Chapter 14
"Lab-on-a-Chip" Dedicated for Cell Engineering

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Abstract In this chapter various microsystems (called Lab-on-a-Chip) dedicated to cell engineering are described. We present methods for microsystems fabrication and also essential parameters, which have influence on cell culture in microscale. This area of research is significant, because microsystems nowadays play an important role in cell studies and drug development. It can be caused by possibility to perform *high-throughput* screening in microscale. In addition, the size scale of microfluidic devices is especially suitable for biological applications at the cellular level, the scale of microchannels corresponds well with the native cellular microenvironment. The volume of cells to extracellular fluid in microsystems is similar to in vivo conditions, the next advantage of microchips. Moreover, a special architecture of microdevices gives the possibility for control of growth factors, reagents, and oxygen inside the system.

14.1 Miniaturization

The development of new technologies enables miniaturization of devices used in research. It also allows to reduce the amount of materials and minimize the quantity of reagents required for determinations. Microbioanalytics is the field, in which for example, process control in biotechnology or *online* monitoring of environmental pollution is performed. New miniaturized analytical systems allowing for fast, cheap, and easy way to carry out such determinations and chemical analysis applicable to the areas of laboratory and environmental investigations were developed. The dynamic development of this branch of science provides a number of

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publications, which describe new technologies or applications of microsystems. Since 2000 the number of publications focused on microsystems increased twice. Whereas in 1998 the number of patents related to microsystems was less than 24, six years later it reached about 300.

Miniature devices called *Lab-on-a-Chip* are an integrated micro-laboratory on the plate, in which it is possible to perform complex and multistep analysis. The origins of microchips are fields such as chemistry, biology, molecular biology, electronics [1]. Analytical chemistry and adaptation of analytical techniques in the microscale have the most important influence on the development of microfluidic systems. The next steps in microtechnology and microbioanalytics development were made after 1980 and were connected to molecular biology. In turn, the possibility of integration of microfluidic devices with electronic systems and utilization of electronic technologies became the consecutive steps leading to the construction of *Lab-on-a-Chip* system [1, 2]. The integration of these fields of science enabled to create a new interdisciplinary science called microbioanalytics. Microfluidic systems were employed in biotechnology, clinical diagnosis, pharmacy, nature science, tissue engineering, and nanomedicine [2, 3]. It is possible to construct a device, which is portable, with small dimensions and dedicated for analysis performed outside laboratory conditions. It is also possible to perform a flow analysis with extremely small reagent volumes and significant reduction of biological materials used. The application of microchips allows also for the reduction of analysis time and control in time and space [4].

14.2 Analytical Techniques in Miniaturization

Analytical chemistry is the main precursor of miniaturized systems. These applications of chips for multi-tests improve efficiently sample analysis. Small samples may be tested and simultaneously high sensitivity obtained. The best concept of microsystems used in analytical chemistry allows to perform a complex analysis which includes sampling, sample processing, component separation and detection, and sample removal. The automated microsystem allows to improve analytical procedures and to use advantages of miniaturization. A miniaturized gas chromatograph developed in silicon was the first microsystem dedicated for analytical chemistry. Microdevices are also applied for extraction, filtration, and separation of samples. Microsystems are miniature devices used in separation techniques such as capillary electrophoresis (CE), capillary iso-electric focusing (CIF), capillary gel electrophoresis (CGE), micellar electrokinetic capillary chromatography (Mecca), capillary electrochromatography (CEC), or high-performance liquid chromatography (HPLC). The usage of microsystems enable to perform series analytical processes on the single plate and elongation of separation way. Moreover, it is possible to design any gradient of mobile phase.

Different methods for analysis of samples are used depending on the research performed in the microchips. Electrochemical and optical detections are performed

in microsystems: spectrophotometry, spectrofluorimetry, photothermal, and Raman spectroscopy are optical methods utilized in microscale. Likewise, amperometry, conductometry, and potentiometry belong to electrochemical methods which are used in microchips [5].

14.3 Cell Cultures

In the past decade, interest in researches related to cell culture and analysis of cell survival significantly increased. Cell cultures play a fundamental role in both biotechnology and pharmaceutical industries. They participate not only in the discovery and production of drugs, but also in the field of regenerative medicine [6]. The continuous increase in popularity of using culture to study the usefulness of new drugs is due to the fact that cells provide a fast and representative response to substances tested. It is also important that they limit the number of tests conducted on live animals, according to the 3Rs rule (Replacement, Reduction, Refinement), which assumes searching for alternative methods used to replace animal testing [7, 8].

Cell cultures are used both for studying biological processes and for application purposes such as tissue engineering. Cell cultures enable to culture selected type of cells and carry out the tests of cellular processes such as proliferation, cell adhesion to the substrate, protein secretion, and differentiation in tissues with specific phenotype [9]. A wide range of applications of cell cultures leads to the search for better methods of optimization which allow to improve the process of cell culturing and assimilation of its terms to the in vivo conditions. The cytotoxicity studies of anticancer drugs should be carried out also on normal cells. It is necessary to determine the extent to which drugs damage healthy cells in the human body [10]. There are many similarities and differences between cancer and normal cells. Understanding the mechanisms which regulate normal and tumor cells proliferation is essential to improve cancer research.

A noticeable difference between normal and cancer cell cultures is the tendency of healthy cells to achieve certain number of divisions and the possibility of programmable death after receiving a signal from the body. The distinguishing feature of the normal cells is also to serve their specific functions in the body. In vitro culture of these cells assume to maintain these functions, due to the fact that they are necessary to obtain material suitable for further research. Cancer cells are characterized by the imbalance between the numbers of dividing and dying cells, moreover, they exhibit a tendency to form multilayer aggregates which impede accurate analysis. Cancer cells can divide indefinitely to form three-dimensional structures. Furthermore, they have the ability to move and occupy the place of normal cells. Therefore, there are numerous publications that compare the cultures of normal and malignant cells [11].

14.4 Microsystems in Tissue Engineering

One of the latest techniques for biological research, which uses biological material, is miniaturized devices called *Lab-on-a-chip*. The utilization of such systems allows for elimination of research in highly specialized laboratories, which usually absorb huge costs. In addition, the volume used during the study is very small, so quantities of biological material used are also small. The usage of miniaturized analytical systems in such studies can also minimize the contribution of the human factor in the whole culturing process [12]. The *real-time* observation of the cultured cells allows to learn their behavior in different environmental conditions. It is especially significant for research carried out, *e.g.*, on cells. Another advantage is the ability to automate a microdevice, which allows for precise identification and elimination of errors in laboratory work. Moreover, these systems exhibit compatibility with most commonly used detection methods such as electrochemical methods, mass spectrometry, and optical methods, including absorption, chemiluminescence, and fluorescence [3]. In comparison with conventional cell culture methods, techniques based on miniature cell culturing systems have important advantages and enable to make an investigation in environment more similar to in vivo conditions [13]. In addition, during the flow of nutrients it is possible to control the shear stress as factor, which influences the cells.

Despite advanced technology, the designing of suitable microsystems dedicated to tissue engineering is still a complicated task. *Lab-on-a-chip* systems used in tissue engineering must fulfill several important functions. It is important that the manufactured chip allows cells to grow and control their behavior, *e.g.*, migration or adhesion to the substrate. It should also ensure a suitable oxygenation and flow of nutrients. Therefore, new miniaturized systems that allow for culturing different cell types and perform various types of analyses are still designed and developed.

14.5 Design and Development of Microsystems

14.5.1 Construction Materials

The structure of the microdevice used for cell analysis determines not only the properties of culture, but also ways of visualizing its results. This chapter presents the most often used materials to manufacture a microdevice dedicated to cellular engineering. The microsystem components should be biocompatible and non-toxic to cells. Furthermore, they should also allow to perform a desirable microstructures in them [14]. There are many currently used materials for production of microsystems, ranging from silicon, glass, and ceramics to various types of plastics. Polydimethylsiloxane (PDMS), polymethyl methacrylate (PMMA), poly [3-mercaptopropyl] methylsiloxane (PMMS), polycarbonate (PC), polycaprolactone

(PCL), polylactic acid (PLLA), poly [lactic-co-glycolic acid] (PLGA) [15–18] are polymers often used in microtechnology.

The most commonly used materials for construction of chip dedicated to tissue engineering are poly(dimethylsiloxane) and glass. The PDMS is nontoxic to cells, impermeable to water and permeable to gases. These are the main advantages of this material. Moreover, it is flexible, inexpensive, and optically transparent. In addition, PDMS is easily treated and allows to perform precise microstructures [19]. It also has the ability to create reversible and irreversible binding to other materials such as glass, silicon, other polymers, or to another layer of PDMS [20]. These bonds may be based on van der Waals forces (reversible) or covalent bonds (irreversible) between the surfaces of individual elements. The seal of microdevice is very important. During the flow of fluid through the microchip it allows suitable flow rates [15]. An important advantage of PDMS-based chips is their relatively simple structure, which allows to easily change the device design and optimization at minimal cost.

Glass is also often used material to create microchips. This material is nontoxic and chemically resistant. Microstructures in the glass are performed by wet etching with hydrofluoric acid [21]. In addition, the glass as a hydrophilic material ensures proper adhesion of cells to the substrate. On the other hand, a significant disadvantage is its limitations during fabrication of the microstructure. The geometry of the fabricated channels has influence on the culture conditions and other factors such as dispersion [22]. The fabrication of microchambers for cell culture in the glass enables to use various types of microscopy including fluorescence, confocal, and phase contrast to monitor cell culture processes.

14.5.2 Fabrication of Microsystem

The material used for construction of miniature analytical systems determines the method for producing a specific microstructures. Various types of materials are used to fabricate *Lab-on-a-chip* systems for cell culture and analysis. Glass and polymers are the most commonly used materials, so the methodology of fabrication of microstructures in these materials is discussed in this chapter. Microstructures in the glass are performed by using photolithography and wet etching techniques with hydrofluoric acid. Glass etching is isotropic, therefore the microstructure formed in the walls are curved. Microstructures in polymers are made by replication methods (hot embosing, injection molding, and casting), and by direct treatment (micromilling, laser micromachining) [2, 16]. The kind of material used to fabricate the microchip, microstructure parameters (geometry and size of the microchannels), and the availability of the components required are very important while choosing the fabrication technique [15]. The design of the geometry of microchannels and microchambers, which will be developed in the materials is the first step in microchip fabrication. Computer programs such as AutoCAD or Corel are used to design the model serving as the basis for manufacturing the microstructures in the material.

14.5.3 Casting

The first step in the casting process is to implement the so-called stamp (matrix). It can be made in different materials such as glass, quartz, nickel, or polymer. There are many techniques for manufacturing such stamps, *e.g.*, micromilling, wet etching, electroforming. The photolithography is the most often used method for stamps fabrication (particular in the case of microsystem made of PDMS) [2]. For this purpose a photoresist is deposited on a plate and exposed to UV light through a photomask [23]. Then, the exposed photoresist is developed using developer (for example water). In this step, it is obtained the stamp which contains the microstructures and microchannel network [16]. There are two kind of photosensitive materials: the negative emulsion—a substance that becomes insoluble by ultraviolet radiation and positives emulsion—a substance soluble in the developer. The stamp is used for replication in PDMS. PDMS prepolimer is mixed with curing reagent and liquid PDMS is poured into the mold and allowed to cure for 1 h at 70 °C. After that, the structure is peeled of the master and the PDMS plate with precisely (with the accuracy of tens of micrometers) formed microchannel network is obtained. This method enables to reduce the time and cost of microchip fabrication process.

14.5.4 Hot Embossing

Hot embossing is a method in which polymer stamps are also used. To obtain microstructures using this technique, stamp and polymer plate (e.g. PMMA) should be placed in a vacuum chamber of hydraulic press and separately heated. The next step is to press the stamp in the polymer. After cooling a microstructure imprinted in the polymer is obtained [2, 16].

14.5.5 Injection Molding

In this method polymer is plasticized by increasing temperature. Then the polymer is injected into the special form containing microdesign by use of high pressure. This is a convenient way to perform the microstructure in the polymer plate allowing for accurate visualization of the design.

14.5.6 Laser Micromachining

Laser micromachining is a direct action of laser-generated UV or IR radiation. This method allows for fast obtaining of microstructures in the material fast. This type of various microstructures preparation is performed on the surface of the polymer or other materials. However, there are some limitations associated with high costs of equipment and a large surface roughness of the resulting shape [2, 16].

14.5.7 Micromilling

Micromilling is a mechanical processing of the material. Microstructures are performed in polymer by use of a microcutter. In this method we use micron-sized cutters covered with hard materials such as, e.g., titanium carbide. The technique enables to obtain a three-dimensional structures in a layer of a polymer. This method allows also to change the shape of the structure during project executing. Microstructures received in materials by micromilling are also used as stamps for structure molding, e.g., in PDMS [2, 16].

14.5.8 Microsystems Sealing

The combination of two plates with fabricated microstructures ensures their sealing. Different techniques can be used depending on the type of material. Polymers such as PMMA or PC can be connected by thermal bonding in thermal hydraulic press. In this method, the thermal properties of material are used. However, it is important not to exceed the temperature limit, since that may cause deformation in microstructures [16]. Another example of microstructures bonding is the use of oxygen plasma. This technique allows to connect materials to each other, e.g., PDMS with PDMS, PDMS with glass or PDMS with silicon.

14.6 Essential Parameters in Microsystem for Cell Culture

14.6.1 Geometry of Microsystem

The important thing which confirms advantages of microsystems is a possibility to manipulate their geometry. The microchannels and microchambers size respond to the cell dimension. The surface area to volume ratio (SAV) in the microsystem is higher than 1 being similar to in vivo conditions [24]. A large SAV ratio gives many advantages. First of all it allows for efficient mass transport of gases via diffusion [22, 25]. The experimental conditions mimicking in vivo environment are important for cell analysis because it increases the meaning of the obtained results. It is possible because in the microscale the cells are in biological interaction between other cells. The microfluidic systems enable also to tests cells in carefully and precisely controlled conditions. Moreover, the microscale gives the possibility to design a suitable geometry and structure of cell culture systems.

14.6.2 Sterilization and Culture Condition

Effective sterilization is critical for maintaining the growth of long-term culture at both macro- and microscale. Autoclaving of microsystems is a fundamental method for sterilization, however, many materials cannot be exposed to high temperatures, because the microchannels developed in these materials can undergo deformation. If autoclaving is not possible the microfluidic systems can be exposed to UV light or oxygen plasma. Flushing the device with ethanol (70 %) is the next method to assure aseptic conditions inside microdevices. In the static cell culture, the microenvironment is uncontrolled. On the contrary, the changes of culture medium in the microsystems is controlled [26]. Suitable preparation of microsystems and in situ monitoring of culture conditions assure a proper cell growth and proliferation. The most important parameters, which must be controlled during system preparation and cell culture are flow rate value of all substances introduced into microdevices, procedure of cell seeding, density of cells introduced into microchamber, and cell-substrate adhesion. The aim of cell culture in the microfluidic systems in not only miniaturization of the conventional cell culture technique, but also usage of microscale benefits.

14.6.3 Gradient Generation

The control of flow rate of culture medium influences the cell culture in the microfluidic system. Unsuitable value of flow rate can indicate shear stress, which disadvantageously affects cell morphology and viability. Moreover, constant flow rate can flush paracrine (affecting other cells) and autocrine (affecting cells that produce it) signaling factors secreted by cells. Too high low rate can also remove cells from the microsystem. On the other hand, too small flow rate can reduce nutrients which leads to a decrease in cell viability [27]. Therefore, a proper flow rate of medium determines optimal cell growth with minimal damage to the cells. Liquid flow in the microscale have three physical phenomena: laminar flow, diffusion, and surface to volume ratio (SAV) [28, 29]. The Reynolds number is at a low level ($10 > \mathrm{Re} > 0{,}001$), which is synonymous with the laminar flow. The ratio of width and height of microchannels is small, therefore the probability of any disturbances in the flow is also low [30]. Three kinds of flows are used in the microscale investigation: electroosmotic flow and flow propelled by centrifugal force or pressure [31]. During the laminar flow the mixing of substances proceeds through diffusion (Fig. 14.1). Scale reduction causes increase in the surface area to volume ratio (SAV). It contributes to increase in the rate of diffusion and heat conduction in microsystem. However, a high value of SAV results in faster adsorption of particles on the microchannel surface. Simultaneously, it reduces the efficiency of fluid flow [28].

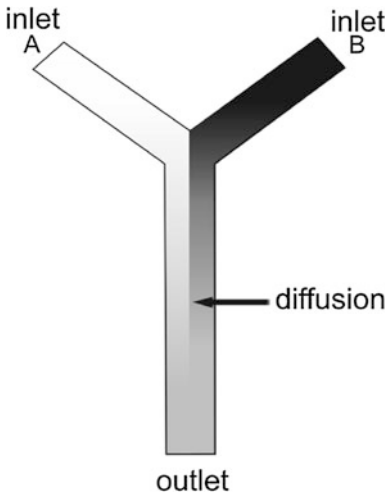

Fig. 14.1 A mixing of stream X and Y. The diffusion rate increasing with time, according to [29]

In miniature systems, it is possible to produce specific chemical concentration gradients similar to that in vivo, which are difficult to obtain at the macroscale. In the first type of gradient, laminar flow is utilized. Control of this kind of gradient can be done by a properly designed network of channels, whose inlets and outlets determine the concentrations obtained (Fig. 14.2) [28]. There is a second kind of gradient generator, in which chemical gradient is achieved by diffusion along the channel between the source and sink compartments (Fig. 14.3). Since mixing without laminar flow is utilized, it can be used for non-adherent cells. This type of gradient is more friendly to the cells and creates an environment with less shear stress on the cells [30].

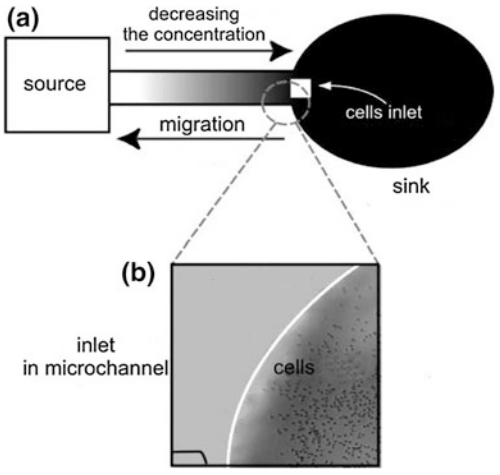

Fig. 14.2 Concentration gradient generator where laminar flow is used. **a** Every microchannel has different concentration of reagent. **b** The outlet with different concentration of substance. Reprinted with permission from Breslauer et al. [28]. Copyright 2006 the Royal Society of Chemistry

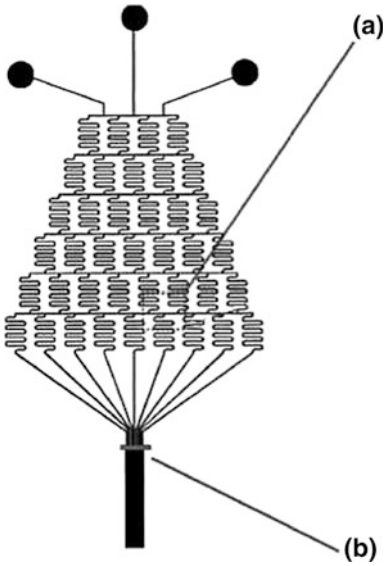

Fig. 14.3 Geometry of chemical gradient generator without flow. **a** The device has source and compartment sink covered with membrane. The compounds diffused through membrane create chemical gradient. **b** Cells are placed in the compartment sink. Reprinted with permission from Chung and Choo [30]. Copyright 2010 the Royal Society of Chemistry

14.6.4 Other Parameters

Temperature, dampness, and concentration of carbon dioxide also influence on the cells cultured in microsystems. These parameters are automatically regulated in the incubator used for cell culture. However, microsystems integrated with heater and devices for temperature and level of carbon dioxide control are also developed. The integrated microsystems assure optimal temperature and pH conditions and allow to eliminate classic incubator during culture and analysis of cells in the microchip.

14.7 Cell Culture in Microscale

The flow rate of cell suspension during introduction into the microsystem is an important parameter. It determines the density of cells in separate microchambers. A non-uniform placement of cells in the growth place is a meaningful problem during cell seeding. Nutrients are consumed faster in microchambers with high density of cells than in those with low cell density. Simultaneously, the secretion of adventive products is increased. When adherent cells are used their density should allow to play appropriate cell–cell and cell–matrix interactions [32]. After introduction into the microsystem, adherent cells need a certain time to achieve an appropriate level of adhesion to the substrate. In contrast, cells cultured in suspension require relatively less time to adapt to the new environment [25]. Another important aspect of adherent cell culture is its response to the modification of

culture medium flow. Cell growth is directly dependent on the flow rate. At low flow rates cell growth is induced by exchange of mass, but there is a shortage of nutrients and excessive accumulation of metabolic products. However, providing large quantities of nutrients at high flow rates may result in a high hydrostatic pressure and a shear stress that inhibits cell growth [33]. Ensuring adequate adhesion of cells to substrate plays a very important role in cell culture. The behavior of the corresponding network structure of intercellular signals is basic for appropriate functions to maintain the biological test material. Adhesion factors are often used to ensure a proper attachment of cells to the substrate. These include proteins like fibronectin [34] or collagen [35]. Adhesion factors regulate several aspects of the cell behavior including proliferation, migration, and protein synthesis [36]. The adhesion of mouse embryonic fibroblasts to the above-mentioned proteins is described in the literature. The impact of factors facilitating the adhesion of cells and their migration iss also examined. The cells that adhered to the uncoated substrate surface have a greater tendency to migrate than in the surface with adhesion improving agent [34]. It should also be noted that the extent to which these factors will enhance bonding with the surface of cells depends on the type of biological material used. The investigation on influence of covering with polylysine on the surface of the PDMS showed that it increased the adhesion of fibroblasts by 32 %, while fibronectin did not exhibit such activity [37]. Park et al. showed that the adhesion affects both the size and the shape of cultured cells [38]. The shape and nature of substrate to which the cells stick are also meaningful. It was examined how the shape of adhesion surface influences growth of cells. For this purpose, adhesive islands of different sizes were coated with extracellular matrix. It was found that cells took the shape of the underlying substrate. Moreover, shape changes had an effect on the cytoskeleton function and cell apoptosis and proliferation [39]. Gaver and Kute [40] investigated the adhesion of the cells on different substrates. Parameters such as pressure, shear stress, flow rate, dimensions of microchannels, and fluid viscosity were examinated. The shear stress increased linearly with increasing flow rate. It was also shown that when the ratio of cell size to channel dimensions is large, the shear stress experienced by cell may differ significantly from the stress acting on microchannel wall. This is the result of significant flow disturbances caused by the cells. These tests show that the presence of a cell changes the velocity distribution of substances. Figure 14.4 shows that the upper part of the cell is exposed to much higher shear stress than its lower part and that in the flow direction is also working on considerable force. The result of these forces is a visible change in cell shape.

Miniaturized analytical systems for cell culture have different geometry of microstructures. Microchips can be used for simultaneous observation and examination of proliferation and controlling the differentiation of one (Fig. 14.5) [19] or six different stem cell lines [41].

Cell adhesion is an important marker of the cell differentiation. Cells could be used as a functional tool for biological research and analysis of procedures used in different therapies, therefore, cell monitoring is very important. Cell growth and adhesion were observed in the microchambers obtained in PMMA (Fig. 14.6).

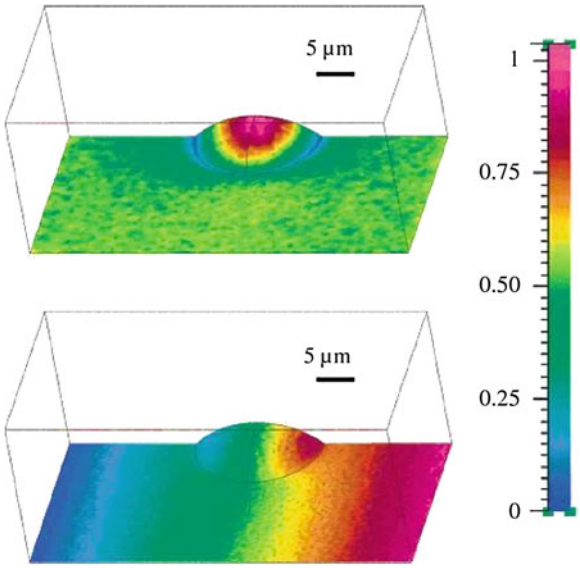

Fig. 14.4 3D model with distribution of forces, which have effect on the cell during the flushing of the microchip. Reprinted with permission from Lu et al. [34]. Copyright 2004 American Chemical Society

The microchambers were also connected to electrodes, used to determine cell-substrate adhesion [42].

14.8 Cytotoxicity Tests in Microsystems

A rapidly growing pharmaceutical industry requires faster and more efficient ways of finding, testing, and refinement of new drugs. Therefore, the main purpose of cytotoxicity testing became to examine the suitability of drugs in the early stages of their placing in the market. Conditions in the cell culture microsystem must be

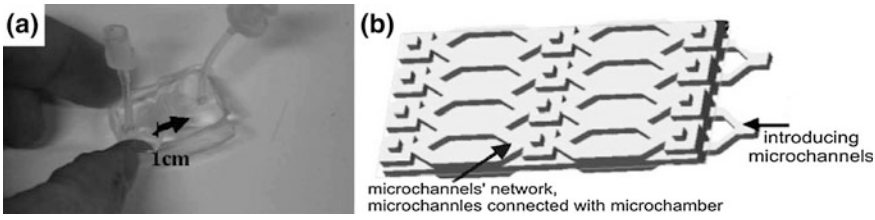

Fig. 14.5 Microsystem (**a**) and the geometry of the microchip (**b**). Reprinted with permission from Leclerc et al. [19]. Copyright 2006 Elsevier

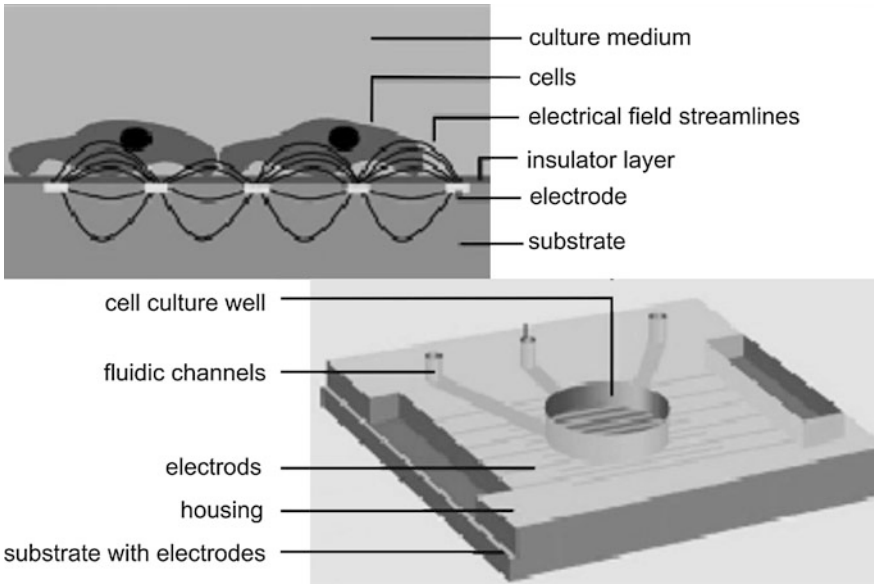

Fig. 14.6 The microsystem for monitoring of cells adhesion. Reprinted with permission from Maercker et al. [42]. Copyright 2008 Wiley–VCH

as close as possible to in vivo conditions for better prediction of the body's response to examined compound. Toxicity tests are carried out sequentially in vitro and in vivo to check whether they are sufficiently safe and effective for further clinical trials. The use of microchips for drug testing is the solution that gives the opportunity to limit not only costs and time-consuming researches, but also to reduce the amount of tests performed on animals.

Microsystems have a great advantage over static cultures, not only because they provide sterile and stable conditions [43], but also by creating a wide range of possibilities in controlling concentrations and dosage of tested substances. It is possible for example to develop a system that allows to simultaneously carry out the test for several concentrations of the tested agent [23]. Moreover, investigations in microscale offer the possibility of testing different types of cells and many substances. It gives the opportunity to perform a more detailed analysis of the effectiveness of tested drug and its safety profile. This is applicable in studying the synergistic effect of combinations of several drugs [44]. The volume of the material required for testing is low and it is especially important when tests are performed with cells derived from the patient. Not without significance are problems arising from two-dimensionality of cells cultured in microsystems. In the natural environment, mammalian cells are exposed to different stimuli including intercellular signals and the effect of extracellular matrix [45]. The ability to predict in vivo effects from in vitro responses of cells cultured in two-dimensional culture are limited. This is significant in the case of tumor cells tending to form

heterogeneous three-dimensional structures [13]. Moreover, it is proved that cancer cells in the case of three-dimensional culture are more resistant to toxic compounds [46]. Despite the clear advantages of the conditions of 3-D cultures, two-dimensional cultures still constitute the majority of the toxicity studies. This is mainly due to relatively low costs of microsystems production and possibility of using simpler detection methods [13].

Studies using the microsystems may be useful in observing and analyzing the effects of drug on both cancer and normal cells [47]. Wang and Kim [48] have designed a microdevice that allowed to examine the response of cells to five different toxins at two different concentrations simultaneously. In these studies they used three types of cells: BALB/3T3, HeLa, and bovine endothelial cells. Another article describes tests carried out only on Balb/3T3 cells, taking into account the continuous monitoring of changes in metabolism and cell adhesion measured by sensors [47].

Microdevice to test the spatial structure cells (cells with this kind of structure better mimic the in vivo conditions) was performed. The microsystem was connected with pneumatic micropumps and microvalves. They enable the flow of nutrients and cells with agarose, which allows cells to achieve the correct spatial configuration and greatly simplifies the mechanism of entering cells to the chip. The microsystem geometry allowed to perform tests a few times in one step [48].

An example of a system used to study the cytotoxicity of chemical compounds can be a device equipped with a wireless magnetoelastic ribbon-like sensor. This solution gives the possibility to monitor the growth of tumor cells in situ and to assess the cytotoxicity of anticancer drugs [49]. The sensor is composed with thick, free-standing (long and narrow) magnetoelastic film, combined with chemical or biochemical layer of receptors. To transfer the energy to magnetoelastic sensor a magnetic pulse is applied. This pulse causes vibrations of the sensor with characteristic resonance frequency, which varies linearly in response to a small increase in weight or change in viscosity. Cell adhesion to the sensor surface causes changes in the resonance frequency and amplitude. Growth curves show the growth and death of cells, allowing for rapid determination of cytotoxicity of chemical compounds. 5+fluorouracil and cisplatin were chosen as model compounds. The addition of these

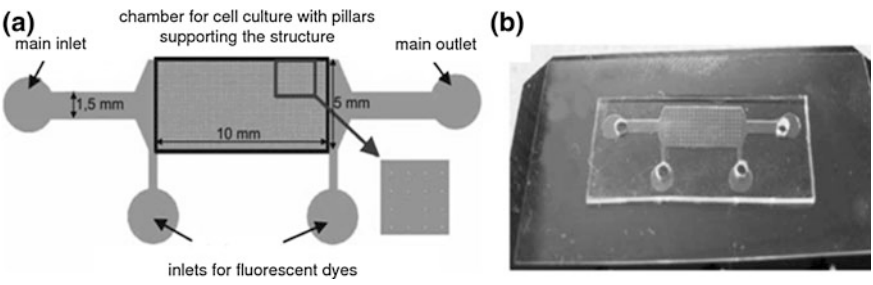

Fig. 14.7 The scheme (**a**) and the fabricated microchip (**b**). Reprinted with permission from Komen et al. [50]. Copyright 2008 Springer

cytostatic agents causes inhibition of cell proliferation. The study was conducted on breast cancer cell line MCF-7 [49]. To assess toxicity of chemical compounds also on the MCF-7 cells another microsystem made of PDMS was used. This device had a different geometry of channels (Fig. 14.7) than the previous one [50]. In this case, the cell viability was assessed after 24 h incubation with staurosporine.

Toxicity tests are also performed in hybrid microsystems built of glass and PDMS with different geometry, using many types of cell lines and various compounds tested [33, 51].

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