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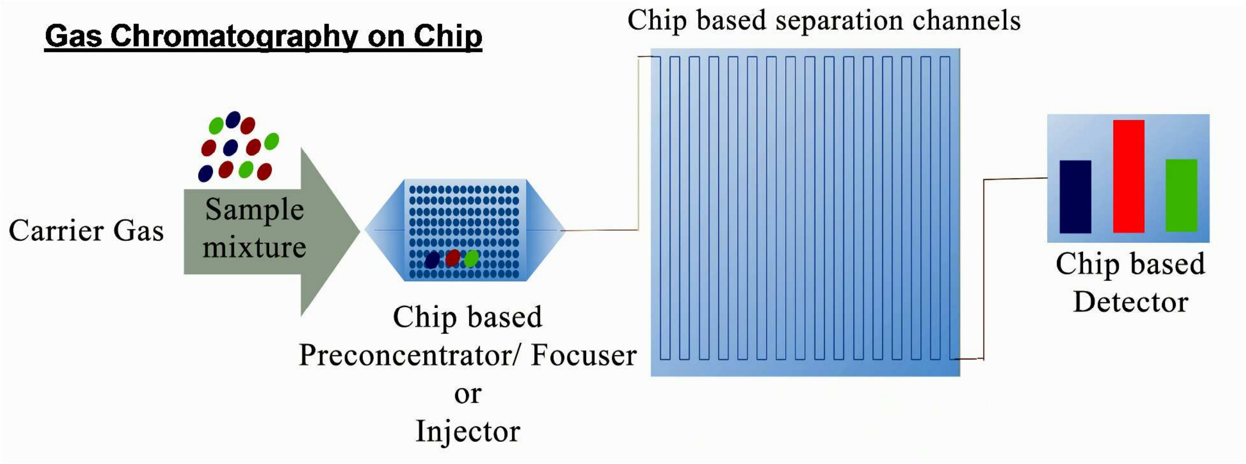
Graphical Abstract



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REVIEW

Through the years with on a chip gas chromatography: a review

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In recent years, the need of measurement and detection of samples *in situ* or with very small volume and low concentration (low sub parts per billion) is a cause for going to miniaturize systems via micro electromechanical system (MEMS) technology. Gas chromatography (GC) is a common technique that is widely used for separating and measuring the semi volatile and volatile compounds. Conventional GCs are bulky and cannot be used for *in situ* analysis, hence in the last decades many studies have been reported with the aim of designing and developing chip-based GC. The focus of this review is to follow and investigate the development and the achievements in the field of chip-based GC and its components from beginning up to now.

1. Introduction

Over the past three decades development of microfluidic devices via microelctomechanical system (MEMS) technology and the critical challenges for analysts i.e. measurement and detection of samples *in situ* or with very small volume and low concentration (low sub parts per billion) has led to creation of the subfield named micro Total Analysis Systems (µTAS) or Lab on a Chip (LOC). Although the emergence of this concept was parallel to introducing the liquid chromatography on a chip in the early 1990s,[1, 2] the first chromatographic separation technique was introduced and fabricated in the late 1970s. This system consist of an injector, circular- spiral channel and thermal conductivity detector integrated on a planar silicon wafer.[3]

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After that, the efforts on microfabrication of this broadly used chromatographic separation technique have been rapidly encompassed by LOC technology.

Gas chromatography is the technique that is most commonly used for separation and measurement of semi volatile and volatile compounds. Briefly, sample components are transported through a long capillary column by a mobile phase consisting of an inert gas (usually H_2, He or N_2). These components are separated based on their boiling points and their relative affinity to the stationary phase coating the walls of the column. The separated components are detected at the exit site using a detector.[4]

A simple bibliographic search with the “gas chromatography” phrase in topic shows that in the last year more than 16000 articles have been published in the various field of science such as: environmental, industrial hygiene, biofuel, petroleum, chemical, agriculture, food and beverage, flavour and fragrance, cosmetic and personal care, cleaning product, pharmaceutical, clinical, forensic and life science. Conventional gas chromatographs are bulky and cannot be used for *in situ* analysis and it might be considered as the main reason toward miniaturization of gas chromatographs, but the other distinct advantages are the faster analysis, reduction in payload requirements (air as carrier gas), power (using battery), waste and sample volume.[5] The miniaturization of gas chromatographs can be done in two ways: one can be built only by scaling down the components (micro GC),[6] and the other via employing machining technology that resulted in planar format (microchip based) which is the focus of this review.

In 1998, Kolesar and Reston reviewed the silicon micromachined GC systems,[7] while Yashin and Yashin reviewed portable chromatographs in 2001 and classified chip-based chromatographs as portable chromatographs.[8] After that in 2002, the development of chip-based chromatography systems has been reviewed.[9] In 2006, SANDIA’s MicroChemLab group discussed about the recent development of gas-phase microlab, where they introduced a new three dimensional micro preconcentrator.[10] Then micro gas analyzers devices for environmental and medical applications were reviewed, in which the authors reconvened about microfabricated GC in short.[11] Ríos et al. further reviewed LOC systems in which they pointed micro GC as a LOCs platform.[1] At the same time, A mini review article was published with the focus on the latest developments in the field of micro and nanostructures in GC, where their authors briefly discussed about microchannels in micro GC.[13] Beside the review articles in this topic that concisely mentioned about GC and its associated components on a chip, two chapters’ books also have been published up to now that discussed about design, fabrication and characterization of chip based gas chromatographs.[14, 15]

In this review, we wish to follow and investigate the development and the latest achievements in the field of chip-based GC and its main components (i.e. micro preconcentrator/injector, micro columns and micro detectors) from the beginning up to now.

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2. Chip-based gas chromatography

In the field of chip-based systems, the work is considered to be ideal when the chip can perform all the steps of analysis automatically on a single chip. Every chip-based analysis system may include sampling, sample preparation, chemical reactions, chemical separation, analyte purification, analyte detection, and data analysis. Such device due to its small size compared to conventional systems has advantages such as portability, reliability, reduced analysis time, reduced cost of operator and analysis, waste reduction, and reducing the volume of the sample, solvent and reactant.[5] Also, many of the chemical reaction products are toxic and harmful which in these systems, human contact with materials is minimized.[16]

The chip-based GC like conventional type consists of an injector, a column coated with stationary phase, and a detector but to be scaled down. Each of these chip-based subsystems as well as the fully integrated system of GC have been developed through the years. Typically, after sampling or injecting samples into the injector or preconcentrator, samples transported through the separation channels by pumping inert gas[17-19] are detected at the exit using a detector. In the following, advances in each of the integrated components are surveyed.

3. Materials and Fabrication

Silicon and glass are the most applicable materials used for micromachining and chip fabrication as substrate due to the advantages like possibility of batch-fabricating (all fabricating process for silicon substrates are well established) and chemical and thermal stability.[20] Polymers have alternatively grown for microfabrication because of several advantages: they are non-toxic, commercially available and inexpensive with fast and easy prototyping possibilities, and have small thermal mass.

The most popular polymer is polydimethyl siloxane (PDMS),[21, 22] while other polymers such as polyparaxylylene (Parylene)[23, 24] have also been used. Metals such as nickel also have been reported as column substrate because of high thermal conductivity which made it suitable for temperature programming works.[25, 26] As most of the reported GC columns microfabricated by machining silicon and bonding with Pyrex, Radadia and co-workers suggested a novel bonding method to fabricate all silicon-based GC device to decreasing alkaline impurities and increasing thermal conductivity and diffusivity compared to Pyrex.[27]

Generally, the fabrication methods include LiGA (lithography, electroplating, and molding) techniques, wet isotropic etching, and deep reactive ion etching (DRIE) which have been used to achieve channels, cavities and etc. with different geometries and shapes that is not discussed in this review and can be followed in mentioned chapter's books and articles.[28-30]

4. Chip-based injector/ preconcentrator

Injector is a device used for introducing liquid or gas samples into the chromatograph. The sample is introduced directly into the carrier-gas stream (e.g., by syringe) or into a chamber temporarily isolated from the system by gas sampling valves.[4] Among all reported studies, several research teams have used commercial injectors with split mode (sample mixture is partly injected into the separation channels)[31] or gas sample valves[32] to introduce samples into micro columns. Some others designed and fabricated the chip-based preconcentrator instead of injector to increase sensitivity and selectivity.[33] In both, the device must be capable of generating sharp injection plugs.[34, 35]

Micro injector was firstly fabricated by Terry et al. with 1 nL sample volume. [3] In 2002, Bessoth et al. further designed a micro injector with two intersecting channel like capillary electrophoresis (Fig 1a), where the size of gas sample reached to approximately 1.6 nL.[36]

Holland et al. miniaturized gas chromatography- mass spectrometry (GC-MS) for *in situ* analysis in planetary exploration, and designed and fabricated MEMS-based injector with programmable gas sample injections of 0.5-15 µL.[37] In 2007, a fully integrated gas chromatograph was reported that injected samples with approximately 5 µL volume with split mode.[26] Also a six low leak microvalves-based micro injector with 250 nL sample volume (Fig 1b) was introduced in 2010. Each valve made from sandwiching polyetheretherketone (PEEK) membranes between silicon substrate and glass. Six valves opened and closed by changing pressure through their actuation hole. In sampling mode valves A, D and E are closed while for injecting sample into separation channels valves B, C and F are closed.[38, 39] The summary of microfabricated preconcentrators for chip-based GC are collected in Table 1.

Alfeeli et al. reported in 2008, a preconcentrator that comprises more than 3500 micropillars coated with Tenax TA as adsorbent for increasing surface area and adsorption capacity.[33]

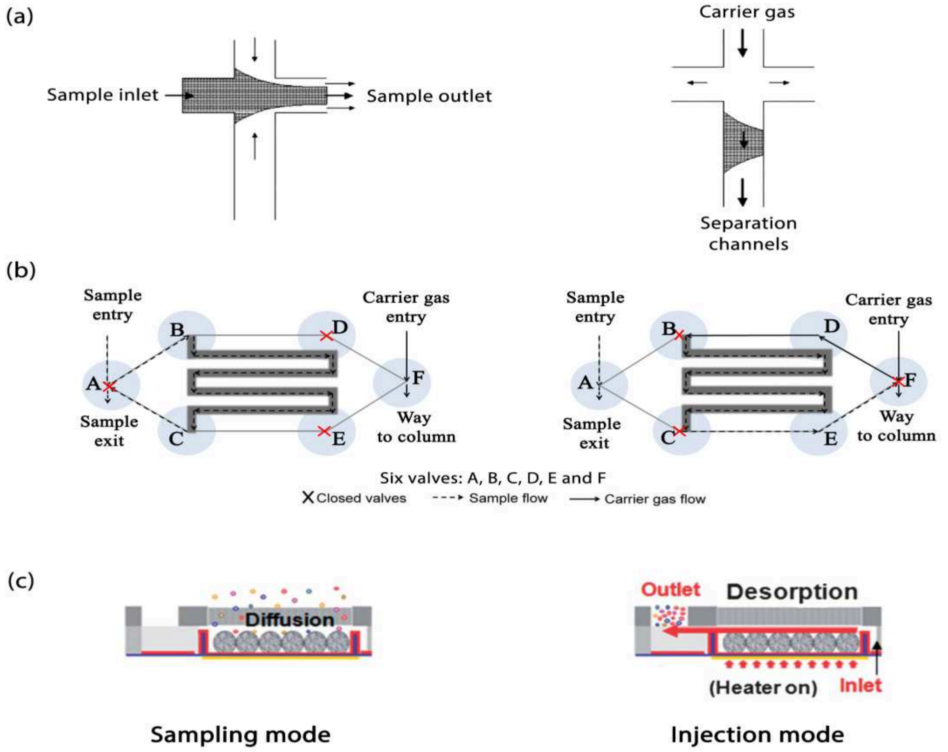

Fig. 1 Different methods of introducing sample mixture into a separation channel; (a) Glassy micro injector with two intersecting channels.[36] Adopted from Ref. 36 with permission from The Royal Society of Chemistry; (b) Six low leak valves with 250 nL sample volume;[38, 39] Adopted and modified from Ref 39 (c) Chip-based micro passive preconcentrator injector.[40] Adopted from Ref. 40 with permission from The Royal Society of Chemistry.

Table 1 Summary of microfabricated preconcentrators reported for chip based GC.

Adsorbing material	Design	Analyte	Working condition	CF[a]	Power	Ref.
Carbopack X	3 mm ×3 mm microfabricated compartment with heating elements separated by 220 µm gaps and thermal isolation air gap around the microheaters	Benzene, m-Xylene, and α-Pinene in dry air	Desorption at 3.3 mL min^{-1}	5600	2.1 W	2003[41]
Carbopack B, Carbopack X and Carboxen 1000	Three-stage adsorbant contains a set of 31 parallel heat exchanger with 27 mm^2 active area	m-Xylene	Desorption at 280˚C	4800	~mW	2005[42]
Tenax TA	7 mm ×7 mm microfabricated compartment with thermal desorption capability and more than 3500 micropillars	C_8, C_9, C_{10}, C_{12} and C_{14}	Desorption at 250˚C	1000	-	2008[33]
QxCav[b]	25 mm ×12 mm ×1.3 mm microfabricated compartment with micromachined silicon cartridge	BETX[c]	Desorption at 100˚C during 5-30 s	-	-	2009[43]
Activated carbon	1cm×1cm alumina substrate with screen printed Pt heater	Benzene and 1,3 Butadiene in air	Desorption at 175˚C during 10 min	> 300	-	2011[44]
Carbopack B and Carbopack X	A sampler, pretrap and micromachined focuser with an integrated heater	TCE[d]	Adsorption & sampling for 26 min/ Desorption at 225˚C	800000	-	2011[45, 46]
Carbopack X	Two layers; a grid of square diffusion channels for vapour sampling, and a cavity for adsorbing analyte with an integrated heater	Toluene	Desorption at 250˚C in 0.23 s	-	1 W	2012[40]
Carbosieve S-II	18.5 mm ×9.3 mm ×1.26 mm microfabricated compartment with 8 parallel adsorption channels and integrated heater	Ethylene in air	Adsorption for 10 min / Desorption at 200˚C during 1 min	23	-	2012[47]
Porous carbon	10 mm ×1mm microfabricated compartment with depositing silver as microheater on cylindrical obstacle arrays	Acetone, Benzene, Toluene and Xylene	Adsorption for 600 s/ Desorption at 300˚C for 90 s	>38000	~ 1 W	2012[48]
Porous carbon	14 mm ×4mm microfabricated compartment with an array of microextraction needles and integrated heater	Toluene	Adsorption for 1 min/ Desorption at 320˚C	13637	3.6 W	2012[49]
Carbopack B and Carbopack Y	A sampler, pretrap and micromachined focuser with an integrated heater	DMNB[e] and 2,4-DNT[f]	Adsorption for 20s/ Desorption at 250˚C	4500 and 1800	-	2013[50]
Carbosieve S-II	microfabricated compartment with micromachined silicon cartridge and integrated heater	Ethylene in air	Desorption at 200˚C during 10 min	-	19-58 W	2014[51]

[a] Concentration factor, [b] Quinoxaline-bridged cavitand, [C]Benzene, Toluene, Ethylbenzene and Xylenes, [d]Trichloroethylene, [e]2,3-dimethyl-2,3-dinitrobutane, [f]2,4-dinitrotoluen

Moreover a alumina-based preconcentrator was fabricated for detecting benzene in presence of 1,3 butadiene and evaluated with conventional GC system.[44]

Recently, an integrated sampler injector on a silicon wafer named micro passive preconcentrator injector (µPPI) was introduced based on Fickian diffusion theory for preconcentration of volatile organic compounds (VOCs) prior to injection to separation channels. This sampler injector is composed of two layers, one layer has a grid for vapour sampling and the other has a cavity containing graphitized carbon for adsorbing analyte with integrated heater for thermal desorption with sampling rate of 9.1 mL min^{-1} (Fig. 1c).[40, 50]

On the one hand, to choose proper adsorbing material via nature of samples (strong affinity with analytes, low activation energy of desorption, large capacity and good binding with preconcentrator substrate) researchers persuaded to introduce and evaluate different adsorbents.[52, 53] On the other hand they considered fabrication of different geometries for increased surface area and sampling volume.

In 2012, a novel preconcentartor was reported, which used laminar flow patterning technique to deposit silver microheater into the channels and then grow carbon on microheaters as an adsorbent. In this study the concentration factors of more than 38000 were obtained.[48] Also in the same year, this research group reported the microfabricated preconcentrator with micro solid-phase microextraction (µSPME) needle coated with porous carbon and evaluated with toluene.[49]

To analyze the trace levels of two explosive markers, Serrano et al. fabricated the preconcentarator/ focuser that contained three main components: membrane filter, sampler and focuser. After sampling, only the volatile compounds pass through the membrane filter and captured by the adsorbent in sampler. They were then thermally desorbed and transformed to the focuser cavity, next the analytes concentrated and thermally injected to the separation channels.[50] Recently, Janssen et al. reported the fabrication of a preconcentrator filled with carbon component as adsorbent and improved their last work[47, 54] to detect ethylene with the 170 part per billion by volume (ppbv) limit of detection.[51]

5. Chip-based separation column

The most critical component and the heart of a GC system is the micro capillary column also called micro-channel, in which the separation of gas components takes place. Type of stationary phases, working modes and geometry of channels are the most important factors that influence on device design and performance.

5.1 Working modes and interface technology

Like conventional gas chromatograph system, chip-based GC can be used in two modes: isothermal and temperature programmed. In the case of a sample mixture containing components with a wide range of boiling points, to obtain better resolution many researchers have integrated micro heaters or used conventional ovens. For the first time Noh et al. fabricated parylene channels integrated with a thin gold film as the heating element for faster heating and cooling processes.[23, 24] Following this publication, Agah research team showed satisfactory separation by using conventional oven for temperature programmed mode[31]. Afterward, they designed and microfabricated GC columns with both integrated heaters and temperature sensors for programming the temperature, as well as integrated sensors for accurate flow control.[55]

The maximum operating temperature reported by chip-based GC system was below 250 ° C because of using Nanoport^{TM} and epoxy, or silicone adhesive for connecting capillaries. Afterward by using the stainless steel and graphite/ vespel ferrules for connecting the capillaries to the channels the maximum operating temperature increased to 450℃, where the system can be used for analysing semi volatile compounds.[56] However, Radadia et al. first used this connection to decrease the dead volume.[57] The other important factor in the case of interface technology is the proper use of inlet/outlet interface without leakage and instability.[84]

5.2 Theory

The separation efficiency is a key characteristic that is used to measure the performance of a GC column. This property is measured by the number of theoretical plates (N) and the height equivalent to a theoretical plate (HETP) as calculated by equation (1):

$$\mathrm{HETP}=\frac{L}{N} \tag{1}$$

Where L is the column length.

Historically, the initial theoretical work on open-tubular GC dates back to the middle of twentieth century when Golay introduced HETP for rectangular channels as equation (2):[58]

$$H=\frac{2D_g}{\bar{u}}f_1f_2+\frac{\left(1+9k+52.5k^2\right)}{105(k+1)^2}\frac{w^2\bar{u}f_1}{D_gf_2}+\frac{2}{3}\frac{k(w+h)^2{d_f}^2}{(k+1)^2D_sh^2} \tag{2}$$

Where D_g and D_s are the binary diffusion coefficients of the solute in the mobile phase (carrier gas) and stationary phases, respectively, k is the retention factor, w and h are the channel width and height, respectively, f_1 and f_2 are the Giddings-Golay and Martin-James gas compression coefficients, respectively, d_f is the thickness of the stationary phase, and $\bar{u}$ as the average linear carrier gas velocity may be calculated by equation (3):

$$\bar{u}=\frac{L}{t_M} \tag{3}$$

Where t_M is the hold-up time i.e. the time it takes for unretained solute (usually methane) to travel from the injector to the detector. In this case, the solute travels through the injector with inner volume, column with the length of L, and detector with the inner volume cell.[4] Since Golay, many researchers have studied the theory of the column's geometry and effects of cross sectional shape on the plate height in a way that different expression of plate height were purposed. They demonstrated that the rectangular cross section channels do not provide better separation characteristics in comparison with circular cross section columns while different plate heights were obtained for different cross-sectional shapes. The longer column with the smaller cross sectional area leads to longer separation time, therefore there is a trade-off between the separation resolution and the analysis time. For more information the authors suggest the mentioned references.[59-75]

Generally, in conventional open tubular capillary columns that are like micro channels because of nearly alike dimensions, the efficiency increases as the radius of the column decreases. Nevertheless, decreasing the radius or width causes a significant decrease in the surface area of the column, which greatly reduces the amount of the analyte that the column can efficiently separate.[4] Furthermore, narrow columns require high pressures which can create drastic limitations on the design of other chip-based GC components. In 2005, a high speed GC system was designed by Agah et al., where they investigated how the number of theoretical plates and hold-up time depends on the column length and width. As can be seen in Fig. 2, they demonstrated that the longer columns have more N and more hold-up time.[55, 76]

Also, to conquest low analyte capacity in open tubular (OT) and pressure drop in packed columns problems, this research team introduced semi-packed[77] and multicapillary[78] microcolumns. In 2013 Yan et al. combined the transport model with conditions including an open, long isothermal column with a flow driven by pressure, and a systematic optimization tool in order to minimize the plate height by adjusting the column's cross-sectional shape.

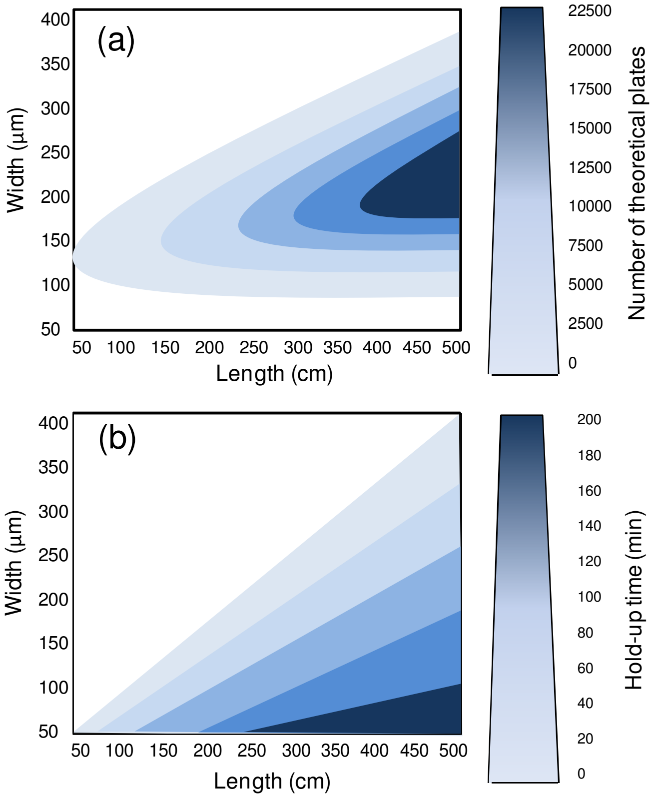

Fig. 2 Counter plot of (a) the number of theoretical plates, (b) hold-up time as a function of column length and width[55]. Adopted and modified from Ref 55.

The plate height was theoretically measured for the transport model and demonstrated that the hypothetical column with shallower optimal shape provides smaller plate height followed by larger plate number per meter but presently, higher pressure is required if the column length is fixed.[75]

Recently, the fabrications of serpentine semi-packed and serpentine channels were reported, and the efficiency of columns by injecting hexane in different velocities compared.

In fact, as Agah research team proved before, the presence of the posts in the semi-packed column results in a more uniform velocity profile (Fig. 3a and 3), shorter mass transfer distances and hence reduction in band broadening.

In fact, when the gas sample moves in areas with no posts, it experiences less variation in velocity and thereby the symmetrical distribution minimizes the eddy diffusion. Thus, when it travels through the posts, it experiences shorter mass transfer distance and less pressure drop leading to reduced ergo band broadening.[77] As it is seen in Fig. 3c, the increase in the gas velocity strongly raised the HETP of open-tubular columns, unlike semi-packed column.[79]

5.3 Geometry of channels

The chip based-GC researchers have used microchannels with different configurations including circular spiral (consists of relatively less sharp turns and no straight segments), square and rectangular spiral (consists of straight length segments and sharp 90^{o} turns), radiator and multicapillary (consists of straight long segments and sharp 180^{o} turns that have channels in each straight segment), serpentine (consists of straight long segments and sharp 180° turns), zigzag (consists of zigzag long segments) and semi-packed (can be designed in each other configuration with posts in channels) up to now. Fig. 4 illustrated these configurations. The first microchannels were fabricated in circular spiral[3], square spiral[80] and rectangular spiral[81] geometries. In 2006, Sanchez, et al. designed radiator geometry[82] and Stadermann et al. fabricated channels in serpentine geometry.[83] The need of comparing the separation performance of different configurations of microcolumns was clear until the study of Radadia and co-workers performed on the effect of micro column geometry on the performance of chip- based GC.[84]

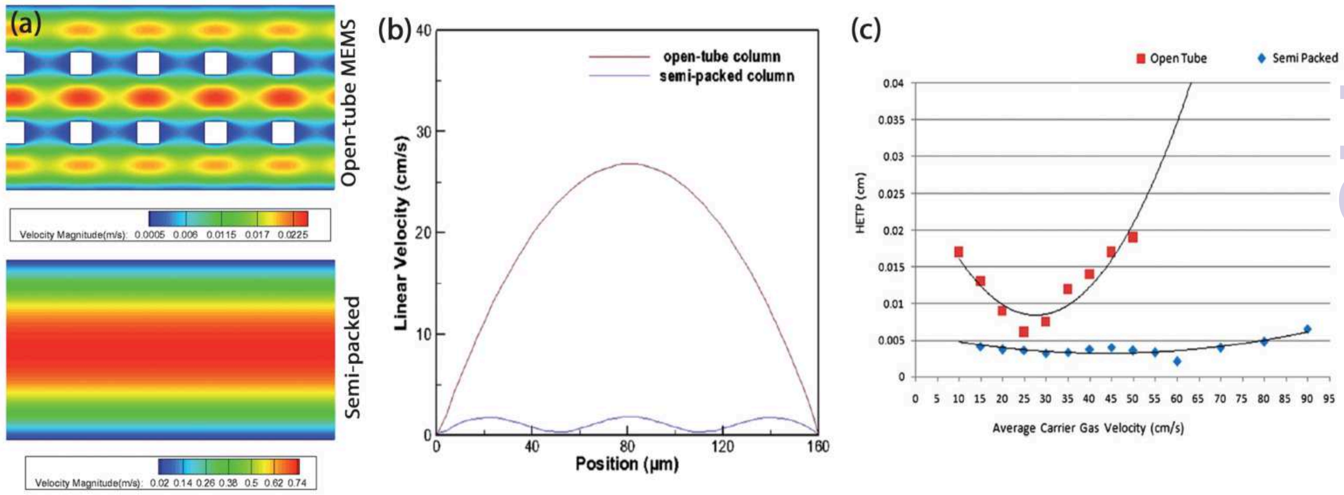

Fig. 3 Comparison between open tubular and semi-packed MEMS column, (a) Velocity contour plot (b) velocity profile along cross-sections for both the MEMS columns. and (c) HETP Golay plot for semi-packed and open tubular MEMS column.[79] Adopted from Ref. 79 with permission from The Royal Society of Chemistry.

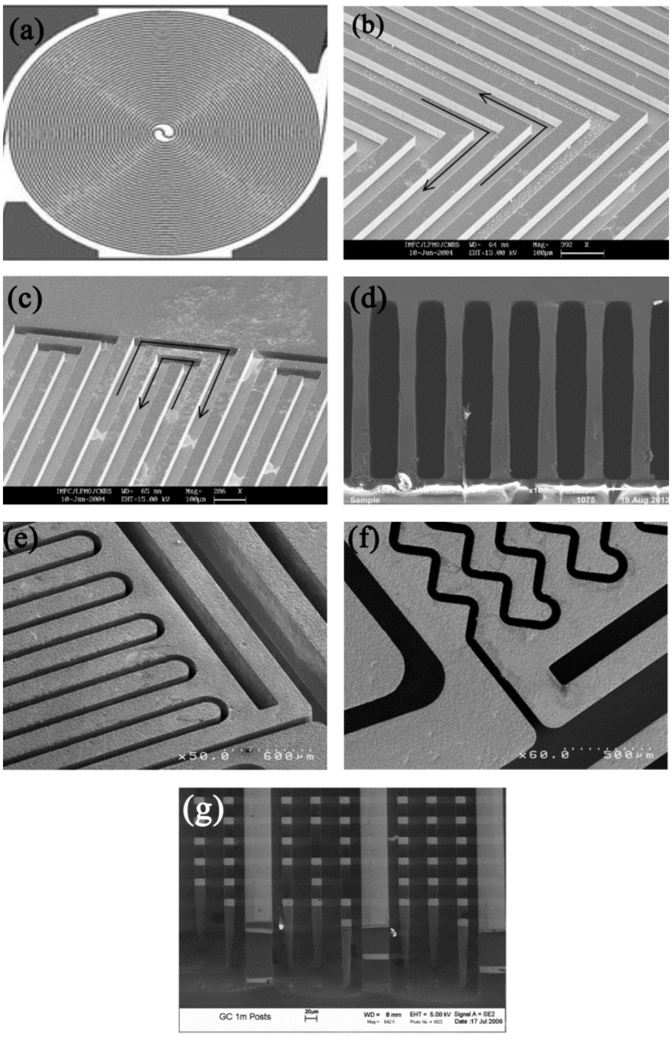

Fig. 4 Photograph showing different microcolumn configurations: (a) circular spiral[85], Adopted with permission from Ref 85; (b) square or rectangular -spiral, (c) Radiator,[82] Adopted with permission from Ref 82; (d) multicapillary with flow splitter[86], Adopted with permission from Ref 86; (e) serpentine, (f) Zigzag,[26] Adopted with permission from Ref 26; (g) semi-packed,[77] Adopted with permission from Ref 77.

They compared three different configurations of microcolumns including square spiral, circular spiral, and serpentine as shown in Fig. 4 a, b and e. For this purpose, to make any entrance effects small, microcolumns were designed to be at the same long and were coated with the same stationary phase.

The microcolumns were tested in the two typical modes of isothermally and temperature programmed.

The isothermal separation characteristics of the three configurations were compared in terms of the number of theoretical plates (N), which is inversely proportional to the band broadening.

For this examination the permeability (average gas velocity) of different uncoated microfabricated column configurations was investigated by injecting an unretained compound. It was concluded that there is negligible difference in the permeability of different microcolumns. Further injection of the iso-octane as retained solute showed that serpentine microcolumns have a higher number of theoretical plates compared to the spiral configurations. For temperature-programmed separation, results were compared in terms of separation numbers (TZ), which is directly proportional to the peak–peak resolution. These give the number of peaks, which can be resolved between the two main peaks, having a 4.7σ resolution between consecutive peaks and may be calculated by equation (4):

$$TZ=\frac{t_{r(z+)}-t_{Rz}}{W_{hz}+W_{h(z+)}}-1 \qquad (4)$$

Where, z and z + 1 refer to two consecutive members of the n-alkane homologous series, t_R is the retention time, and w_h is the full width at half maximum of the peak. For this purpose, separation of n-alkane mixture with the temperature-programmed mode showed that serpentine microcolumns resulted in higher separation numbers which can be attributed to the more favourable hydrodynamic flow.[84] In all three microcolumns configurations microfabricated until 2009 (i.e square spiral, circular spiral, serpentine) the stationary phase is only supported by the column wall and the sample capacity can be increased by having a thicker stationary phase, while it causes a reduction in separation efficiency. When only three sides of the column sidewalls are coated (while the glass side may not be coated), the non-coated glass side can contribute in peak broadening and loose of efficiency. Moreover, packed columns have more surface area, but they produce larger pressure drops and more eddy diffusion, thereby reducing the separation efficiency. As mentioned formerly in the theoretical section, to conquest these problems, two new classes of microcolumns have been introduced by Agah research team named "multicapillary" and "semi-packed". Fig. 4d illustrates the geometry of multicapillary columns designed with bundle of very narrow-width rectangular capillaries similar to the radiator configuration shown in Fig. 4c. Besides, theoretical analysis showed how this configuration could enhance separation efficiency.[78, 87] Another new configuration for increased capacity of column i.e semi packed column, was introduced for the first time by Ali et al in 2009. These columns contain embedded posts along the length of channel as shown schematically in Fig. 4g and fabricated like a square spiral configuration. Moreover, they have pointed that the semi-packed configuration has made it possible to achieve a two folds improvement in the separation efficiency and a higher sample capacity as compared to open tubular MEMS with capillary columns of the same dimensions (width/diameter).[77] In the recent work semi-packed microcolumn was microfabricated like a serpentine configuration by Sun et al. In order to improve the separation efficiency, the location of the micro-posts in the linear channels and the configuration of curved channels were optimized through numerical simulation.[88]

Beside the importance of channel's configuration, the geometry

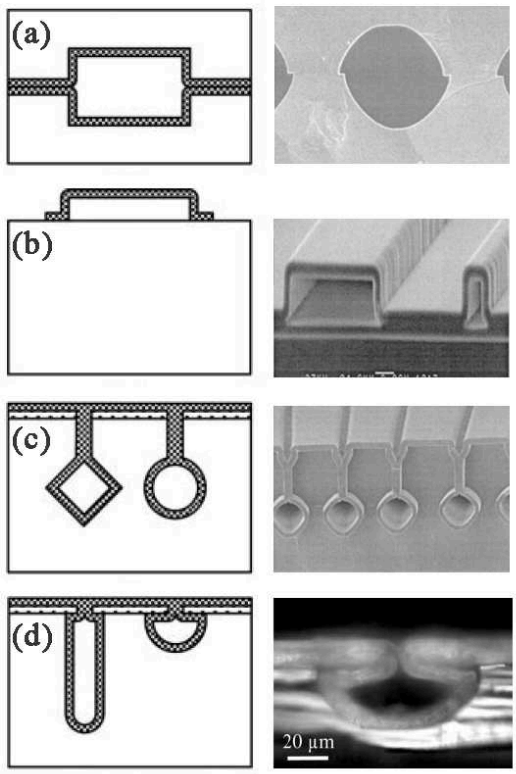

Fig. 5 The schematics and scanning electron microscope image of channels fabrication technologies: (a) surface micromachined channel, (b) wafer-bonded channel, (c) buried channel, and (d) embedded channel.[89, 90] Adopted with permission from Ref 89 and 90.

of channel's cross-section and accuracy of alignment process are affective factors that influence the separation efficiency. In 2000, De Boer and colleagues introduced a new method for fabrication of channels, cavities and etc., named "buried channel technology" that solved the alignment problems (Fig. 5 a and b). As can be seen in Fig. 5c this method does not require alignment bonding, where the channels are completely enclosed inside the silicon substrate. They introduced these channels in four different cross sectional shapes: hemicircular or semicircular at surface, circular in bulk, V-groove in bulk, and V-groove at surface.[89] Another new method for fabrication of channels i,e embedded channels was introduced by chen et al. in 2005 with two cross sectional shapes: quasi-hemi-circular and quasi-rectangular embedded parylene channel (Fig. 5d).[90] Later on, Agah and Wise used this technology was used to make low thermal mass semicircular cross-section oxynitride columns[91]. Radadia and co-workers further adopted this technology to fabricate partially buried channels with rounded edge to improve separation performance by having more uniform stationary phase compared with square edge deep reactive ion etched (DRIE).[92]

5.4 The stationary phase

The stationary phase could be loaded as wall coated or packed. In the case of wall coated, the thickness of the stationary phase is to be considered. Thinner coatings usually provide higher efficiency (higher N or lower HETP) because the mass transfer is quick between the mobile and stationary phases. Beside the thickness, the uniformity and stability of the stationary phase film are important factors that are assumed to be effective on the separation efficiency. For packed columns, the particle sizes and the packing quality are the most important factors. There is no regularity for choosing the stationary phase and it is only dependents on the nature of sample (i.e. polar or non-polar). Generally, for separation of non-polar compounds non-polar stationary phase is used, and vice versa. Even for separation of complex and difficult compounds two or more mixed stationary phase can be utilized.[4, 15] Typically, prior to introducing the stationary phase or after that, the inner surface is deactivated. One method of deactivation is to react the free or residual silanol groups with reagents such as tri-methylsilylchloride (TMCS), 1,3-diphenyltetramethyldisilazane (DPTMDS),[93] phenyltris (dimethylsiloxy) silane (Ah3P)[92], or hexamethyldisilazane (HMDS).[45, 94] The stationary phase is usually applied by either static or dynamic coating methods as the wall coated stationary phases. In static method the column is filled with the stationary phase dissolved in a volatile solvent. Then one end of the column is sealed, a vacuum is applied and the solvent is further evaporated, leaving a coating of the stationary phase on the column wall. The thickness of the stationary phase is calculated from the weight and density of the filling solution.[81] In dynamic method a stationary phase solvent is injected into and flown through the GC column under the pressure. The thickness of stationary phase can be controlled by altering the flow rate and the concentration of the stationary phase solvent. The stationary phase solution is pushed out of the other side of the GC column, while the nitrogen gas is delivered through the column for several hours to completely evaporate the solvent.[15, 95]

Stationary phases used for chip-based GC up to now are represented in Table 2. The most frequently reported stationary phase used by GC-on-a-chip researchers are polydimethylsilosane (PDMS) and poly (trifluoropropylmethyl) siloxane (PTFPMS). Further to increased selectivity of the analyte and efficiency of separation other stationary phases were introduced and used. In 2003, Gross et al. reported the use of monolayer-protected gold nanoparticles (MPNs) as stationary phase for GC.[96, 97] Later on, square cross section capillary with dodecanethiol MPNs as stationary phase was used to model the chip-based GC.[98] The application of monolayer protected gold as stationary phase for chip-based GC shows a good stability and high surface area. Moreover, this material can be easily functionalized with different groups ergo such that they can separate a wide range of analytes. [87]

Vial et al. further deposited the thin film silica and graphite onto microchannels as the novel stationary phase. For obtaining different thicknesses, they were varying the time of sputtering.[99, 100] An extensive review has been published about stationary phase for chip-based GC in 2014. [101] The other reviews about porous layers membrane for microfluidic devices can be found in mentioned references.[102-105]

6. Chip- based detector

After separating the compounds, a detector is used to monitor the outlet stream from the column. The detector determines the time at which each component reaches the outlet as well as the amount of that component. The miniaturization of detectors into chip-based GC not only enables total analysis in a single chip, but also provides a higher sensitivity, selectivity and safety.[106] Several chip-based detectors have been published for chip-based GC systems, such as flame ionization detector (FID)[106] differential mobility spectrometer (DMS)[107], thermal conductivity detector (TCD)[108], photoionization detector (PID)[109, 110], flame photometric detector (FPD)[111], plasma detector [112] and several other sensors.

6.1 Planar flame ionization detector (FID)

One of the most common and popular detectors in conventional GC system is the FID which first time was suggested in 1958 by Harley and co-workers.[113] This detector is destructive and used for analysis of trace levels of organic compounds with a very wide dynamic range and high sensitivity.[4] As the eluted components and carrier gas flow were introduced into a hydrogen flame inside the FID, any hydrocarbons containing components in the sample degrade and produce ions. Ions are collected by a metal collector. This recorded current depends upon the concentration of H-C bond in the sample gas. The study of planar FID fabrication goes back to Kuipers's research team. In 2000, they fabricated planar flame ionization detector [106] and in 2002 they investigated it in more details.[114] Since then, Kuipers and Müller fabricated a planner FID in which the oxyhydrogen flame burns inside a glass–silicon–glass sandwich. Also, they integrated the guard electrode between detector's electrodes to intercept leak current past the picoammeter.[115] In 2010, they demonstrated that the sensitivity of microfabricated planar FID increases with decreasing molecule size, increasing hydroxygen flow, or premixing the sample with hydroxygen.[116] The latest work in this area has been carried out by Kuipers and Müller that microfabricated a counter current planar FID (Fig. 6a), hydrogen and oxygen are supplied from opposite directions and react in vicinity of so-called stagnation point, where gas flow velocities are small. Also they have investigated the effect of many parameters such as the sample gas flow and the sample concentration on the response of cc- FID.[117]

6.2 Planar thermal conductivity detector (TCD)

TCD is a non-destructive detection system. It measures the difference in thermal conductivity between pure carrier gas and carrier gas containing sample components.[4] For this aim it needs to be made at least two cell cavities, although cells with four cavities are more common because the detection response of the four filament cell cavity was 2 times more.

These are drilled into a metal block, typically constructed of stainless steel. Each cavity contains high resistance tungsten or a tungsten-rhenium alloy filament, incorporated into a Wheatstone bridge circuit.

The first chip-based TCD integrated with separation channels is referred to 1979.[3] After that in 1994, Reston and Kolesar designed and fabricated a dual detector system, a selective chemiresistor as the primary detector and a TCD as a secondary detector for better analysis of the analytes.[32]

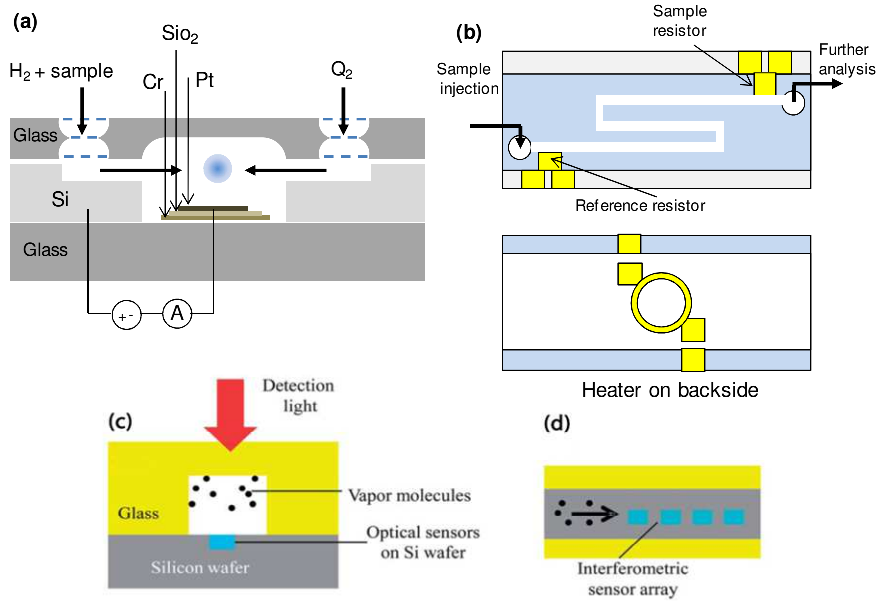

Fig. 6 The schematic design of detectors on a chip, (a) cross-section of the counter current- flame ionization detector, [117] Adopted and modified from Ref 117; (b) Conceptual picture showing the operation of single-chip separation column with an embedded thermal conductivity detector.[118] Adopted and modified from Ref 118; The schematic diagram of on- column detection: (c) cross-sectional and (d) Top-view view of the FP sensor array fabricated on etched silicon wafer inside a 1 mm deep and 450 mm wide microfluidic.[119] Adopted with permission from Ref 119.

Since then, several studies has been published in the case of planar TCD. [108, 118, 120-125]. Also a separation channel integrated monolithically with TCD was fabricated in 2010.[108] In another study, the ability of integrating TCD cells on channels was demonstrated. As illustrated in Fig. 6b, before and after introducing a sample, the conductivity of both carrier gas and the separated samples are recorded at the reference cell and sample cell, respectively. Therefore, the concentration of samples is proportional to the conductivities differences. [118, 123]

6.3 On- column detection

The utilization of on-column detection for chip-based GC started with the fabrication of optical ring resonator (OFRR) by Fan and co-workers. The OFRR was connected to the regular GC separation column, where the inner surface of capillary was coated with single type polymer. The optical detection was carried out at the end stage by measuring the sample transmission through a tapered optical fiber in contact with the OFRR.[126, 127] After that, the Fabry-Pe´rot (FP) cavity sensor was suggested by this research team. The principle detection of this method is shown in Fig. 6c and d.[34, 119, 128, 129] Shortly, FP sensor was fabricated by depositing a thin layer metal followed by a layer of gas sensitive polymer. As the analyte passes through the module, it interacts with the polymer and changes the refractive index or the thickness of polymer layer.

6.4 Gas sensors

Many sensors such as chemiresistor array and metal oxide (MOX) sensors have been reported for chip-based GC. The response mechanism of these sensors is mainly relies on the impedance changes. Typically, a chemiresistor consists of a conductive or semi-conductive polymer, or emulsion and organometallic compounds. Reston and Kolsar used a copper phthalocyanine coated chemiresistor for detecting gas mixture.[32, 130] Also two different gold thiolate monolayer protected clusters (Au-n-octanethiol and Au -2 phenylethanethiol) were used for gas chemical sensing with electron tunneling or hopping mechanism in dual chemiresistor array.[131] Moreover different MNPs as sensitive layer for chemiresistor-based array sensor were introduced.[42, 132] MOX sensors consist of semiconductor bead (usually SnO_2) and integrated microhotplate since they are functional in high temperature condition. In 2005, Lorenzelli et al. fabricated a gas sensor with SnO_2 sensitive layer for chip-based GC and used it for diagnostic and biomedical applications.[81] The latest work in this case was published by Sklorz and co- workers. In this study, the metal oxide sensor based on SnO_2 layer was fabricated coupled with humidity/temperature sensor to analyze low molecular weight gas, especially ethylene in air samples.[54] The summary of articles published for chip-based GC platforms, the constituting components and the applications are illustrated in Table 2.

7. Chip-based multidimensional gas chromatography

In 1984, Giddings suggested that the usage of two columns for separation instead of one, would be associated with better resolution.[133] In 1991, comprehensive two-dimensional gas chromatography (GC×GC) was developed by Liu and Phillips

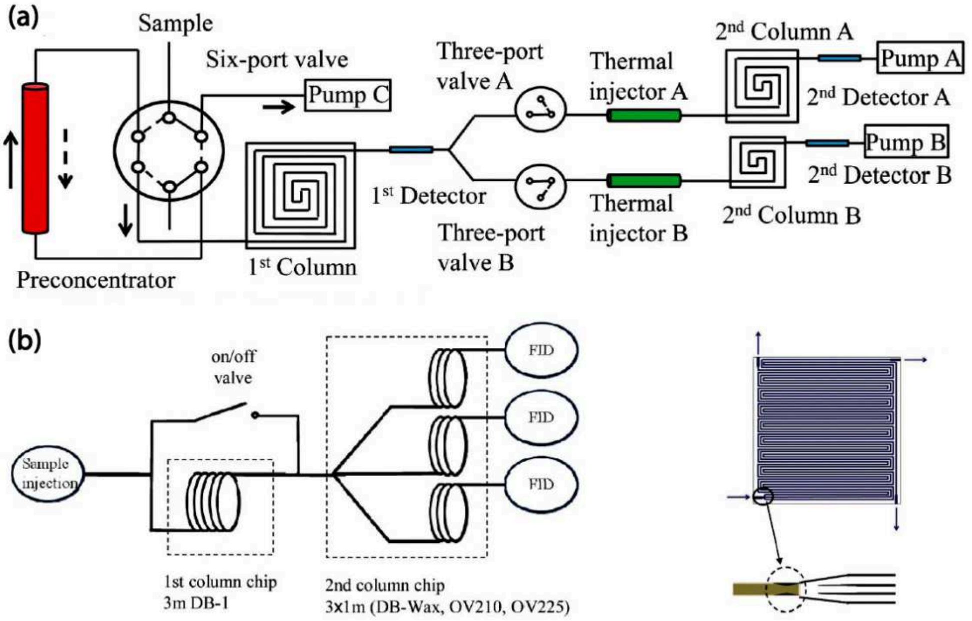

Fig. 7 The schematic diagram of chip-based multidimentional gas chromatography, (a) each column has separate injector and on-column optical fiber detector,[134] Adopted with permission from Ref 134; (b) each column has a separate flame ionization detector (Left) and three second channels all fabricated in a single chip (Right).[135] Adopted with permission from Ref 135.

and the first article in this field was published.[136] Today, multidimensional gas chromatography with different polarities and length columns has become a powerful technique for separating volatile and semi-volatile compounds in complex mixtures. In the field of chip-based GC, usage of micromachined channels for 2D separation was first considered by Wiranto et al[80] and after that has been developed as a second column by Gross and coworkers[97, 98] and Reid and co-workers.[137] In 2005, Lambertus and Sacks reported the two dimensional chip-based GC with stop-flow valve, the first column was filled with PDMS as the non-polar stationary phase, while the second column filled with trifluoropropylmethyl polysiloxane as the polar stationary phase. As a result, 14 multifunctional compounds were separated with isothermal mode less than 300 s.[138] After that in the same time, in 2013, Liu et al.[134] and Chen et al.[135] designed and introduced chip-based multidimensional GC with two single microchannels chips (Fig. 7a) and three microchannels on a single chip (Fig. 7b) as the second column, respectively. The first column was filled with non-polar stationary phase, and the other columns were filled with the same or different polar stationary phases. To separate and detect compounds, researchers have also used Y connector to control connection between the first and the second column while the exit of each column was detected with separate detector.[134, 135]

8. Applications

The main goal of developing GC-on-chip technology is to perform real-time analysis of organic mixture vapors with a reasonable performance and a high efficiency using an integrated platform with all of the steps of analysis performed in a single chip. Early applications of such chip-based GC systems were only reported in analyses of hydrocarbons[3] and gas samples.[80] However, as shown in Table 2, the development of these systems has been extended across a wide variety of application areas such as health service,[45, 51, 57, 81, 111, 134, 139, 140] industry pollution monitoring,[56, 57, 111] environmental analysis,[32, 54, 56, 57, 82, 88, 111, 134, 141] homeland security,[50, 142, 143] petrochemical industries[143], and as the second dimension of comprehensive two-dimensional gas chromatography (GC × GC).[97, 98, 111, 80, 137] Nowadays chip-based gas chromatograp instruments are commercially available by companies such a Dolomite[144], C2V[145] and etc.

Table 2 The summary of chip-based GC systems reported from the beginning up to now.

Columns feature							Anal. Time (s)	Detector	Application	Ye
Geometry	Length (cm)	Width (μm)	Depth (μm)	Stationary phase	N_{max}[a]	Mode				
Circular-spiral	150	200	30	PDMS[b]	NR	Isothermal	10	TCD[c, **]	Gaseous hydrocarbons (8)	1979
Spiral	90	300	10	CuPc[d]	NR	Isothermal	NR	CR[e] & TCD [**]	NO_2 & Ammonia	1994
Square-spiral	125	100	20	PDMS	2193	Isothermal	85	FID[f]	Hydrocarbons	1999[illegible]
Circular-spiral	100	100	350	NR	NR	Isothermal	NR	NR	NR	2002[illegible]
Square-spiral	300	150	240	Rtx-1 & Rtx-200	8200	Temperature programmed	600	FID	Multifunctional components (20)	2004[31]
Square-spiral	300	150	250	PDMS	17000	Temperature programmed[*]	360	Sensor array[**] & FID	Multifunctional components (20)	2005[55]
Square-spiral	300	150	240	PDMS	5500	Temperature programmed	450	DMS[g, **]	VOCs[h] (45)	2005[illegible]
Rectangular-spiral	130	200	20	PDMS	NR	NR	40	SnO_2 sensor[**]	HVA[i] & VMA[j]	20[illegible]5[81]
Circular-spiral	75	800	800	Carbograph 1 + 5%Carbowax	NR	Isothermal	1800	SnO_2 sensor[**]	Beneze, Toluene & Xylene	2005[illegible]
Square-spiral	300	150	240	PDMS	6500	Temperature programmed[*]	90	4 CR[**]	VOCs (11)	20[illegible][42]
NR	100	150	240	PDMS	4000	Temperature programmed[*]	24	cc-FPD[k, **]	OP[l] & OS[m] compounds	2006[111]
Square-spiral	25-300	150	240	PDMS	12500	Temperature programmed	150-500	FID	Multifunctional components	2006[illegible]
Rectangular-spiral Radiator	200	30	50	Silica	NR	Isothermal	600	SnO_2 sensor[**]	HF[n], Toluene and aceton	2006[82]
Serpentine	50	100	100	SWNTs[o]	NR	Temperature programmed[*]	2	FID	Multifunctional components	2006[83]
Serpentine	50-200	50	600	OV-1	17500	Isothermal[*]	2	FID	Hydrocarbons & CWAs[p]	2007[25, illegible]
Circular-spiral	25	45	45	PDMS	5000	Temperature programmed[*]	200	FID	n-Alkanes (6)	2007[illegible]
Square-spiral	25-300	150	240	PDMS	12000	Temperature programmed[*]	12	FID	Multifunctional compounds (30)	2007[147]

Table 2 *continued*

Columns feature							Anal. Time (s)	Detector	Application	Year
Geometry	Length (cm)	Width (μm)	Depth (μm)	Stationary phase	N_{max}[a]	Mode				
Circular-spiral	76	280	30 & 50	PDMS	360	Isothermal	180	VOC sensor	Beneze & Xylene	2008
Serpentine	35	100	100	OV-5	NR	Isothermal	NR	SWNT sensor[**]	DMMP[q]	2008
Serpentine	300	100	100	OV-5	16500	Isothermal	420	FID & MS[r]	OP & OS compounds	2008
Semi-packed-Square-spiral	100	150	180	OV-1	10000	Temperature programmed	270	FID	Multifunctional compounds (8)	2009
Semi-packed-Serpentine	100	160	230	Parylene diX-AM	NR	Temperature programmed	30	FID	n-Alkanes (5)	2009
Circular-spiral	50	440	500	Styrene divinylbenzene	NR	Isothermal	600	SAW & TCD	n-Alkanes (3)	2009[150]
Circular-spiral	856-1700	100-200	50-100	SE-54	35000	Temperature programmed[*]	600	FID	Multidimensional compounds (12)	2009
Serpentine	34	165	65	OV-5	872	Temperature programmed	3.8	FID & MS	Multifunctional compounds (8)	2009
NR	30	50	50	CNTs[s]	NR	Temperature programmed[*]	1.5	FID	Multifunctional compounds (10)	2009
Square-spiral	50-300	150	240	PDMS & PTFPMS[t]	4900	Temperature programmed[*]	210	FID	Multifunctional compounds (19)	2009
Serpentine	600	100	100	OV-1	4850	Isothermal[*]	185	FID	Benzene & Toluene	2009
Square-spiral	50	800	800	Carbograph 2 + 0.2 % Carbowax	NR	NR	660	MOX sensor[w, **]	BTEX[x]	2009[43]
Multicapillary	NR	25	NR	OV-1	12500	Isothermal[*]	120	FID	n-Alkanes (7)	2009
Square-spiral	300	150	240	PDMS	NR	Temperature programmed[*]	120	CR[**]	TCE[y]	2010
Serpentine	50	400	200	Carbopack & HayeSep A	900 & 1160	Isothermal	30	TCD[**]	N_2, CH_4 & CO_2	2010
Square-spiral	750	320	320	OV-101	2000	Temperature programmed[*]	300	FID & PID[**]	BETX	2010
Serpentine	50	140	70	PDMS	NR	Isothermal	120	TCD[**]	n- Alkanes (4)	2010
Serpentine	35	100	100	OV-5	NR	Temperature-programmed[*]	35	FID	n- Alkanes (6)	2010
Multicapillary	25	25	250	MPG[z]	20000	Temperature-programmed[**]	300	FID	n- Alkanes and alcohols	2010[87]
Square-spiral	300 * 300	150	240	PDMS	4550	Temperature-programmed[**]	200	4 CR[**]	TCE & 11 VOCs	2011[45]
Serpentine	320	250	250	Carbowax	9750	Isothermal[**]	300	FID	Benzene & Toluene	2011
Circular-spiral	86	100	400	PDMS	8000	Temperature-programmed[**]	210	Sensor[**] & FID	CWAs	2011[142]
Serpentine-Semi-packed	220	75	100	Sputtered silica	5000	Isothermal	60	FID	Alkanes (4)	2011
Serpentine-Semi-packed	220	75	100	Sputtered silica or graphite	NR	Temperature-programmed	9-15	FID	Multifunctional components	2012
Serpentine	100	100	250	OV-1	NR	Isothermal[*]	90	TCD[**]	Multifunctional components (8)	2012[118]
Square-spiral	25-250	400	100	OV-1 & Carbowax	NR	Isothermal	125	4 FP[aa, **]	Multifunctional components (4)	2012
Circular-spiral	280	240	NR	PDMS	NR	Isothermal	600	SAW[**] & FID	Multifunctional components (5)	2012
Multicapillary	25	30	250	MPG	7300	Temperature-programmed	200	FID	Alkanes	2013[155]
Square-spiral	100	150	240	PDMS	NR	Temperature-programmed[*]	80	FID	Multifunctional components (24)	2013
Circular-spiral	75	1000	800	Carboxen 1000	962	Isothermal[*]	1000	MOX-sensor[o, **]	Ethylene	2013
Serpentine-Semi-packed	200	300	350	SE-54 & Carbowax-20M	9500	Isothermal[*]	60	PID[ab]	Aromatic compounds (5)	2013[88]
Circular-spiral	75	40	40	Carboxen 1000	NR	Isothermal[*]	NR	MOX-sensor[**]	Ethylene	2014
Circular-spiral	200	50	50	PDMS	2420.6	NR	160	NEMS sensor[ac, **]	TEOX[ad]	2014

Table 2 *continued*

Geometry	Length (cm)	Width (μm)	Depth (μm)	Stationary phase	N_{max}[a]	Mode	Anal. Time (s)	Detector	Application	Year
Serpentine-Semi-packed	200	350	320	SE-54 & PEG-20M	10000	Isothermal*	65	sensor	Multifunctional components (6)	201
double Circular-spiral	200	100	100	PDMS	67000	Temperature-programmed*	1500	FID	PAHs[ae] (18)	2014
Serpentine-Semi-packed	100	160	250	SE-54	55366	Temperature-programmed	240	NR	Alkanes	2014
Serpentine	200	70	240	PDMS	NR	Isothermal	300	PID**	Multifunctional components (4)	2014[109]

NR: Not Reported, [a]The max obtained theoretical plate, [b]Polydimethylsiloxane, [c]Thermal conductivity detector, [d]Copper phthalocyanin, [e]Chemiresistor, [f] Flame ionization detector, [g]Differential mobility spectrometer, [h]Volatile organic compounds, [i]Homovanillic acid, [j]Vanillylmandelic acid, [k]Countercurrent flame photometric detector, [l]Organophosphorus, [m]Organosulfur, [n]Hydrogen fluoride, [o]Single wall nanotubes, [p]Chemical warfare agents, [q]Dimethyl methylphosphonate, [r]Mass spectrometry, [s]Carbon nanotubes, [t]Poly (trifluoropropylmethyl) siloxane, [w]Metal-oxide gas sensor, [x]Benzene, Toluene, Ethylbenzene and Xylenes, [y]Trichloroethylene, [z]Monolayer-protected gold nanoparticles, [aa]Fabry-Pe´rot cavity sensor, [ab]Photoionization detector, [ac] Nano electro mechanical systems sensor, [ad]Toluene, ethylbenzene, Octane, and xylene, [ae] Polycyclic aromatic hydrocarbons, * Integrated heater, ** Microfabricated detector

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