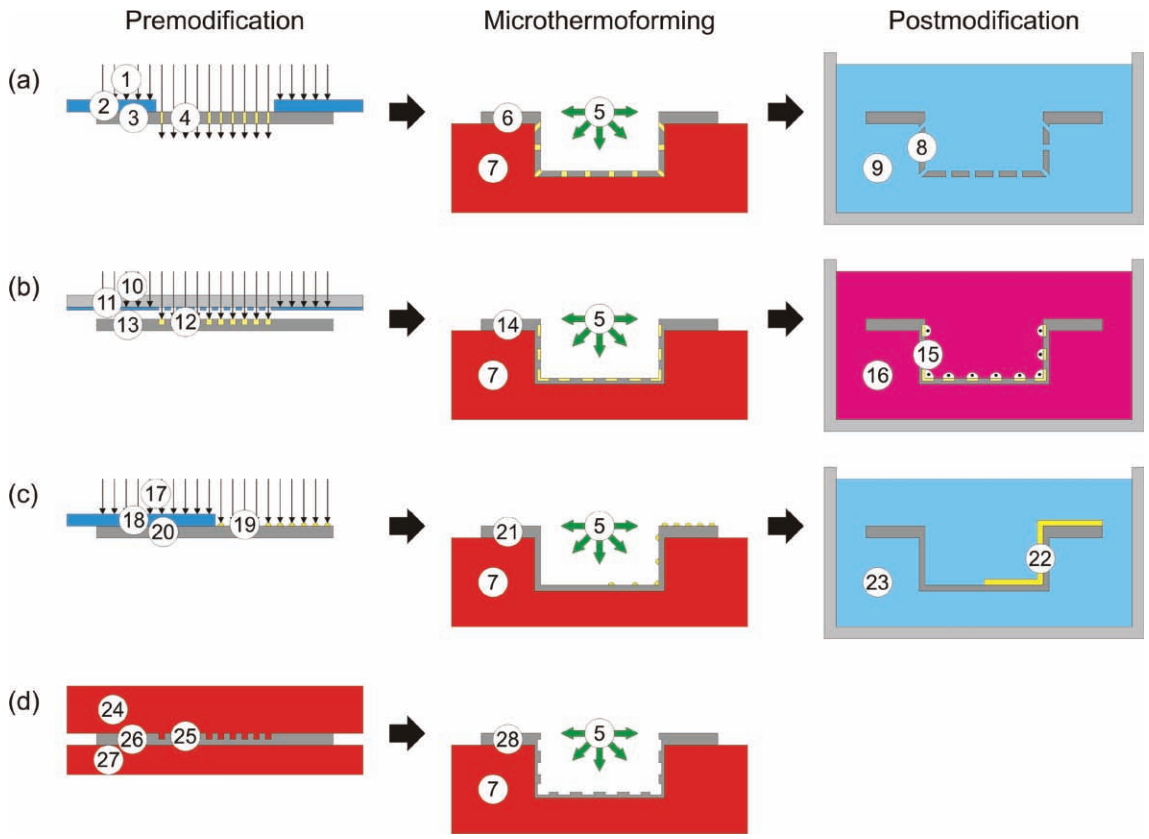

Figure 5. SMART processes for patterned modification of thermoformed microdevices: Modification with (a) micro- or nanopores, (b) cell adhesion micropatterns, (c) microelectrodes or (d) surface micro- or nanotopographies (simplified schemes; (1) heavy ion radiation, (2) ion absorber mask, (3, 26) polycarbonate (PC) film, (4) latent ion tracks, (5) compressed nitrogen, (6, 14, 21, 28) thermoformed film, (7) heated thermoforming mould, (8) pores, (9) etch bath, (10) deep-UV radiation, (11) photomask, (12) UV-modified domains, (13) polystyrene (PS) film, (15) adhering cells of the mouse fibroblast cell line L929, (16) cell culture medium, (17) gold vapour, (18) sputter mask, (19) gold cluster seeds, (20) rough(ened) PC film, (22) thin-film electrodes from gold, (23) chemically reductive fine-gold bath, (24) heated imprint stamp, (25) surface topographies, (27) heated substrate wafer). (a)–(c) Reproduced with permission;[49] Copyright 2008, The Royal Society of Chemistry.

or surface micro- or nanotopographies (Figure 5d and 6d). In the latter case as well as in case of cell chips with cell-repellent micropatterns, a more straightforward version of SMART was applied where modifications are performed only before thermoforming.[40,50,52] For the fabrication of porous microfluidic devices by thermoforming, a comparable approach was also reported by Ikeuchi and Ikuta.[36,37] Of course, modifications can also be carried out solely after forming.[43] This is the only way it can be done in case of the other polymer micromoulding processes. The consequences can be, among others, big loss of patterning resolution, strong pattern distortion and even shadowing.

The SMART processes are only feasible because two preconditions are satisfied. The first precondition is the usage of plane semi-finished products in the premodification processes. This allows full access typically perpendicular to the surface of the semi-finished products to be modified without unwanted proximity gaps in all sorts of mask-based lithographic modification processes. The second precondition is the material coherence of the semi-finished products in the forming process. This enables the preservation of the material modifications. Besides microthermoforming, no other micromoulding process satisfies both conditions.

Interfacial friction or resulting near-surface shear stress can damage or destroy surface and bulk premodifications or their patterns. The negligible gas friction therefore favours negative forming by differential gas pressure over the other negative forming processes or positive forming where the surface of the modified film comes into contact with the soft or hard pressure medium, counter tool or mould.

6. First Applications

6.1. Introductory Remarks on Properties of Thermoformed Microdevices and Derived Applications

Thermoformed microdevices have some unique properties compared to otherwise moulded microdevices or macroscopic thermoformed parts. These properties result from the combination of their microscale dimensions and their special, with respect to microdevices, unusual morphology or architecture.

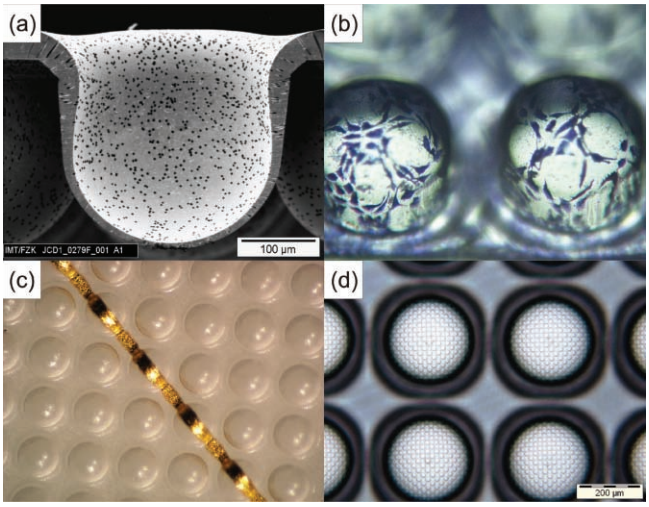

Figure 6. Application of the SMART technology to cell culture chips: (a) Microcontainer of a cell chip from PC with track-etched pores perpendicular to the container walls (SEM image; cross-sectional view; inner container diameter and depth: approximately 300 µm). (b) PS microcontainers with fixed and crystal-violet-stained L929 cells seeding only in the domains of the deep-UV-irradiated chess board pattern (back view). (c) PC microcontainers with electroless plated, crack-free conducting path from gold crossing (back view). (d) PC microcontainers with imprinted pillar pattern (back view). (a), (b) Reproduced with permission;[49] Copyright 2008, The Royal Society of Chemistry. (c) Reproduced with permission;[51] Copyright 2007, The Royal Society of Chemistry.

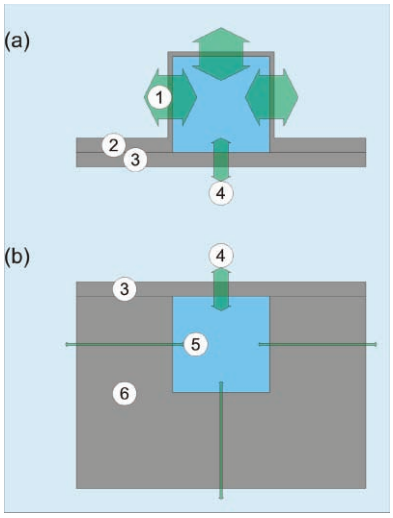

Figure 7. Heat and mass transfer through the walls of a sealed fluidic microstructure fabricated by (a) thermoforming, or (b) hot embossing or injection moulding, for example (simplified schemes; (1, 4, 5) heat or mass transfer, (2) thin thermoformed film, (3) sealing film, (6) thick hot-embossed film or plate; arrow widths proportional to heat or mass transfer rates through the corresponding wall elements).

The structures of microthermoformed devices are free-standing and have thin walls with thicknesses partly in the range of only a few micrometres. This morphology can hardly be obtained using the other polymer micromoulding processes. In case of hot embossing and micro injection moulding, for instance, this is due to the fact that a micromould and a matching counter mould, or their microstructures, would have to be fabricated very precisely. They also would have to be very accurately aligned to each other and, during closing and opening of the embossing machine or the injection moulding tool, very accurately moved towards or away from each other. Under the time- and position-dependent impact of heat and mechanical load in these thermal moulding processes, the latter two things are almost impossible. Additionally, in micro injection moulding, one would have to squeeze the polymer melt through the long narrow gaps between the two micromoulds, which is also nearly impossible. Another part of the morphology of thermoformed microdevices or their structures is their surface roughness. It can be in the same order of the typically very small roughness depth of the film semi-finished products. For microstructures negative-formed by differential gas pressure, this holds true at least on their functional, inner surfaces. The film-based microstructures have properties such as small volume and mass, high flexibility, low heat capacity and thermal resistance, and high permeability. The latter two are due to small distances and large surface areas for heat or mass transfer in comparison with, for example, hot-embossed or injection-moulded microstructures (**Figure 7**a and b). Due to small optical path lengths, the film structures can have a high transparency and a low autofluorescence. From the morphology of thermoformed microdevices and the resulting properties, improved or even new applications or application techniques can be derived (**Table 4**).

By using barrier or light blocking films, thermoformed microdevices otherwise being permeable and transparent can become impermeable or light proof. That way, it is possible to protect oxygen, humidity and light sensitive biochemical substances from degradation or prevent volatile substances from evaporating. Such substances can be prestored in thermoformed and sealed microdevices by adapting macroscopic "form-fill-and-seal" processes.[24] In the context of protecting goods in thermoformed and sealed parts or packages, the combination of miniature or microscale film forming and "modified atmosphere packaging"[60,61] could be an interesting option. The same is true for the combination with other modern packaging technologies such as "(inter)active packaging",[62] "intelligent packaging" or "smart packaging".[63] The special morphology of microdevices thermoformed from multilayer films and therefore having multilayered walls could open up further opportunities. In case of microfluidic devices, for example, the fluid contacting inner film or wall layer can be different from the outer layer which is exposed to the environment, and from further functional layers in between these two layers. In the following sections, first applications of the microthermoforming technology from various fields of application are presented (**Table 5**; summary and overview; see end of Section 6.).

6.2. Membrane Switches

Kurosawa et al. reported on thermoforming of plastic sheets with dome-shaped structures to use them in "click" membrane

Table 4. Properties of thermoformed microdevices and derived exemplary applications.

Properties of thermoformed microdevices	Derived improved or new applications or application techniques
Thin walls	• Chip-based CE with 3D electrodes for contactless conductivity detection surrounding the separation channels • Hermetically closed microfluidic point-of-care testing devices with prestored substances which can be accessed at the time and place of their use just by peeling, ripping, puncturing or punching
Small material quantities (volume and mass)	• Microdevices from expensive high-performance or biopolymers • Extreme low-cost devices • Biodegradable human implants with faster and physiologically less burdening decomposition • Single-use applications with small quantities of contaminated biomedical or clinical waste
High flexibility	• Medical use on the freeform surface of the human skin ('intelligent plaster') • Implantation under the skin or into soft tissue • Integration into functional, 'smart' textiles • Combination with flexible 'poly(mer elec)tronic' circuits • Disposable microfluidic chips with micropumps actuated by pushing button-like reservoirs with the fingertips • Reel-to-reel processes not only in production, but also in application
Low heat resistance and capacity	• Chip-based PCR • CE chips • Micro heat exchangers
High permeability for gases,[a] liquids or solid particles[b]	• Chips for 3D cell or tissue culture, or film-based scaffolds • Microdevices for liquid-liquid or liquid-gas reactions
Low light absorption and background fluorescence	• Imaging through the walls of biochips

[a] Or low permeability, for example for oxygen or water vapour, through the usage of (multilayer) barrier films. [b] Provided appropriately porous polymer films.

switches of, for example, keyboards or operating panels of all kinds of portable electronic devices.[31] In such applications, they can substitute domes made from metal sheets. The plastic membrane domes were fabricated from polyethylene terephthalate (PET) sheets. For forming, matched-die moulding was used. Compared to membrane switches based on metal domes, the simpler constructed switches based on thermoformed plastic domes have production and application-technological advantages as well as economical advantages. Cost savings result to a greater extent from reduced material and assembly costs.

6.3. Electrostatic Microactuator

Dreuth and Heiden reported on thermoforming of micro corrugated sheets.[32] They were fabricated from biaxially oriented PET foils with thicknesses smaller than 10 µm. The crystallinity of these foils was approximately 50%. In one case, a corrugated sheet from an only 1.5 µm thick foil was fabricated in a sandwich between two 6 µm thick PET foils (**Figure 8**a). For forming, continuous micro matched-die moulding was used. The periodicity of the wave pattern was 450 µm. Metallised with a 30 nm thick aluminium layer and glued on a 600 nm thick plane PET foil with a similar metallisation, this corrugated sheet was used to fabricate an electrostatic microactuator. When supplied with a voltage, the actuator performed bending movements with an electromechanical conversion factor of 50 µm V^{-1}. By using thinner foils, as in this case, such foil-based electrostatic actuators can reach the same forces at lower voltages. Currently, microthermoforming seems to be the only moulding process which is capable to economically fabricate microdevices such as this very thin-walled microactuator. Potential applications for thermoformed electrostatic microactuators and also -sensors are loudspeakers or microphones. Another potential application for thermoformed microdevices from metallised very thin polymer foils, and that in the field of cryotechnology, is super-insulation.[32] This application could benefit from the fact that while the heat resistance perpendicular to the foil plane is very low, it is very high in the foil plane.

6.4. Microfluidic Chips

6.4.1. CE Chips

Compared to buried channels in bulky capillary electrophoresis (CE) chips fabricated, for example, by injection moulding or hot embossing, freestanding thin-walled channels in film-based CE chips fabricated by thermoforming could be advantageous. One advantage could be the higher heat transfer rates from the inside of the channels to the outer chip environment due to the lower thermal resistance of the channel confining structures. Another advantage could be a more sensitive measurement in case of contactless conductivity detection due to the possibility

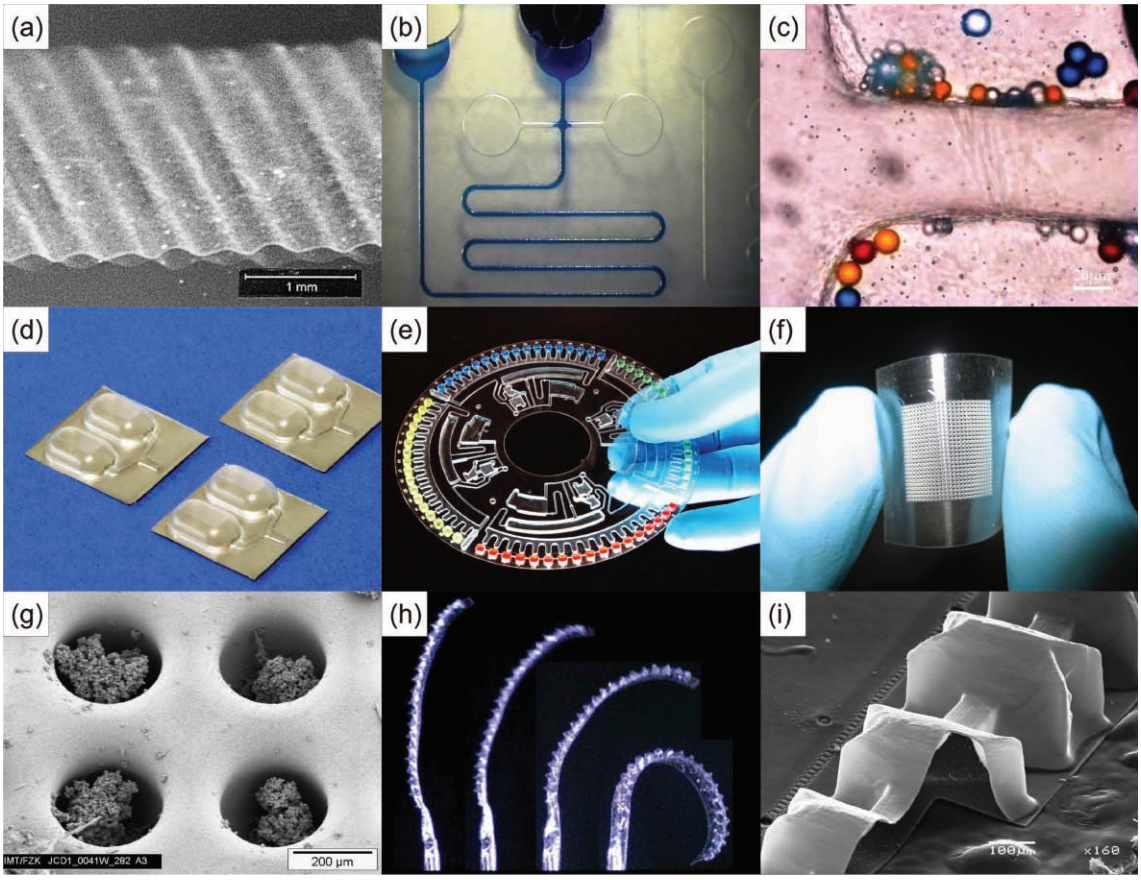

Figure 8. Applications of thermoformed microdevices: (a) Micro corrugated sheet from PET used to fabricate an electrostatic microactuator. (b) Microchannel structure of a CE chip from PS (showpiece; buffer and buffer waste reservoir opened by punching; separation channel filled with coloured, contrasting liquid; inner width of injection and separation channel: approximately 150 µm). (c) Microchannel intersection of a mesoporous polymer membrane microfluidic device from PLA for on-site size-selective particle sampling (scale bar: 20 µm).[36] (d) Disposable microfluidic blister chips from PP-COC-PP (showpiece; length, width and height of the fluid reservoirs: approximately 7.5, 5 and 2 mm).[56] (e) Cartridge from COP for real-time PCR (reaction cavities filled with coloured liquids). (f) Cell chip from PC for 3D cell culture (bent between the thumb and the forefinger of a hand). (g) Cells of the human hepatocyte cell line HepG2 cultured in the microcontainers of the cell culture chip from (f) (SEM image).[47] (h) Pressure-driven micro active catheters from PLA for intravascular surgery applications performing bending movements (catheter diameter: approximately 300 µm).[39] (i) Bellows units of the microcatheter from (h) (SEM image; partially cut open and still on the support substrate).[39] (a) Reproduced with permission;[32] Copyright 1999, Elsevier. (b) Reproduced with permission;[42] Copyright 2002, Institute of Physics Publishing. (e) Reproduced with permission;[55] Copyright 2010, The Royal Society of Chemistry. (f) Reproduced with permission;[49] Copyright 2008, The Royal Society of Chemistry.

of having 3D measuring electrodes surrounding the thin-walled channels. Truckenmüller et al. reported on thermoforming and sealing of showpieces of CE chips,[41,42,44] the first-ever microdevices thermoformed by pressure forming. The CE chips were fabricated from biaxially oriented (high-impact) polystyrene (PS) films with thicknesses of 25 and 250 µm, the former for forming, the latter for sealing. The film for sealing was coated with a 5 µm thick heat sealing layer from polyester-polyether-polyurethane. For sealing, the corresponding process described in Section 4. was used. In one case, the CE chip contained 16 microchannel and reservoir structures arranged in four rows and columns (Figure 8b).[42,44] The smallest injection and separation channels had an inner width of approximately 150 µm, the corresponding greatest inner channel depth or height was approximately 75 µm.

6.4.2. 3D Microfluidic Device

Ikeuchi and Ikuta reported on thermoforming and sealing of a 3D microfluidic device in the form of a honeycomb-like microchannel network.[35] The membrane microfluidic device was fabricated from two 5 µm thick polylactic acid (PLA) membranes, one for forming, the other for sealing. The membranes in turn were fabricated by spin coating. For forming and sealing, the MeME process was used. The sealed membrane microchannels had a width and height of 50 µm. The thin-walled channels of such thermoformed microfluidic devices significantly enhance heat and mass transfer through the channel walls compared to traditional microfluidic devices. These characteristics can extend the overall application of fluidic microdevices for chemical and biological analysis to temperature- and environment-dependent reactions.

6.4.3. Microfluidic Device for On-Site Size-Selective Particle Sampling

Ikeuchi and Ikuta also reported on thermoforming and sealing of a mesoporous polymer membrane microfluidic device with tunable pore diameter and density for on-site size-selective particle sampling.[36] The fabrication and the device were more or less identical to the one described in Section 6.4.2. The exceptions were that the layout of the channel network was a mesh with square instead of hexagonal openings and that the membranes were fabricated as porous, not as dense ones. The porosity was generated by liquid-induced phase separation following spin coating. When a suspension of microbeads was offered at the outside of the microchannel network, beads with a diameter smaller than 1 μm entered the inside of the channels by penetrating through their permeable, porous walls, whereas larger beads did not (Figure 8c). Thus, the porous membrane device worked as a size-selective filter with a cut-off diameter of 1 μm. Unlike existing microfluidic devices adding filtration components such as pillar arrays, packed beads or porous membranes to microchannels, in case of the thermoformed membrane microfluidic device, the microchannels as a whole work as thin-walled large-area filters. This enables the miniaturisation of high-throughput on-site size-selective sampling. A potential application for such thermoformed microdevices is size-selective sampling as an essential first step in many biological analysis processes. In these preparation steps, for instance, blood cells are separated from whole blood or proteins are extracted from cell lysates. Other potential applications for thermoformed microfluidic devices based on porous membranes which can benefit from large interfacial areas and short diffusion lengths are liquid-liquid and liquid-gas reactions.

6.4.4. Blister Chip

Disch et al. reported on thermoforming and sealing of a showpiece of a disposable microfluidic "blister chip" in the form of a microchannel and reservoir structure (Figure 8d).[56] The microfluidic chip was fabricated from a 300 μm thick high-moisture-barrier laminate for forming and an aluminium-based film laminate for sealing. The former was a laminate of a thicker inner COC layer embedded between two thinner outer polypropylene (PP) layers. For forming and sealing, combined pressure forming and hot embossing, and the corresponding sealing process described in Section 4. were used. The thermoformed fluid reservoirs of the chip, the "blisters", had a length, width and height of approximately 7.5, 5 and 2 mm. The embossed microfluidic main channel had an inner width of 1 mm and an inner height of 250 μm. The usage of barrier films enables applications where substances need to be stored and preserved in the reservoirs of microfluidic chips over a longer period of time, see also Section 6.1. In case different substances can only be stored separately and not mixed with each other, they can be filled in different reservoirs before, at another time and place, they are then mixed, and, immediately after mixing, applied.

6.4.5. Cartridges for Nucleic Acid Analysis

Already in the 1990s, thermoformed miniaturised devices for analytical or diagnostic biomedical applications were developed.[55] This included self-contained disposable film cartridges for performing polymerase chain reaction (PCR)[55,64] or immunoassays[55,65] with prefilled liquid and dry reagents. The fluid transport was carried out by a roller squeezing fluidic reservoirs or via centrifugal actuation.

In PCR, the time for thermocycling and thus the duration of the whole assay can be decreased by increasing the heating and cooling rates. Therefore, the time from sample to result can be reduced using thermoformed foil-based PCR cartridges with enhanced heat transfer through the thin walls of their reaction cavities. Focke et al. reported on thermoforming and sealing of such a lab-on-a-chip (LOC) cartridge for real-time PCR, and that in the form of a centrifugal microfluidic platform (Figure 8e).[53,55] The circular-disc-shaped foil cartridge was fabricated from 100–200 μm thick cycloolefin polymer (COP) foils. For forming and sealing, miniature pressure forming and the corresponding sealing process described in Section 4. were used. The foil cartridge contained four fluidic networks, in each case comprising a chamber for the DNA sample, a chamber for the dilution buffer, a chamber for mixing both substances, an aliquoting channel, and 17 metering chambers and downstream PCR reaction cavities. The fluidic microstructures had sharp corners with corner angles down to 60° and aspect ratios up to 3.

A similar cartridge, but now for nucleic acid analysis based on recombinase polymerase amplification (RPA), was reported by Lutz et al. and Focke et al.[54,55] The disc-shaped foil cartridge was fabricated from 188 μm thick COP foils using the same processes as for the PCR cartridge described in the last paragraph. The RPA rehydration buffer, which was sealed in glass ampoules, and the lyophilised RPA reagents were prestored in the foil cartridge by placing them in corresponding chambers of the thermoformed cartridge before sealing it. After pipetting the DNA samples into the inlets of the PCR reaction cavities and subsequently sealing them with adhesive tape, and before starting the processing of the assay in a modified thermocycler for real-time PCR, the rehydration buffer was released from the glass ampoules. For this, the ampoules were crushed by compressing the storage chambers containing them with a fingertip.

6.5. Cell and Tissue Culture Chips

6.5.1. Cell Chips

Giselbrecht et al., Truckenmüller et al. and Reinhardt et al. reported on thermoforming and functionalisation of chips for 3D cell culture in the form of microcontainer arrays. In one case, the cell culture chips were fabricated, for example, from 40–50 μm thick COP, polycarbonate (PC, Figure 8f) and biaxially oriented high-impact PS films.[43–51] For forming and modification, micro high-pressure forming in the form of negative forming and the SMART processes were used. For microwell arrays, besides the compatibility with surface-modified films, negative forming has several advantages compared to positive forming. Among others, the wells can have thinner bottoms or bottoms with a rounded or spherical shape (compare Figure 6a–d), the latter by free forming

into appropriately deep blind or through holes. Due to the fact that the events of forming the wells are highly decoupled from each other, the wall thickness distribution of wells at the edges of the arrays and from the array's other regions is highly identical. The cell chips were based on an originally injection-moulded chip[51,66,67] which later on was also fabricated by hot embossing.[48] The chips contained 625 circular containers arranged in 25 orthogonal rows and columns (Figure 8g). The inner diameter and depth of the cell containers were approximately 300 µm. For porous versions of the cell chips, for instance, thermoforming has several advantages compared to injection moulding or hot embossing, and that concerning chip fabrication[43,48] as well as chip application. Porous chips fabricated by a combination of thermoforming and ion track technology allow an all-side supply of cell aggregates in their containers with nutrients and gases through the track-etched thin walls. Schober et al. reported on the fabrication of a porous 3D cell support using the microthermoforming and corresponding cell chip technologies previously developed by Giselbrecht and Truckenmüller.[68]

In another case, the cell culture chips were fabricated from a 30 µm thick biaxially oriented PLA film.[40] For forming and premodification, micro back moulding and thermal micro- or nanoimprinting, respectively, were used. The cell chips contained approximately 1200 hexagonal containers arranged in honeycomb fashion. The cell containers had an inner incircle diameter of approximately 150 µm and an inner depth of approximately 100 µm. The spatially curved inner container walls were provided with micro- and nanogroove patterns. For this, the grooved topographies were imprinted in the PLA film prior to temporary back moulding the film with the softened polymer of an approximately 500 µm thick stack of low-density polyethylene (PE) films. Cells of the mouse premyoblast cell line C2C12 were cultured in the containers and shown to adapt to the underlying microtopographies of the container walls by aligning along the grooves.

6.5.2. Artificial Capillary Network Chip for In Vitro 3D Tissue Culture

Ikeuchi and Ikuta reported on thermoforming and sealing of an artificial blood capillary network chip for thick 3D tissue culture *in vitro*.[37] The fabrication and the device were more or less identical to the ones described in Section 6.4.2. with the exception of the membranes, which in turn were similar to the porous ones in Section 6.4.3. (5 µm thick PLA membranes with approximately 1 µm wide pores). Cells can be cultured in a soft 3D hydrogel matrix on the outside of the capillary network with the thick 3D cellular construct being supplied with nutrients and gases through the porous walls of the capillaries. Thus, the capillary network can act as an artificial vascular system. Compared to cells cultured on the buried channels of conventional, bulky microfluidic chip scaffolds, cells cultivated on and between the freestanding thin-walled capillaries of the thermoformed film-based chip scaffold can grow in higher and more uniform cell densities. The volume or mass ratio of cells to scaffold can be higher, too. As the film scaffold is much more flexible, it is more suitable for implantation into soft tissue. There, it could then be degraded faster and physiologically less burdening because of its much smaller volume and its much higher surface-to-volume ratio. The thermoformed capillary network chip could be applied, for example, to study cellular dynamics under 3D conditions or, in the near future, to regenerate or engineer large tissues *in vitro* for subsequent implantation. Thick tissues can be built up by multiple stacking of the chip scaffolds covered with cell-laden hydrogel.

6.6. Pressure-Driven Micro Active Catheter

Ikeuchi and Ikuta also reported on thermoforming, sealing and cutting out of the world's smallest micro active catheters in the form of pressure-driven catheters for safe intravascular surgery applications, even in narrow, branched blood vessels.[38,39] The microcatheters were fabricated from 5 µm thick spin-coated PLA membranes. For forming, sealing and trimming, the MeME-X process was used. When cutting out the microcatheters, at the same time, an opening was cut at one end. Before then removing the paraffin support substrate by dissolving it in hexane, a microtube was connected to the catheter opening by adhesive bonding. One side of the catheters' bodies was designed as a microbellows. In case of the latest catheter version (Figure 8h), the bellows was constructed as a series of folded microchambers, and of microchannels in between the chambers connecting them (Figure 8i).[39] The catheter had a diameter of approximately 300 µm and a length of 4 mm. A single microchamber-microchannel unit in its unexpanded, initial state had a length of 300 µm. When supplied with saline water, depending on the water pressure, the fluidic microactuator performed bending movements in an angle range of 0 to 180° (Figure 8h). The bending was due to the expansion of the bellows under a differential pressure between the catheter in- and outside. The special construction of the bellows prevented its undesirable inflation in circumferential direction during the longitudinal expansion. For demonstration purposes, the catheter was advanced, rotated and actuated in a blood vessel model from PDMS with vessels of 1–3 mm diameter to reach a target aneurysm situated behind a bifurcation. It seems that microthermoforming presently is the only moulding process being capable to fabricate such small and thin-walled catheters. Due to its nature as a moulding process, thermoforming allows to easily monolithically integrate microcapillaries parallel to the blind actuating capillary with the bellows. These additional capillaries can then be used, for instance, for on-site pharmaceutical injections or blood sampling. Instead of recurrent laborious tube assembly for every single catheter to be fabricated, it only needs one-time adding of the corresponding structures to the thermoforming mould.

7. Latest Developments

An important development is the further or new development of SMART processes. This includes new processes for the generation of micro- and nanopores in thermoformed microdevices. In these processes, besides track etching, alternative

Table 5. First applications of microthermoforming technology.

Application	Functional structures	Used semi-finished product	Applied forming variant[a]	Characteristic dimensions	Figure and references
Membrane switches	Dome-shaped structures	PET sheet[b]	Matching counter tool	–	[31]
Electrostatic actuator	Micro corrugated sheet	1.5 µm thick PET foil[c]	Matching counter tool; continuous forming	Periodicity: 450 µm	Figure 8a[32]
-/test structure	Micro corrugated sheet	1.5 µm thick PET foil[d]	Softened second polymer[e]	Periodicity: 1 µm[d]	[32]
-/test structure	Micro corrugated sheet	25 µm thick PS film	Elastomeric counter tool[f]	Periodicity: 200 µm; curvature radius: 50 µm	[33,34]
CE chip (showpiece)	Microchannel and reservoir structures	25 µm thick PS film	Compressed gas; negative forming	Inner channel width: ~150 µm; inner height: ~75 µm	Figure 8b[42,44]
3D microfluidic device	Channel network in the form of a mesh with hexagonal openings	5 µm thick PLA membrane	Softened paraffin[g]; positive forming	Channel width and height: 50 µm	[35]
Microfluidic device for on-site particle sampling	Channel network in the form of a mesh with square openings	5 µm thick, porous PLA membrane	Softened paraffin; positive forming	Channel width and height: 50 µm	Figure 8c[36]
Microfluidic blister chip (showpiece)	Microchannel and reservoir structure	300 µm thick PP-COC-PP three-layer laminate[d]	Compressed gas; positive forming	Inner main channel width: 1 mm[d]; inner height: 250 µm	Figure 8d[56]
Cartridge for real-time PCR	Miniature channel and chamber networks	100–200 µm thick COP foils	Compressed gas; positive forming	Aspect ratios of up to 3	Figure 8e[53,55]
Cartridge for RPA (recombinase polymerase amplification)	Miniature channel and chamber networks	188 µm thick COP foil	Compressed gas; positive forming	–	[54,55]
Passive microvalve for highly wetting fluids	Sequence of microcapillaries and heart-shaped chambers	COP foils	Compressed gas; positive forming	Inner capillary width and height: 200 µm	[69]
-/microfluidic test structures	Channels and circular pits	30 µm thick PS film	Compressed gas; negative forming	Channel width and height: 400 µm; pit diameter and height: 400 µm	[28]
Cell chip	Circular microcontainers	40–50 µm thick COP, PC or PS films	Compressed gas; negative forming	Inner container diameter and depth: ~300 µm	Figure 8f and g[43–51]
Cell chip	Hexagonal microcontainers	30 µm thick PLA film	Softened polymer; negative forming	Inner container incircle diameter: ~150 µm; inner depth: ~100 µm	[40]
Microchips for extrahepatic transplantation of islets of Langerhans	Circular microcontainers	~50 µm thick PEOT-PBT[h] block copolymer film	Softened polymer; negative forming	Inner container diameters: ~130 µm or ~330 µm	[70]
Artificial capillary network chip for *in vitro* 3D tissue culture	Channel network in the form of a mesh with hexagonal openings	5 µm thick, porous PLA membrane	Softened paraffin; positive forming	Channel width and height: 50 µm	[37]
Pressure-driven micro active catheter	Microbellows	5 µm thick PLA membrane	Softened paraffin; positive forming	Catheter diameter: ~300 µm	Figure 8h and i[39]

[a] Unless otherwise stated, discontinuous forming. [b] Pressed in a sandwich together with an additional 'cushion sheet'. [c] Sandwiched between two 6 µm thick PET foils. [d] According to the remarks in Section 2.2.1., the films were mainly embossed. [e] Stack of three approximately 100 µm thick transparency foils on an unpatterned polished steel plate. [f] 6.4 mm thick unpatterned sheets from different grades of a high-temperature silicone rubber with a hardness between 30 and 80 Shore A. [g] With melting points of 60 and 70 °C. [h] Polyethylene-oxide-terephthalate-polybutylene-terephthalate.

methods to generate porosity such as particulate leaching and phase separation shall be combined with microthermoforming. Furthermore, the generation of pores shall be combined with other film modifications such as the generation of surface topographies by imprinting.

The development of SMART processes also includes new processes for the generation of micro- and nanotopographies on the surfaces and also in the bulk of thermoformed (PMMA) films. Here, in combination with microthermoforming, deep-UV[71] or X-ray direct lithography is used instead of hot embossing or thermal imprinting as reported by Reinhardt et al. and Giselbrecht et al.[40,50] Especially X-ray lithography (XRL) enables the realisation of film layouts with topographies exceeding a certain depth compared to their lateral dimensions or to the film thickness. These layouts would be difficult to realise with hot embossing because of problems in demoulding. Demoulding of embossed films carrying topographies with depths in the order of the film thicknesses often results in overstretching or tearing of the films. This is due to the relatively high static and dynamic friction of the embossed topographical structures in their mould cavities in connection with a relatively low stiffness and strength of the residual film layer

connecting these structures. Besides the realisation of comparatively high topographies, using XRL in combination with thermoforming could enable the realisation of regularly arranged and shaped through holes which would be hardly feasible with hot embossing.

8. Future Trends

For some time past, in polymer (micro)moulding, there is a trend towards moulding of multiscale devices, or multiscale moulding. This means moulding of devices in one single piece which combine functional structures with dimensions ranging from the micro- or nanoscale to the macroscale. This has not necessarily to be done in one single moulding step, see next paragraph. The functional dimensions often span over seven, eight or even more orders of magnitude. One reason for this trend is the increased added value when extending plastic parts by small-scale substructures adding functionality to the parts. Examples for such moulded multiscale devices are devices with biomimetic micro- or nanoscale surface topographies such as polymer lenses with antireflective surfaces on the basis of the "moth eye effect". Similar bioinspired topographies can have self-cleaning, superhydrophobic properties based on the "lotus effect", "shark-skin-effect"-based properties reducing water drag, or biofouling or -deterioration suppressing properties. Another reason for multiscale moulding is the cost reduction when substituting assembled parts by parts moulded in one piece.

The chances are that the trend towards multiscale moulding will be carried over to thermoforming. In thermoforming, however, the thickness of the semi-finished product has to be adapted to the size of the final part to a certain extent. Therefore, when realising devices with structure dimensions spanning several orders of magnitude solely by thermoforming, films or plates with different thicknesses in different areas would be needed. Much more feasible seems to be the realisation of multiscale devices by thermoforming combined with overlaid embossing or imprinting. By this means, for instance, very-large-area plastic parts with functional surface topographies similar to the ones described in the last paragraph could be moulded. The topographies could be imprinted into the films already before thermoforming the films, analogous to the fabrication of the cell culture chips with the textured container walls described in the Sections 5. and 6.5.1. Alternatively, the topographies could be imprinted during thermoforming. The required complex, multiscale mould for the simultaneous imprinting and thermoforming process can be derived from a corresponding part moulded using the sequential process by copying the part. The presence of positive locking between formed film and mould can make it necessary to restrict the topographies to be imprinted to flat textures and to use elastomeric moulds.

Another potential trend which, in case microthermoforming is successfully developing further, can be anticipated is the hybrid integration of microthermoformed devices in devices replicated by micro injection moulding or hot embossing. In this way, the advantageous properties of thermoformed, flexible and adaptable film microdevices can be combined with the rigidity and shape definition of injection-moulded or embossed devices. An example for such hybrid devices could be thermoformed porous cell culture chips integrated in the bottoms of injection-moulded inserts for multiwell plates, comparable to Transwell® membrane inserts. Another example are similar chips integrated in injection-moulded chip-type bioreactors in microscope slide format.[72] The assembling of the film microdevices in their carriers or frames can be performed by various micro joining techniques, but also by partial insert moulding. Derived from thermoforming of cell containers using imprinted films as previously described by the first authors of this paper,[40,46,50] Heilig and coworkers lined hot embossed microfluidic channels and reservoirs with a film which carried nanoimprinted surface textures.[73] For this, instead of a micromould, an embossed substrate was used, in each thermoforming cycle a new one. In the course of thermoforming, the film was thermally bonded to the substrate with the substrate and the film polymer being similar.

9. Conclusions and Outlook

In this progress report, we review the state of the art of microthermoforming technology as well as its first applications. It becomes clear that, in spite of its comparatively young history, microthermoforming has already developed to a versatile technology with manifold applications. The applications so far are mainly in the biomedical field with an emphasis on chip-type microdevices becoming apparent. Due to the favourable properties of the various processes for thermoforming of microdevices and the thermoformed microdevices themselves, also compared to the other polymer micromoulding processes, this development can be expected to further continue.

For a sustained establishment of microthermoforming as a mass production capable process in the near future, there could be some crucial points to pay attention to. One might be the successful transition from the variotherm film heating concepts of the lab scale microprocesses used so far to the concepts commonly used in the macroscopic processes. This measure is essential for the realisation of competitive, short cycle times. For similar reasons, in some cases, the successful implementation of continuous production processes might be another decisive point. In this regard, for LOC-type microdevices, continuous processes throughout the whole product life cycle from film production to chip disposal, that is also during the application, could be an interesting option. A promising approach for continuous microthermoforming might be by temporary back moulding with the back moulding performed as roller embossing. For this, two films, the film to be thermoformed and the film for providing the back moulding polymer, one upon the other, would be fed between a micropatterned mould roller and an unpatterned counter roller. Peeling off the thermoformed film from the backing film could then benefit from the possibility to definably put films under tension in continuous processes. Replacing the two separate films to be fed between the rollers by a single peelable double-layer film might be an attractive

subvariant of a potential roller-embossing-based thermoforming process.

All in all, the potential great diversity of microthermoforming technology and therefore its adaptability to specific moulding tasks could be, comparable to macroscopic thermoforming, the basis of a long lasting success of this technology in the area of microtechnology and plastics engineering. Referring to this, the scalability of microthermoforming in terms of production throughput could play a major role. At the lower end of throughput, for a research lab in the area of biomedical engineering with an interest in film-based microdevices, it finally needs only an appropriate micromould, and a hot press or another combination of a heat source and a pressing or clamping mechanism to step into the world of microscale thermoforming.

Acknowledgements

R. T. gratefully acknowledges financial support from the "Spearhead" program "Advanced Polymeric Microstructures for Tissue Engineering" of the MIRA Institute for Biomedical Technology and Technical Medicine of the University of Twente, The Netherlands.

Received: September 28, 2010
Published online: January 31, 2011

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