Microfluid Nanofluid (2010) 9:995–1001
DOI 10.1007/s10404-010-0611-6

SHORT COMMUNICATION

A gravity-actuated technique for flexible and portable microfluidic droplet manipulation

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Received: 25 January 2010 / Accepted: 25 March 2010 / Published online: 8 April 2010

Abstract In this study, an inexpensive and robust microfluidic droplet manipulation device based on gravity-actuated technique is described. The device is mainly composed of a turntable and some disposable infusion sets. The movement of oil-phase and water-phase in the microchannel is controllable. Droplet volume of different sizes is precisely generated by controlling droplet length using the turntable. A series of essential functional units have been demonstrated including on-demand sampling, droplets generation of controllable size and controllable number, droplets fusion of different sizes and contents, even droplets-stopping. These functions can well meet the requirements of routine droplet-based microfluidic biological/chemical assays, cell research, and high content drug screening. The presented technique shows unique advantages in inexpensiveness, flexibility, and portability when compared with general droplet manipulation systems containing precision syringe pump and complicated micromechanical/pneumatic valve. Furthermore, this device can be used as a portable droplet manipulation tool in outdoor and remote areas, because it does not need electrical source and is very facile to set up in any place.

Keywords Microfluidic · Droplet · Gravity · Manipulation · Technique

Electronic supplementary material The online version of this article (doi:10.1007/s10404-010-0611-6) contains supplementary material, which is available to authorized users.

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1 Introduction

Droplet-based microfluidic systems have attracted increasing attention in the past 10 years due to its remarkable advantages in miniaturized bio-analytical and chemical field (Song et al. 2006; Fair 2007, Teh et al. 2008; Huebner et al. 2008a, b; Zhang et al. 2008, Chiu et al. 2009). A series of droplet-based microfluidics successful applications have been reported, including chemical reaction (Cygan et al. 2005), synthesis of micro- and nano-particles (Tan and Takeuchi 2007; Rondeau and Cooper-White 2008; Um et al. 2008; Prasad et al. 2009), cell sorting (Baret et al. 2009) and assay (Clausell-Tormos et al. 2008), enzyme assay (Srinivasan et al. 2004; Huebner et al. 2008a, b; Wang et al. 2009a, b), and drug discovery (Zheng et al. 2003; Dittrich and Manz 2006). All the above applications are based on the mature droplet manipulation technique, therefore it is crucial whether droplets are precisely manipulated or not.

Essential droplet manipulation technique mainly includes droplet generation, transport, fusion, and mixing. Usually precise syringe pump and syringe needle are necessary for droplet generation by T-junction (Garstecki et al. 2006) or flow-focusing configuration (Anna et al. 2003). Although the method shows extremely good capability in

obtaining monodisperse droplets (Thoren et al. 2001; Yobas et al. 2006), it lacks flexibility in the process of droplet manipulation. Therefore, a series of styles, including passive and active, for enhancing flexible performance have been developed. According to the principles of fluid dynamics, microchannel structures with specific function have been successfully designed and fabricated for the control of droplet fission, fusion, mixing, and sorting (Song et al. 2003; Tan et al. 2004; Tan et al. 2008; Maenaka et al. 2008). The main shortage of passive style chips is difficult to integrate multiple functional units into a chip although relatively easy to fabricate. For the active style chips, droplets are manipulated by external force mainly including valve actuation force (Lin and Su 2008) and electrical force (Velev et al. 2003; Xu and Attinger 2008). Microvalve is a highly efficient tool to precisely and flexibly control the generation, size, composition, and fusion of droplets in microfluidic devices (Sassa et al. 2008; Lee et al. 2009; Zeng et al. 2009). Although it does not require the precise control of fluid velocity, syringe pumps controlled by computers are still necessary. Another important approach for flexible droplet manipulation is to integrate microelectrodes into chips (Zeng and Korsmeyer 2004), including dielectrophoresis (DEP) (Jones et al. 2001; Gascoyne et al. 2004) and electrowetting on dielectric (EWOD) (Moon et al. 2002; Cho et al. 2003). The size and uniformity of the droplets depend on the magnitude and the frequency of the applied voltage. By the technique, some essential functional units have been demonstrated including creating, transporting, cutting, and merging. However, the complexity of chip design and fabrication are greatly increased by the integration of electronic components.

In addition to the methods mentioned above, other active droplet manipulation techniques have also been developed including magnetic force (Shikida et al. 2006; Pipper et al. 2007; Zhang et al. 2009), optical force (Chiou et al. 2003), surface acoustic wave force (Franke et al. 2009), and thermocapillary force (Darhuber et al. 2003; Glockner and Naterer 2005). Most of them are either lack in enough flexibility to meet diverse requirements of droplet manipulation, or make chips too complicated to fabricate for common laboratories due to integrating micromechanical/pneumatic valves and electronic components into devices. Furthermore, outdoor operation and application are greatly limited by bulky and expensive external control facilities.

Gravity is economical and easy to use (Yamada et al. 2008), which provides an alternative method for droplet manipulation. However, for most of published papers in relation to droplet manipulation, playing as a driving force, gravity is just like a pump (Huh et al. 2007) and fluid flow velocity is difficult to adjust (Liu et al. 2008). These passive droplet manipulation methods lack independence and flexibility. Herein, we first systematically present a facile and robust gravity-actuated technique for active flexible microfluidic droplet manipulation. The overall process, from sampling to on-demand droplets generation, transport, collision, fusion, mixing, and stopping, is accomplished by the technique. The necessary driving force of promoting fluids movement in the microchannel is provided by the gravity of oil-phase (silicon oil) stored in a reservoir. And all the reservoirs are hanged on both the sides of a turntable which is used to adjust the height difference between reservoirs and chips. The main advantages of this system are the capabilities for meeting the requirements of flexible droplet manipulation as well as completely eliminating the demand of electrical resource, complicated fabricate techniques, and bulky external control facilities.

2 Experimental section

Standard PDMS (Sylgard 184 polydimethysioxane silicone elastomer, Dow Corning, USA) fabrication techniques were used to fabricate microchips (Duffy et al. 1998) and all the depth of microchannels were 100 μm. Before use, the chips were left at 100°C for 2 h to ensure full recovery of the PDMS hydrophobicity. Dimethylsilicon oil (with dynamic viscosity at room temperature of 35 mPa s and a density of 950 kg m^{-3}, purchased from Hangping, China) as oil-phase was filtered through a 0.22-μm Nylon membrane filter (Jinteng, China), and HP Inkjet inks of different colors (viscosity 2 mPa s) were used as water-phase. No surfactant was used in the experiment. The necessary gravity was provided through disposable infusion sets (each length 30 cm, OD 4 mm, and ID 3 mm, provided by hospital) filled with oil-phase. PTFE tubings (each length 5 cm, OD 1.4 mm, and ID 0.6 mm, purchased from Xingchen, China) used to store water-phase (samples/reagents) were inserted directly into the PDMS holes connected with the channels. The diameter of PTFE tube was slightly larger than that of PDMS hole (1.2 mm). Since PDMS has excellent elasticity, no leakage phenomenon is observed. Images were obtained and analyzed using a CCD (Daheng, China).

3 Results and discussion

Precision syringe pumps and syringes are commonly considered to be the essential tools in microfluidic-based droplet generation. Both sampling and droplets generation are accomplished only by gravity through the technique, which completely eliminates the use of any syringe pump/syringe and also further reduces the demand of samples/reagents volume. Oil-phase is first loaded into disposable infusion sets, and then water-phase (samples/reagents) is pumped and stored into PTFE tubing by utilizing the gravity of oil-phase

(see Fig. 1a). The method of sampling is easy to operate and the consumption of samples/reagents volume is extremely decreased by reducing the diameter of the PTFE tubing (typical volume consumption between 1 and 30 μl). Usually a drop of sample/reagent (~20 μl) is enough in the experiment. After sampling, the two reservoirs are hanged on both the sides of the turntable (diameter 7 cm) with the same length of Nylon line (each 10 cm, see Fig. 1b). The turntable fixed on a plastic board can be smoothly turned to left/right manually with a screwdriver. Each inlet is manipulated by individual reservoir.

The main principle of this technique is that the size of fluid pressures (P, Pa), including oil-phase (P_O) and water-phase (P_W), at the T-junction can be varied quickly and precisely by turning the turntable to left/right. When water-phase height difference (Δh_W, m) is higher than that of oil-phase (Δh_O, m), the droplets are generated. We call this state switch-on. According to the Pascal's expression:

$$P = \rho g \Delta h \tag{1}$$

where ρ is the fluid density (kg m^{-3}), g is the gravity acceleration (m s^{-2}), and Δh is the height difference

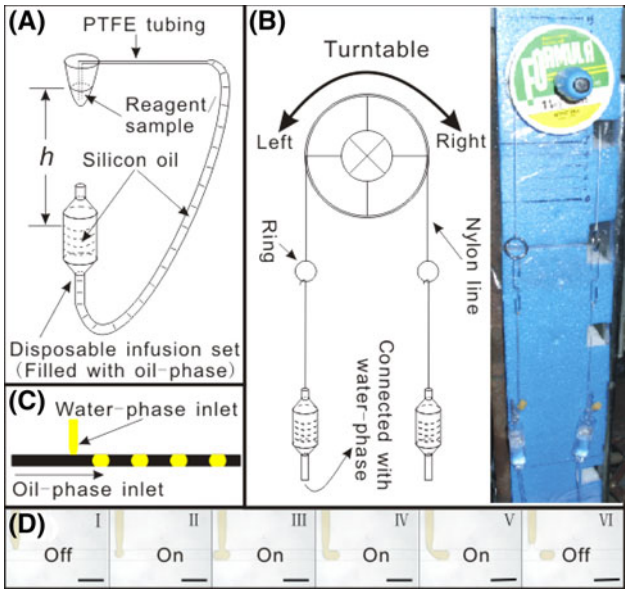

Fig. 1 Schematic diagrams of the gravity-actuated technique for microfluidic droplet manipulation. **a** Oil-phase (silicon oil) is first filled into a disposable infusion set. Then water-phase (reagents/samples) is easily pumped and stored into PTFE tubing by utilizing the gravity of oil-phase. **b** Experimental manipulation platform only includes a turntable, a vertical plastic board, several disposable infusion sets, rings, and Nylon lines. Two reservoirs are, respectively, hanged on both the sides of the turntable and one of them connects to the PTFE tubing loaded with water-phase. Droplets are generated only by turning the turntable to right/left. **c** Design of microchip 1 of two inlets. **d** Sequential microscope photographs of droplet generation. $P_W > P_O$ represents the state of switch-on, namely droplet generation, and $P_W < P_O$ represents the state of switch-off, namely no droplet generation. The longer the state of switch-on, the larger the droplets volume would be. *Scale bar* 400 μm

between the reservoir and channel (m). P is proportional to Δh. Therefore, $P_W > P_O$ (or $\frac{P_W}{P_O} = \frac{\Delta h_W}{\Delta h_O} > 1$) represents the state of switch-on, namely droplet generation, and $P_W < P_O$ (or $\frac{P_W}{P_O} = \frac{\Delta h_W}{\Delta h_O} < 1$) represents the state of switch-off, namely no droplet generation (see Fig. 1d).

The sizes of droplets by this method are closely related to total flow velocity in the main channel (v_T, m s^{-1}), time period of the state of switch-on (t_{on}, s) and the size of $\frac{P_W}{P_O}$. However, the volume of each droplet ($V_{droplet}$, m^3) is difficult to be precisely controlled by managing t_{on} and $\frac{P_W}{P_O}$ simultaneously unless v_T matches well with the turntable sensitivity. Flow velocity (v, m s^{-1}) is described by Poiseuille equation (Morier et al. 2004; Liu et al. 2008):

$$v = PR^2/8\eta l \tag{2}$$

where R is the radius of fluid channel (m), η is the fluid viscosity (Pa s), and l is the length of fluid channel (m). Combining Pascal and Poiseille equations:

$$v = \rho g \Delta h R^2/8\eta l \tag{3}$$

We can see from the Eq. 3 that v is proportional to Δh and R^2 but inversely proportional to η. However, for a given liquid and a given microfluidic chip, the effects of variation of R and η on the experiments can be ignored because PDMS channels are perfectly wetted by oil-phase. Therefore, it should be possible to control v by manipulating Δh. When the turntable is fixed at a height, the total height difference (Δh_T, $\Delta h_T = \Delta h_O + \Delta h_W$) is always constant. So v_T ($v_T = v_O + v_W$) is also constant whether the state is switch-on or switch-off. The phenomenon has been verified by observing droplets movement. In the experiment, the typical v_T ranges from 0 (called droplet-stopping v_T) to 10^3 μm s^{-1} (called droplet transport v_T), and corresponding range of Δh_T and range of total fluid pressure (P_T, $P_T = P_W + P_O$) are 0–40 cm and 0–10^4 Pa, respectively. However, in order to precisely control droplet length in the channel ($L_{droplet}$, m), a relatively low flow velocity range (called droplet generation, v_T, 1–300 μm s^{-1}) is selected for droplet generation. Within the range of droplet generation v_T, the turntable has a good sensitivity and $L_{droplet}$ can be precisely controlled with the help of the standard scale. According to the theoretical analysis (Eq. 4), we find that $V_{droplet}$ can be quantitatively expressed by $L_{droplet}$ no matter what the state of droplet is "slug" or "plug" (see Fig. 2):

$$V_{droplet}\begin{cases} = \frac{1}{6}\pi L_{droplet}^3 \,|\text{slug}; & L_{droplet} \le H \\ \approx \frac{1}{4}\pi H L_{droplet}^2 \,|\text{slug}; & H \le L_{droplet} \le 2H \\ = \pi H^3 + 2H^2\left(L_{droplet} - 2H\right)|\text{plug}; & L_{droplet} \ge 2H \end{cases} \tag{4}$$

where H is the depth of microchannel (m). Therefore, $V_{droplet}$ of different sizes can be precisely generated by the

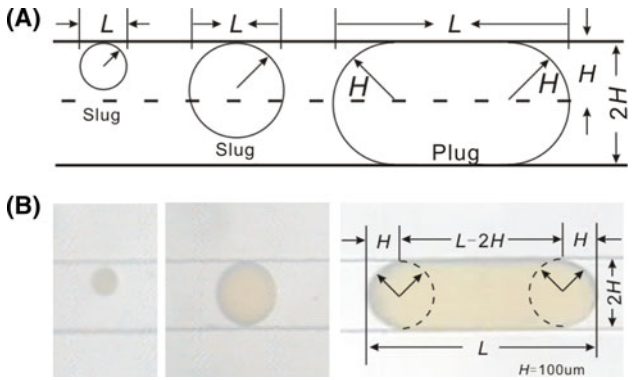

Fig. 2 The relationships between volume and length of droplets. **a** Schematic diagram of droplets of different sizes demonstrates that the volume of each droplet is proportional to its length. **b** Three microscope pictures of droplets in the microchannel

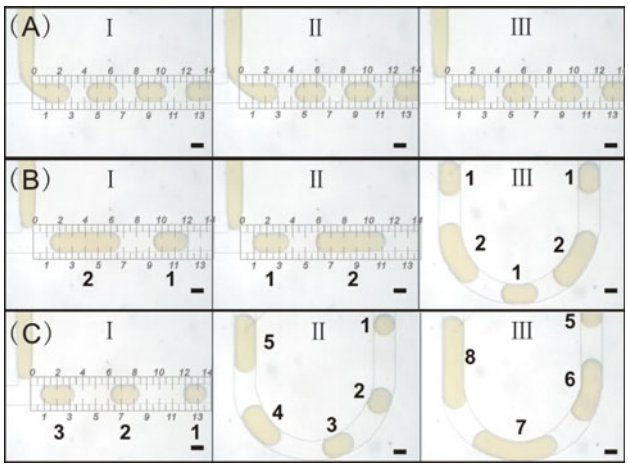

Fig. 3 Gravity-actuated technique controlled generation on-demand individual droplets. The length of each droplet is precisely measured with the help of the standard scale. **a** Droplets of the same size are steadily generated ($v_T = 83$ μm/s). **b** Droplets of two different sizes are generated continuously and alternately ($v_T = 165$ μm/s). **c** Continuous increase of the volume of individual droplets ($v_T = 220$ μm/s) The droplets marked with the same number have the same sizes in image (**b**, **c**), respectively. *Scale bar* 100 μm

control of $L_{droplet}$ using the turntable, and turning angle (θ) and t_{on} do not require repeatable manipulation during droplet generation. Typical θ of droplet generation ranges from $-45°$ ($\frac{P_W}{P_O} = 0.76$, no droplet generation) to $+45°$ ($\frac{P_W}{P_O} = 1.32$, droplet generation). Considering the combined effect of t_{on} and θ, the actual droplet generation frequency ranges from 0 to 30 droplets per minute and $V_{droplet}$ ranges from picoliter (10^{-12} l) to microliter (10^{-6} l). The approach for droplet manipulation is simple, flexible, and reproducible (RSD $< 5\%$). Moreover, no unwanted satellite droplets (Xu and Attinger 2008) are generated due to low values of the Capillary number ($Ca = v\eta/\gamma$, 0–3.75 $\times$ 10^{-4}, dimensionless) and low values of the Reynolds number ($Re = vl\rho/\eta$, 0–8 $\times$ 10^{-4}, dimensionless). Where v is the flow velocity in the channel (0–10^{-4} m s^{-1}), η is the fluid viscosity (35 $\times$ 10^{-3} Pa s), γ is the surface tension at the water-phase/oil-phase interface (20 $\times$ 10^{-3} N m^{-1}), l is the diameter of fluid channel (10^{-4} m), and ρ is the fluid density (0.95 $\times$ 10^3 kg m^{-3}).

Monodisperse droplets of the same length are obtained (see Fig. 3a; movie 1). The droplet generation technique is not only very simple but also flexible. On-demand individual droplets can be continuously generated, including alternate droplets of different sizes (see Fig. 3b; movie 2) and droplets of any size (see Fig. 3c; movie 3). As the state of switch-on/off can be varied easily and precisely, the number and spacing of droplets can also be well controlled to meet the requirements of a wide range of experiments. Moreover, droplets-stopping (at droplet-stopping v_T) at designated position in the microchannel is achieved by reducing the height of turntable (see movie 4), which allows in situ monitoring, real-time detection, and study of the biological/chemical assays process without need of a high speed camera (Wang et al. 2009a, b).

Droplets fusion is very important for droplet-based microfluidic system. Therefore, in addition to flexible way to generate individual droplets, as a practical droplet manipulation technique it should have the capability for highly efficient fusing two or more droplets of different reagents/samples. The gravity-actuated technique demonstrates a good ability in this aspect.

All four reservoirs are hanged on both the sides of the turntable and two of them connected with water-phase (1 and 2) are separated (see Fig. 4a). Microfluidic chip 2 of four inlets is fabricated and the connection between chip and tubings is showed in Fig. 4b. In order to clearly observe the fusion process of two droplets, red and yellow ink solutions are used to represent the different reagents/samples, respectively. No droplet is generated when the system is in the balance (namely the state of switch-off), i.e., $P_{O1} > P_{W1}$ and $P_{O2} > P_{W2}$. Red and yellow droplets are generated in sequence by turning the turntable to right firstly ($P_{W1} > P_{O1}$, $P_{O2} > P_{W2}$, only red droplet generation, see Fig. 4cII) and then left ($P_{W2} > P_{O2}$, $P_{O1} > P_{W1}$, only yellow droplet generation, see Fig. 4cIII). In order to ensure synchronous arrival of the two droplets to the microchannel expansion, P_2 ($P_2 = P_{O2} + P_{W2}$) should be slightly larger than P_1 ($P_1 = P_{O1} + P_{W1}$). P is inversely proportional to the length of Nylon line (l_N) which is easily implemented by adjusting connected circle, therefore l_{N2} ($l_{N2} = l_{NO2} + l_{NW2}$) is supposed to be shorter than l_{N1} ($l_{N1} = l_{NO1} + l_{NW1}$). The experimental results demonstrate that when the total difference of l_N is about 4 cm (namely $l_{NO1} = l_{NO2} + 2$ and $l_{NW1} = l_{NW2} + 2$), the two droplets almost simultaneously reach the expansion. The oval-shaped microchannel expansion (1000 μm in length

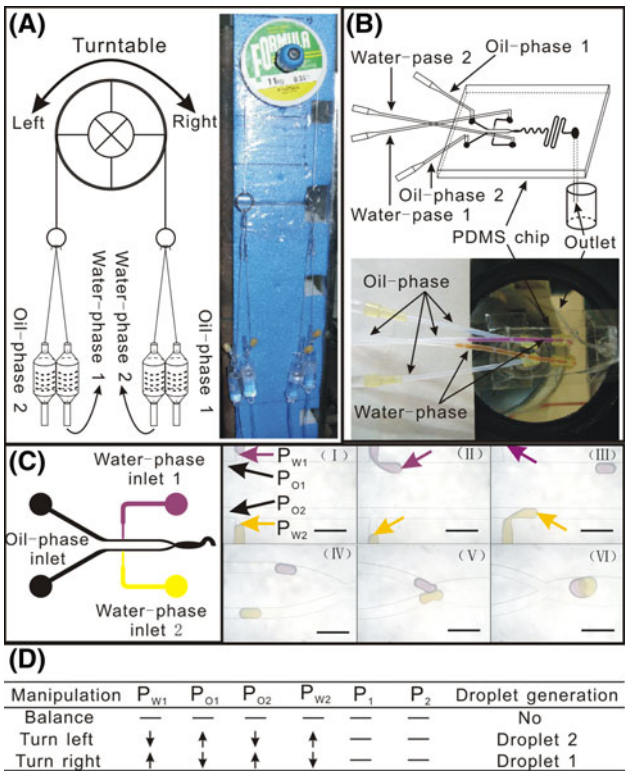

Fig. 4 Schematic diagrams of the gravity-actuated technique for droplet fusion. **a** Four reservoirs are averagely hanged on both the sides of the turntable, and two of them connected with water-phase (1 and 2) are separated. **b** Design of microchip 2 of four inlets and the connection between chip and tubings. **c** Two droplets containing different *colors* of ink solution are generated in sequence and then the collision and fusion occur at the expansion of microchannel. The main process includes balance (I), generation of droplet 1 (II), generation of droplet 2 (III), droplet transport (IV), droplet collision (V), and two droplets fusion (VI). The fluid pressures (P) at the position of droplet generation are shown by four *arrows*, respectively. *Scale bar* 400 μm. **d** The fluid pressures vary with turning the turntable. No droplet is generated when all the fluid pressures are in the balance ($P_O > P_W$). Droplets 1 and 2 are, respectively, generated when the turntable is turned to right first and then to left. P_2 is slightly larger than P_1, which ensure highly efficient droplets fusion. $P_1 = P_{W1} + P_{O1}$, $P_2 = P_{W2} + P_{O2}$. "—", "↑", and "↓", respectively, represent the fluid pressure in three states: "invariableness", "increase", and "decrease"

and 400 μm in width, see Fig. 4c) is specifically designed to increase the possibility of two droplets fusion. Since the shape changes from "plug" to "slug" and the flow velocity reduces, the opportunities of droplets contact with droplets increase when the droplets flow into the expansion. As no surfactant is added into the oil-phase, the two droplets will highly efficient fuse when they collide with together (see Fig. 4c; movie 5). The variation of fluid pressures has been listed in detail (see Fig. 4d).

The various mixed droplets of different concentration gradients are generated because the size of each droplet is precisely controllable. Here, blue ink and yellow ink are

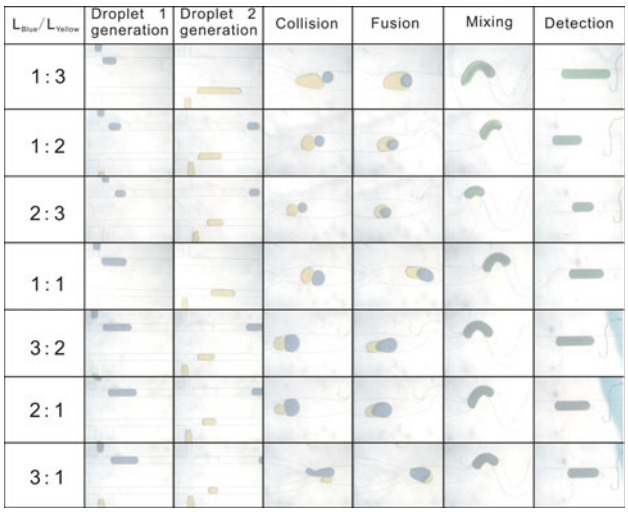

Fig. 5 The gravity-actuated technique for controlled on-demand fusion of two droplets. *Blue* and *yellow* droplets are generated in sequence, and then the collision and fusion occur since the two droplets almost simultaneously reach the expansion. After fully mixed in a serpentine microchannel, mixed droplets can stop at the designated position for detection. The mixed droplets of seven concentration gradients are rapidly obtained

used to represent different reagents/samples, respectively. Seven kinds of mixed droplets of different length ratios (L_{Blue}/L_{Yellow}) are continuously obtained, including 1:3, 1:2, 2:3, 1:1, 3:2, 2:1, and 3:1 (see Fig. 5). The described method is more simple and flexible when compared with other approaches generating droplets of concentration gradients (Lorenz et al. 2008; Damean et al. 2009). Moreover, the generation of array droplets of different compositions and sizes can also be simply implemented by our technique, which might promote the development of a cartridge approach so as to perform screening experiments (Li et al. 2007; Zeng et al. 2009).

As an alternative active droplet manipulation approach, the gravity-actuated technique offers obvious advantages in flexibility, simplicity, economy, and portability. However, limitations still exist in this technology. First, fast droplet generation is relatively difficult within the range of current turntable sensitivity. Secondly, owing to manual operation, it is hard to generate droplets for a long span of time. The two limitations may be easily resolved using a small motor (less than 10 dollars) which can precisely control turntable to-and-fro movement. Future work would include measures to increase the sensitivity of the system and also the use of real biological samples.

4 Conclusions

In summary, we have systematically presented a facile, flexible, and robust gravity-actuated technique for

microfluidic droplet manipulation. The total cost of the device is less than 1 dollar and a series of essential functional units have been demonstrated by our technique, including gravity-based sampling, droplets generation of controllable size and controllable number, on-demand fusion of two droplets containing different contents, even droplets stopping for end-point detection. All these can meet the requirements of routine microfluidic biological/chemical assays, cell research and high content drug screening. Since the overall system is simple to set up and related materials are very easy to obtain without involving any syringe pump/syringe, bulky external control facility or complicated fabrication technique, the device can also be used as a portable tool which may accelerate the application of droplet-based microfluidic systems in outdoor and remote areas.

Acknowledgments This research was supported by funding from National Basic Research Program (973 Program) of China (2007CB714505) and Ministry of Education of China (No. 20080031012).

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