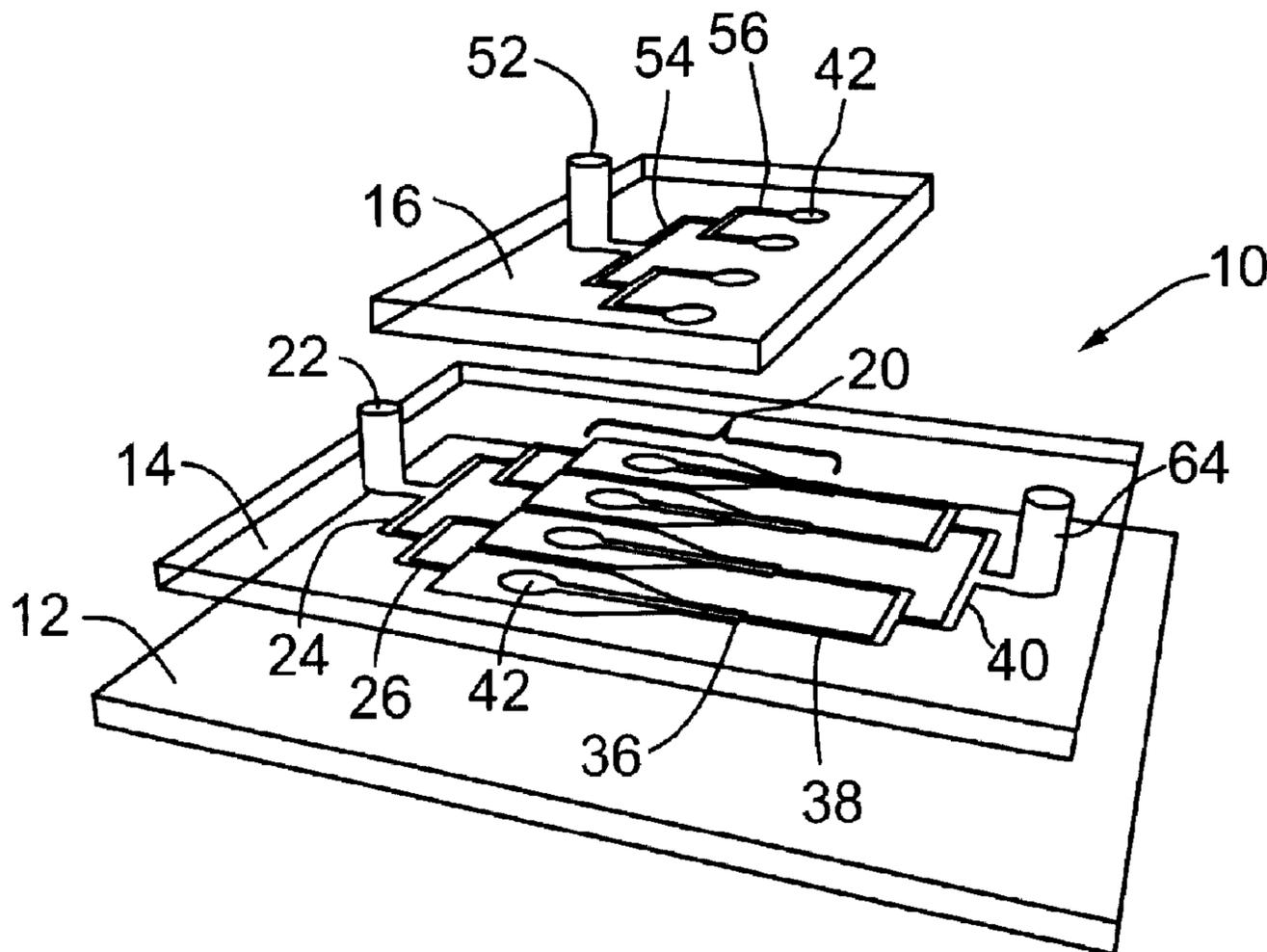




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(54) Titre : REACTEURS A MICROFLUIDES CONTINUS MULTIPLES PERMETTANT UNE SYNTHESE AMELIOREE DE PARTICULES DE GEL OU POLYMERES
 (54) Title: MULTIPLE CONTINUOUS MICROFLUIDIC REACTORS FOR THE SCALED UP SYNTHESIS OF GEL OR POLYMER PARTICLES



(57) **Abrégé/Abstract:**

This present invention provides devices for the parallelization of the formation of droplets in a multiple droplet generator integrating two or more parallel flow-focusing devices (FFDs) with either identical, or different, geometries. In the parallel identical FFDs, emulsification generates droplets with a narrow (below 4%) polydispersity despite weak coupling between the identical flow-focusing devices. Formation of droplets in the integrated droplet generator comprising FFDs with different dimensions of the microchannels occurs with strong coupling between the FFDs and produces droplets with varying sizes and size distributions. For such devices the regime in which emulsification produces droplets with varying dimensions and a narrow size distribution have been identified. The results of this work can be used in scaling up the production of droplets and in the simultaneous production of droplets and particles with different dimensions.



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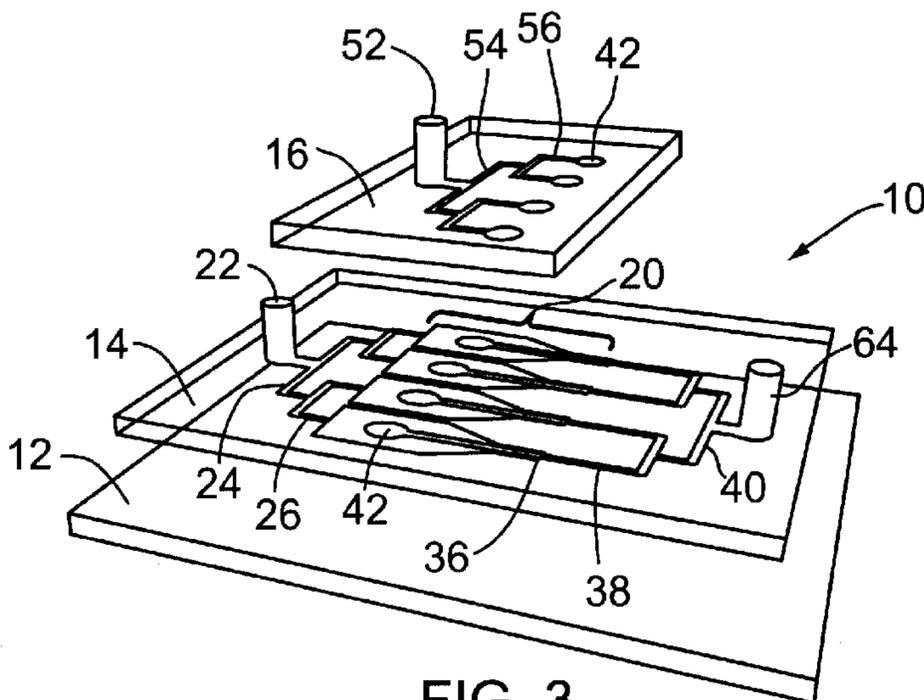


FIG. 3

(57) Abstract: This present invention provides devices for the parallelization of the formation of droplets in a multiple droplet generator integrating two or more parallel flow-focusing devices (FFDs) with either identical, or different, geometries. In the parallel identical FFDs, emulsification generates droplets with a narrow (below 4%) polydispersity despite weak coupling between the identical flow-focusing devices. Formation of droplets in the integrated droplet generator comprising FFDs with different dimensions of the microchannels occurs with strong coupling between the FFDs and produces droplets with varying sizes and size distributions. For such devices the regime in which emulsification produces droplets with varying dimensions and a narrow size distribution have been identified. The results of this work can be used in scaling up the production of droplets and in the simultaneous production of droplets and particles with different dimensions.

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MULTIPLE CONTINUOUS MICROFLUIDIC REACTORS FOR THE SCALED UP SYNTHESIS OF GEL OR POLYMER PARTICLES

5

FIELD OF THE INVENTION

The present invention relates to microfluidic reactors for parallel scaled up synthesis in droplets and methods of use. The microfluidic devices include multiple parallel flow-focusing droplet generators with an individual inlet and outlet and an integrated microfluidic reactor.

10

BACKGROUND OF THE INVENTION

Microfluidics is the science and technology of systems that process or manipulate small (10^{-9} to 10^{-8} L) amounts of fluids, using channels with dimensions of tens to hundreds of micrometers (see G. M. Whitesides. *Nature* 442, 368 (2006)). Over the last decade, a broad range of applications of microfluidics has been developed that included bioanalyses, syntheses of organic, inorganic, and bioorganic compounds, and the screening of conditions for protein crystallization.

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Recently, microfluidic syntheses of polymer particles with controllable dimensions, shapes, and structures have attracted significant industrial interest. Potential applications of the microreaction technology include the production of ion exchange resins, calibration standards, spacers for electrochromic windows, microbeads for chromatography and biomedical purposes, and for the encapsulation of liquid ingredients. Currently, the productivity of a single microfluidic reactor is on the order of grams/hour. It is unlikely that without a significant increase in the productivity of microfluidic reactors this technology will ever find major industrial applications.

5 Recently, microfluidic emulsification allowed for the generation of droplets with precisely controlled compositions, morphologies, and volumes. Synthesis performed in these droplets has attracted great interest in materials and polymer science, and proved useful in the chemical, pharmaceutical, food, nutrition, and cosmetics fields. Miniaturization of continuous chemical reactions by compartmentalizing them in droplets provided efficient heat and mass transfer, precise control of the timing of reactions, and the ability to synthesize and transport gaseous, liquid and solid reagents and products (see H. Song; D. L. Chen; R. F. Ismagilov. *Angew. Chem., Int. Ed.* 45, 7336 (2006)). The use of these droplets as microreactors has generated a rapidly growing field of research and led to a number of new technology platforms (see H. Song; D. L. Chen; R. F. Ismagilov. *Angew. Chem., Int. Ed.* 45, 7336 (2006); M. Seo; S. Xu; Z. Nie; P.C. Lewis; R. Graham; M. Mok; E. Kumacheva. *Langmuir* 21, 4773 (2005); and A. Gunther, K F. Jensen. *Lab Chip* 6, 1487 (2006)).

15 Presently, applications of droplets produced by means of microfluidics can be tentatively categorized in two groups, namely, “*discovery*” and “*development*.” The first group of applications aims at studies of fast reactions and processes in e.g., drug discovery, gene expression analysis, bioassays, and the optimization of formulations for chemical synthesis. These applications generally require reactions to be performed on a microscale, since reagents are generally expensive or are only available in limited amounts. The second group of applications embraces microfluidic synthesis and fabrication of new materials with specific and sometimes, unique properties. Examples of such materials include silica colloids, microgel capsules, and polymer particles with specific morphologies (see Whitesides, G.M., Stone, H. A. *Angew. Chemie, Intl. Ed.* 44, 724 (2005); (b) D. Dendukuri, K. Tsoi, T. A. Hatton and P. S. Doyle, *Langmuir* 21, 2113 (2005); S. A. Khan, A. Gunther, M. A. Schmidt, and K. F. Jensen, *Langmuir* 20, 8604 (2004); and (a) A. S. Utada, E. Lorenceau, D. R. Link, P. D. Kaplan, H. A. Stone, and D. A. Weitz, *Science* 2005, 308, 537 (2005); (b) Nie, Z.; Xu, S.; Seo, M.; Lewis P. C., Kumacheva, E. *J. Amer. Chem. Soc.* 127, 8058 (2005)).

Both groups of applications require multiple reactions and processes to be performed in parallel. For the second group, this requirement is vital: future progress in the development and production of new materials by microfluidic

synthesis will be determined by the ability to scale up their production in multiple parallel continuous processes.

Currently, two groups of conventional technologies are used for the production of polymer colloids in the range from tens to hundreds of micrometers. In the first group, namely suspension polymerization methods, polymer particles are obtained by polymerizing monomer droplets that comprise oil-soluble initiators (see E. Vivaldo-Lima, P. E. Wood, A. E. Hamielec *Ind. Eng. Chem. Res.*, 36, 939 (1997)). Droplets are produced by emulsifying liquid monomers in an aqueous phase in the presence of a stabilizing agent. Typically, particles obtained by suspension polymerization have a broad range of sizes, due to the insufficient control of the emulsification process and coalescence of droplets during their transportation to the reactor and in the course of polymerization. Generally, when a narrower distribution of sizes is required, the microbeads are fractionated. This time-consuming process leads to the loss of material. Although, membrane emulsification enhances droplet size distribution, coalescence of droplets in the course of polymerization still results in a broadened size distribution of the resulting particles (see G.-H. Ma, H. Sone, S. Omi. *Macromolecules* 37, 2954 (2004)).

The second group, is referred to as the multi-step swelling method (the Ugelstadt method, see (a) J. Ugelstad, K.H. Kaggerud, F.K. Hansen, A. Berge. *Macromol. Comm.* 180, 737 (1979); (b) J. Ugelstad, L. Söderberg, A. Berge, I. Bergström, *Nature* 303, 95 (1983)). This time-consuming process involves the synthesis of small "precursor" particles that are used as seeds for the multi-stage synthesis of larger microbeads. When a monomer is added to the dispersion of precursor particles, it partitions and swells the seed particles. Subsequent polymerization of the swollen beads yields particles with an incremental increase in size. In order to obtain particles with dimensions exceeding 50 μm , the procedure is repeated several times.

At present, the microfluidic production of polymer particles includes (i) microfluidic emulsification of monomers or liquid pre-polymers and (ii) *in-situ* hardening of droplets by on-chip free-radical or condensation polymerization. In contrast with conventional suspension polymerization, microfluidic synthesis in an *individual* microreactor produces particles with an extremely narrow size distribution, due to the specific mechanisms of microfluidic emulsification and

continuous “on-chip” polymerization of the droplets that prevents droplet coalescence. In addition, microfluidic polymerization yields particles with a range of precisely controlled shapes and morphologies.

5 A single microfluidic droplet generator typically has a productivity in the range from 10^3 to 10^6 droplets/hour, which corresponds to the productivity in particle synthesis. In order to favorably compete with conventional polymerization strategies, the generation of droplets has to be scaled up by producing them in multiple parallel droplet generators. Furthermore, to preserve the advantages of microfluidic emulsification, the droplets obtained in parallel
10 devices should maintain their narrow size distribution.

Scalable *polymerization* of polymer particles has been reported in sixteen individual microfluidic reactors with eight inlets for the monomer droplet phase and sixteen inlets for the continuous aqueous phase, that were placed in a concentric manner on a single microfluidic chip (T. Nisisako, T. Torii, T.
15 Takahashi, Y. Takizawa, Adv. Mater. 18, 1152-1156 (2006)). Although detailed analysis of the variation in sizes of particles produced in multiple microchannels has not been reported, the authors claimed that polymerization of monomer droplets yielded up to 20 g h^{-1} of particles with polydispersity 3 %. This device requires multiple (at least 16) syringe pumps to supply two liquids to each
20 microfluidic such that such a system is quite expensive.

The challenge in the scaled up microfluidic synthesis of polymer particles in multichannel microfluidic reactors is to preserve the advantages of synthesis in a single-channel microfluidic reactor: a narrow size distribution and controllable structure of particles, arising from the highly controlled microfluidic
25 emulsification and the high conversion of monomers, without a significant increase in the microreactor dimensions and the use of multiple pumps supplying liquids to each microreactor. The last two requirements can be satisfied requirements in a combined microfluidic reactor with two inlets for the droplet and continuous phases.

30 Multichannel microfluidic devices have been used for DNA separation, parallel PCR assays, detection of enzymatically-generated fluorescence and linear temperature gradients, capillary electrophoresis for immunoassays, and chiral separation (see Zheng, B.; Ismagilov, R. F. Angew. Chem., Int. Ed. 2005, 44, 2520; J. S. Marcus, W. F. Anderson, and S. R. Quake, Anal. Chem., 2006,

78, 956, A. T. Woolley, G. F Sensabaugh, and R. A. Mathies, *Anal. Chem.*, 1997, 69, 2181; Y. Shi, P. C. Simpson, J. R. Scherer, D. Wexler, C. Skibola, M. T. Smith, and R. A. Mathies, *Anal. Chem.* 1999, 71, 5354; H. Mao, T. Yang, and P. S. Cremer, *J. Am. Chem. Soc.*, 2002, 124, 4432; M. Herrmann, T. Veres, and M. Tabrizian, *Lab Chip*, 2006, 6, 555; Y. Gao, Z. Shen, H. Wang, Z. Dai, and B. Lin, *Electrophoresis*, 2005, 26, 4774; S.B. Cheng, C. Skinner, J. Taylor, S. Attiya, W.E. Lee, G. Picelli, and D.J. Harrison, *Anal. Chem.*, 2001, 73, 1472).

In these reports, emulsification in parallel combined microfluidic channels was not used. Typically, implementation of multiple droplet generators on a planar microfluidic chip entails experimental challenges such as an easy supply of liquids, realization of identical geometries of individual droplet generators, and controlled and reproducible flow rates of liquids in microchannels. Recently, several approaches to the production of droplets or plugs with identical or alternating composition were proposed that employed break up of liquid plugs at T-junctions, geometrically mediated breakup of droplets and flow-focusing devices placed *in a series* (see V. Barbier, H. Willaime, and P. Tabeling, *Phys. Rev. E*, 2006, 74, 046306; 26. B. Zheng, J. D. Tice and R. F. Ismagilov, *Anal. Chem.*, 2004, 76, 4977; B. Zheng, L. S. Roach and R. F. Ismagilov, *J. Am. Chem. Soc.*, 2003, 125, 11170; D. N. Adamson, D. M. John, X. J. Zhang, B. Zheng, and R.F. Ismagilov, *Lab Chip*, 2006, 6, 1178; D. R. Link, S. L. Anna, D. A. Weitz, and H. A. Stone, *Phys. Rev. Lett.*, 2004, 92, 054503; P. Garstecki, M. J. Fuerstman, H. A. Stone, and G. M. Whitesides, *Lab Chip*, 2006, 6, 437; P. Garstecki, M. J. Fuerstman and G. M. Whitesides, *Nat. Phys.*, 2005, 1, 168; H. Song, J. D. Tice and R. F. Ismagilov, *Angew. Chem. Int. Ed.*, 2003, 42, 768).

To date, a single report exists on the synchronization of formation of droplets in the device comprising *two parallel combined* microfluidic droplet generators with T-junctions with two inlets (see V. Barbier, H. Willaime, P. Tabeling. *Phys. Rev. E* 74, 046306 (2006)). The authors showed the broadening in droplet size distribution due to the parametric coupling between the individual devices, and, found that a narrow polydispersity of the droplets was achieved when emulsification in the two microchannels was synchronized.

In comparison with formation of droplets at T-junctions, the flow-focusing mechanism used in the present invention discussed hereinafter has higher emulsification efficiency and allows better control over droplet size and size

distribution. It is also not obvious whether the results obtained in two droplet generators can be projected to the *multichannel* device with *combined* microchannels; with an increasing number of microchannels, the requirement for synchronization between them may become problematic.

5 In addition to the scaled up synthesis of polymer particles, emulsification in parallel droplet generators is also important in fast-throughput screening of the effect of a particular event or variable in a chemical or physical process, e.g., in optimization of conditions of chemical reactions or in studies of the effect of the surface energy and geometry of the microfluidic device on the formation of
10 droplets.

SUMMARY OF THE INVENTION

 This present invention provides multiple continuous microfluidic reactors for parallel scaled up synthesis in polymer particles, and methods of use thereof.
15 The requirements of such synthesis include a high conversion (up to 98%) of monomer to polymer and the production of microbeads in the diameter in the range from 10 to 500 μm that also have a narrow size distribution and a well-defined structure.

 Accordingly, the present invention provides embodiments of a multiple
20 microfluidic droplet generator containing two or more parallel flow-focusing devices (FFDs), with a single overall inlet branching into multiple inlets associated with each of the flow-focusing devices depending on the number of FFDs in the generator, and a single outlet. Upon using FFDs with an identical design, the production of droplets is scaled up and the variation in their size
25 distribution is examined, in comparison with droplets formed in a single droplet generator. Using the FFDs with distinct geometries we simultaneously generate several populations of droplets with different volumes, yet a narrow size distribution. The results of this work can be used in parallelization (scaling up) of the production of droplets, as well as in simultaneous production of polymer
30 particles with different dimensions and fast throughput screening of the effect of droplet volume on polymerization reactions.

 Droplets produced in the multiple parallel droplet generators are used for chemical reactions. Activation of reactions occurs by applying heat, irradiation, electric or magnetic fields. For example, photoinitiated polymerization of

monomers is triggered by irradiating droplets with UV-light. For monomers undergoing fast polymerization, e.g. multifunctional acrylates, continuous polymerization is conducted on-chip in the integrated extension channel, as shown in **Figure 11** for an individual microfluidic reactor. For monomers

5 undergoing slow polymerization such as styrene in situ pre-polymerization is followed by post-polymerization in the of-chip additional extension channel (**Figure 11**). For such polymers, the rate of polymerization is additionally increased by using a mixed initiator approach: a monomer is mixed with a thermoinitiator and photoinitiator. Exothermic photopolymerization generates

10 heat which triggers thermoinitiated polymerization thereby increasing monomer conversion.

Thus, in one aspect of the present invention there is provided multiple microfluidic reactor for scaled up synthesis in emulsion droplets, comprising:

a) a first base sheet having a planar top surface;

15 b) a second sheet having:

i) relief patterns of a plurality of microfluidic flow-focusing devices, each including an inlet and an outlet,

ii) a relief pattern for a first inlet manifold distributor having a fluid inlet and microfluidic flow channels each in fluid communication with the first manifold fluid inlet and the inlets of the plurality of microfluidic flow-focusing devices,

20 iii) a relief pattern for an outlet manifold distributor connected to the outlets of the plurality of microfluidic flow-focusing devices, the outlet manifold distributor having a fluid outlet,

25 iv) said relief patterns being formed in a bottom surface of the second sheet,

v) each of said plurality of microfluidic flow-focusing devices having an opening in the top surface of the second sheet in flow communication with an interior of the associated microfluidic flow-focusing device; and

30 c) at least a third sheet having a relief pattern of a second inlet manifold distributor in a bottom surface of said third sheet, the relief pattern of the second inlet manifold distributor including an inlet and a plurality of microfluidic flow channels each in fluid communication with the second manifold fluid inlet and with one of said openings in the top surface of the second sheet when said third

sheet is assembled on a top surface of the second sheet with the bottom surface in physical contact with the planar top surface in sealing relationship, and wherein assembling the second sheet on the planar top surface of the first base sheet with the bottom surface in physical contact with the planar top surface in sealing relationship forms the plurality of microfluidic flow-focusing devices and the first inlet and outlet manifold distributors; and

d) wherein in operation two immiscible liquids, a droplet phase, **A**, and a continuous phase, **B**, are supplied to the first manifold fluid inlet and to the second manifold fluid inlet respectively, and wherein said two immiscible liquids **A** and **B** are forced through a narrow orifice in which a thread of liquid **A** breaks up and produces emulsion droplets.

In another aspect of the present invention there is provided a method for producing emulsion droplets, comprising the steps of:

a) providing a multiple microfluidic reactor for scaled up synthesis in emulsion droplets, comprising:

i) a first base sheet having a planar top surface;

ii) a second sheet having relief patterns of a plurality of microfluidic flow-focusing devices, each including an inlet and an outlet, a relief pattern for a first inlet manifold distributor having a fluid inlet and microfluidic flow channels each in communication with the first manifold fluid inlet and the inlets of the plurality of microfluidic flow-focusing devices, the first inlet manifold distributor having a fluid inlet, a relief pattern for an outlet manifold distributor connected to the outlets of the plurality of microfluidic flow-focusing devices, the outlet manifold distributor having a fluid outlet, said relief patterns being formed in a bottom surface of the second sheet, each of said plurality of microfluidic flow-focusing devices having an opening in the top surface of the second sheet in flow communication with an interior of the associated microfluidic flow-focusing device; and

iii) at least a third sheet having a relief pattern of a second inlet manifold distributor in a bottom surface of said third sheet, the relief pattern of the second inlet manifold distributor including a plurality of microfluidic flow channels each in fluid communication with a second manifold fluid inlet and one of said openings in the top surface of the

second sheet when said third sheet is assembled on a top surface of the second sheet with the bottom surface in physical contact with the planar top surface in sealing relationship, and wherein assembling the second sheet on the planar top surface of the first base sheet with the bottom surface in physical contact with the planar top surface in sealing relationship forms the plurality of microfluidic flow-focusing devices and the first inlet and outlet manifold distributors; and

5 b) supplying at least two immiscible liquids, a droplet phase, **A**, and a continuous phase, **B**, to the first manifold fluid inlet and to the second manifold fluid inlet respectively, and wherein said two immiscible liquids **A** and **B** are forced through a narrow orifice in which a thread of liquid **A** breaks up and produces emulsion droplets.

A further understanding of the functional and advantageous aspects of the invention can be realized by reference to the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the present invention are described in greater detail with reference to the accompanying drawings.

20 **Figure 1** is a schematic of droplet formation in an individual planar microfluidic flow-focusing droplet generator.

Figure 2 is a top-view of an individual droplet generator depicting the direction of fluid flow in the microfluidic droplet generator.

25 **Figure 3** is a 3D illustration of a microfluidic quadra-droplet generator (QDG).

Figure 4 is a top-view of the geometry of the microchannel relief patterns in the bottom surface of sheet **14**.

Figure 5 is a top-view of the geometry of the microchannel relief patterns in the bottom surface of sheet **16**.

30 **Figure 6** is a top-view of **Figure 4** showing a non-limiting example of dimensions (in mm) of microchannels in the quadra-droplet generator (QDG) fabricated in sheet **14**. In the present non-limiting embodiment, sheet **14** is 5 cm × 7.5 cm.

Figure 7 is a top-view of **Figure 5** showing a non-limiting example of dimensions (in mm) of microchannels in the quadra-droplet generator fabricated in sheet **16**. In the present non-limiting embodiment, sheet **16** is 5 cm × 3 cm.

Figure 8 is a top-view of **Figure 1** showing a non-limiting example of dimensions (in μm) of microchannels in the outlet **36** of the fluid-focusing device in sheet **14**.

Figures 9a and **9b** show optical microscopy images of droplets formed in four-flow-focusing devices (**Figure 9a**) and collected at the outlet of the quadra-droplet generator (**Figure 9b**).

Figure 10a, 10b show optical microscopy images of droplets formed in a four FFDs with the mean orifice width: $41 \pm 1 \mu\text{m}$ (FFD **101**); $50 \pm 1 \mu\text{m}$ (FFD **102**); $61 \pm 1 \mu\text{m}$ (FFD **103**), and $75 \pm 1 \mu\text{m}$ (FFD **104**). In **10a**, $Q_A = 0.2 \text{ mL/hr}$ and $Q_B = 1.0 \text{ mL/hr}$; in **10b**, $Q_A = 0.2 \text{ mL/hr}$ and $Q_B = 2.0 \text{ mL/hr}$. The height of quadra-droplet generator (QDG) is $150 \pm 2 \mu\text{m}$.

Figure 11 shows an individual microfluidic polymerization reactor combining emulsification and on-chip polymerization for rapidly polymerizing monomers and on-chip and off-chip polymerization for slowly polymerizing monomers

Figures 12a, 12b shows variation in mean diameter of droplets generated in four parallel FFDs, plotted as a function of the flow rate of the droplet phase, Q_A , at (**12a**) $Q_B = 1.0 \text{ mL/hr}$ and (**12b**) $Q_B = 1.4 \text{ mL/hr}$. Q_B is the flow rate of the continuous phase **B** supplied to inlet **22**

Figures 12c, 12d show variation in polydispersity of droplets produced in individual FFDs and in the quadra-droplet generator (QDG) (\blacksquare). Orifice width in FFD **101** is $50.7 \pm 1.0 \mu\text{m}$ (\diamond), FFD **102**, $50.8 \pm 1.0 \mu\text{m}$ (\square); FFD **103**, $48 \pm 1.0 \mu\text{m}$ (Δ) and FFD **104**, $48.8 \pm 1.0 \mu\text{m}$ (\circ).

Figures 13a, 13b show variation in mean diameter of droplets generated in FFD **102**, plotted as a function of the flow rate, Q_A , of the droplet phase at (a): $Q_B = 1.0 \text{ mL/hr}$ and (b): $Q_B = 1.4 \text{ mL/hr}$. Q_B is the flow rate of the continuous phase **B** supplied to inlet **22**.

Figures 13c, 13d show variation in polydispersity of droplets produced in FFD **102** in three consecutive emulsification experiments (open symbols) and of the total population of droplets (\blacksquare). Orifice width of FFD **102**: $50.8 \pm 1.0 \mu\text{m}$.

Figure 14 shows the variation in volume fraction of droplets generated in FFD with different geometry plotted as a function of ratio of flow rates of continuous to droplet phases for FFD 101 (■), FFD 102 (Δ), FFD 103 (◇), and FFD 104 (□).

5 **Figure 15** shows experimentally measured volume fraction of droplets generated in the quadra-droplet generator 10 (QDG) with different geometry plotted as a function of the ratio of flow rates of continuous to droplet phases in the quadra-droplet generator 10 (QDG). The horizontal dashed lines represent the volume fraction of an orifice in an individual FFD to the total volume of
10 orifices in the QDG (bottom to top lines correspond to FFD 101 to FFD 104, respectively).

Figure 16 shows the variation in the droplet size plotted along with the width and height of the orifice in the integrated droplet generator comprising sixteen individual droplet generators 20.

15 The following reference numbers are incorporated herein to describe elements within the figures. In the quadra-droplet generator (QDG) shown generally at 10,

12 First sheet

14 Second sheet

20 16 Third Sheet

In sheet 14,

20 Fluid-focusing device (FFD)

22 Fluid B inlet

24 Inlet manifold distributor

25 26 Inlet microfluidic flow channels

28 FFD inlet

30 Fluid A microchannel inlets to the FFD

32 Fluid B microchannel inlets to the FFD

34 Orifice in the FFD

30 36 FFD outlet

38 Outlet microfluidic flow channels from the FFD

40 Outlet manifold distributor

42 Openings for fluid A

62 Fluid A droplets

64 Fluid outlet

In sheet **16**,

52 Fluid **A** inlet

54 Inlet manifold distributor

5 **56** Inlet microfluidic flow channels

In microfluidic polymerization reactor **70** in **Figure 11**,

72 Pumps for inserting the fluid **B**

74 Pump for inserting the fluid **A**

76 Fluid inlets

10 **78** Orifice

80 Polymerization compartment

82 First outlet

84 Microfluidic flow channels

88 Extension tube

15 **90** Off-chip polymerization compartment

92 Second outlet

Elsewhere, **101**, **102**, **103**, and **104** are four flow-focusing devices **20** (FFDs) in a quadra-droplet generator **10** (QDG) used in experimentation and for demonstrative purposes.

20

DETAILED DESCRIPTION OF THE INVENTION

Generally speaking, the systems described herein are directed to multiple flow-focusing microfluidic droplet generators. As required, embodiments of the present invention are disclosed herein. However, the disclosed embodiments are merely exemplary, and it should be understood that the invention may be embodied in many various and alternative forms. The figures are not to scale and some features may be exaggerated or minimized to show details of particular elements while related elements may have been eliminated to prevent obscuring novel aspects. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting but merely as a basis for the claims and as a representative basis for teaching one skilled in the art to variously employ the present invention. For purposes of teaching and not limitation, the illustrated embodiments are directed to multiple flow-focusing microfluidic droplet generators.

25

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As used herein, the term “about”, when used in conjunction with ranges of dimensions of particles or other physical properties or characteristics, is meant to cover slight variations that may exist in the upper and lower limits of the ranges of dimensions so as to not exclude embodiments where on average most of the dimensions are satisfied but where statistically dimensions may exist outside this region. It is not the intention to exclude embodiments such as these from the present invention.

Figures 1 through 8 illustrate a quadra-droplet generator (QDG) used in the present work, shown generally at **10** in **Figure 3**. **Figure 1** shows a schematic drawing of an individual planar flow-focusing droplet generator. Two immiscible liquids, a droplet phase **A**, and a continuous phase **B**, are supplied to the central channel **30** and side channels **32** of the flow-focusing device (FFD), respectively. The liquids are forced through a narrow orifice **34** in which a thread of liquid **A** breaks up and releases droplets **62**. The separation of the time scales between the slow progression of collapse and the fast equilibration of the interfacial tension and hydrostatic pressure results in the formation of droplets **62** with a narrow size distribution.

Figure 2 depicts the fluid flow path in a single planar flow-focusing device shown generally at **20**. Liquid **A** enters via opening **42** and travels downstream via the central microchannel **30** through orifice **34** to the outlet microchannels **38**. Liquid **B** enters via side microchannels **26** and travels through microchannel **32** through orifice **34** to the outlet microchannels **38**.

Figure 3 shows a 3D illustration of the quadra-droplet generator **10** (QDG) with four parallel flow-focusing devices **20**. Liquids **A** and **B** are supplied to the flow-focusing devices **20** (FFDs) in a manifold fashion through inlets **52** (liquid **A**) and **22** (liquid **B**). The bottom component of the device is a planar, non-patterned base sheet **12** having a planar top surface.

The intermediate and the top components of the device (sheets **14** and **16**, respectively) are patterned, as shown in **Figures 4** and **5**. Particularly, sheet **14** has a relief pattern of four (4) (but it may be a plurality) microfluidic flow-focusing devices **20**, each including an inlet **28** and an outlet **36**, microchannels **30** and **32**, a relief pattern for a first inlet manifold distributor **24** having a plurality of microfluidic flow channels **26** connected to the inlets **28** of the plurality of microfluidic flow-focusing devices **20**. The first inlet manifold distributor **24** has a

fluid inlet **22**. Sheet **14** includes a relief pattern for an outlet manifold distributor **40** connected via relief patterns of microchannels **38** to the outlets **36** of the plurality of microfluidic flow-focusing devices **20**. The outlet manifold distributor **40** has a fluid outlet **64**. The relief patterns are formed in the bottom surface of sheet **14**, and each of the microfluidic flow-focusing devices **20** has an opening **42** in the top surface of sheet **14** in flow communication with microchannel **30** on the interior of the associated microfluidic flow-focusing device **20**.

The device includes a third sheet **16** having a relief pattern of a second inlet manifold distributor **54** in a bottom surface of the third sheet **16**, with this relief pattern including a plurality of microfluidic flow channels **56** each in communication with a fluid inlet **52** and one of the openings **42** in the top surface of sheet **14** when sheet **16** is assembled on the top surface of sheet **14** with its bottom surface in physical contact with the planar top surface of sheet **14** in a sealing relationship. Assembling sheet **14** on the planar top surface of the base sheet **12** with the bottom surface in physical contact with the planar top surface in sealing relationship forms the plurality of microfluidic flow-focusing devices **20** and the first inlet manifold distributors **24** and outlet manifold distributors **40**.

Liquid **B** is supplied through inlet **22** and is split between four channels **26** of identical width and height and further split between eight channels **32** of identical width and height. Liquid **A** is injected in inlet **52** and is split between four channels **56** of identical width and height. When the three sheets **12**, **14** and **16** are sealed, as shown in **Figure 3**, the openings **42** in sheet **14** and **16** are superimposed, so that liquid **A** enters the microchannels **30** in the intermediate sheet **14**. Thus sheet **16** serves as an "adapter," while the generation of droplets occurs between sheets **12** and **14**. The droplets produced in the individual flow-focusing devices **20** (FFDs) enter a common downstream channel **38** and exit from the outlet **64**. The distribution of sizes of droplets **62** is examined in the downstream channels of individual FFDs **20** and at the exit from the quadra-droplet generator **10**.

Figure 6 shows a non-limiting example of dimensions of microchannels in the quadra-droplet generator (QDG) fabricated in sheet **14**, in millimeters. The width of microchannels **24** and **38** is 800 micrometers, **26**, 400 micrometers, **30** and **32**, 200 micrometers, and **38**, 450 micrometers. These dimensions of

disclosed embodiments are merely exemplary, and it should be appreciated that the microchannel widths may vary from about 20 to 1000 micrometers.

It is noted that in **Figure 3** there is shown a single sheet **16** having an inlet manifold distributor **54**. It will be appreciated that additional sheet(s) may be included with additional inlet manifolds, and in the case of **Figure 3** if an additional sheet with an inlet manifold is provided, there are holes **42** through the third sheet located at the termination of the microfluidic flow channels **56** in the third sheets which are in registration with the terminations of the microfluidic flow channels **54** in the additional sheet(s). These additional sheet(s) may be useful in some embodiments where mixing, concentration, dilution, or change in composition of droplet phase or continuous phases is needed.

Microfluidic devices were fabricated from poly(dimethylsiloxane) (PDMS) using a soft lithography technique as disclosed in Y. Xia, G. M. Whitesides, *Angew. Chem.* 110, 568 – 594 (1998); Y. Xia, G. M. Whitesides, *Angew. Chem. Int. Ed.* 37, 550-575 (1998); D. C. Duffy, J. C. McDonald, O. J. A. Schueller, G. M. Whitesides *Anal. Chem.* 70, 4974- 4984 (1998). The actual widths of the microchannels, especially the widths of the orifices in the individual flow-focusing devices (FFDs), were measured prior to the emulsification experiments. Herein, we used two types of quadra-droplet generators (GDGs) in which the flow-focusing devices had *identical* or *different* widths of the orifice **34**.

Filtered, deionized water was used as a droplet phase (introduced as liquid **A**). A 2 wt% solution of a non-ionic surfactant Span 80 in a light mineral oil was used as a continuous phase (introduced as liquid **B**). Liquids **A** and **B** were supplied to the quadra-droplet generator **10** (QDG) using two separate syringe pumps (PHD 2000, Harvard Apparatus, MA). An optical microscope (Olympus BX41) coupled with a CCD camera (EvolutionTM VF) was used to acquire images of droplets (**Figures 9** and **10**). The distribution of sizes of droplets was determined by image analysis of the micrographs using a software Image-Pro Plus 5.0.

Typically, we measured the diameters of at least 100 droplets. Polydispersity of droplets was characterized by determining coefficient of variance (CV) of the diameters of droplets (defined as $(\sigma/d_m) \times 100\%$ where σ is the standard deviation and d_m is the mean droplet diameter).

Emulsification is performed in a quadra-droplet generator (QDG) with identical flow-focusing devices. **Figures 9a** shows typical optical microscopy results of droplets generated in four identical FFDs **20** and **Figure 9b** shows droplets collected from the outlet **64** of the quadra-droplet generator **10**. The width of the orifices and the height of channels in the FFDs were $50\pm 2\ \mu\text{m}$ and $150\pm 2\ \mu\text{m}$, respectively. The flow rate of water and oil, introduced liquids **A** (inlet **52**) and **B** (inlet **22**) are 0.02 mL/hr and 1.0 mL/hr, respectively. We varied the flow rate, Q_A , of the droplet phase **A** supplied to inlet **52** from 0.02 to 0.08 milliliters/hour and the flow rate, Q_B , of the continuous phase **B** supplied to inlet **22** from 1.0 to 1.6 milliliters/hour. In this range of flow rates of liquid, the droplets formed via the flow-focusing mechanism, and the formation of large discoid droplets squished between the top and the bottom walls of the microchannels was avoided.

Figures 12a and **12b** show a typical variation in the diameter, D_m , of droplets **62** generated in the individual flow-focusing devices **20** (FFDs), plotted as a function of the flow rate, Q_A , of the droplet phase for two different values of Q_B . As expected, the size of droplets increased with an increasing value of Q_A and a decreasing value of Q_B . More importantly, for each value of Q_A and Q_B a small but finite difference existed in the dimensions of droplets **62** generated in the individual FFDs **20**. The difference between the mean diameters of droplets **62** generated in different FFDs **20** was up to $8\ \mu\text{m}$ (for the size of droplets in the range from 80 to $135\ \mu\text{m}$). This variation did not notably change with the value of Q_B .

Because of the small difference between the mean diameters of droplets **62** generated in the individual FFDs, polydispersity of the total population of droplets produced in the multiple droplet generator was approximately 1-2 % higher than CV of the droplets generated in the individual combined devices, however, the total value of CV did not exceed 4.0 % (**Figures 3c** and **3d**). Polydispersity did not significantly change with increasing flow rates of the liquids

We ascribed the broadening in the distribution of sizes of the droplets emulsified in the quadra-droplet generator **10** (QDG) to the weak parametric coupling between the individual droplet generators. Close inspection of images of droplets moving through the downstream channels in the *individual* FFDs

revealed that the difference in distances between the two neighbouring droplets did not exceed 5 μm whereas for the droplets produced in the *different* FFDs the variation in the spacing was up to 20 μm . This result suggested that droplets in the parallel FFDs were generated at varying frequencies, i.e., emulsification was not completely synchronized. This effect resulted in the broadening of polydispersity of the total population of droplets.

To rule out a possible effect of occasional flow instabilities on size distribution of droplets obtained in the QDG, we examined polydispersity of droplets produced in four independent FFDs **20** that were not combined in the QDG. The increase in CV of the total population of droplets did not exceed 0.7 % and in most cases, it did not exceed 0.5 %, in comparison with the value of CV of the droplets obtained in the individual FFDs.

Table 1. Diameters of droplets and coefficients of variance (CV) of droplets obtained in four individual microfluidic FFDs

	FFD 101	FFD 102	FFD 103	FFD 104	Total population of droplets	Q_B (mL/hr)	Q_A (mL/hr)
Width of orifice (μm)	50.7 \pm 1.0	50.8 \pm 1.0	48 \pm 1.0	48.8 \pm 1.0			
Mean droplet diameter (μm) / CV(%)	105.5/1.4	103.2/1.5	102.2/1.4	104.1/1.2	103.8 1.7		0.005
	104.3/1.3	104.6/1.3	103.1/1.2	103.9/1.3	104.0 1.5	0.25	(T1)
	105.0/1.3	103.6/1.4	102.9/1.5	102.2/1.6	103.4 1.9		(T2)
							(T3)
	112.1/1.3	113.0/1.0	112.9/1.2	111.2/1.4	112.3 1.5		0.0125
	112.8/1.6	114.2/1.1	111.2/1.5	110.6/1.1	112.2 1.6	0.25	(T1)
	114.2/1.5	112.6/1.3	110.6/1.5	114.3/1.2	112.9 1.7		(T2)
							(T3)
	132.6/1.1	132.4/0.9	129.7/1.0	130.5/1.1	131.3 1.6		0.020
	130.6/1.3	135.1/1.0	130.6/0.9	133.2/0.9	132.4 1.4	0.25	(T1)
	131.5/1.1	134.3/1.2	132.9/0.9	130.6/1.1	132.3 1.6		(T2)
							(T3)
91.9/1.1	93.8/1.4	95.3/1.4	93.3/1.6	93.6 1.9		0.005	
91.0/1.2	92.6/1.6	93.6/1.5	92.6/1.2	92.5 1.7	0.30	(T1)	
90.5/1.4	93.5/1.5	93.1/1.1	93.7/1.2	92.7 1.6		(T2)	
						(T3)	

Mean droplet diameter (μm) / CV(%)	107.2/1.3	109.3/1.4	107.0/1.3	106.5/1.5	107.5	1.6		0.005
	108.2/1.5	108.6/1.2	107.9/1.2	106.6/1.4	107.8	1.8	0.30	(T1)
	106.9/1.2	109.9/1.4	105.4/1.4	104.9/1.1	106.8	2.0		(T2)
								(T3)
	116.7/1.1	118.4/1.0	115.9/1.1	116.7/1.2	116.9	1.7		0.0125
	116.2/1.4	116.5/1.2	116.8/1.4	115.5/1.1	116.3	1.6	0.30	(T1)
								(T2)
	115.2/1.3	117.2/1.1	118.3/1.5	114.3/1.5	116.3	1.8		(T3)
	81.1/1.5	82.3/1.6	80.4/1.7	80.8/1.4	81.2	1.9		0.005
	80.6/1.4	82.9/1.4	80.1/1.5	79.3/1.6	80.7	2.0	0.35	(T1)
								(T2)
	82.0	81.6/ 1.3	81.6/ 1.2	79.0/ 1.7	81.1	1.9		(T3)
	96.9/ 1.3	98.1/ 1.5	98.5/ 1.0	97.2/ 1.5	97.7	1.6		0.0125
	95.3/ 1.2	97.5/ 1.4	97.6/ 1.5	98.9/ 1.2	97.3	1.7	0.35	(T1)
								(T2)
	97.2/ 1.5	97.0/ 1.6	96.9/ 1.4	97.7/ 1.4	97.2	1.7		(T3)
	105.6/1.5	107.2/1.3	105.8/1.3	106.3/1.4	106.2	1.8		0.020
	105.8/1.4	106.4/1.6	106.8/1.2	104.9/1.6	106.0	1.9	0.35	(T1)
								(T2)
	104.3/1.2	105.9/1.5	108.0/1.6	103.7/1.6	105.5	2.0		(T3)
	73.5/ 1.7	76.5/ 1.6	74.2/ 1.8	73.1/ 1.6	74.3	2.1		0.005
	72.4/ 1.6	75.5/ 1.6	70.6/ 1.2	71.2/ 1.4	72.4	1.8	0.40	(T1)
								(T2)
	73.9/ 1.7	74.9/ 1.7	72.6/ 1.3	70.6/ 1.5	73.0	1.9		(T3)
83.5/ 1.8	85.6/ 1.6	83.5/ 1.5	86./1.4	84.7	1.7		0.0125	
82.1	86.3/ 1.5	85.3/ 1.1	85.5/ 1.2	84.8	1.7	0.40	(T1)	
							(T2)	
83.1/ 1.4	84.9/ 1.6	86.3/ 1.6	84.2/ 1.5	84.6	1.9		(T3)	
92.9/ 1.6	94.9/ 1.6	91.9/ 1.2	93.7/ 1.4	93.4	1.8		0.020	
91.3/ 1.6	93.0/ 1.3	93.1/ 1.1	91.1/ 1.4	92.1	1.8	0.40	(T1)	
							(T2)	
90.8/ 1.5	94.1/ 1.6	92.7/ 1.5	90.6/ 1.5	92.1	1.8		(T3)	

The data denoted as T1, T2 and T3 correspond to three experiments conducted for the same values of Q_A and Q_B .

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Furthermore, we studied reproducible formation of droplets in the QDG
10 by examining the distribution in sizes of droplets obtained with a one-day time

interval. **Figures 13a, 13b** shows a representative change in the mean diameter of droplets obtained in FFD **102**, plotted as a function of the flow rate of the droplet phase, Q_A . In the same range of flow rates as in **Figure 12**, the difference in mean diameter of droplets formed in the successive emulsification experiments was from 1 to 5 μm . **Figure 13c, 13d** shows that the value of the CV of droplets generated in each emulsification experiment was in the range from 1.6 to 2.5 %, while the CV of the entire collection of droplets produced in three experiments did not exceed 3.0%.

We thus conclude that in the range of flow rates of liquids studied, weak coupling between parallel FFDs integrated in the multiple droplet generator broadened the polydispersity of droplets; however, the droplets generated in the multiple droplet generator could be defined as “monodispersed” (According to the standards of the National Institute of Standards and Technology (NIST): “a particle distribution may be considered monodisperse if at least 90% of the distribution lies within 5% of the median size” (Particle Size Characterization, Special Publication 960–961, January 2001). In the second series of experiments, emulsification was carried out in a quadra-droplet generator integrating flow-focusing devices with distinct geometries. The width of the orifice in the individual FFDs was varied from 40 to 75 μm (all other dimensions of the microchannels were kept identical). Here, our objective was to achieve simultaneous formation of droplets with different volumes.

We used the values of flow rates of liquids, Q_B/Q_A , yielding droplets in the flow-focusing regime and obtained droplets with different sizes and varying size distributions, as illustrated in **Figure 10a** and quantified in **Table 1**. At low values of Q_B/Q_A , emulsification in the FFDs with wide orifices (FFD **103** and FFD **104**) generated a single population of monodispersed droplets whereas two populations of droplets, each with $CV \approx 2\%$ were obtained in the FFDs with narrower orifices. With increasing values of Q_B/Q_A this trend narrowed to FFD **101** and for $8 < Q_B/Q_A < 10$ all FFDs produced a single population of droplets with polydispersity of 2-3% (**Figure 5b**). The mean diameter of droplets decreased with a decreasing width of the orifice. At $Q_B/Q_A \geq 40$, the stream of the droplet phase did not enter the orifice with the smallest width of 40 μm .

Table 2. Mean diameter (d_m) of droplets formed in individual droplet generators and of the total population of droplets generated in quadra-droplet generator.

	Q_B (mL/hr)	Q_B/Q_A^*	FFD 101	FFD 102	FFD 103	FFD 104	$V_1/V_2/V_3/V_4^{**}$
Orifice width (μm)			41	50	61	75	1/1.22/1.49/1.83
	1	5	144+63	166+83	170	188	1/1.30/1.34/1.68
	1.2	6	136+41	152	159	180	1/1.42/1.57/1.83
Mean droplet diameter (d_m) (μm)	1.4	7	130+29	142	147	174	1/1.56/1.73/2.79
	1.6	8	120	139	143	166	1/1.87/2.03/2.92
	1.8	9	115	132	137	161	1/2.27/2.45/3.82
	2.0	10	108	122	130	152	1/2.40/2.71/3.87

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* $Q_A = 0.2$ mL/hr.

** $V_1/V_2/V_3/V_4$ is the mean volume ratio of droplets formed in four parallel FFDs, normalized by V_1 .

We note that for the parallel FFDs with distinct geometries, coupling was significantly stronger than in the FFDs with identical design. Close inspection of the optical microscopy images revealed that the difference in spacing between the droplets generated in each FFD was up to $20 \mu\text{m}$, in comparison with $1-5 \mu\text{m}$ measured for the FFDs with similar geometry. To elucidate the role of geometric coupling, we examined the ratio of volumes of droplets generated in the parallel FFDs with different geometries. The ratio between the volumes of droplets generated in the individual parallel FFDs was found by analyzing optical microscopy images. With an increasing value of Q_B/Q_A the ratio of volumes of droplets changed, as shown in Table 1, right column. For example, when Q_B/Q_A doubled from 5 to 10, the ratio of volumes of droplets generated in FFD 104 and FFD 101 increased from 1.68 to 3.89, i.e., increased by a factor of 2.32.

Figure 14 shows the effect of flow rate ratio Q_B / Q_A on the volume fractions of droplets produced in parallel FFDs. The volume fraction of droplets formed in an individual FFD was defined as $R_i = (V_i / V_{\text{tot}})$ where V_i is the total volume of droplets produced per unit time in individual FFD and V_{tot} is the total volume of droplets obtained in the quadra-droplet generator. Dashed lines in

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Figure 15 show the ratio of volume of an orifice **34** in an individual FFD **20** to the total volume of orifices **34** in the quadra-droplet generator **10** (QDG). For ratios of $Q_B / Q_A > 6$, the value of R_i for FFD **104** increased, the value of R_i for FFD **101** decreased, and the values of R_i for FFD **102** and FFD **103** did not change. These effects implied that with an increasing ratio of flow rates of liquids, the FFD with the widest orifice consumed an increasing volume of the droplet phase, at the expense of the liquid entering the FFD with the narrowest orifice. We attribute the re-distribution of droplet size between the FFDs to the difference in hydrodynamic path resistances to the liquids in the devices with different geometry, in addition to the non-synchronized break up of the liquid threads (see V. Barbier, H. Willaime, and P. Tabeling, Phys. Rev. E, 74, 046306 (2006)).

Figures 15 shows the effect of the flow-rate ratio Q_B/Q_A on the volume fractions of droplets produced in parallel FFDs. The variation in experimental volume fraction R_i of droplets generated in FFDs with different geometry is plotted as a function of the flow rate ratio $[Q_B / Q_A]$ of continuous to droplet phases for FFD **101** (■), FFD **102** (Δ), FFD **103** (◇), and FFD **104** (□). The horizontal dashed lines represent the volume fraction of an orifice in an individual FFD to the total volume of orifices in the QDG (bottom to top lines correspond to FFD **101** to FFD **104**, respectively).

Figure 16 shows that the dimensions of droplets produced in the integrated droplet generator comprising sixteen individual droplet generators. The diameters of droplets show weak correlation with the width and the height of the orifices of the individual droplet generators.

Figure 11 shows a functional schematic of a microfluidic polymerization reactor, shown generally at **70**. Pumps **72** and **74** propel continuous phase fluid **B** and droplet phase fluid **A** respectively to inlets **76** which are in fluid communication with orifice **78** via microfluidic flow channels **84**, wherein droplets **62** of fluid **A** suspended in fluid **B** are formed. Orifice **78** is in flow communication with polymerization compartment **80** for in-chip polymerization, as described herebelow. In the polymerization compartment **80**, the droplets **62** undergo solidification and are collected at the first outlet **82**. If solidification is insufficient, the droplets can be transferred via the extension tube **88** to the off-

chip polymerization compartment **90** where they undergo complete solidification and are collected at the second outlet **92**.

Droplets produced in the multiple parallel droplet generators may be polymerized induced by various types of polymerization agents to give different types of polymerizations, including photoinitiated free-radical polymerization. For polymers undergoing fast polymerization, e.g. multifunctional acrylates, continuous polymerization is conducted *in situ* in the polymerization compartment **80**, as shown in **Figure 11** at the outlet of the flow focusing device for an individual microfluidic reactor. For monomers undergoing slow polymerization such as styrene, *in situ* pre-polymerization is followed by post-polymerization in the off-chip polymerization compartment **90** fabricated in glass (**Figure 11**). The pre-polymerization step is used to preserve a narrow size distribution of particles. Furthermore, the rate of polymerization is increased by using a mixed initiator approach developed in the applicant's group: a monomer is mixed with a thermo- and photoinitiator. Exothermic photopolymerization generates heat which triggers thermoinitiated polymerization thereby increasing monomer conversion.

The various polymerization agents induce any one or combination of free-radical, polymerization including reversible addition-fragmentation chain transfer polymerization (RAFT) and atom transfer radical polymerization (ATRP), ionic polymerizations or polycondensation. The polymerization may be induced or triggered by light so that the resulting polymerization process is thus photoinitiated. The droplet phase **A** contains one or more polymerization agents such that the emulsion droplets contain one or more polymerization agents. Alternatively the liquid phase **B** may contain one or more polymerization agents which diffuse into the emulsion droplets such that the emulsion droplets contain one or more polymerization agents.

The polymerized particles so produced may be substantially rigid particles. Alternatively the droplet phase **A** may contain prepolymer agents such that the emulsion droplets contain prepolymer agents. These prepolymer agents localized in the emulsion droplets transform the emulsion droplets into a gel and yields microgel particles.

It is noted that each droplet can be used for solution polymerization, i.e., the droplets would not be transformed into rigid beads. In this embodiment the droplets may act as pico or nanoreactors for solution polymerization.

We designed and implemented a multiple droplet generator integrating
5 four parallel flow-focusing devices (FFDs) with *identical* or *different* geometries. Emulsification conducted in the droplet generator combining identical FFDs shows that weak coupling between the devices led to the moderate broadening in their size distribution, yet, the droplets produced in the QDG could be characterized as “monodispersed”. Emulsification in the droplet generator
10 combining parallel FFDs with distinct geometries occurred with strong coupling and produced droplets with varying size and size distributions.

As used herein, the terms “comprises”, “comprising”, “including” and “includes” are to be construed as being inclusive and open ended, and not exclusive. Specifically, when used in this specification including claims, the
15 terms “comprises”, “comprising”, “including” and “includes” and variations thereof mean the specified features, steps or components are included. These terms are not to be interpreted to exclude the presence of other features, steps or components.

The foregoing description of the preferred embodiments of the invention
20 has been presented to illustrate the principles of the invention and not to limit the invention to the particular embodiment illustrated. It is intended that the scope of the invention be defined by all of the embodiments encompassed within the following claims and their equivalents.

THEREFORE WHAT IS CLAIMED IS:

1. A multiple microfluidic reactor for scaled up synthesis in emulsion droplets, comprising:
 - a) a first base sheet having a planar top surface;
 - b) a second sheet having:
 - i) relief patterns of a plurality of microfluidic flow-focusing devices, each including an inlet and an outlet,
 - ii) a relief pattern for a first inlet manifold distributor having a fluid inlet and microfluidic flow channels each in fluid communication with the first manifold fluid inlet and the inlets of the plurality of microfluidic flow-focusing devices,
 - iii) a relief pattern for an outlet manifold distributor connected to the outlets of the plurality of microfluidic flow-focusing devices, the outlet manifold distributor having a fluid outlet,
 - iv) said relief patterns being formed in a bottom surface of the second sheet,
 - v) each of said plurality of microfluidic flow-focusing devices having an opening in the top surface of the second sheet in flow communication with an interior of the associated microfluidic flow-focusing device; and
 - c) at least a third sheet having a relief pattern of a second inlet manifold distributor in a bottom surface of said third sheet, the relief pattern of the second inlet manifold distributor including an inlet and a plurality of microfluidic flow channels each in fluid communication with the second manifold fluid inlet and with one of said openings in the top surface of the second sheet when said third sheet is assembled on a top surface of the second sheet with the bottom surface in physical contact with the planar top surface in sealing relationship, and wherein assembling the second sheet on the planar top surface of the first base sheet with the bottom surface in physical contact with the planar top surface in sealing relationship forms the plurality of microfluidic flow-focusing devices and the first inlet and outlet manifold distributors; and
 - d) wherein in operation two immiscible liquids, a droplet phase, **A**, and a continuous phase, **B**, are supplied to the first manifold fluid inlet and to the second manifold fluid inlet respectively, and wherein said two immiscible liquids **A** and **B** are forced through a narrow orifice in which a thread of liquid **A** breaks up and produces emulsion droplets.

2. The multiple microfluidic reactor according to claim 1 wherein said first base sheet, said second sheet and said third sheet are made of poly(dimethylsiloxane) (PDMS).
3. The multiple microfluidic reactor according to claim 1 or 2 wherein said second sheet includes apertures right through the second sheet at a location corresponding to a termination of each microfluidic flow channel where each microfluidic flow channel communicates with the openings in the top surface of the second sheet when said third sheet is assembled on the top surface of the second sheet, including at least one additional third sheet having a relief pattern of at least one additional third inlet manifold distributor in a bottom surface of said at least one additional third sheet, the relief pattern of the at least one additional third inlet manifold distributor including a plurality of microfluidic flow channels each in communication with an at least one additional third manifold fluid inlet and one of said openings in the top surface of the second sheet wherein said at least one additional third sheet is assembled on a top surface of the second sheet with the bottom surface in physical contact with the planar top surface in sealing relationship, and wherein assembling the second sheet on the planar top surface of the first base sheet with the bottom surface in physical contact with the planar top surface in sealing relationship forms the plurality of microfluidic flow-focusing devices and the first inlet and outlet manifold distributors.
4. The multiple microfluidic reactor according to claim 1, 2 or 3 wherein said fluid outlet in said manifold distributor on the second sheet is connected to a polymerization compartment configured for polymerization of said emulsion droplets.
5. The multiple microfluidic reactor according to claim 4 wherein said polymerization compartment is an on-chip polymerization compartment, and wherein an outlet of said on-chip polymerization compartment is in flow communication with an extension tube, and wherein said extension tube is in flow communication with an off-chip polymerization compartment for post-polymerization of droplets pre-polymerized in said on-chip polymerization compartment.
6. A method for producing emulsion droplets, comprising the steps of:

a) providing a multiple microfluidic reactor for scaled up synthesis in emulsion droplets, comprising:

i) a first base sheet having a planar top surface;

ii) a second sheet having relief patterns of a plurality of microfluidic flow-focusing devices, each including an inlet and an outlet, a relief pattern for a first inlet manifold distributor having a fluid inlet and microfluidic flow channels each in communication with the first manifold fluid inlet and the inlets of the plurality of microfluidic flow-focusing devices, the first inlet manifold distributor having a fluid inlet, a relief pattern for an outlet manifold distributor connected to the outlets of the plurality of microfluidic flow-focusing devices, the outlet manifold distributor having a fluid outlet, said relief patterns being formed in a bottom surface of the second sheet, each of said plurality of microfluidic flow-focusing devices having an opening in the top surface of the second sheet in flow communication with an interior of the associated microfluidic flow-focusing device; and

iii) at least a third sheet having a relief pattern of a second inlet manifold distributor in a bottom surface of said third sheet, the relief pattern of the second inlet manifold distributor including a plurality of microfluidic flow channels each in fluid communication with a second manifold fluid inlet and one of said openings in the top surface of the second sheet when said third sheet is assembled on a top surface of the second sheet with the bottom surface in physical contact with the planar top surface in sealing relationship, and wherein assembling the second sheet on the planar top surface of the first base sheet with the bottom surface in physical contact with the planar top surface in sealing relationship forms the plurality of microfluidic flow-focusing devices and the first inlet and outlet manifold distributors; and

b) supplying at least two immiscible liquids, a droplet phase, **A**, and a continuous phase, **B**, to the first manifold fluid inlet and to the second manifold fluid inlet respectively, and wherein said two immiscible liquids **A** and **B** are forced through a narrow orifice in which a thread of liquid **A** breaks up and produces emulsion droplets.

7. The method according to claim 6 wherein said first base sheet, said a second sheet and said third sheet are made of poly(dimethylsiloxane) (PDMS).

8. The method according to claim 6 or 7 wherein said second sheet includes apertures right through the second sheet at a location corresponding to a termination of each microfluidic flow channel where each microfluidic flow channel communicates with the openings in the top surface of the second sheet when said third sheet is assembled on the top surface of the second sheet, including at least one additional third sheet having a relief pattern of at least one additional inlet manifold distributor in a bottom surface of said at least one additional third sheet, the relief pattern of the at least one additional third inlet manifold distributor including a plurality of microfluidic flow channels each in communication with an at least one additional third manifold fluid inlet and one of said openings in the top surface of the second sheet wherein said at least one additional third sheet is assembled on a top surface of the second sheet with the bottom surface in physical contact with the planar top surface in sealing relationship, and wherein assembling the second sheet on the planar top surface of the first base sheet with the bottom surface in physical contact with the planar top surface in sealing relationship forms the plurality of microfluidic flow-focusing devices and the first inlet and outlet manifold distributors.
9. The method according to claim 6, 7 or 8 wherein said fluid outlet in said outlet manifold distributor in said second sheet is in flow communication with a polymerization compartment, said method further comprising flowing said emulsion droplets through said polymerization compartment and exposing said emulsion droplets to a first polymerizing agent or initiator for at least initiating the polymerization of the emulsion droplets.
10. The method according to claim 9 wherein said first polymerization agent induces any one or combination of free-radical polymerization including reversible addition-fragmentation chain transfer polymerization (RAFT) and atom transfer radical polymerization (ATRP), ionic polymerizations or polycondensation.
11. The method according to claim 10 wherein said polymerization initiator is light.
12. The method according to any one of claims 9 to 11 in which the droplet phase, **A**, contains one or more polymerization agents such that the emulsion droplets contain one or more polymerization agents.

13. The method according to any one of claims 9 to 12 in which the polymerized particles are substantially rigid particles.
14. The method according to any one of claims 9 to 11 in which the droplet phase, **A**, contains prepolymer agents such that the emulsion droplets contain prepolymer agents.
15. The method according to claim 14 in which the prepolymer agent localized in the emulsion droplets transforms said emulsion droplets into a gel and yields microgel particles.
16. The method according to any one of claims 9 to 15 including a wave channel connected to an outlet of said extension tube, and wherein said emulsion droplets are flowed through said extension tube at a rate such that upon exposure to said polymerizing agent they are pre-polymerized to form a polymerized outer shell, and wherein said pre-polymerized emulsion droplets are flowed through said wave tube at a selected rate and exposed to a second polymerizing agent to completely polymerize, including a particle collector located at an outlet of said wave tube for collecting the completely polymerized particles.
17. The method according to claim 9 wherein said polymerization compartment is an on-chip polymerization compartment, and wherein an outlet of said on-chip polymerization compartment is in flow communication with an off-chip polymerization compartment, and wherein said emulsion droplets are pre-polymerized in said on-chip polymerization compartment to produce pre-polymerized droplets, said method further comprising flowing said pre-polymerized droplets through said off-chip polymerization compartment and post-polymerizing said pre-polymerized droplets in said off-chip polymerization compartment.
18. The method according to claim 17 wherein said emulsion droplets are flowed through said on-chip polymerization compartment at a rate such that upon exposure to said polymerization agent they are pre-polymerized to form a polymerized outer shell, and wherein said pre-polymerized droplets are flowed through said off-chip polymerization compartment at a selected rate and exposed to a second polymerizing agent to completely polymerize the pre-polymerized droplets into particles.

19. The multiple microfluidic reactor according to claim 5 further comprising a particle collector located at an outlet of said off-chip polymerization compartment.

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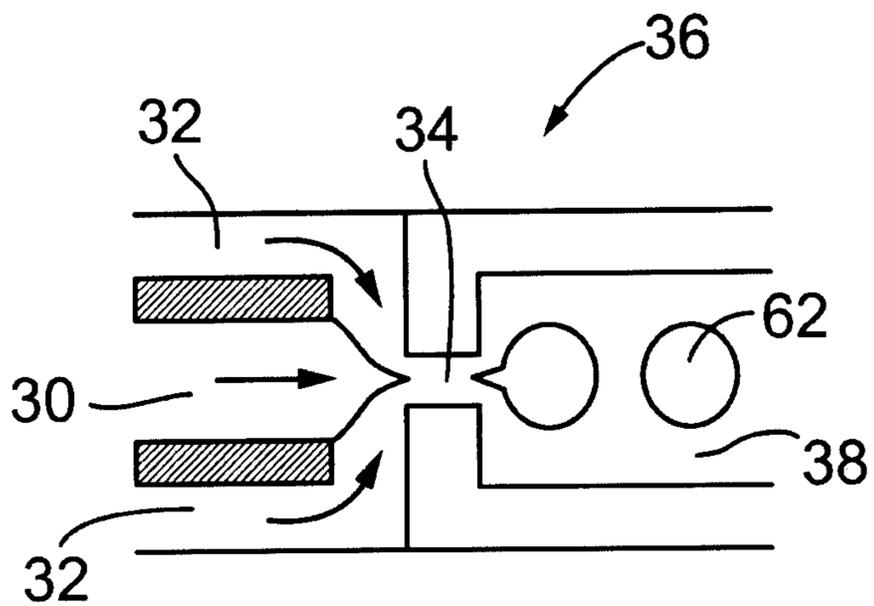


FIG. 1

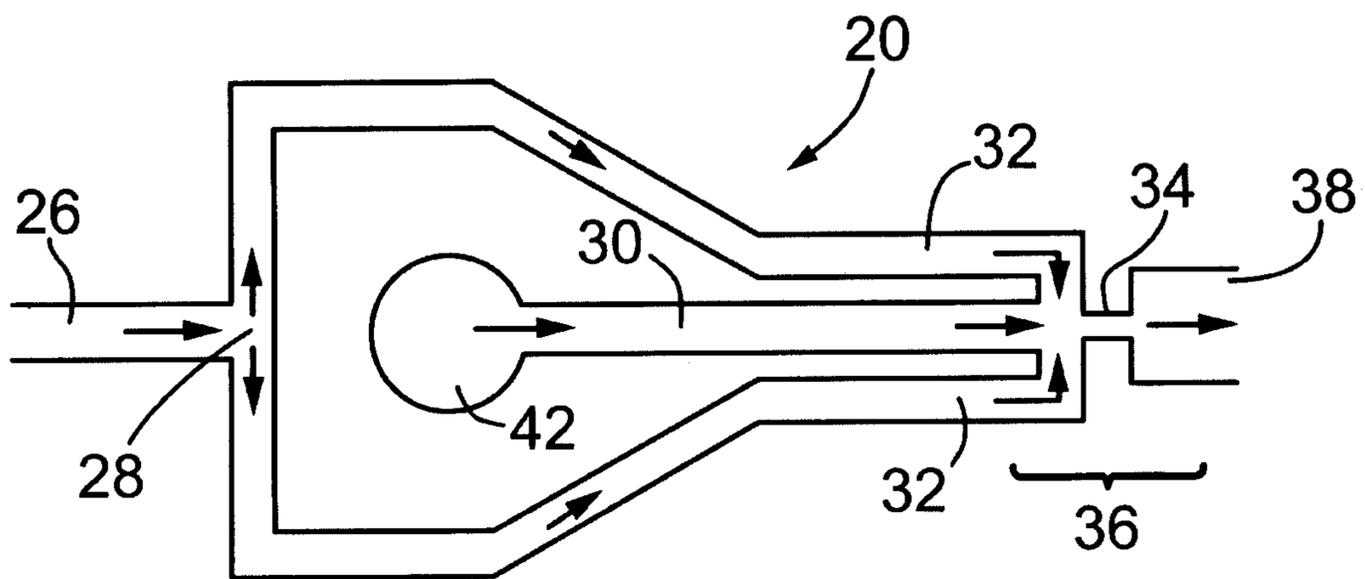


FIG. 2

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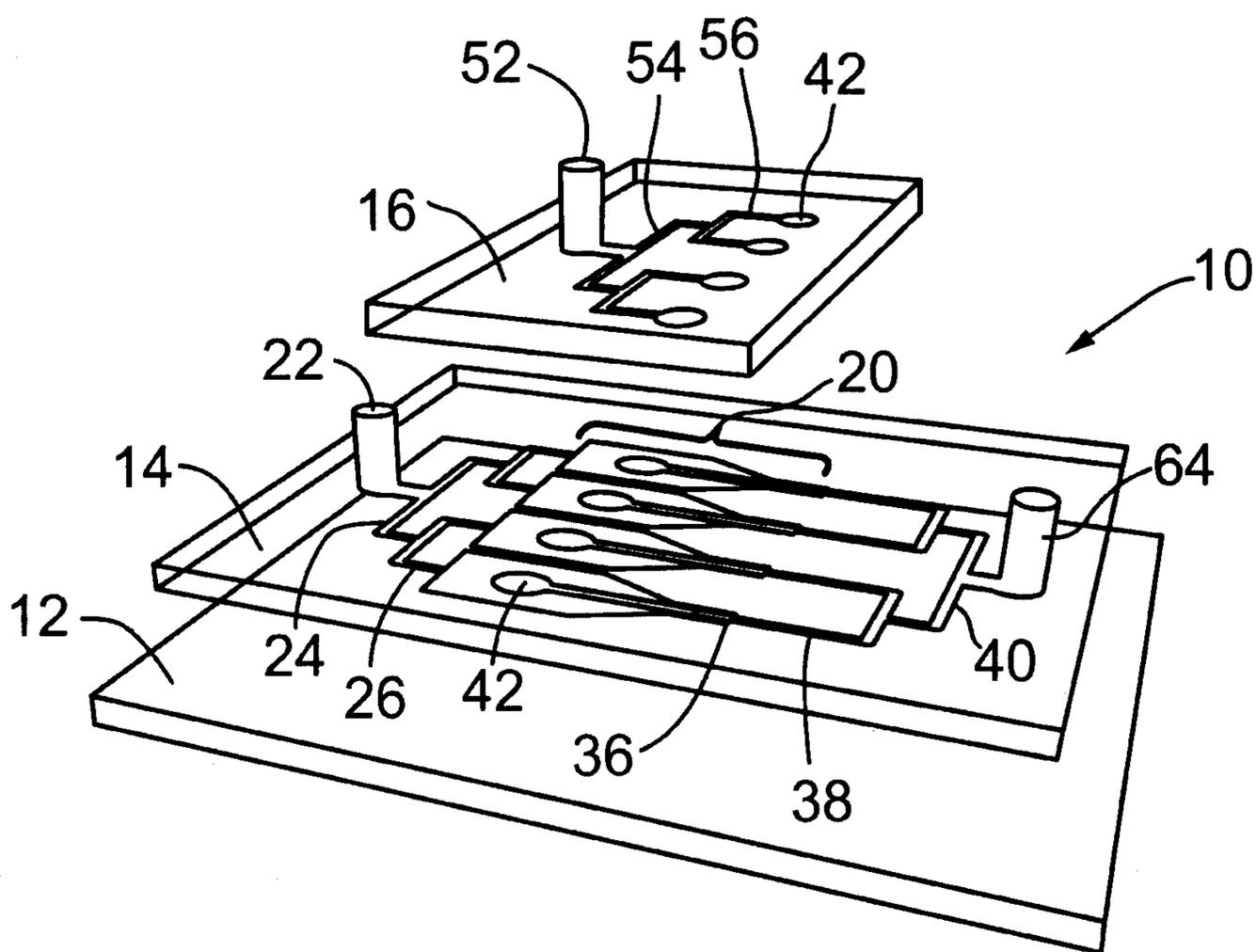


FIG. 3

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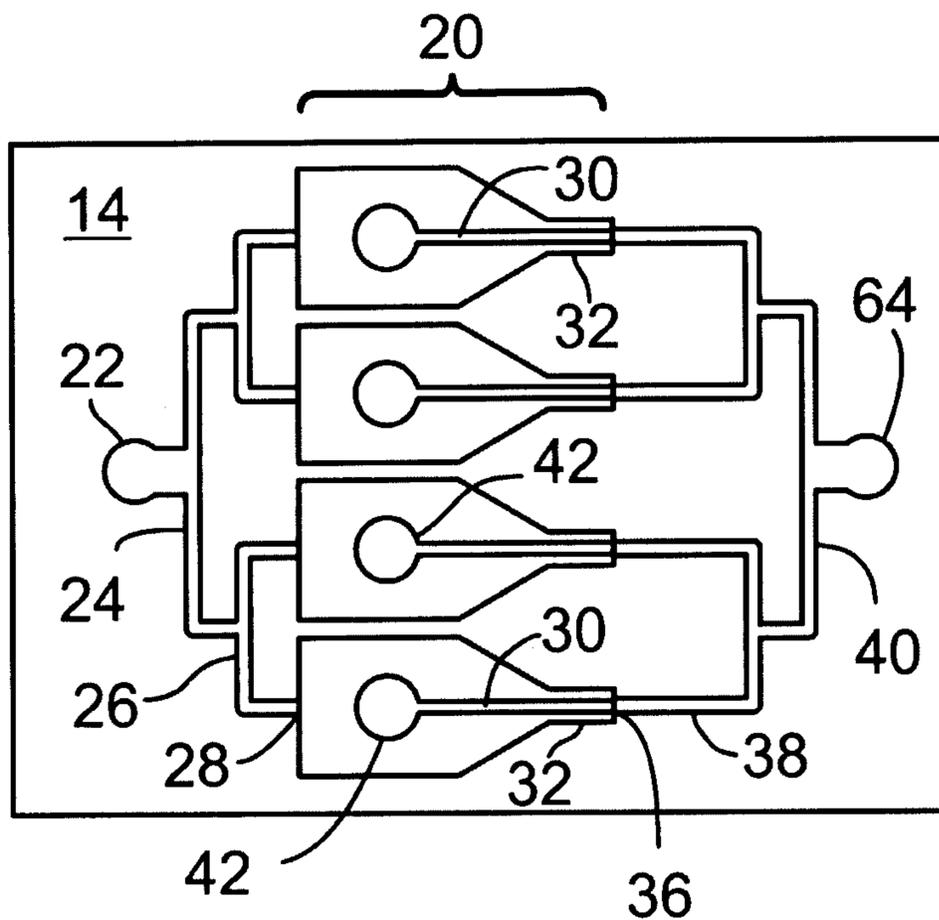


FIG. 4

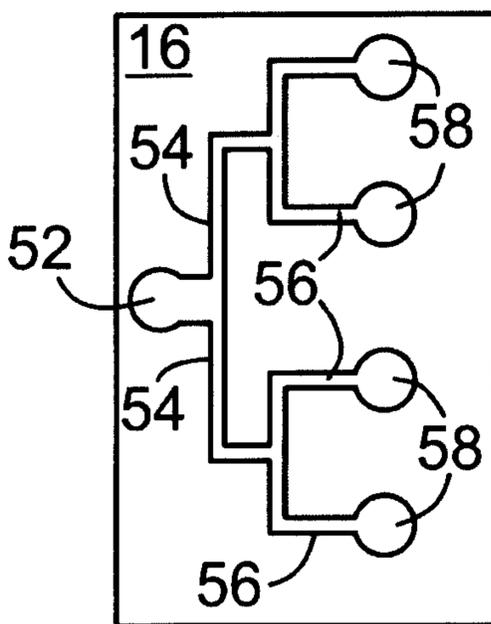


FIG. 5

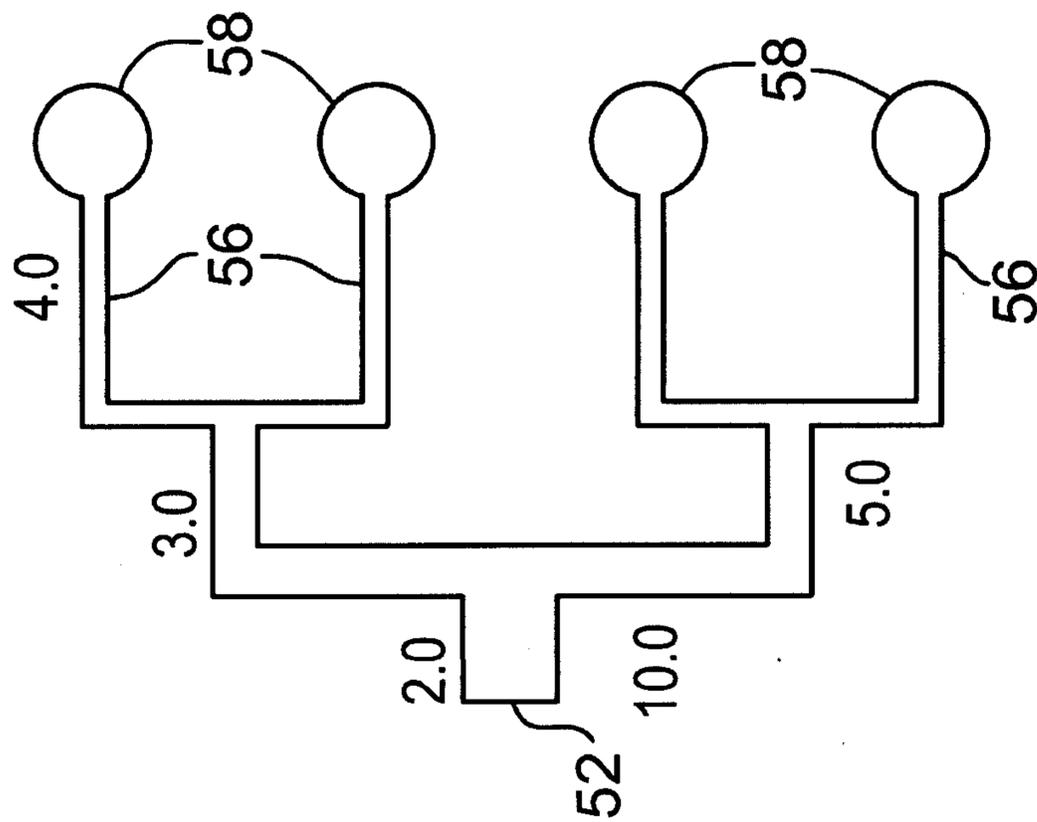


FIG. 7

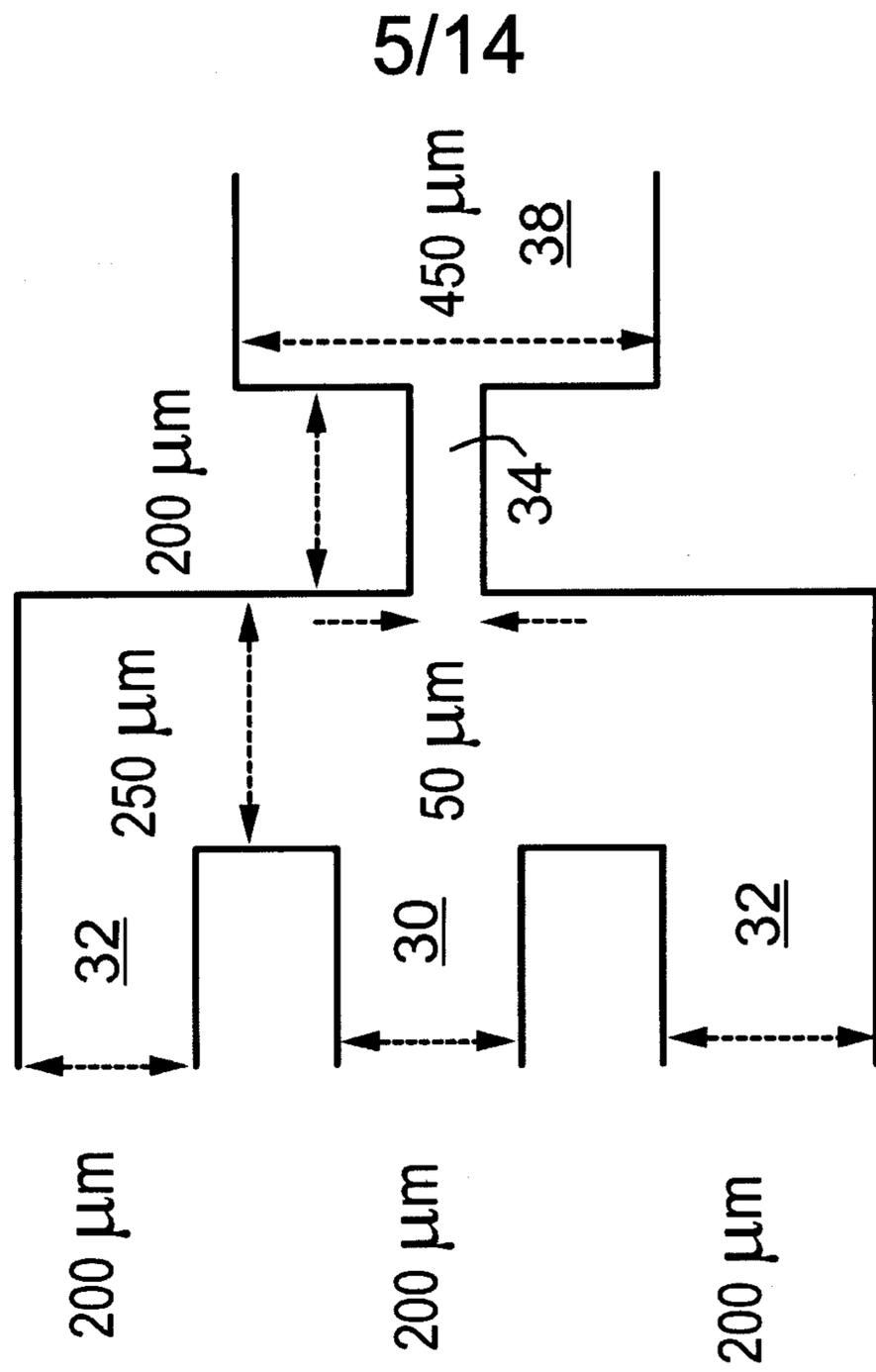


FIG. 8

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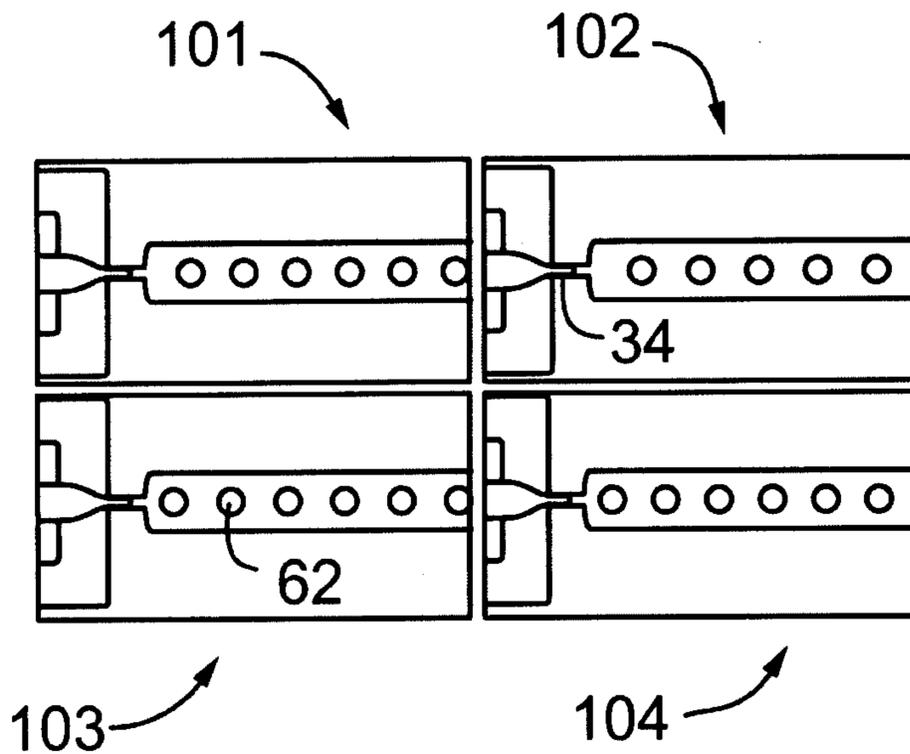


FIG. 9(a)

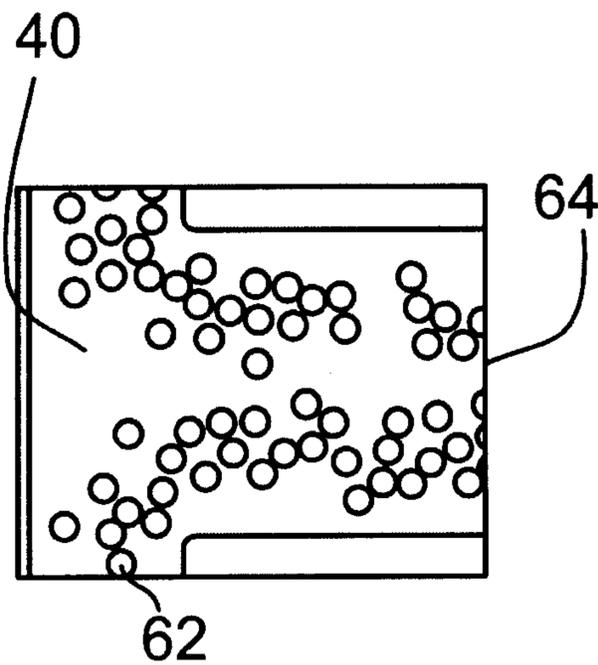


FIG. 9(b)

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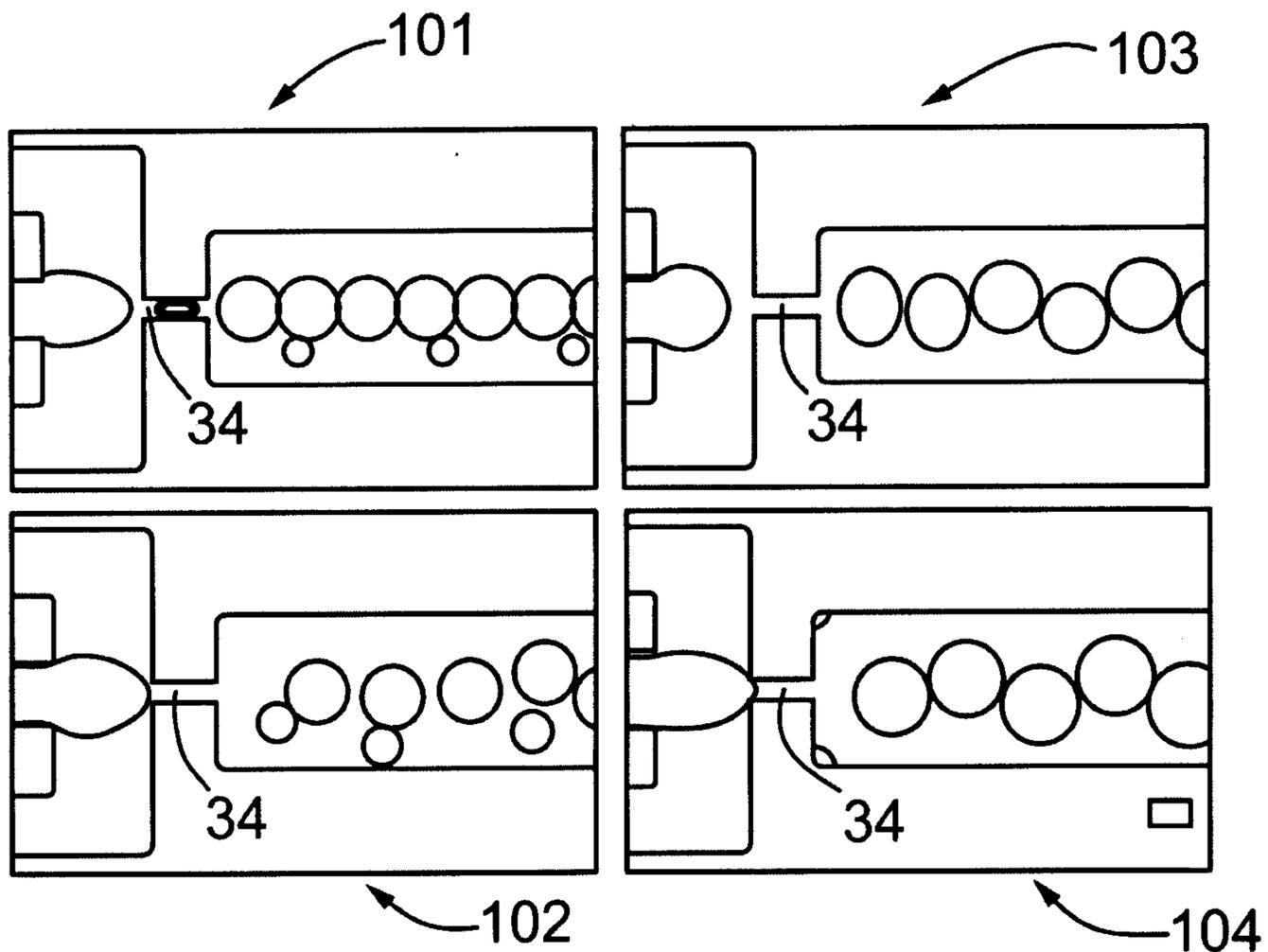


FIG. 10(a)

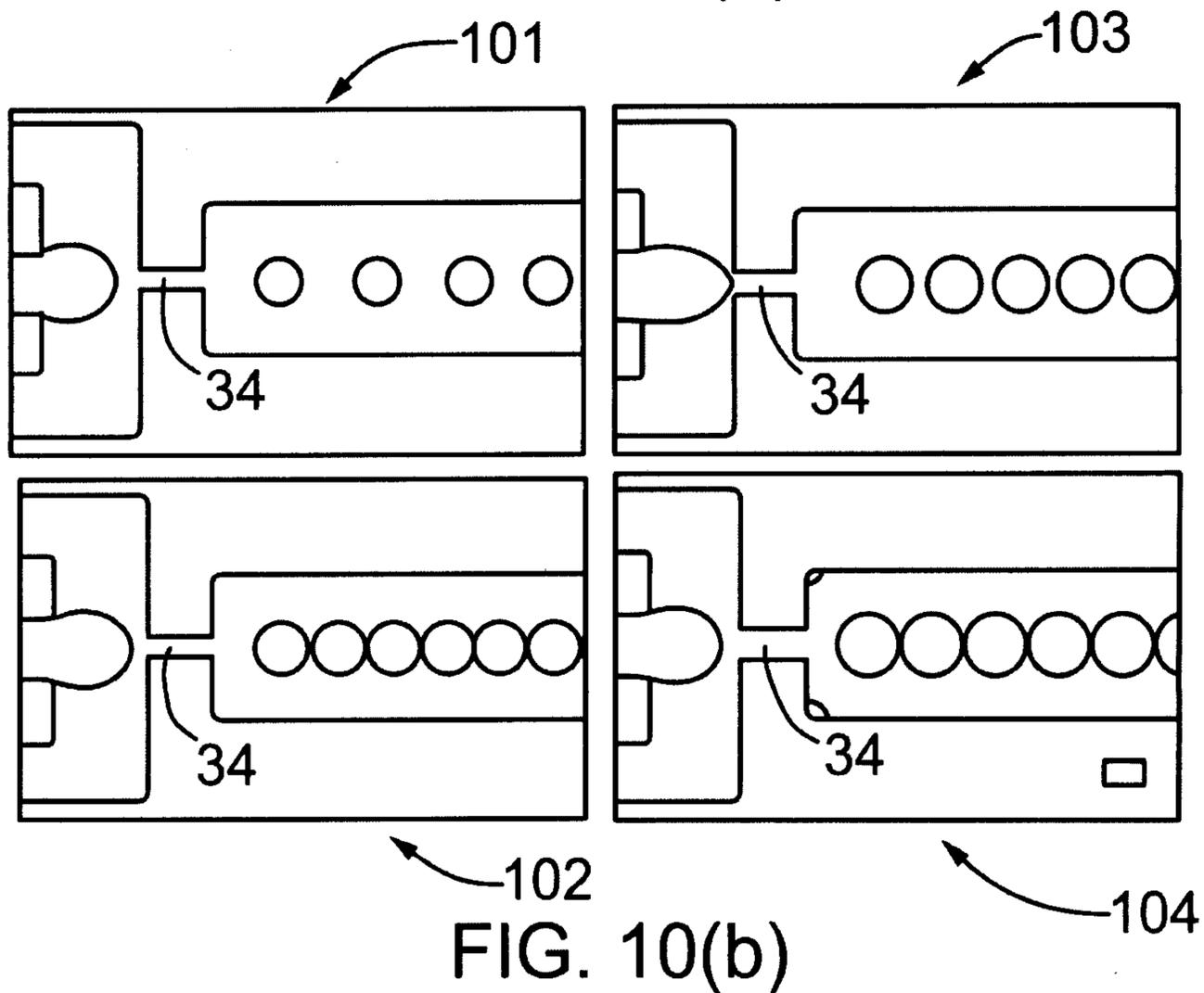


FIG. 10(b)

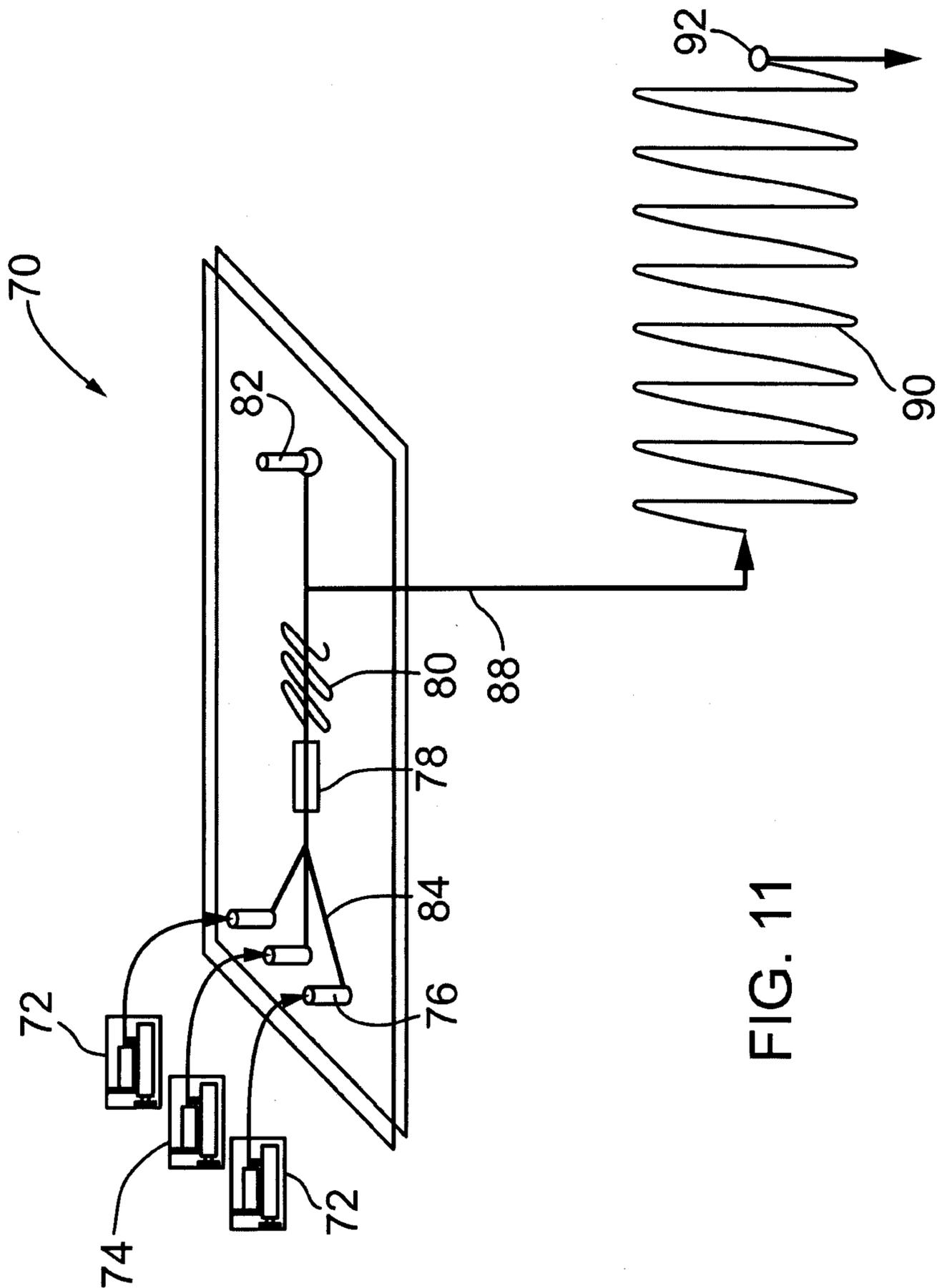


FIG. 11

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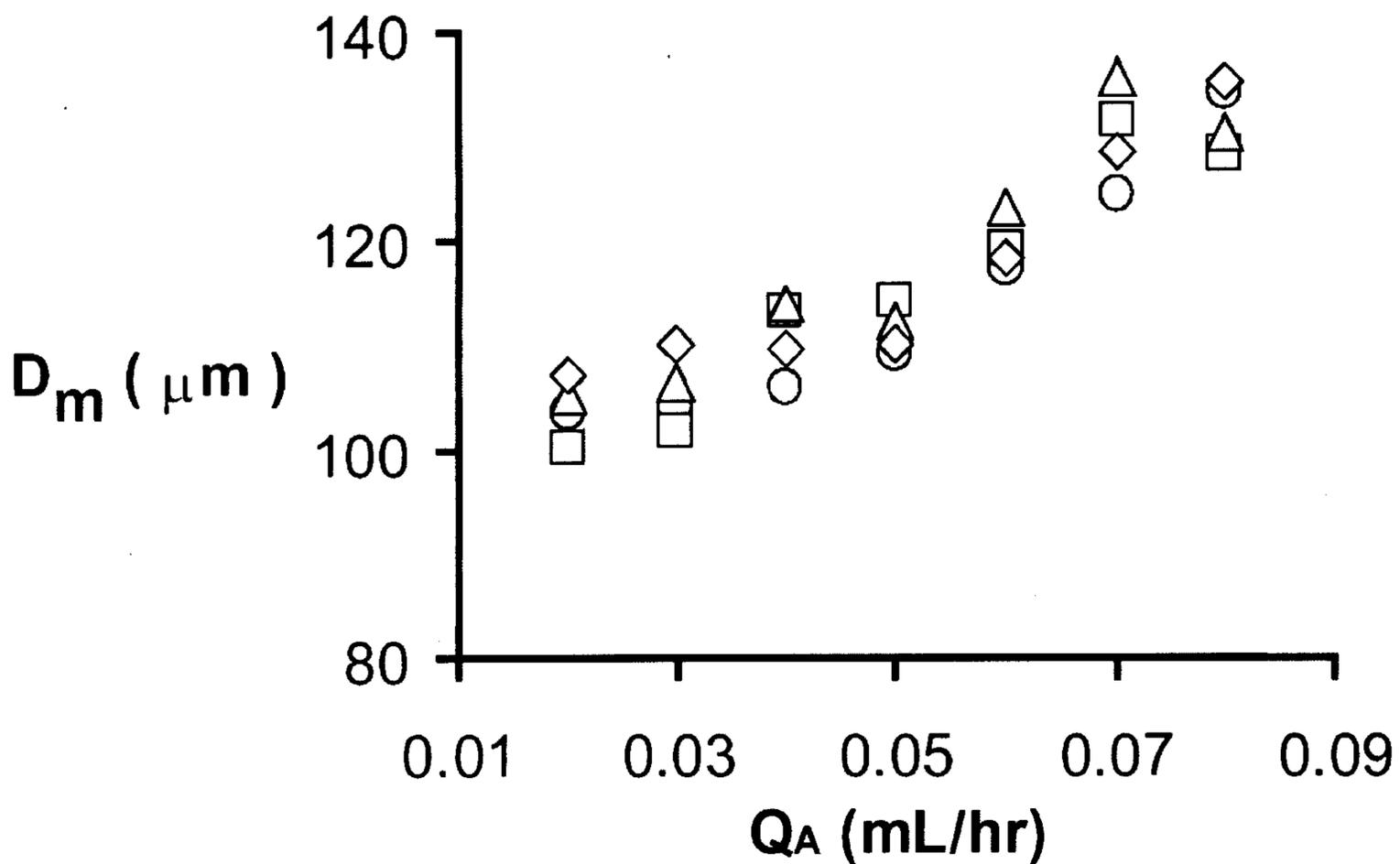


FIG. 12(a)

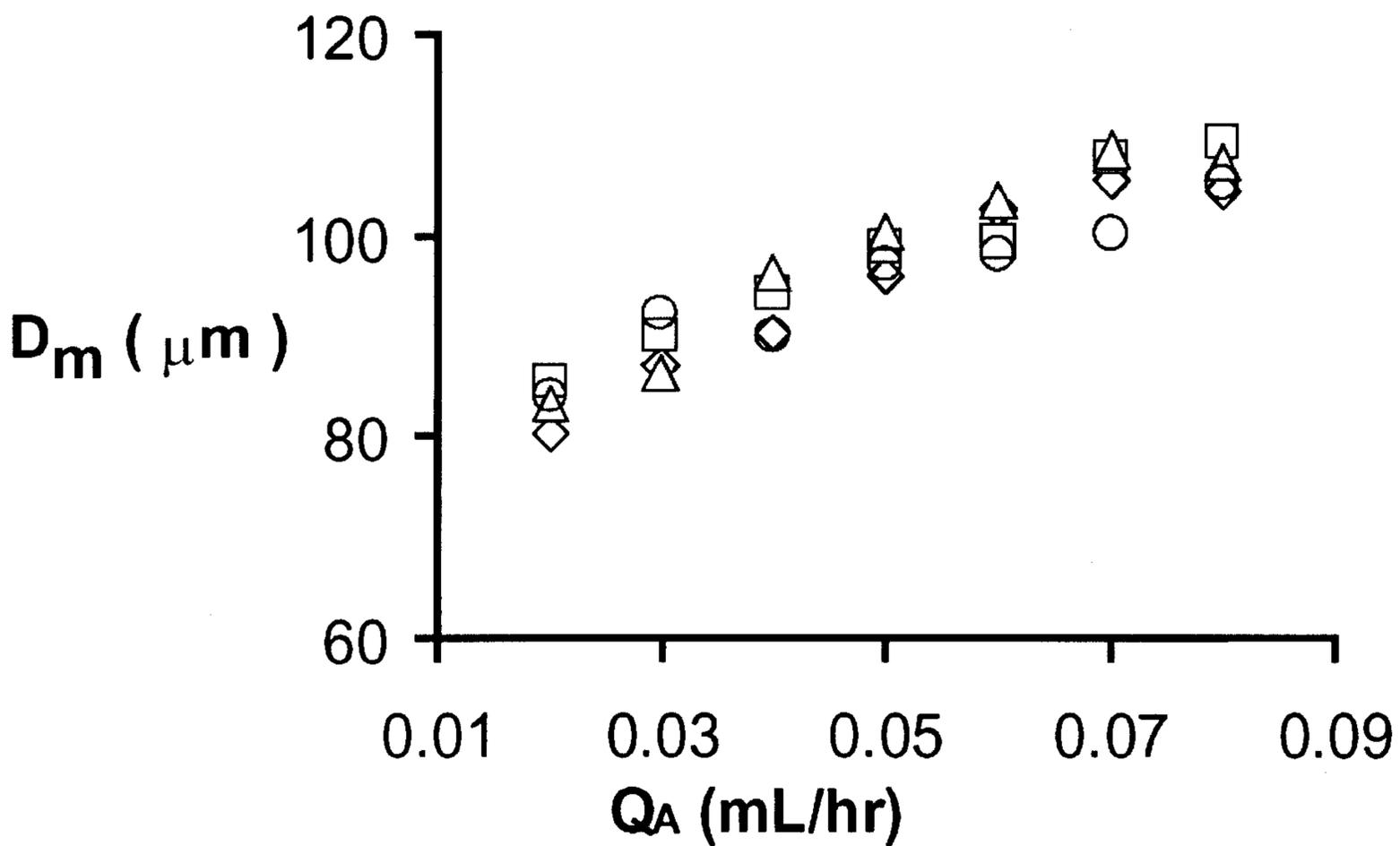


FIG. 12(b)

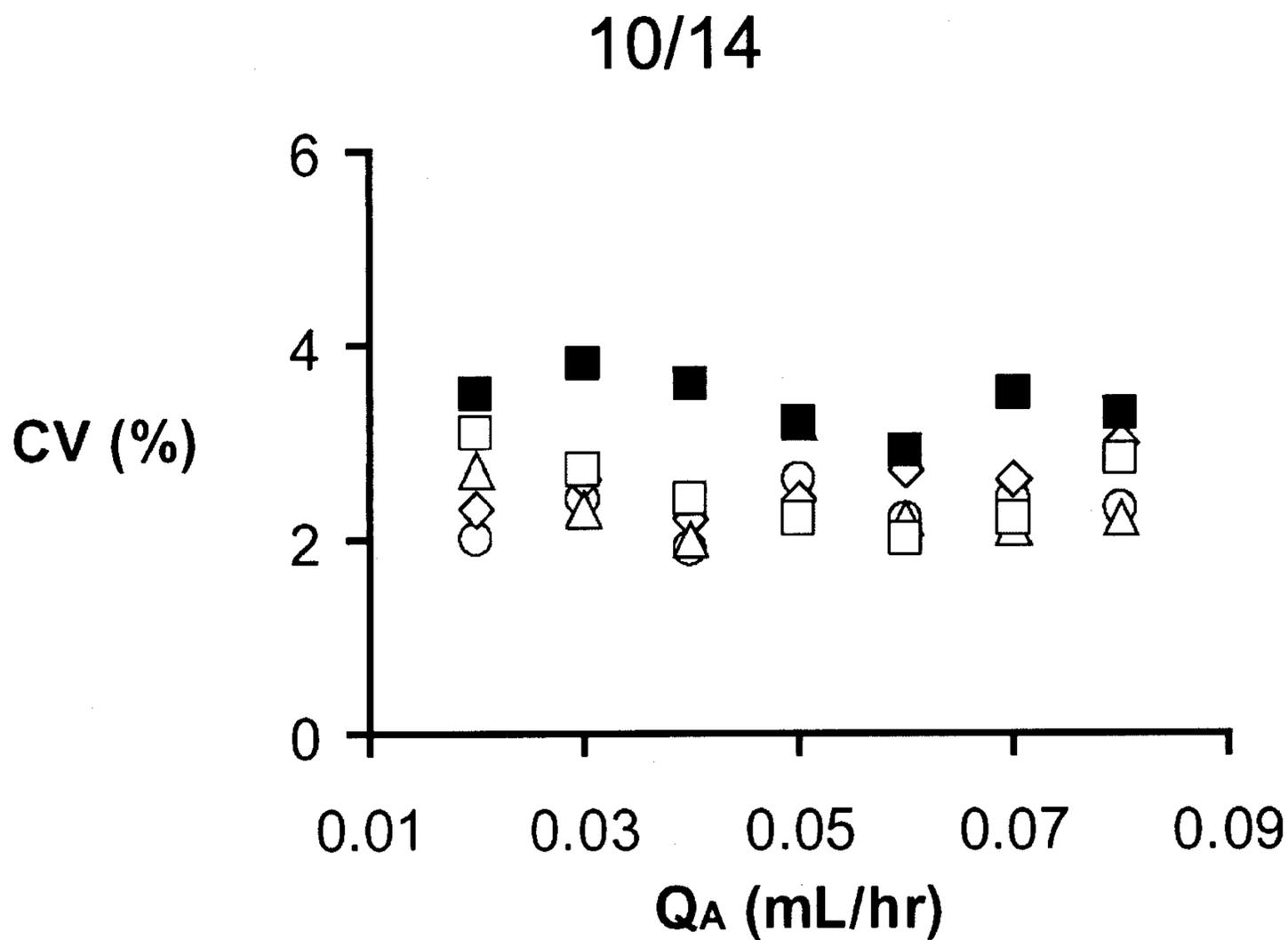


FIG. 12(c)

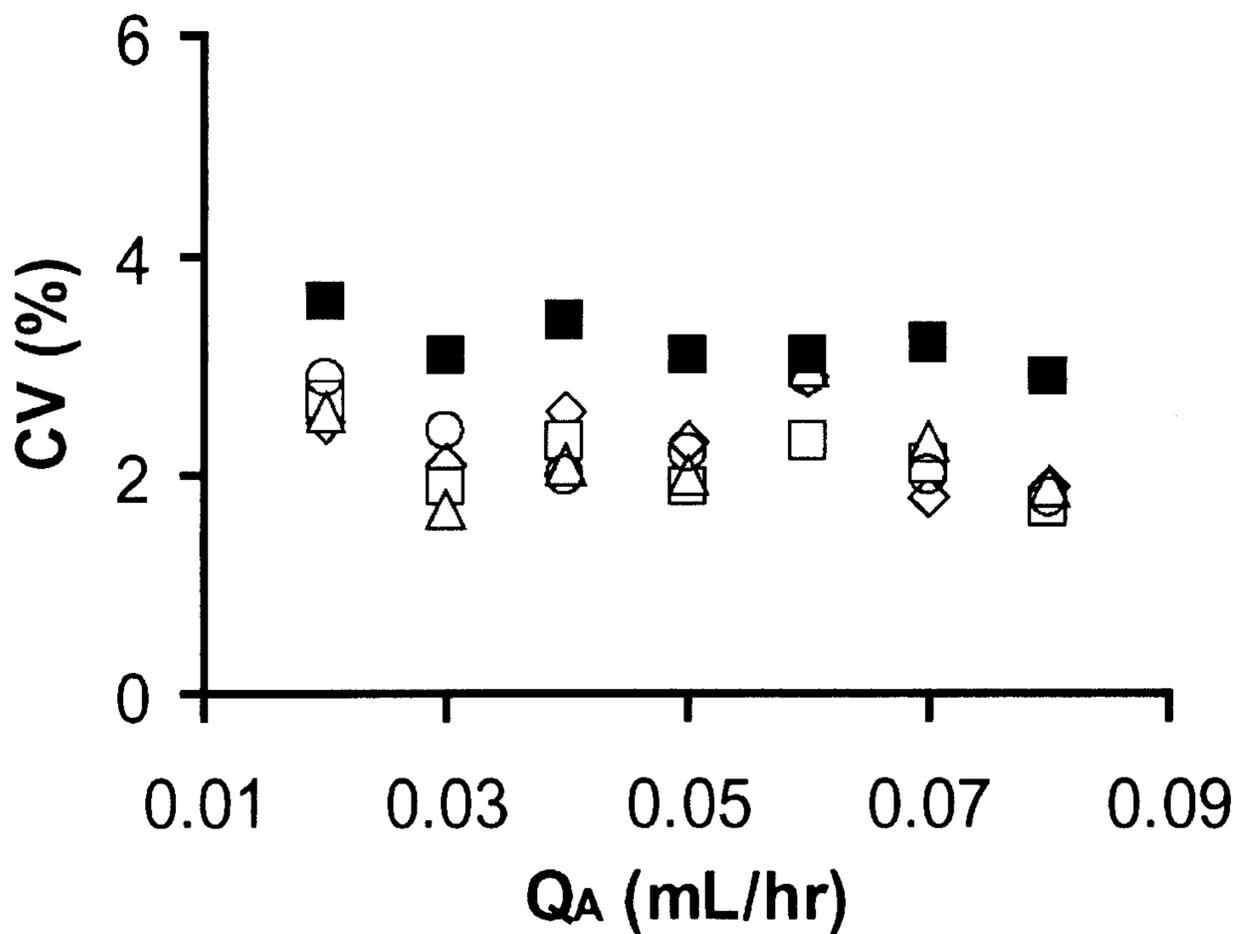


FIG. 12(d)

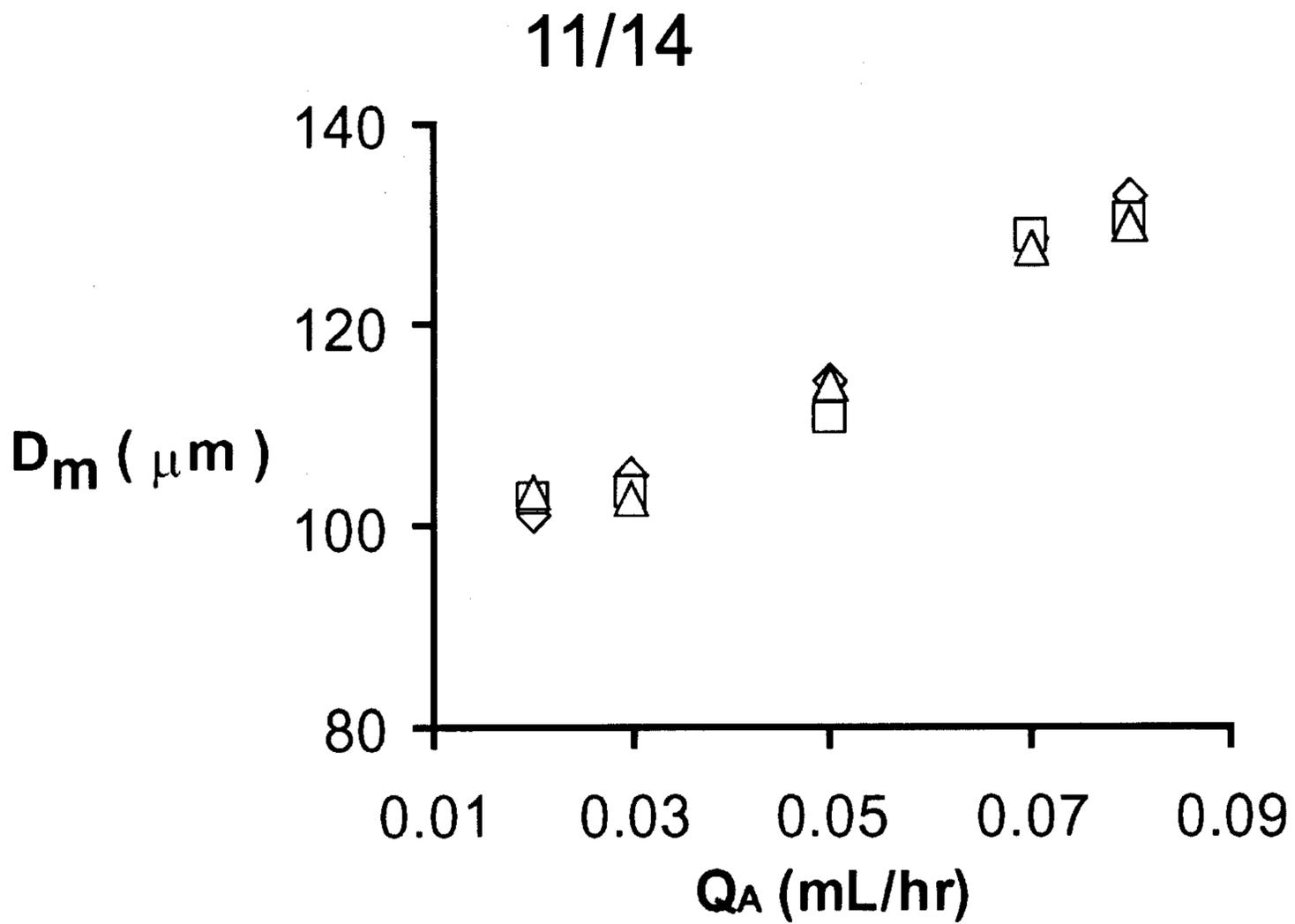


FIG. 13(a)

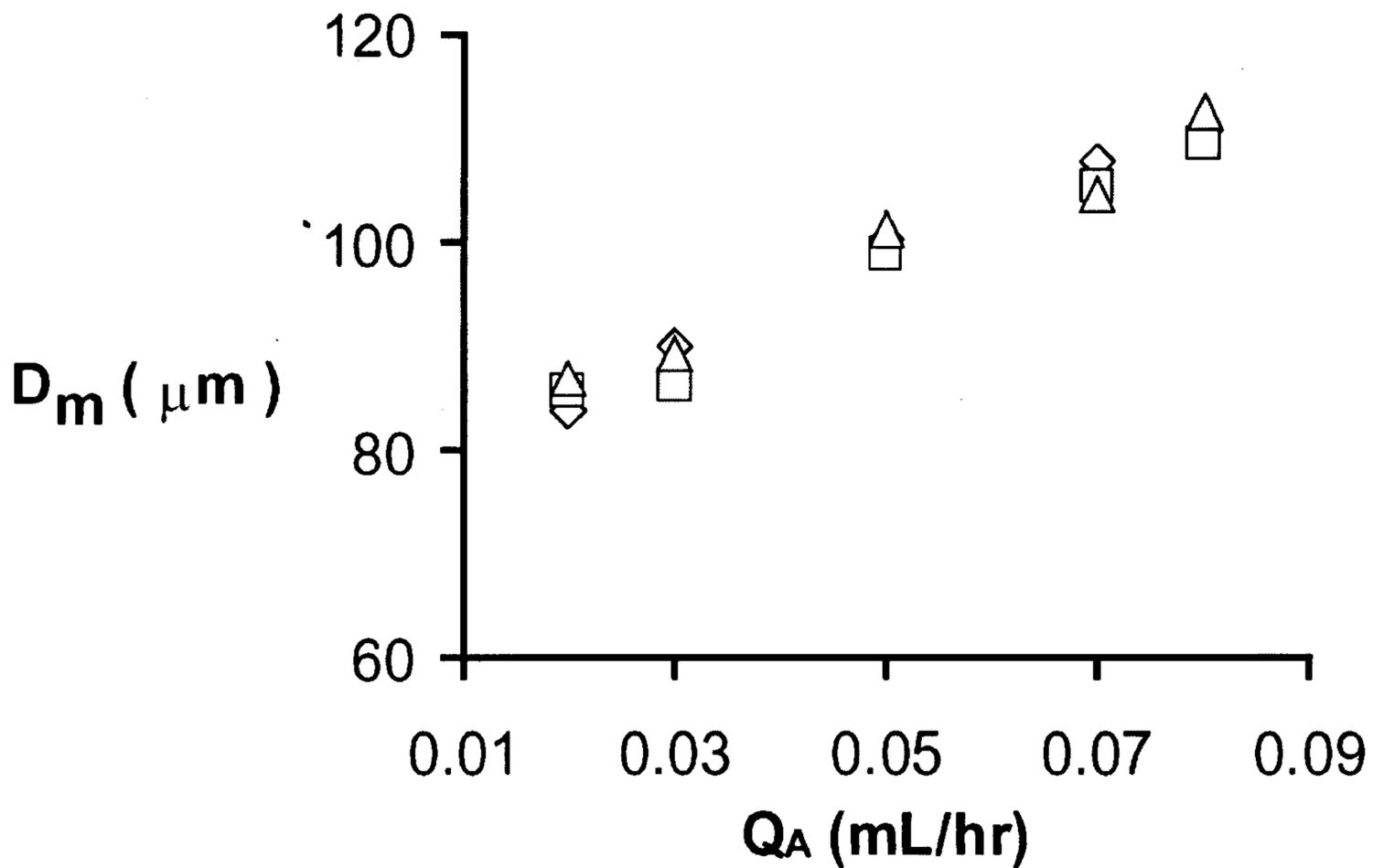


FIG. 13(b)

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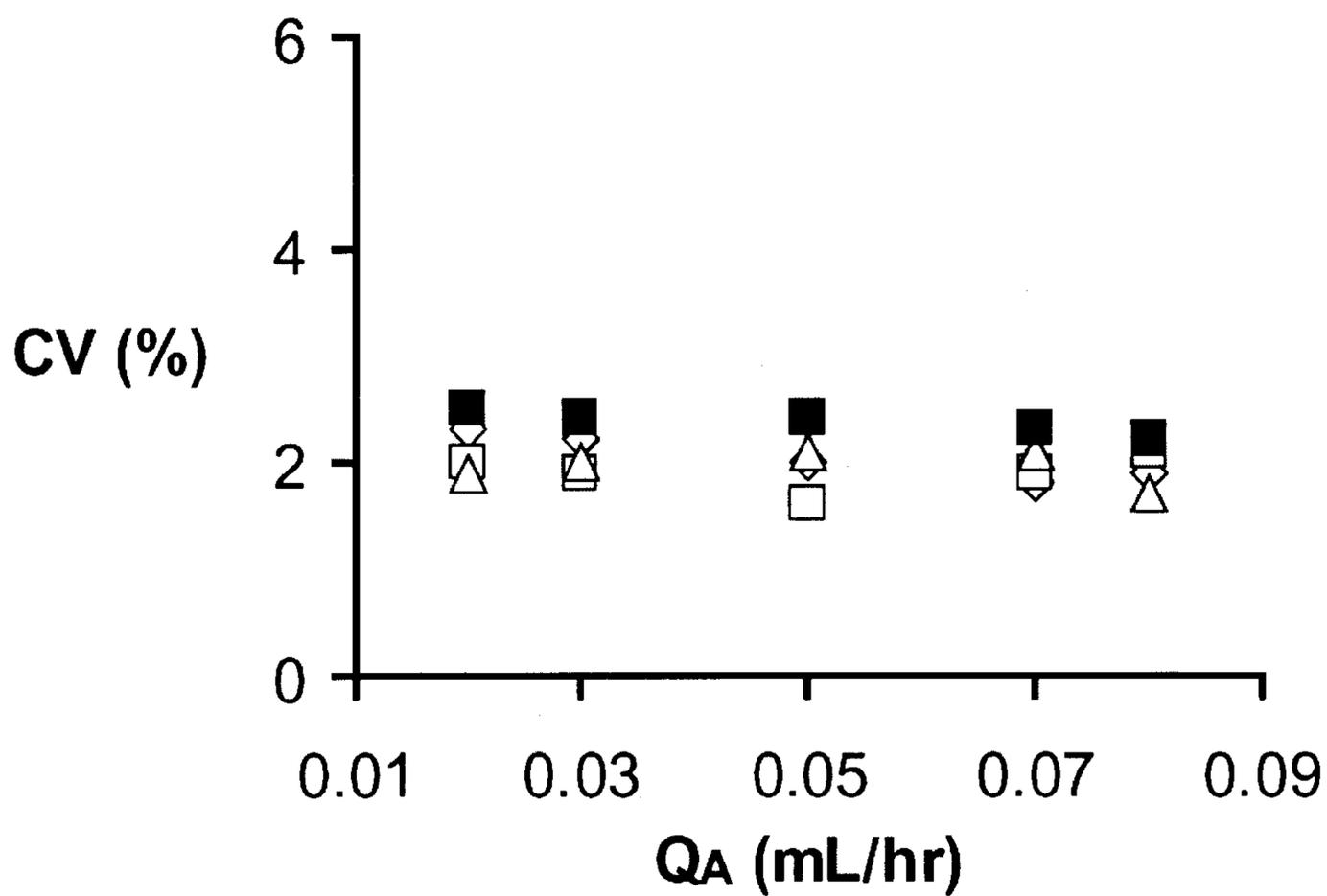


FIG. 13(c)

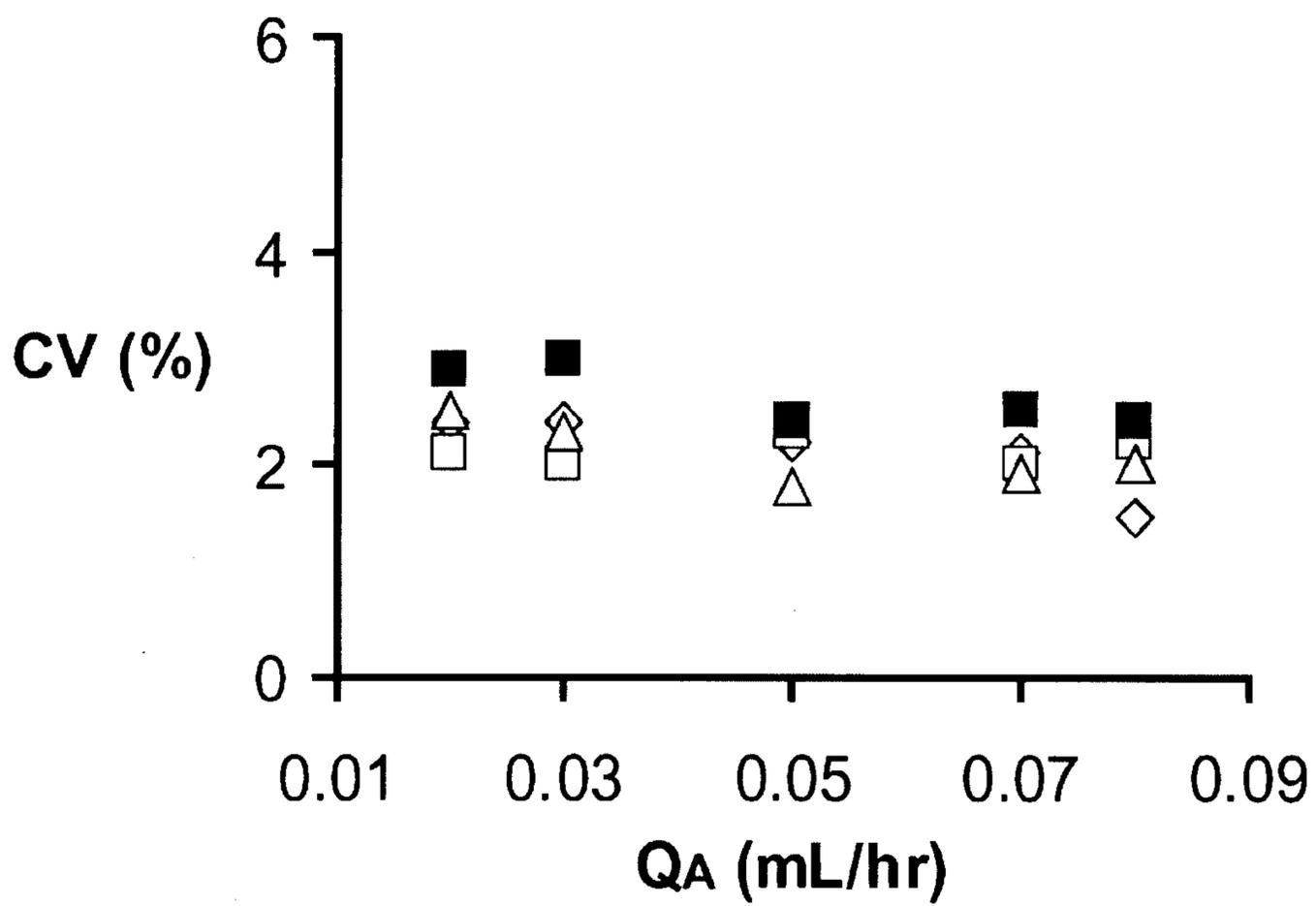


FIG. 13(d)

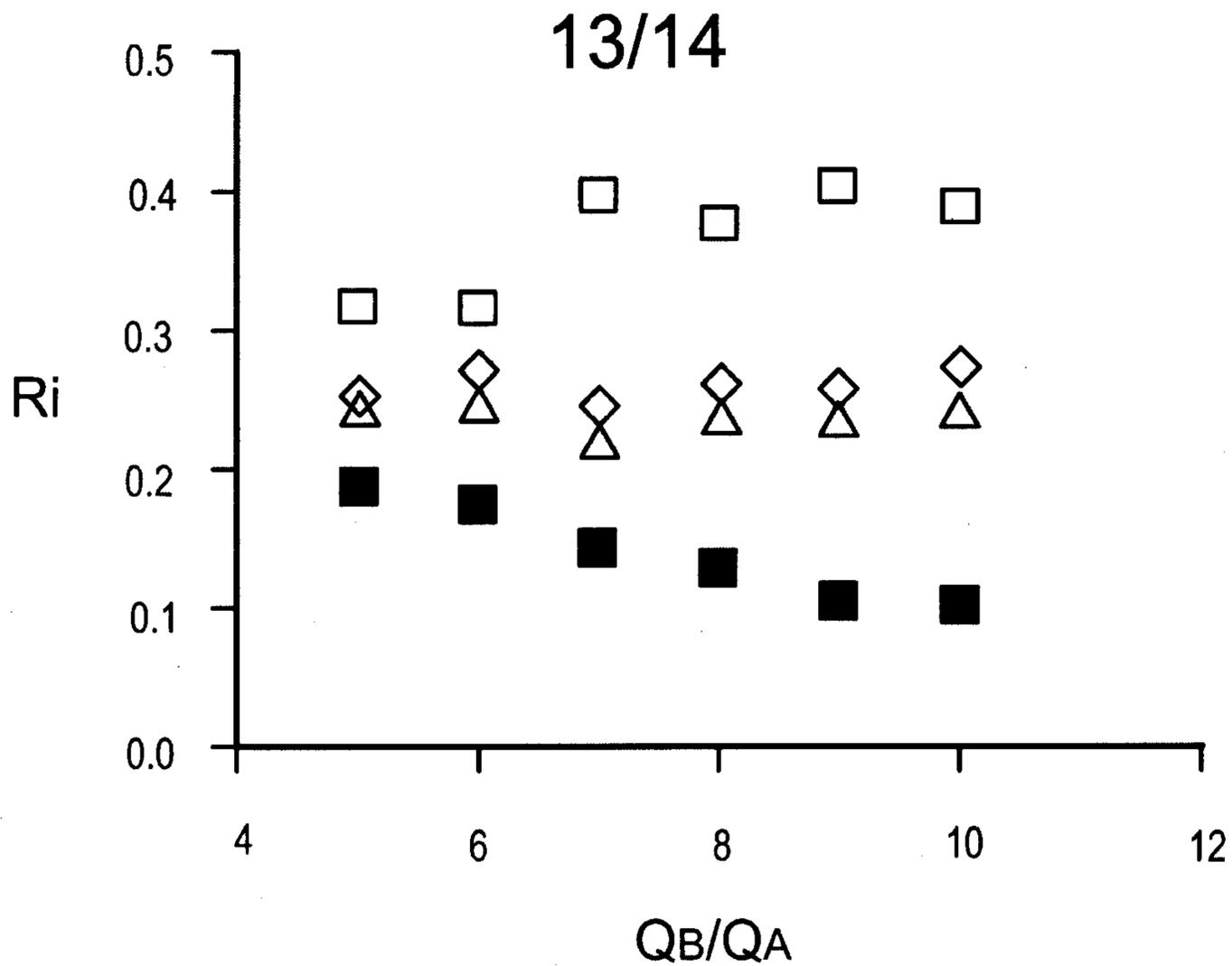


FIG. 14

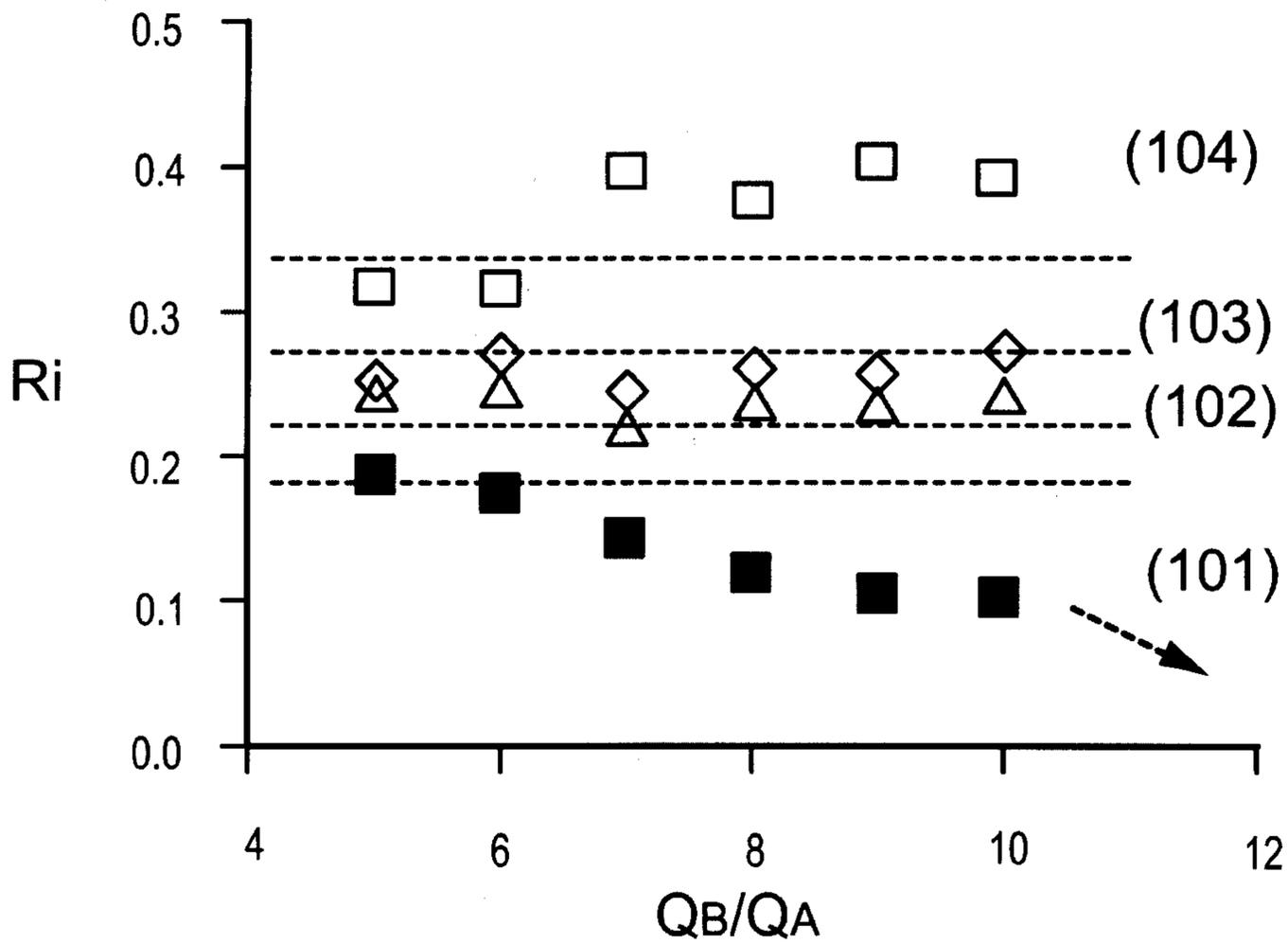


FIG. 15

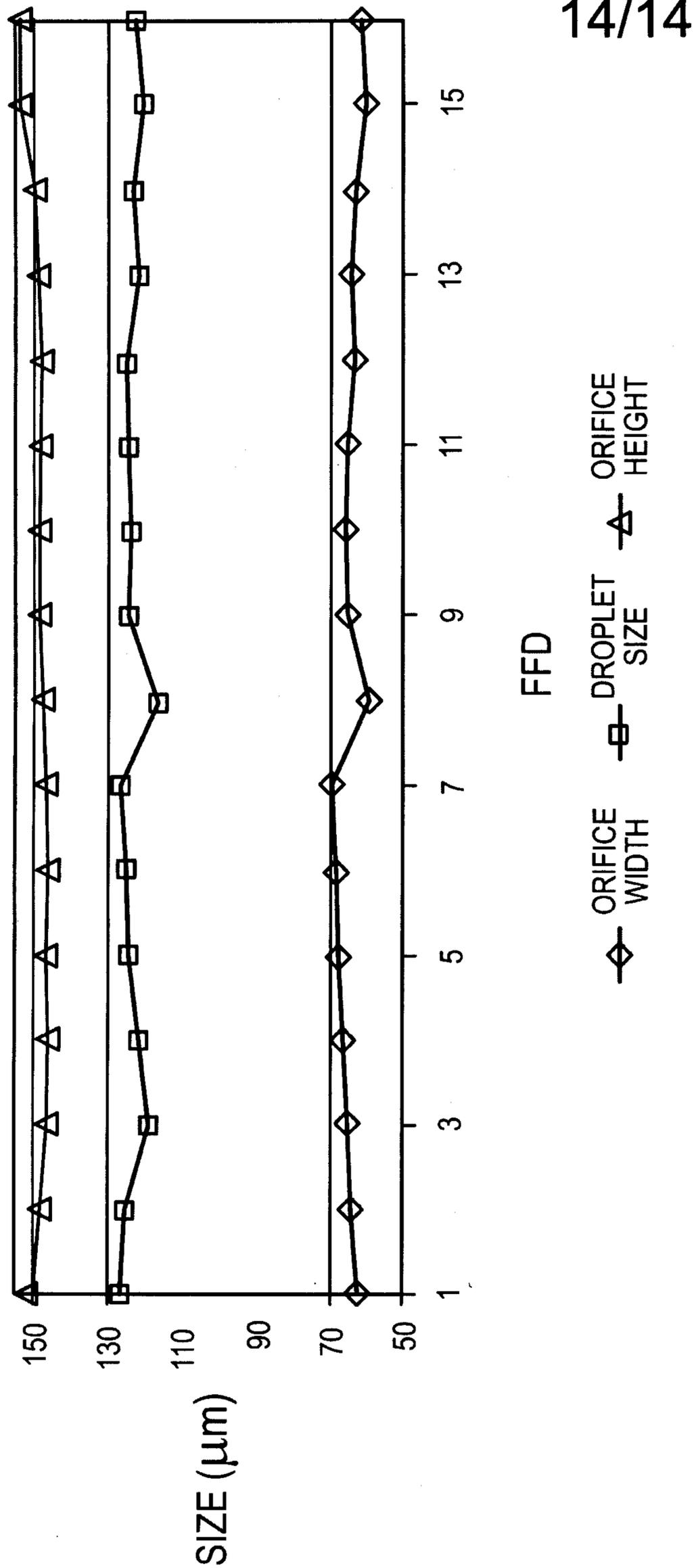


FIG. 16

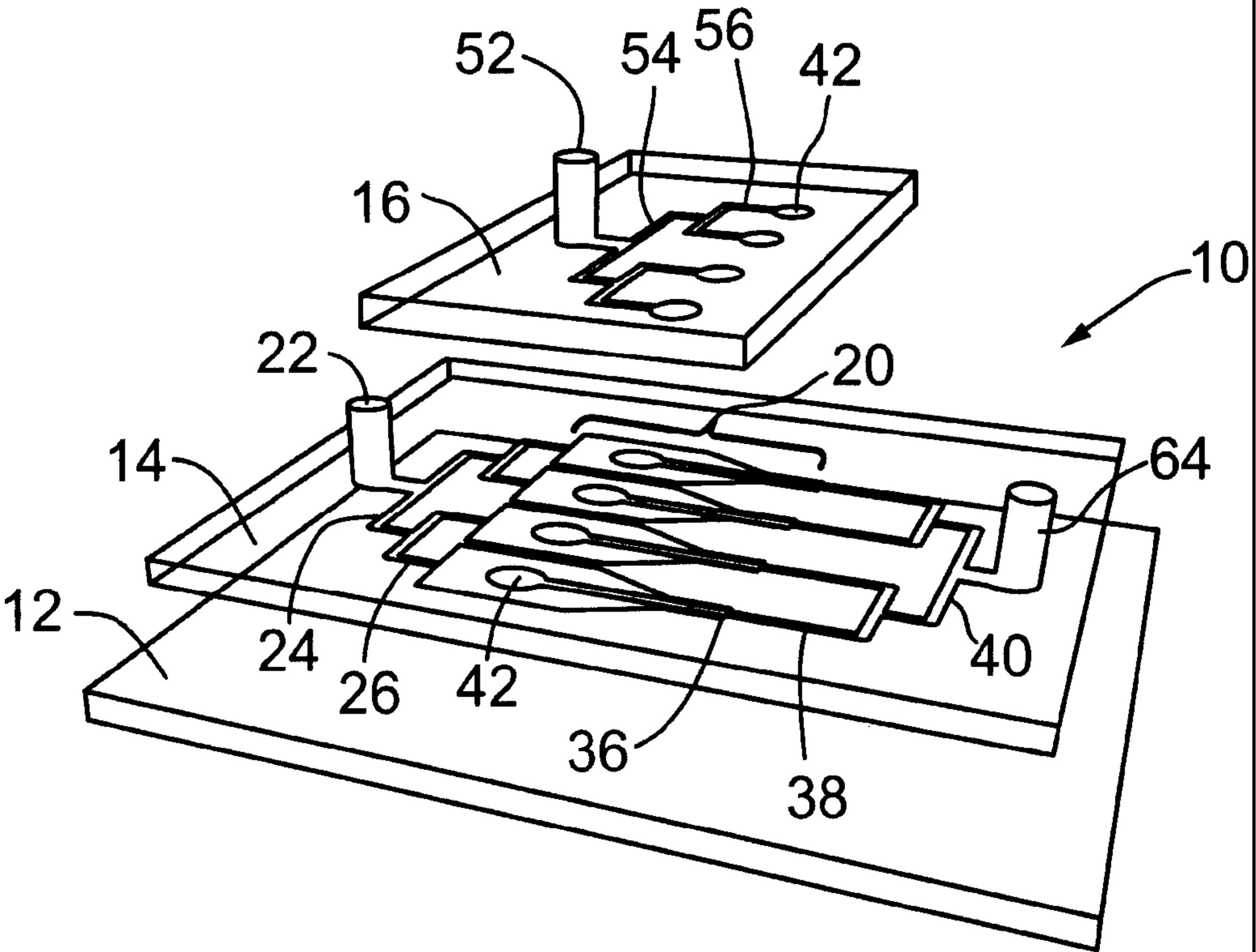


FIG. 3