Ultrahigh Speed Femtosecond Laser Fabrication of Numerous Glass Micro-chambers for Molecular Analysis

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Quantitative measurements of trace number of targets in biochemical samples are essential in the early detection and monitoring of various pathogens and genetic variants. Real-time polymerase chain reaction (PCR) has been under continuous development for decades and found widespread applications in clinical molecular diagnostics. Compared to conventional real-time quantitative PCR (qPCR), digital PCR (dPCR) features partitioning biochemical samples into numerous chambers for independent PCR reactions, which shows significant advantages in sensitivity and quantification. Owing to the nature of statistics, dPCR requires tens of thousands of micro-chambers for accurate quantification. Among various material platforms for the micro-chambers, glass provides outstanding properties such as high biocompatibility, low fluorescence, and flexibility for surface modification. However, high-quality, high-speed micro-fabrication of numerous micro-chambers in glass is challenging to conventional fabrication methods. Here we apply femtosecond laser with axicon lens to efficiently fabricate an array of chambers with nano litter volume on glass substrate. Femtosecond laser pulses at repetition rate of several hundred Hz are focused onto glass substrates with a thickness of 300 μm at a scanning speed of several centimeters per second such that a single pulse is separately irradiated at each spot. Irradiated spots are then treated with selective wet etching using hydrofluoric acid (Figure (a)). A chamber array with 20 000 though-holes with a diameter of ~100 μm can be typically fabricated within 5 minutes without micro-cracking (Figure (b)). Such a glass chip enables simple reagent loading within several seconds and can contribute to the simplification and accessibility of dPCR tests (Figure (c)).