SYNTHESIS OF MICRO- AND NANOPARTICLES IN MICROFLUID REACTORS FOR BIOMEDICAL APPLICATIONS

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ABSTRACT

Currently, microfluidic devices are striving for implementation in many areas of biomedicine: drug synthesis, theranostics, biosensors. Such devices provide fast and sufficient mixing in microfluidic channels, make it possible to obtain monodisperse particles, including nanoscale ones, to control the synthesis conditions and to precisely regulate the physicochemical properties of the resulting substances. Sensors based on microfluidics allow detecting various pathological processes. The presented review gives an idea of the principles of constructing microflow devices, chip materials, and reagent dosing systems. Examples of the use of microfluidics in various fields are given.

Key words: biosensors, microfluidics, theranostics.

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INTRODUCTION

Microfluidic reactors are devices designed for the synthesis of substances and particles using small fluid flows in channels of micro- and nanometer size. Although microfluidic reactors were first developed in the early 90s of the last century, new design solutions in reactor topologies have found applications in medicine, pharmaceuticals and chemical industries for diagnostics, crystallization, chemical and combinatorial synthesis, as well as rapid analysis methods.

The development of miniature reactors has many potential advantages over more traditional methods of synthesizing chemicals and particulates. Due to good reaction control, low reagent consumption, high sensitivity and safer working environment, microfluidic devices have proven themselves well for larger production of chemical compounds with clearly defined and predetermined properties. This improves the quality of chemical substances for pharmaceutical industries as well.

APPLICATIONS OF MICROFLUIDIC SYNTHESIS

Microfluidic technologies play an extremely important role not only in chemical synthesis, but also in the synthesis of nanoparticles. Nanoparticles obtained using microfluidic synthesis have found application in such areas as medicine [1], electronics [2], cosmetology [3], solar energy [4] and others. In general terms, the application areas of microfluidic synthesis can be illustrated by Figure 1.

Due to the fact that the physical and chemical properties of nanoobjects depend on the size, shape and crystal structure, in order to obtain materials with the necessary characteristics and properties, their synthesis requires precision control of kinetic and thermodynamic parameters. Thus, the role of microreactors in the synthesis of nanomaterials is reduced to two main tasks: synthesis with controlled size, shape and structure and regulation due to continuous flow processes.

MATERIALS FOR MAKING MICROFLUIDIC CHIPS

The choice of microfluidic chip material (MFC) depends on the purpose of its use and the reagents used in the research.

Silicon, quartz, and glass are traditional materials for large-scale production of microfluidic devices. MFCs from these materials are made by photolithography [5]. Glass and silicon are used because of their thermal stability and compatibility with chemical solvents in crystal reactions [6], droplet formation [7] and extraction [8].

For rapid prototyping and research in the laboratory, polymeric materials are usually used, which were chosen because of the lower price and simpler MFC manufacturing technology. One of the most commonly used materials is Sylgard 184 polydimethylsiloxane (PDMS). This is due to a number of reasons. The liquid PDMS Prepolymer is thermally cured at moderate temperatures (40-70 °C) and can be cast with nanometer resolution using soft lithography from master molds made from silicon, glass or photoresist SU-8 [9], its low surface tension makes it much easier to peel off the templates after curing. The PDMS chip can be reversibly and conformally sealed with another part made of PDMS, glass or other substrate material by a simple connection. However, when using PDMS, more attention should be paid to the chemical compatibility of polymers with the reagents used. In addition, many polymers are not designed for use at high temperatures.

PRODUCTION OF PDMS-BASED MICROFLUIDIC CHIPS

PDMS-based MFCs are made using soft lithography methods.PDMS The sequence in the manufacture of such chips is shown in Figure 2. To do this, the PDMS base is first mixed with a hardener in a mass ratio of 10:1 and poured into a master mold, usually made of silicon by photolithography, with a macroscale pattern. A vacuum desiccator with a pump is used to remove air bubbles. Degassed PDMS is placed in a hardening oven for 4 hours at 60° C. The cured PDMS replica is removed from the mold using a sharp blade. The sealing of a PDMS replica with a glass plate can occur in various ways, for example, by plasma treatment and exposure to high-frequency currents [10]. After that, the ready-made MFC is ready for operation. The above manufacturing protocol is constantly being reviewed and improved [11]. In this form, it has been used in microfluidic studies in recent decades [12—14].

MICROFLUIDIC DEVICE DESIGN AND TOPOLOGY

The choice of the type of microfluidic device used for the synthesis of nanomaterials should be approached taking into account all possible factors. The simplicity of the design leads to easy scalability of the process, but reduces the quality of the nanomaterials produced.

Microreactors with more complex designs allow better control over the properties of nanoparticles, but scaling up the process can be a challenge. In this case, it is preferable to use MFCs with topologies that assume continuous operation, especially for nanomaterials that are less sensitive to changes in reaction conditions.

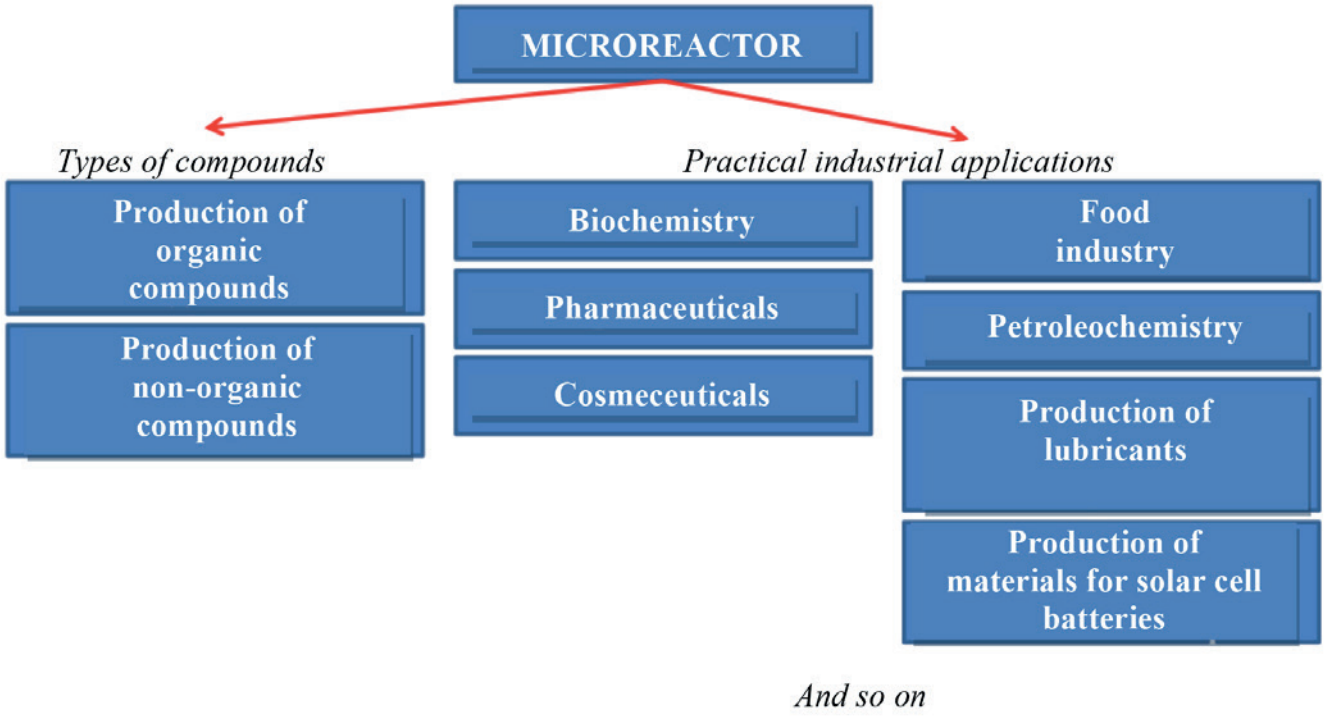


Figure 1. General application schematic for microfluidic synthesis

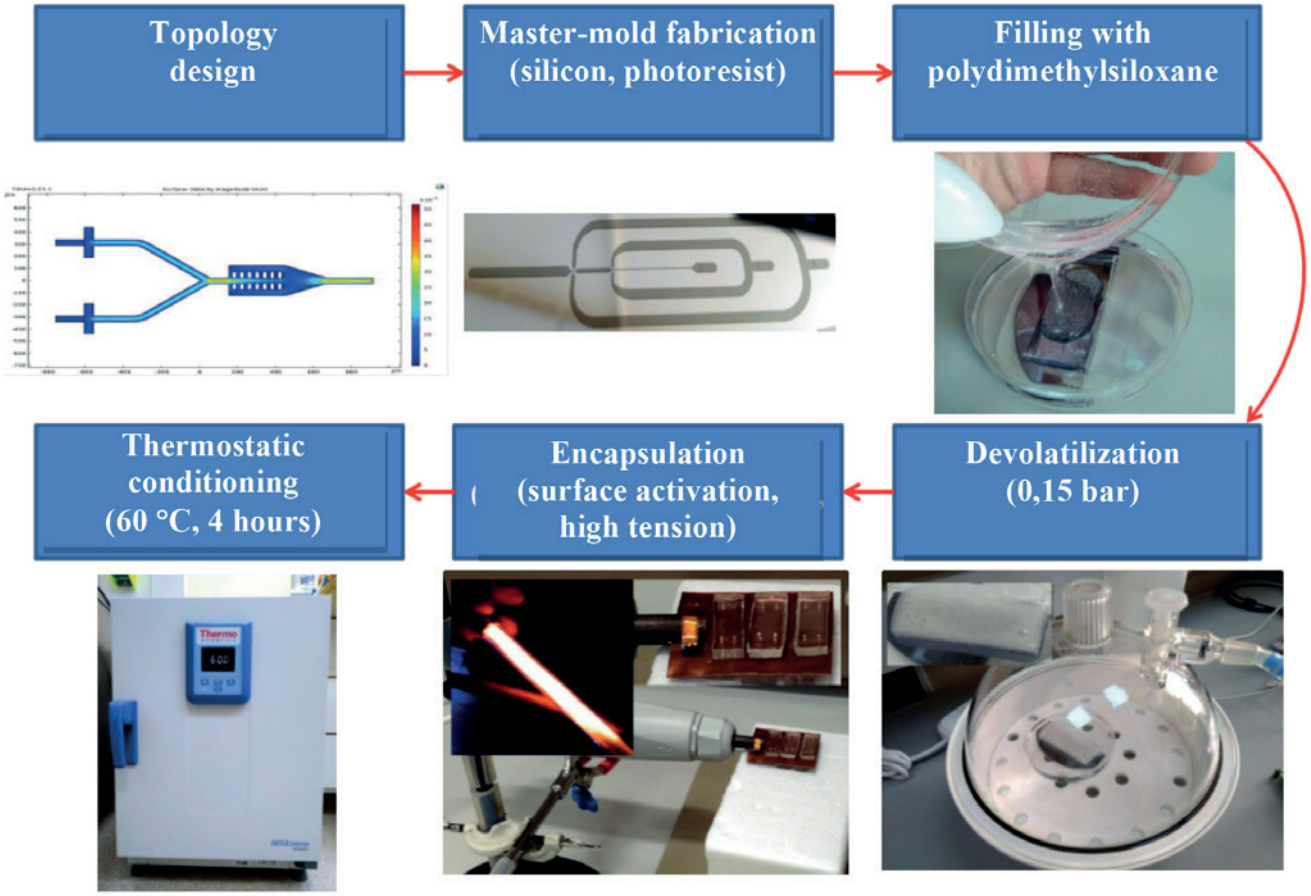


Figure 2. PDMS-based MFC manufacturing schematic

Microfluidic reactors for chemical synthesis can be divided into three main categories: continuous laminar flow reactors, segmented flow reactors and droplet-based reactors [15].

Continuous laminar flow microreactors include only single-phase fluid flows. Several liquid reagents of different composition and concentration are fed to the MFC through the inlets. In these laminar flow-dominated microreactors, mixing is a key process for optimizing production.

The mixing methods can be divided into two large groups. MFCs with flow focusing topologies can be attributed to the first group. Hydrodynamic focusing is one of the most important methods in microfluidic synthesis of materials [16, 17]. Hydrodynamic focusing always occurs in MFPs with topologies involving a triple-input channel consisting of one central inlet channel and two lateral inlet channels positioned vertically or at an angle (less than 90 °) to the central one. In addition, the flow rate of the central channel is smaller than the lateral ones, so that the average flow can be focused and mixed with the lateral flows quickly and sufficiently. The mixing time mainly depends on the flow ratio of the lateral and central inlet channels.

The second group of mixing methods concerns MFCs with topologies for conventionally more efficient mixing. The simplest topologies most often represent two inlet channels of a Y-shaped microfluidic reactor, creating a supersaturated region at the boundary of diffusion mixing between two mutually diffusing flows of reagents.

The use of microstructures, such as straight microchannels [18], curved microchannels [19], spiral microchannels [20] and spinal mixers [21], can further increase the mixing efficiency by introducing disturbances and prolonging the mixing time of flows during the synthesis of nanoparticles.

Segmented flow microreactors typically include several liquid phase flows for reagents and one gas phase flow for creating gas bubbles in order to isolate different segments of reagents. Gas bubbles are formed due to differences in surface tension between the gas and liquid phases. In a typical design, two or more reagents in liquid phases are introduced into the microreactor through the inlets. Additional inlets and sections can be added to the design depending on the requirements for the reaction. Segmented flow microfluidic reactors may become contaminated due to physical contact between the reagents and the walls of the channel. Sometimes this problem can be solved by analyzing the hydrophobicity of the channel walls.

One of the biggest advantages of droplet-based microreactors is the separation into parts, which helps achieving rapid mixing, good time and reagents control, as well as contamination-free microenvironment. Such microreactors usually include several flows of dispersion liquid phase of reagents and a flow of immiscible dispersion medium to form droplets. The simplest geometric designs for droplet formation are T-shaped and Y-shaped injectors [22]. The droplet size depends on the channel width and flow rate.

One of the types of droplet-based reactors is an MFC with a flow-focusing topology, designed for the manufacture of suspensions. The principle of operation of such reactors is based on the “blowing off” of droplets in a continuous stream. The application of this topology is shown in Figure 3. At different flow rates, different droplet sizes are obtained from 30 microns (Figure 3, a)

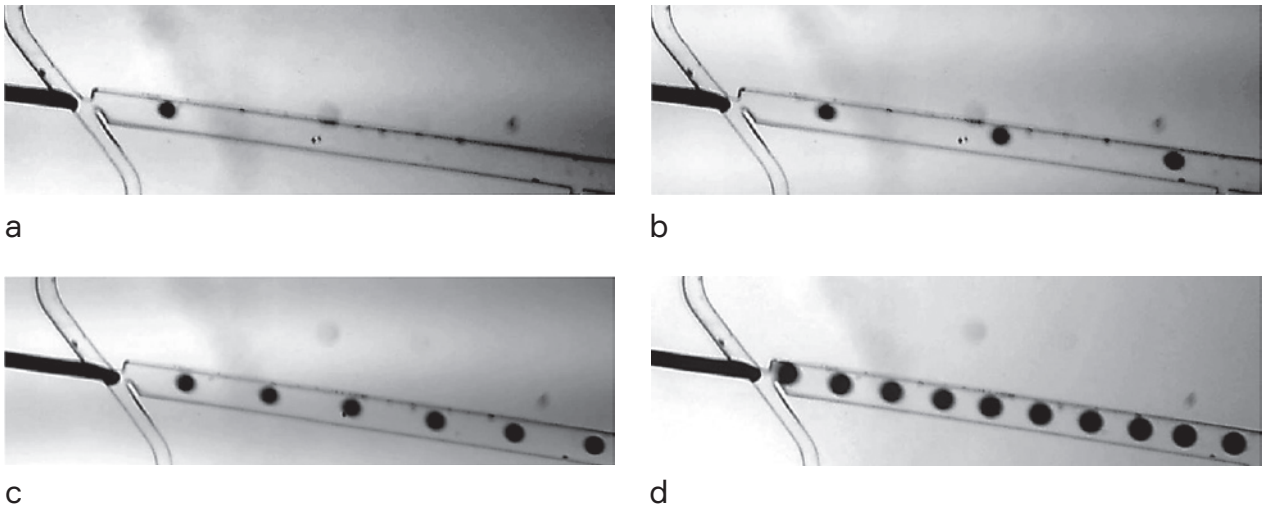


Figure 3. Examples of obtaining magnetic fluid suspension at different feed pressure of mineral oil (P1 = 6.0 kPa) and magnetic fluid (P2):
a — P2 = 6.2 kPa; b — P2 = 6.8 kPa; c — P2 = 7.5 kPa; d — P2 = 8.5 kPa

to 60 microns (Figure 3, d), which makes it possible to regulate not only the suspension formation rate, but also the dispersion.

REAGENT SUPPLY SYSTEMS

Fluids can be supplied to the microfluidic device by a syringe pump (Figure 4, a) or under the action of the applied pressure (Figure 4, b) [23]. The advantage of syringe pumps is a fixed volumetric flow rate, but they also have a long response time and periodic pulsations. The low response time makes syringe pumps unsuitable for advanced droplet pattern formation, since the flow rate and the resulting droplet formation rate cannot be changed quickly. Pressure monitoring systems are able to individually control the flow of multiple fluids simultaneously. They have a response time of up to 40 ms.

The flow in such systems is pulse-free, however, there is a possibility of reverse fluid movement.

In addition to these traditional fluid supply systems, manual syringes [24] and laboratory analogues [25] are sometimes used.

For synthesis under laboratory conditions, a small system can be used (Figure 5), consisting of a light microscope, a microfluidic pressure controller with a compressor, capillaries and a personal computer with a program for controlling the reagent supply system. Such a system was developed at the Almazov National Medical Research Centre in collaboration with the Institute for Analytical Instrumentation.

MICROFLUIDIC SYNTHESIS OF MAGNETIC NANOPARTICLES

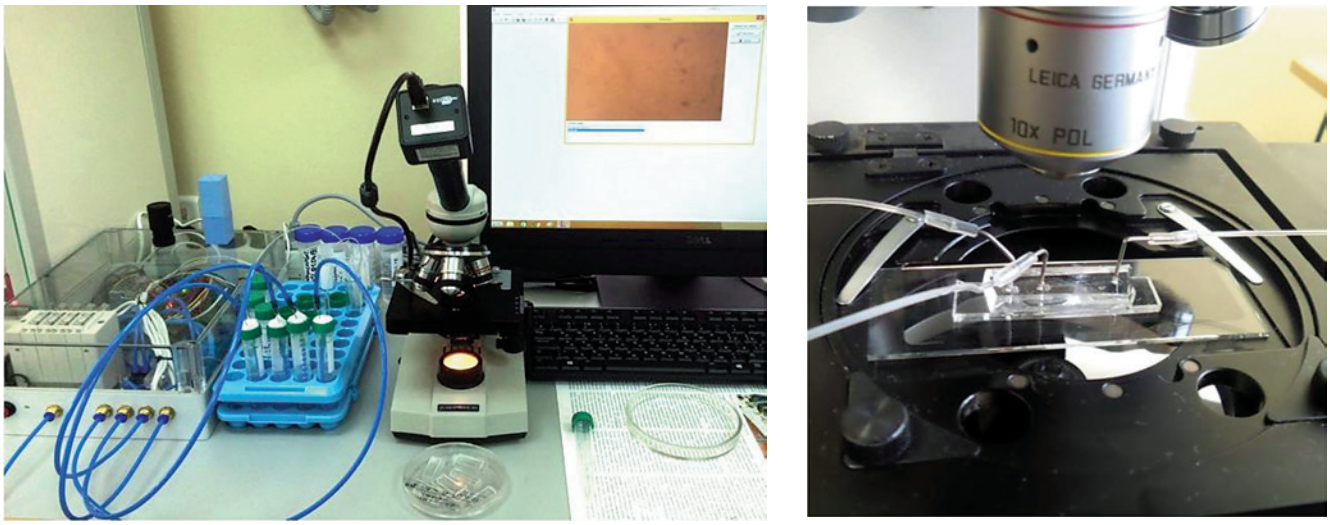
Over the past decade, experiments using microfluidic reactors have demonstrated that it is possible to control with high accuracy the physical properties of various nanomaterials, such as quantum dots, nanoparticles, nanotubes, nanowires and nanocomposites by controlling the growth parameters of nanocrystals and the kinetics of processes. In addition to microfluidic approaches based on laminar flow, experiments using microfluidic droplet methods for the synthesis of nanoparticles have also been successful. At the same time, the development of microfluidic devices for the synthesis of magnetic nanomaterials is still at the initial stage of development. Nevertheless, information available from the literature indicates that there is potential for obtaining better control over size, size distribution, crystal structure and shape of magnetic nanoparticles (MNP) both in small-scale and large-scale processes [26, 27].

The compact process control system is an effective tool that accelerates the optimization of synthesis parameters and the determination of the characteristics of the MNP for nanomedical, theranostic and biosensor applications based on nuclear magnetic resonance (NMR). An automated system has been developed and tested [28] combining a miniature NMR relaxometer and a flow-through microreactor for the synthesis and determination of the characteristics of iron oxide-based MNPs. The properties of NMR relaxation were quantified in a permanent magnet field with an induction of 0.5 T to measure the transverse (T2) and longitudinal (T1) relaxation time. Nanoparticles with a crystallite size of about 25 nm were obtained by codeposition in a microfluidic reactor with three-dimensional hydrodynamic flow focusing to avoid clogging of the channels.

A microfluidic method for the synthesis of magnetic fluorescent liposomes has been proposed [29]. The MNP were functionalized by an amino group in a microfluidic reactor and then covalently bound to carboxyl groups immobilized inside the liposomes. Such liposomes had good biological binding and accumulation under the influence of a magnetic field.

a b

Figure 4. Examples of reagent supply systems:
a — Harvard Apparatus Pump 11 Elite syringe pump;
b — Elveflow OB1 MK3+ microfluid flow controller



a b

Figure 5. Example of a microfluidic synthesis system: a — general view; b — chip microscopy

It was demonstrated in [30] that microfluidic electroporation can effectively promote the synthesis of MNPs coated with a biomimetic cell membrane. Fe_3O_4 magnetic nanoparticles and vesicles obtained from erythrocyte membranes (RBC vesicles) were introduced into a microfluidic device. When a mixture of magnetic nanoparticles and RBC vesicles flowed through the electroporation zone, electrical impulses contributed to the penetration of the MNPs into the RBC vesicles. After that, the resulting RBC-coated MNPs were collected from the chip and injected into experimental animals for testing *in vivo*. Due to the good magnetic and photothermal properties of the MNPs nuclei and the prolonged circulation in the blood, characteristic of the membrane membranes of red blood cells, the obtained nano-objects were used for contrast- enhanced magnetic resonance imaging of tumors and photothermal therapy.

$KGdF_4$ nanoparticles functionalized with hyaluronic acid and doped with lanthanides were synthesized in two stages on a microfluidic platform [31]. Microfluidic synthesis of KgDF nanoparticles doped with Ln^{3+} was carried out at room temperature in a continuous mode using a chip with four inputs. At the second stage, in a separate MFC with T-topology on the surface of $KgDF_4$ nanoparticles doped with Ln^{3+}, hyaluronic acid was continuously immobilized by electrostatic adsorption. The dispersed composition of the obtained nanoobjects was homogeneous; they showed high biocompatibility, targeted cellular absorption, photoluminescent and magnetic resonance properties.

The Almazov National Medical Research Centre in collaboration with the Institute for Analytical Instrumentation developed an MFC topology for the synthesis of MNPs. Initially, it was revealed that magnetite particles during a chemical reaction settle on the walls of the channel, creating aggregates, which in a narrow aperture passage leads to the formation of a blockage of the channel and greatly impedes the flows (Figure 6, *a*). By increasing the pressure, it is still possible to break through the blockage, but in the end the entire surface of the channel becomes dirty, and synthesis is impossible (Figure 6, *b*). The addition of various surfactants does not solve the problem either.

For these reasons, it was decided to abandon the synthesis of MNP in MFCs with T-shaped topology and develop a more complex synthesis scheme. It is a system of 4 input and 1 output interfaces connected by a system of channels (Figure 7). Interfaces 1 and 2 are designed to supply a continuous medium from mineral oil. Two different inputs for the same medium are necessary for the supply of oil at different speeds, which implements the supply of microemulsions of aqueous solutions at different speeds and thus allows efficient mixing using internal recirculation inside the droplet. Interfaces 3 and 4 are designed to feed the channels with aqueous solutions of iron sulfate and ammonia hydrate, which are dispersed phases. In cross-lines 5, droplets of aqueous solutions are formed by by focusing the flow. Then the droplets enter the reaction chamber 6 with an array of walls for inhibiting droplets. Here they merge and move further along the channels. The serpentine section of the channels 7 is necessary for better mixing of the droplet volume through the reaction of the dispersed phase on the channel walls. Interface 8 is used to output reaction products from the MFC.

MICROFLUIDIC SYNTHESIS AND THERANOSTIC SYSTEMS

Theranostics is defined, among other things, as an approach to the development of pharmaceutical compositions, which consists in a comprehensive solution of therapeutic and diagnostic problems by creating drugs that are both a means of early diagnosis and a therapeutic agent [32].

The American scientific community identifies theranostics as part of personalized, precision medicine, in which drugs are selected individually for each patient based on their predicted response or individual risk of disease [33]. In both cases, the use of multi-cascade microfluidic systems is quite interesting for the synthesis of such objects. According to the PubMed database, publications on theranostics originate from the 90s, where a systematic approach based on accuracy and selectivity began to be used for drug development [34]. At the same time, the term itself was introduced by Funchauser in 2002 and defined as the integration of two modalities, that is, therapy and medical imaging into a single "package" of material to overcome undesirable variations in bio-distribution and therapeutic efficacy [35]. At the same time, the number of publications on this topic is constantly growing (Figure 8 a). Microfluidics began to develop actively in the early 2000s (Fig. 8. b), and the number of articles is also steadily increasing. However, there is only a limited number of publications on the use of microfluidics in theranostics, currently not exceeding one hundred publications per year (Figure 8. c). Apparently, this is due to the difficulties of synthesis and modification of nano-objects in narrow channels. Currently, the task of synthesizing theranostics objects based on microfluidic technologies is reduced to two aspects: the synthesis of nanoparticles themselves and their modification. For this purpose, MFCs of various topologies are used [36]. The general schematic of such synthesis can be illustrated in Figure 9. It includes the synthesis of nanoparticles, spacer, immobilization of the active substance, coating, contrast immobilization, as well as purification from intermediate reaction products [37]. Operation control is possible at each stage. In the synthesis of nanoparticles, this is the size distribution control by dynamic light scattering (DLS) [38], FT-IR analysis [39] at the stages of immobilization of active substances and the fluorescence analysis [40, 41] during immobilization of fluorophores. All these types of analysis, as well as PCR and others, can be implemented in separate microchips [42-46].

SENSORS BASED ON MICROFLUIDIC SYSTEMS

The integration of micro-devices with different chip designs has led to an increase in the analysis functionality using such systems. For example, fast and sensitive microfluidic systems can detect various biological objects, such as proteins, nucleic acids, cells, pathogens, etc. [47—49]. However, the objects of interest to researchers may not only have a biological nature, but also contain specific ions, dissolved gases, drugs and toxins [50]. Therefore, microfluidic biosensors are used in various fields, for example, for the diagnosis of diseases [51], food safety control [52] and environmental monitoring [53].

Currently, the most commonly used microfluidic platform is known as a "laboratory-on-chip" (LOC) or a total microanalysis system (micro-TAS) [54, 55].

Devices based on LOC technology combine several laboratory functions on a single crystal ranging in

a b

Figure 6. Contamination of T-shaped topology MFC in the process of MNP synthesis: a — initial contamination; b — complete filling

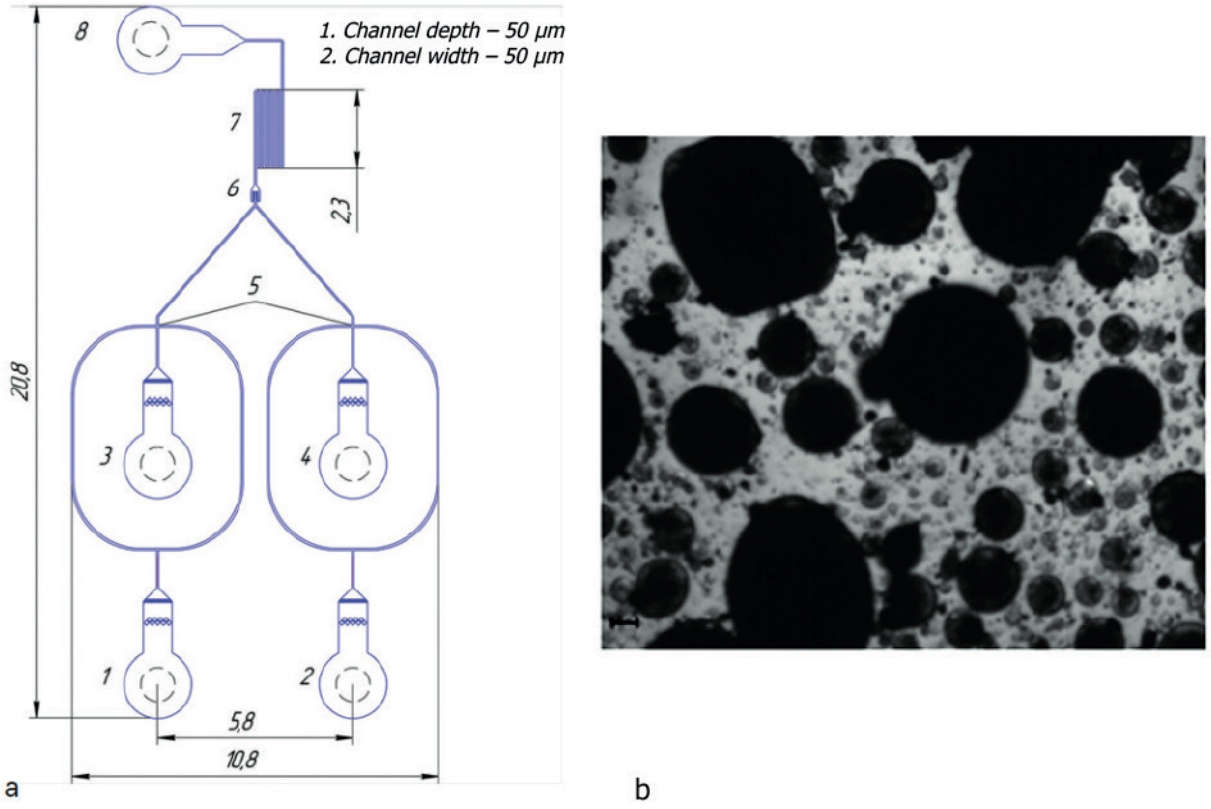


Figure 7. MFC topology for the synthesis of magnetic nanoparticles (a) and suspension of droplets containing nanoparticles (b)

size from a few square millimeters to several square centimeters. Compared to conventional systems, these platforms have many advantages, for example, a high surface-to-volume ratio, precise fluid control, low sample consumption and a high degree of integration with functional components [56]. There are chip-integrated microfluidic biosensors designed for so-called point-of-care diagnosis (POC) [57]. Microfluidics provides simple and fast analysis of small samples. Moreover, several sensors and sensing zones can be built into microfluidic chips to increase their usefulness. It is assumed that the ideal chip-integrated biosensor will be inexpensive, compact, fast and sensitive.

Recently, a flexible and easily stretchable MFC-integrated electrochemical sensor [58] has been manufactured. This makes it possible to simulate physiological and biomechanical parameters of blood vessels *in vivo* and simultaneously monitor mechanically induced biochemical signals in real time. A microfluidic biosensor has been developed for online sensitive detection of salmonella based on immuno-magnetic separation, fluorescent marking and video processing on a smart phone [59]. Magnetic nanoparticles were used to separate and efficiently concentrate the target bacteria, resulting in the formation of magnetic bacteria, which were then marked with fluorescent microspheres. After that, fluorescent bacteria were continuously injected into the MFC and illuminated by a fluorescent microscopic system, and fluorescent spots were counted online using an application for smart phone based on the interframe difference algorithm to determine the number of bacteria.

One of the varieties of LOC is the "organ on chip" (OOC) technology which arose from the desire to replace experimental models with animals [60].

OOC platforms are a new generation of three-dimensional models of cell cultures that better simulate the dynamic, physico-chemical, biochemical and microarchitectural properties of the microenvironment of living organs. Organ-on-chip microphysiological systems are flexible and can be designed to simulate the required types of organs and tissues for the opening process and drug development [61, 62]. For example, the lung-on-chip model is used to study the physical and physiological aspects of alveolar tissue [63].

An important direction in the development of test microfluidic systems is the diagnosis of viral diseases. Such systems can be based on both OOC technology and biosensors for POC. One of these sensors is a smart phone-based platform for highly sensitive and selective detection of avian influenza virus based on colorimetric detection using nanomaterials [64]. Three-dimensional nanostructures that serve as a framework for the conju-

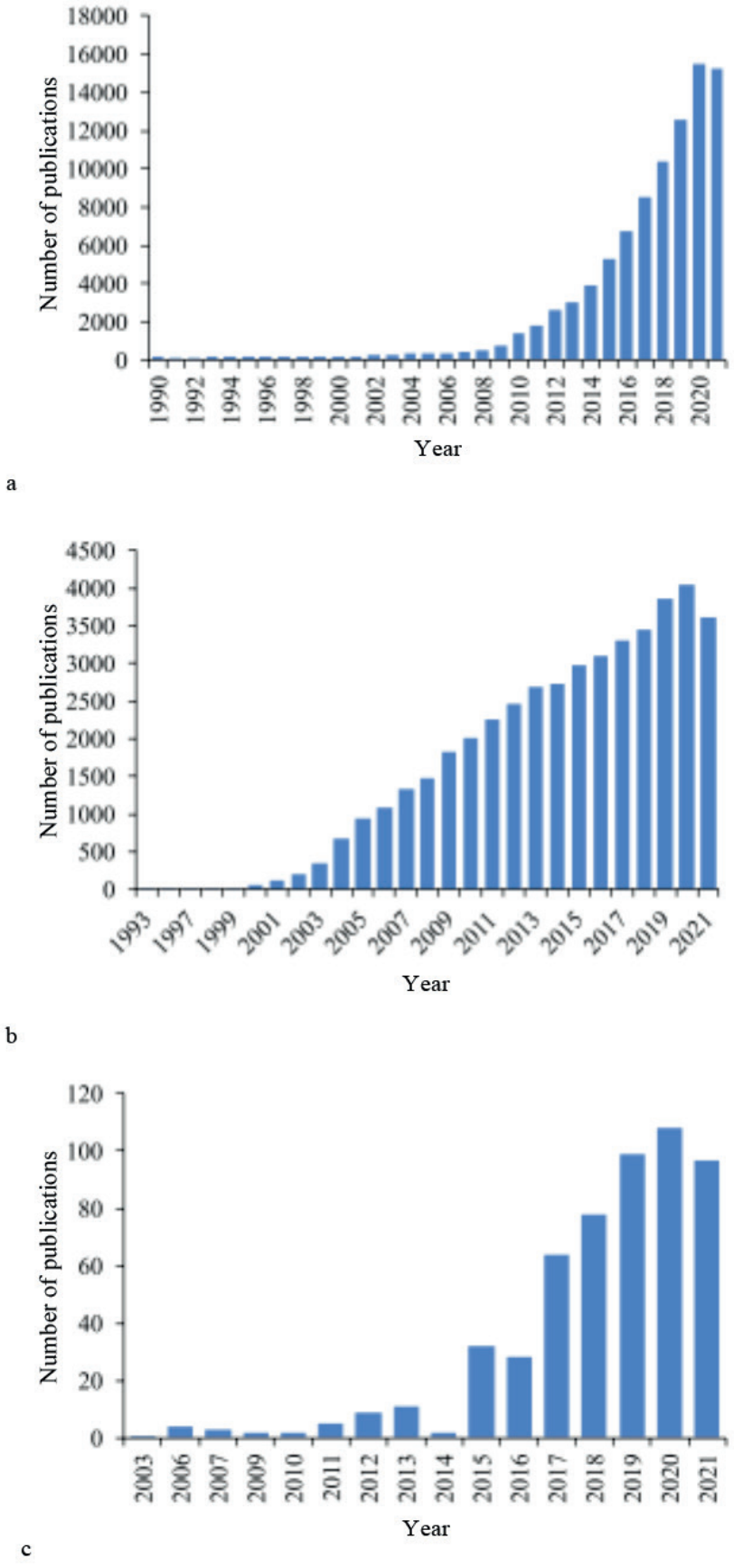


Figure 8. Number of publications:
a — theranostics; b — microfluidic; c — microfluidic & theranostics

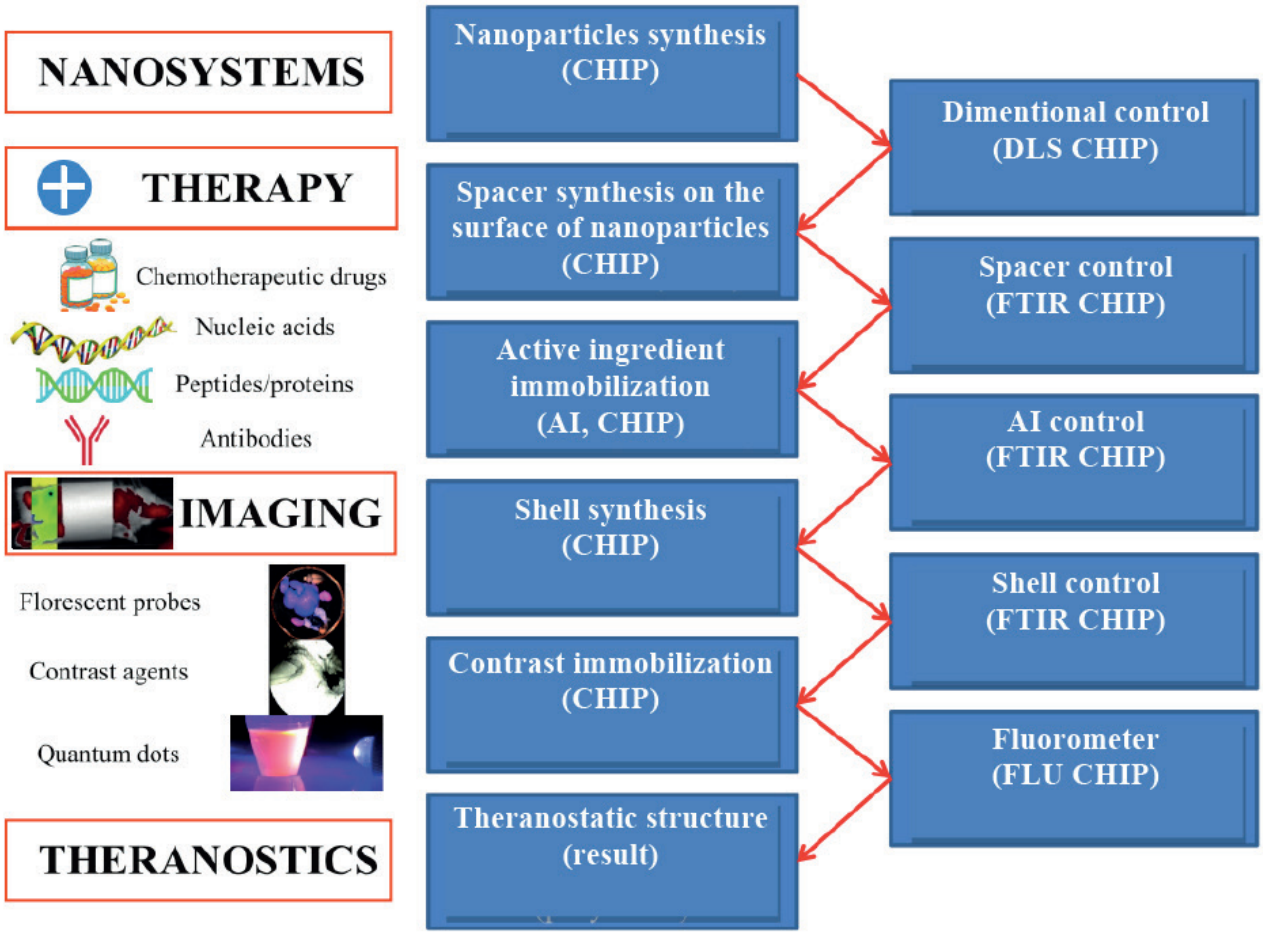


Figure 9. General flowchart diagram for synthesizing objects for theranostics

gation of antibodies to capture the avian influenza virus are made on their PDMS structures in the form of a herringbone using a template of ZnO nanorods. After the virus is captured, a colorimetric reaction based on gold nanoparticles on a crystal makes it possible to detect the virus with the naked eye. An example of a test system based on OOC is the study on virus-host interactions and human reactions on the "lungs-on-chip" and "intestine-on-chip" models [65] .

Today, the problem of detecting the SARS-CoV-2 virus is an acute problem. The main diagnostic methods are now genomic (including PCR, real-time RT-PCR, sequencing) and serological/immunological tests (focused on detection antibodies or antigens in biological samples taken from patients). With a high degree of reliability of these methods, they have a number of significant disadvantages expressed in high cost, duration of analysis and dependence of the accuracy of the results on the methods of material collection, compliance with storage conditions, transportation and sample preparation. All this complicates mass screening, especially in remote regions with insufficient infrastructure [66—69]. Some of these problems can be solved by immobilizing viral antigens or proteins of its targets on the surface of nanoparticles, followed by their use to determine the markers of viral infection (both nucleic acids and viral proteins, and antibodies against them). In recent years, new methods of nanodiagnostics for early sensitive detection of viral infections have been considered as the most accessible and effective in the context of an epidemic. They do not require a large volume of the test sample or a special sample preparation and can be used even at home, which reduces the risk of cross-infection of others [70]. In order to enhance the signal when detecting pathogens, the surfaces of nanoparticles are easily modified with polyvalent ligands or other biomolecules [71]. Surface functionalization gives nanoparticles the ability to interact with specific biomarkers of infection, such as viral RNA, viral proteins and virus-specific antibodies [72, 73]. The unique physico-chemical characteristics of nanoparticles (optical, reaction and/or fluorescent properties) allow them converting the fact of interaction with biomarkers into measurable detection signals [74, 75]. All this makes it possible to formulate a new scheme for detecting viruses and, in particular, COVID-19 (Figure 10).

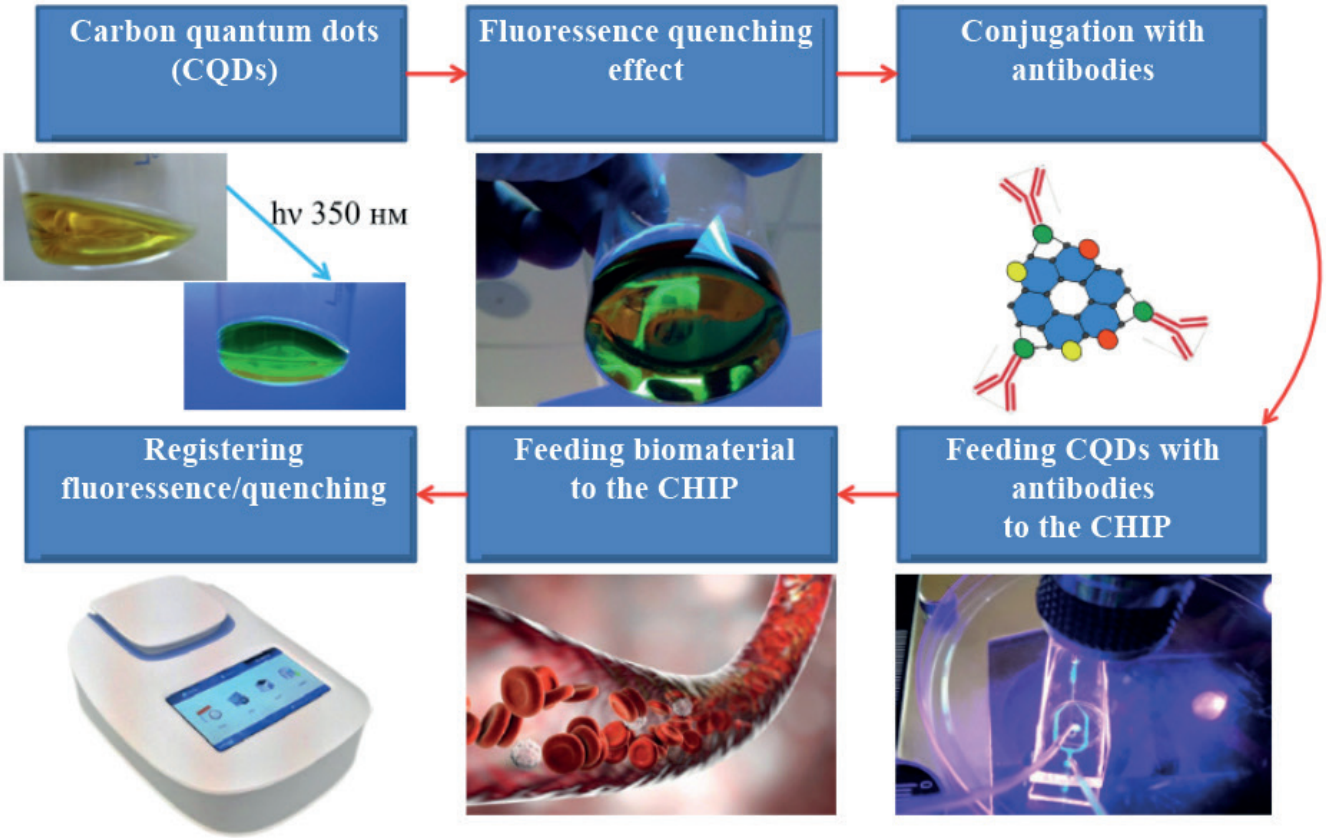


Figure 10. General schematic of a sensor based on fluorescent quenching of carbon quantum dots

The main component of the system is a fluorescent agent (FA), which is characterized by fluorescent quenching while reducing the intensity of the inducing radiation or shifting its wavelength. Colloidal quantum dots (QDs), which by their physical nature are nanoparticles, can act as FAs. QDs are conjugated with antibodies to the virus or with a protein that is tropic to any part of the virus. Such a conjugate can be launched into the channel of a microfluidic chip, where it mixes with blood and enters another chip for detection. The scheme can be portable and adapted for various viruses.

CONCLUSION

Despite the relatively recent introduction of microfluidic synthesis, it has proved highly efficient in reproducing micro- and nanoparticles in a controlled environment.

Successful synthesis and application of micro- and nanoparticles based on microfluidics have the following features:

1. Fast and sufficient mixing in microfluidic channels leads to monodisperse particles with a relatively high yield.
2. Control over the synthesis conditions allows you to accurately regulate the physical and chemical properties and minimize their deviation from batch to batch.
3. Systematic integration of several procedures into a single microfluidic device makes it possible to produce micro- and nanoparticles with the desired complex structure in one step.
4. Microreactor technology provides improved process control based on well-defined active unit cell microstructures that can be reproduced to obtain higher chemical production volumes.

All these advantages allow us to draw a conclusion about the prospect of large-scale use of microfluidics for biomedical purposes. Currently, the use of microfluidic devices in such areas as synthesis of drugs [76], PCR analysis [77], cell research [78], synthesis of radiopharmaceuticals [79] and many others is already close to practical implementation.

Conflict of interest
The authors declare no conflict of interest.

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