

LTCC Based Microfluidic Structures for the Controlled Synthesis of Antioxidant Polymers

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Abstract:

Low Temperature Co-fired Ceramic (LTCC) based microfluidic structures have been designed and applied to the controlled polymerization of a new type of biomaterial, antioxidant polymers. Oxidation mediated tissue injury can occur due to the local accumulation of degradable byproducts of polymeric biomaterials. In order to avoid these effects, polymers composed of synthetic antioxidant Trolox have been synthesized. Trolox, released as a degradation product, can theoretically attenuate or prevent this material induced oxidative stress mechanism and site inflammation by providing slow antioxidant release. Despite success with the synthesis of oligomers of Trolox, the synthesis of longer chain polymers has represented a significant technological challenge.

The current paper reviews the fabrication and design of LTCC based microfluidic reactor modules and flow conditions required to provide improved control the Trolox polymerization process. Microfluidic channels have been fabricated using commercial LTCC materials and traditional LTCC processing technologies. Patterning of channels has been conducted using CNC micromilling and laser ablation tools. The application of computer assisted LTCC fabrication technologies has allowed a large degree of design flexibility and the rapid deployment of reactor design revisions. The proposed reactor utilizes three streams of co-laminar flow to allow for the controlled introduction of monomer and condensation pairs into the reaction stream. Reactor design and flow conditions have been refined to provide an improved method for control of the degree of polymerization and polydispersity in the product stream. This work demonstrates the inherent advantages of microfluidic based synthesis techniques for the production of highly customized polymeric materials.

Keywords: Microfluidic, LTCC, Trolox, Biomedical devices

Introduction:

Microfluidics is the science and technology of designing and manufacturing devices that manipulate small volumes of fluids on the order of nanoliters. Scaling down fluidic processes to the microscale offers precise control and rapid analysis of small amounts of precious samples and reagents, high selectivity and sensitivity in separations and detections, low cost, and short analysis time [1]. The laminar flow behavior of fluids in microchannels enables precise control of mixing and metering of multiple streams of fluids and exploitation of the interfaces between them [2]. Integrated microfluidic devices (known as “lab-on-a-chip” or “micro total analysis systems”) incorporating these advantages have generated considerable interest for a wide range of applications from biological and chemical analysis to molecular and medical diagnostics [3].

A microfluidic approach to chemical synthesis may enable the development of novel reactions or processing conditions due to the unprecedented control of fluids at the microscale. Chemical reactions performed and controlled in microfluidic devices have been shown to provide superior results compared to those performed in macroscale systems [4, 5].

While it is thought that biodegradable polymers (e.g. poly(lactic acid)) can evade long term biocompatibility concerns through degradation, recent studies have found that the local accumulation of degradation byproducts can trigger radical forming, oxidation mediated tissue injury [6]. Trolox is a water soluble analogue of Vitamin E which can scavenge free radical oxidants. Trolox can theoretically attenuate or prevent biomaterial- induced oxidative stress and local inflammation by providing slow

antioxidant release through polymer degradation. One-pot polymerization of Trolox results in low molecular weight oligomers of Trolox with high polydispersity. Also, it results in formation of a side-product, N-acyl urea, preventing greater degrees of polymerization. The use of a micro-channel reactor for the polymerization of Trolox will: 1.)improve reaction yield by minimizing side reactions, 2.)provide better control over the molecular weight of the polymer, and 3.) reduce the polydispersity of the synthesized polymer by operating in a continuous semi-batch type mechanism.

Microfluidic systems for chemical synthesis have been fabricated in a number of materials including silicon, glass, metal, and polymers [7]. LTCC materials and processing, used commercially for twenty years, were originally developed as a multilayer substrate electronic packaging technology for packaging integrated circuits [8]. Recently, use of LTCC materials for microfluidic systems has been developed to capitalize on the significant advantages offered by this technology. LTCC utilizes a layered assembly process and is compatible with wide range of metallic and ceramic materials, making LTCC a logical choice for the integration of 3-D structures and multifunctional materials. As a true packaging technology, LTCC modules are more robust and durable than polymeric substrates and there is no need for an additional protective envelope, as required for Si-Based microsystems. Finally, the layer manufacturing process utilized for LTCC allows design changes in a single layer to be rapidly incorporated into the final device, leading to short development time and low cost production [9, 10]. The chemical inertness, temperature and pressure stability, solvent compatibility, and ease of fabrication and integration suggest that low temperature co-fired ceramic (LTCC) materials and fabrication processes are appropriate for the current purpose.

The commercial LTCC process begins with flexible “green tapes” composed of ceramic particles, glass frits, and organic binders. LTCC tapes can be easily patterned in the “green” state (before firing) and become rigid once fired. Fig.1 shows the typical LTCC fabrication process. Traditionally, electrical circuitry and interconnects are produced by punching and filling electrical via holes, followed by screen printing of conductor, resistor and capacitor inks on each layer of “green” tape. The individual layers are then stacked and laminated at the manufacturers recommended pressure and temperature. The laminated stack is then cofired, to remove organics and sinter the ceramic and electronic components into a dense monolithic ceramic part. Following co-firing additional electronic components may be soldered or

bonded on the surfaces. This processing route is extensively used for fabrication of RF components, microwave communication modules, and for packaging sensors and MEMS devices. Minor modifications to the LTCC process allow the integration of complex 3-D structures (e.g. cavities, reservoirs, beams, and microchannels) for microsystems and microfluidic devices [11].

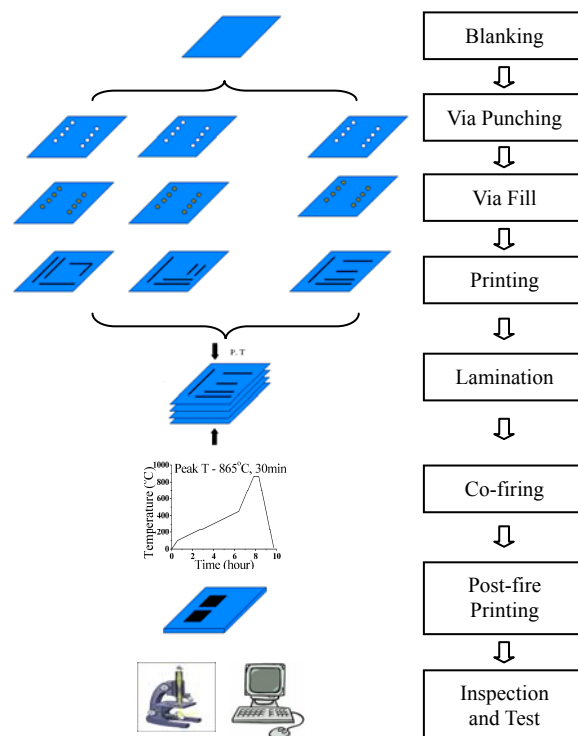


Fig.1 The commercial LTCC processing route.

In this study, microfluidic reactor modules have been fabricated using commercial LTCC materials and modified LTCC processing technologies. The designed reactor utilizes three streams of co-laminar flow to allow for the controlled introduction of Trolox and condensation pairs (DCC and DMAP) into the reaction channel. A schematic diagram of the microchannel reactor is shown in Fig.2. Optimization of the reactor design and flow conditions will provide improved control of the degree of polymerization and polydispersity in the product stream.

Experimental Procedure:

Sample preparation: (±)-6-Hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox), *N,N'*-Dicyclohexylcarbodiimide (DCC), 4-(Dimethylamino)pyridine (DMAP) and acetone were purchased from Sigma-Aldrich and used as it is without further purification. Trolox, DCC and DMAP were dissolved in acetone at 20, 18.14 and 9.76

mg/ml respectively. All reagent solutions were freshly prepared just before the experiment was conducted.

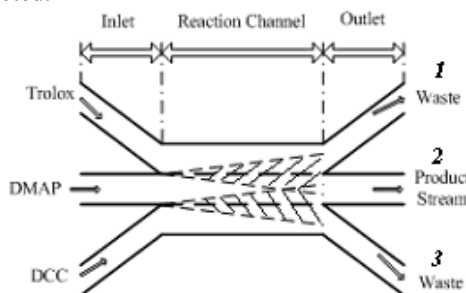


Fig.2 Illustration of synthesis conditions via co-laminar flow in a microfluidic reactor.

LTCC fabrication process: The fabrication process for LTCC microfluidic systems has been modified from the typical LTCC process. Starting from the initial CAD design, channels and cavities on each layer were patterned mechanically by CNC machining or chemically by laser ablation. Individual layers were then aligned and stacked sequentially, laminated using a uniaxial press, and finally co-fired to form the desired 3D structure.

In this study, Heraclon[®] HL2000 tapes (Heraeus Quartz America) with layer thickness of 360 μ m (3-layer stack) were used. The initial LTCC based microreactors consist of three layers: a bottom layer, an intermediate layer containing the microchannels (an S-shaped main reaction channel linked with three inlet/outlet channels) and reservoirs and a top layer containing the inlet/outlet ports (see Fig.3A). The designed microchannel dimensions were 300 μ m deep by 1350 μ m wide for the reaction channel and 450 μ m wide for each of the six inlet and outlet channels. These dimensions were confirmed by optical microscopy of sintered parts (see Fig.3B).

The final 3D structure of microreactor was designed in a CAD program (AutoCAD[®] 2007) and was then sliced into individual layers, containing the required features, for output to either the micromilling or laser ablation tool. The design step typically must account for shrinkage in each of the x, y and z directions during the sintering process. However, constrained sintering LTCC materials exhibit nominal sintering shrinkage in the x, y directions (in the plane of the tape). This allows for “near net shape” fabrication in which the patterned feature dimensions are conserved in the final sintered component. In the current work self-constrained Heraclon[®] tapes (Heraeus) were used. These tapes exhibit sintering shrinkage in x, y direction of less than 0.2%, however the large z (thickness) shrinkage of 32% needed to be considered.

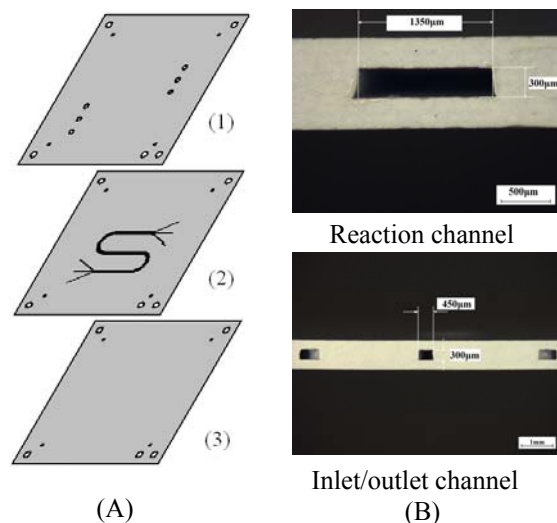


Fig.3 (A) Design of layers used to fabricate the LTCC microfluidic reactor; (B) feature dimensions of sintered microchannels.

A CNC micromilling machine (FP-21T, MITS Electronics) and a CO₂-Laser system (VLS 3.50, VersaLASER[®]) were utilized to transfer the designed patterns, alignment holes and fiducial marks to “green” tapes simultaneously. The size of features fabricated using CNC machine is mainly determined by the diameter of tool. End mills with diameter of 530 μ m were used and milling speed was 3mm/sec. The same or smaller feature sizes could be achieved by using laser machine.

Alignment of individual layers was implemented using a fixture with five registration pins and corresponding holes in the corner of each patterned layer. A uniaxial hydraulic press (3851-0, CARVER[®]) with temperature controllable platen was used for the lamination process. The stacked layers placed between the heated platens (75°C) and pressed first at 200psi for 3 minutes and then at 1500psi for 10 minutes. Finally, the laminate was sintered at 865°C for 30 minutes on a flat alumina setter in a box furnace (Isotemp[®] Programmable Muffle Furnace, Fisher Scientific) in air atmosphere using recommended firing profile.

Fluidic connections were made using polypropylene Luer connectors (Small Parts) and Teflon tubing (Fisher Scientific) with inner diameter of 3/32 inches. Inlet and outlet connectors were epoxied (Devcon[®]) to the ceramic module and connected with Teflon tubing.

Polymer synthesis and detection: Microchannels, reservoirs and connectors were primed with acetone before infusing reactant solutions. Trolox (Tx), DMAP, and DCC solutions were loaded into three 1ml medical syringes

(Henke-Sass, Wolf GmbH) and injected through syringe pumps (210, Kd Scientific). Flow rates for the three streams were equivalent, with total flow rates equaling 300 $\mu\text{L}/\text{min}$, 600 $\mu\text{L}/\text{min}$, and 900 $\mu\text{L}/\text{min}$. In order to quench the reaction, outflow samples were flash-frozen using liquid N_2 as soon as they were collected and stored in microcentrifuge tubes (500 μL) for further analysis. The microreactor was rinsed by acetone after the experiment. All samples were centrifuged to remove precipitated urea and the supernatants were analyzed using Gel Permeation Chromatography (GPC, Shimadzu Prominence LC-20 AB HPLC system, with waters 2410 refractive index detector.).

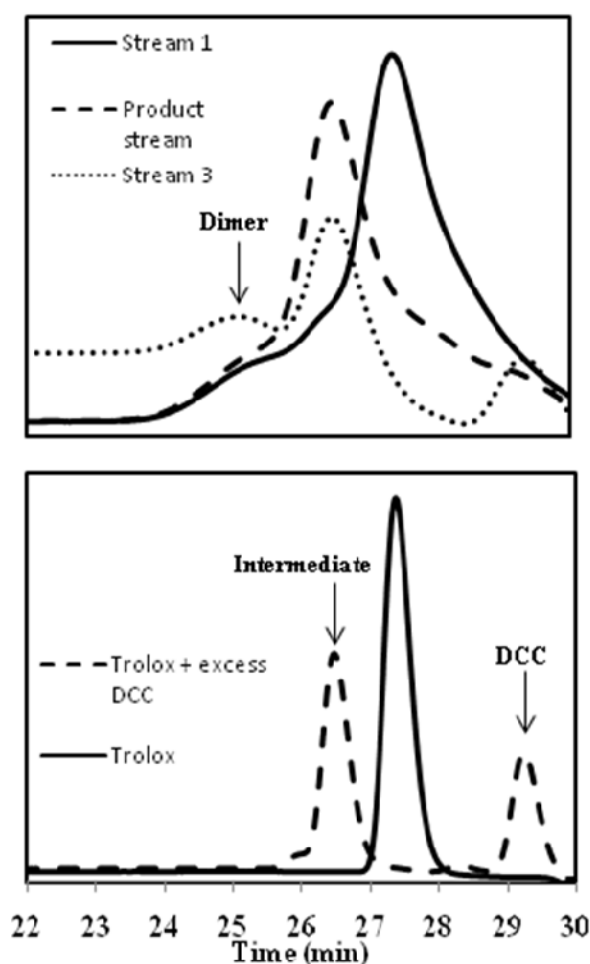


Fig. 4 Chromatograms of samples collected from output streams at 300 $\mu\text{L}/\text{min}$ (top). All three streams demonstrate presence of Trolox dimer, indicating mixing between streams. Peak identification was obtained by comparing to reference peaks of the pure reactants (bottom).

Results and Discussion:

At the flow rates of 300, 600 and 900 $\mu\text{L}/\text{min}$, the calculated residence times based on volume of the microchannel were 6.9, 3.4 and 2.3 sec respectively. When DCC is added in excess to trolox, it results in formation of a Tx-DCC intermediate. A GPC peak at ~ 26.4 min corresponds to this intermediate. Chromatograms of output streams indicate that this intermediate is present in all three streams, as shown in Fig 4. A peak at ~ 25 min corresponds to the dimer. Chromatograms obtained from samples of product stream using 600 and 900 $\mu\text{L}/\text{min}$ (data not shown) were identical to the chromatogram in Fig 4. If we assume that dn/dc (i.e. change in refractive index with respect to concentration) values for all reactants and products are the same, then a ratio of, area under a peak to total area, should be equivalent to its mass ratio.

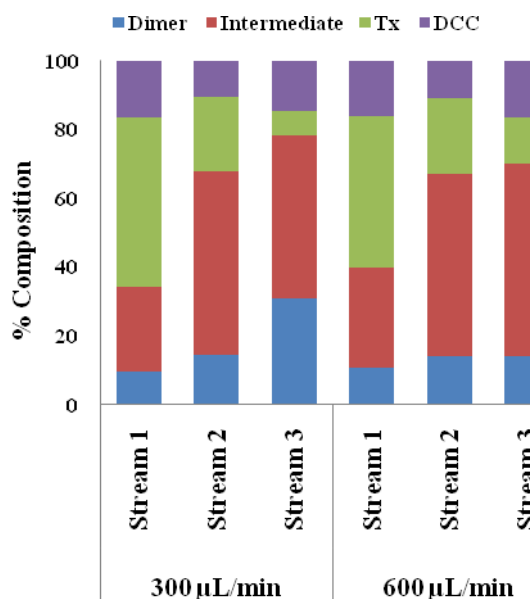


Fig. 5 Output Stream composition for flow rates of 300 $\mu\text{L}/\text{min}$ and 600 $\mu\text{L}/\text{min}$, as determined by relative chromatographic peak area. Stream 2 is the desired product stream.

At all flow rates, the dimer, and intermediate were similarly distributed across all 3 streams, as shown in Fig 5. These results indicate a similar reaction profile. Similarly, DCC was distributed almost evenly in all the three streams.

It was hypothesized that the lack of residence time dependence on the extent of reaction was likely due to too slow polymerization kinetics. Kinetics of Trolox polymerization were investigated by monitoring the turbidity of the solution in a single pot reactor. Initially turbidity will increase as the

reaction progresses, as the by-product dicyclohexyl urea precipitates out of solution. Turbidity of solution was monitored at a wavelength of 450 nm using a Varian Cary 50 Bio UV-Vis Spectrophotometer. At trolox, DCC and DMAP concentrations of 15, 13.6 and 7.32 mg/ml respectively, turbidity of solution started increasing gradually after ~ 2.5 min (Fig. 6). Interestingly, while the carbodiimide ester conjugation proceeds over a rate of minutes, the formation of the DCC-trolox intermediate is extremely fast, occurring well within 3.4 seconds.

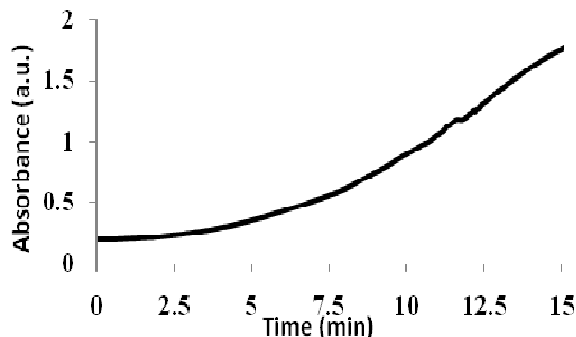


Fig. 6 Turbidity of trolox polymerization reaction mixture monitored at 450 nm.

Conclusions:

The absence of any high molecular weight peaks, as determined from GPC results, suggests that the residence time was insufficient for esterification of trolox. Results do however indicate rapid formation of trolox-DCC intermediate, which is a precursor for esterification of trolox. This is an indication that higher residence times should result in formation of high molecular weight products. Therefore, increased the residence times, on the order of 5 minutes, can result in a higher molecular weight polymer synthesis. Revised reactor designs suggest a reactor length of 3 meters can easily be fabricated in a planar 3"x3" LTCC module. This revised design will allow residence times appropriate for trolox polymerization, as indicated by kinetics results.

The results obtained from the LTCC microfluidic reactor developed in this work clearly indicate the promise of this approach for the controlled synthesis of biomaterials. The precise control of the reaction time and ability to separate and analyze reactant and product output streams separately allowed detailed analysis of reaction kinetics, mass transfer rates, and flow dynamics. Based on these findings an improved reactor design has been suggested which will enable controlled synthesis of synthetic anti-oxidant Trolox polymers.

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