FULLY AUTOMATED STICK-PACKAGING FOR PRECISE LIQUID REAGENT PRE-STORAGE AND RELEASE IN LAB-ON-A-CHIP DISPOSABLES

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ABSTRACT

We demonstrate for the first time the highly precise and fully automated manufacturing of tubular-shaped composite-foil pouches for the pre-storage of liquid reagents in lab-on-a-chip disposables. Those stick-packs are miniaturized and easy to handle packages and enable: i) the protection of reagents from external influences (e.g. irradiation, vaporization) and ii) on-demand release by delamination of a well-defined peel-seal. Based on previous work, we successfully expanded the volume range from 80 - 500 µL to 50 - 1200 µl and fabricated batch sizes of 2,400 parts at significantly reduced cycle times of 1.5 seconds with a fully automated stick-packaging machine.

KEYWORDS: reagent pre-storage, stick-packaging, centrifugal lab-on-a-chip

INTRODUCTION

Only few concepts exist for long-term stable pre-storage of liquid reagents in lab-on-a-chip systems, although it is a vital requirement for a self-contained test, which can be operated by untrained users [1]. Recently, the use of stick-packs was introduced for reagent pre-storage and automated release on a centrifugal microfluidic platform [2] (Fig. 1).

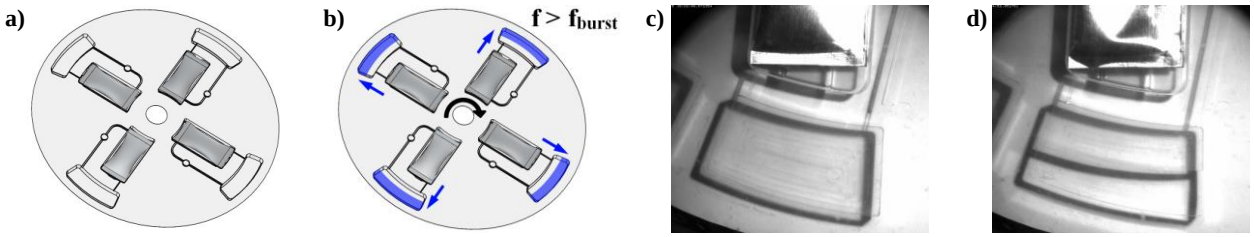

Figure 1: (a) Lab-on-a-chip cartridge with pre-stored liquid reagents in stick-packs. (b) Release of the liquid is done by centrifugation above the burst pressure frequency. (c) Stick-pack before and (d) after delamination of the peel-seal.

Also for a pressure driven platform the novel stick-pack reagent pre-storage concept has been reported [3]. This system released liquids by pushing a flexible membrane through pneumatic pressure onto the stick-pack. However, the permanent and peel-seals were so far manufactured manually using ultrasonic-welding, a process that is challenging to automate. Here we demonstrate fully automated, cost-efficient fabrication by thermal sealing resulting in significantly reduced cycle times and improved precision.

EXPERIMENTAL

A commercially available stick-packaging machine (SBL50, Merz Verpackungsmaschinen GmbH, Germany) was modified by adapting the forming and sealing station to obtain miniaturization of stick-packs. This resulted in stick-packs with widths of 9 mm or 15 mm and variable lengths from 10 to 100 mm. The used composite foil consisting of 12 µm polyethylene terephthalate (PET), 9 µm aluminum

and 70 µm polyethylene (PE) (JG Service AG, Germany) enables peelable sealing. Sealing strength was adjustable by varying the sealing parameters temperature, pressure and duration.

The high-throughput manufacturing process is illustrated in Figure 2. For this work, deionized water and DNA extraction reagents (Magnamedics Diagnostics B.V, The Netherlands) were packaged fully automated in stick-packs. We demonstrated process reliability by fabricating batches of 2,400 parts with a cycle time of 1.5 seconds per stick-pack.

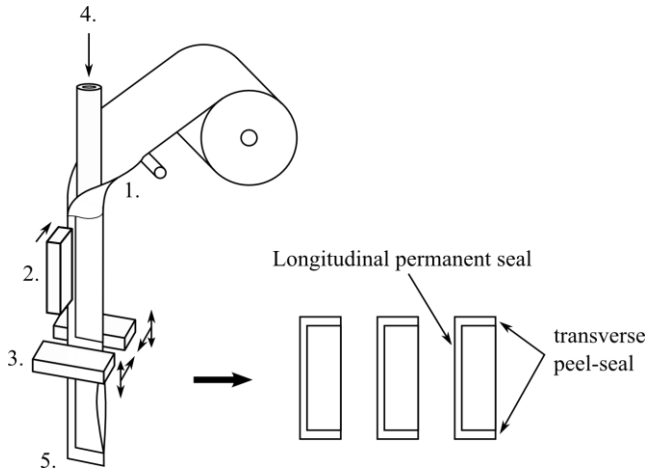

Figure 2: Setup for the automated production of stick-packs: 1. Forming of a tube of the composite foil. 2. Longitudinal permanent sealing. 3. Transverse peel-sealing. 4. Pump-induced dispensing of liquids. 5. Cutting.

RESULTS AND DISCUSSION

Stick-packs from the beginning and the end of a production cycle as well as randomly chosen parts were characterized for packaged liquid volume (CV < 1.0%, n=15), and dimensional characteristics (CV < 0.5%, n=15). In addition, liquid release by delamination of the peel-seal was tested by centrifugation at a radial position of r = 51 mm at different sealing temperatures (Fig. 3). Consequently stick-packs with different release frequencies can be fabricated enabling on-demand and sequential release of liquid reagents.

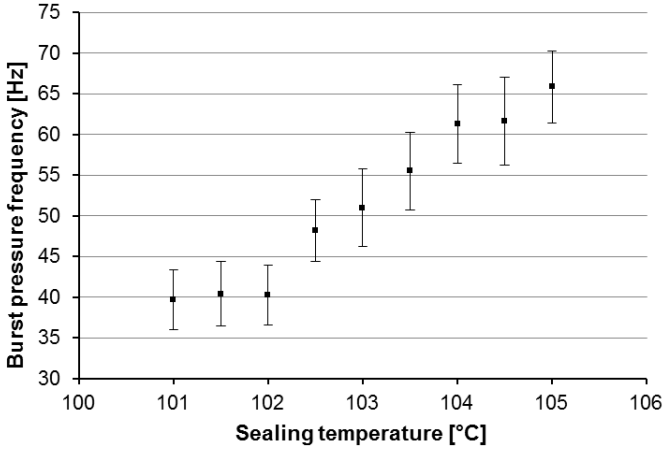

Figure 3: Burst pressure frequencies at variable sealing temperatures for stick-packs filled with 400 µl deionized water. The stick-packs with a width of 15 mm were tested at a radial position of r = 51 mm. The corresponding CV ranges from 7.5% to 9.7% (n=20).

Biochemical functionality of the DNA extraction reagents packaged in stick-packs was demonstrated on the centrifugal microfluidic platform. Automated purification of DNA from Salmonella Typhi (S. Typhi, Mast Diagnostica GmbH, Germany) spiked into whole blood was done using magnetic silica beads.

The DNA eluate obtained by this process was detected using loop mediated isothermal amplification (LAMP) (Fig. 4).

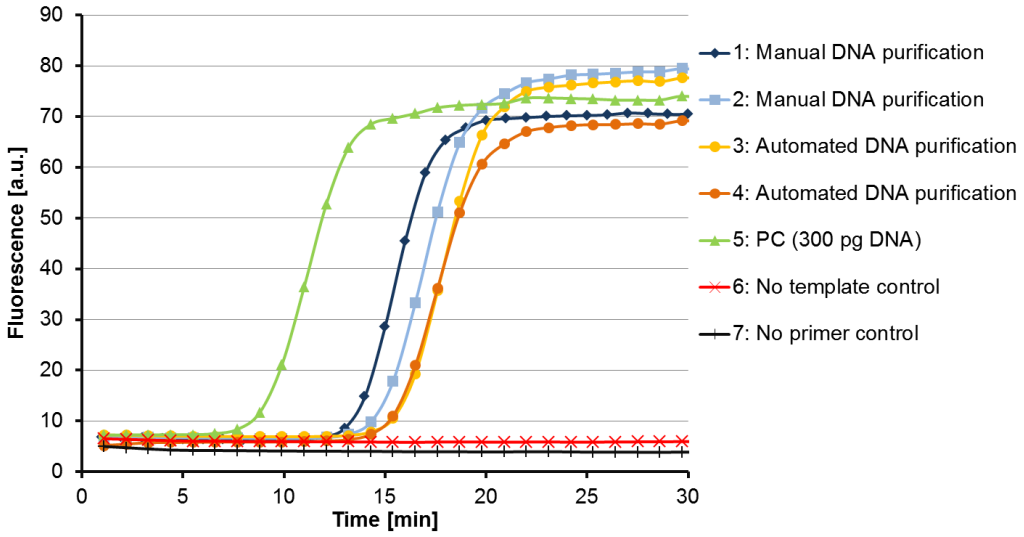

Figure 4: Result plot of LAMP to verify functionality of packaged reagents for DNA purification. Two whole blood samples (50 µl) spiked with plasmid DNA of S.Typhi (600 pg) were used for manual DNA purification with stock reagents and automated DNA purification on the centrifugal microfluidic platform LabDisk using the produced stick-packs, respectively. Successful amplification was detected with the DNA of both purification protocols, namely the manual DNA purification protocol (signal 1 and 2) and the automated DNA purification protocol with packaged reagents (signal 3 and 4). Positive control (signal 5) contained 300 pg plasmid DNA from S. Typhi. No template control (signal 6) and no primer control (signal 7) show no positive amplification result.

CONCLUSION

A reliable process with significantly increased production rate, volume accuracy and dimensional accuracy was demonstrated. We believe this will render stick-packaging to be the preferred technology for on-chip liquid reagent pre-storage in lab-on-a-chip disposables.

For future work, a gas inflation device will be implemented to inflate the stick-packs simultaneously to liquid dispensing. This enables the use of protective gas and a possible increase of the filling capacity.

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