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M.Sc. in Mechanical Engineering

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**UNIVERSITY OF GAZIANTEP
GRADUATE SCHOOL OF
NATURAL & APPLIED SCIENCES**

**INVESTIGATION OF THE EFFECTS OF TUBE
GEOMETRY IN THE MICROFLUIDIC DEVICE USED TO
GENERATE NANOSPHERES**

**M.Sc. THESIS
IN
MECHANICAL ENGINEERING**

**BY
AUSSAMA AL-HAMADANI
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**Investigation of the Effects of Tube Geometry in the Microfluidic Device Used
to Generate Nanospheres**

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University of Gaziantep

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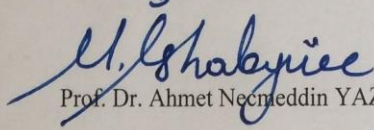
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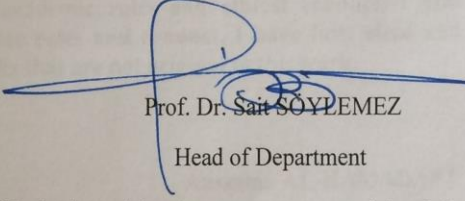
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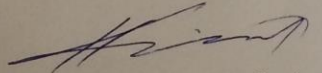

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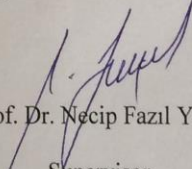
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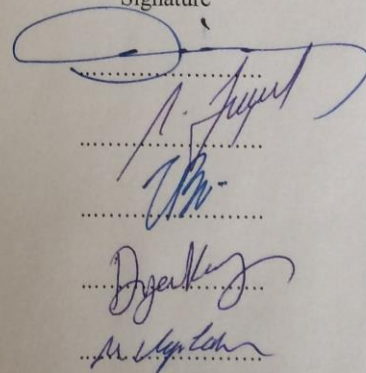
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ABSTRACT

INVESTIGATION OF THE EFFECTS OF TUBE GEOMETRY IN THE MICROFLUIDIC DEVICE USED TO GENERATE NANOSPHERES

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M.Sc. in Mechanical Engineering

Supervisor: Assoc. Prof. Dr. Necip Fazıl YILMAZ

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This study describes polymethylsilsesquioxane (PMSQ) nanospheres formation from microbubble bursting in a 100 μm capillaries embedded combined microfluidic device based on effects of junction angle and flow rate of liquid solution. The understanding of polymer nanosphere generation from microbubble bursting in the device with thin capillaries used could be very useful for many applications, such as cell transplantation in biomedical therapy, advanced therapeutic applications and food industry. The effects of the junction angle ($\theta=0^\circ$ to 60°) between the liquid and gas channels and the gas pressure ratios (50 to 400 kPa) are considered. The digital microscope results indicate that the microbubble size during the bubble generation process generally decreases with the increase of junction angle at the same flow rate and gas pressure. A junction angle of around 60° was figured out as the most efficient angle at which alternating microbubbles are still formed at lower capillary numbers (Ca). In addition, the nanosphere size in the combined microfluidic junction device with 100 μm capillaries decreases as junction angle increases with the same flow and gas pressure conditions. The microbubble formation in the device used in this work depends significantly on the gas pressure, and the combined microfluidic junction device with thin capillaries becomes a microbubble generation when N₂ gas pressure is greater than 50 kPa.

Keywords: Microbubble Generation, Microfluidic Device, Junction Angle, Gas Pressure, Polymer Nanospheres

ÖZET

NANO KÜRELERİN ÜRETİLMESİNDE KULLANILAN MİKRO AKIŞKAN CİHAZDA TÜP GEOMETRİ ETKİLERİNİN İNCELENMESİ

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Bu çalışmada, birleşme açısının ve sıvı çözelti akış hızının mikro akışkan cihaz içine yerleştirilmiş 100 µm'lik bir tüp içinde mikro baloncuk patlamasından elde edilen polimetilseskiokson (PMSQ) nano-küre oluşumuna etkileri incelenmiştir. Kullanılan mikro akışkan cihazda mikro baloncuk patlamasından elde edilen polimer nano küre üretiminin anlaşılması, biyomedikal tedavide hücre naklini, ileri terapötik uygulamalar ve gıda endüstrisi gibi birçok uygulama için çok yararlı olabileceği görülmüştür. Sıvı ve gaz kanalları arasındaki bağlantı açısının ($\theta = 0^\circ$ ila 60°) ve gaz basıncının 50 ila 400 kPa olduğu zaman ki etkileri dikkate alınmıştır. Dijital mikroskop sonuçları, baloncuk oluşturma işlemi sırasında mikro baloncuk boyutunun, genellikle aynı akış hızında ve gaz basıncında birleşme açısının artmasıyla azaldığını göstermektedir. Yapılan deneylerde değişken mikro baloncukların oluşturulduğu en verimli açının yaklaşık 60° 'lik bir bağlantı açısı olduğu görülmüştür. Ayrıca, 100 µm çapında tüp kullanılan birleşik mikro akışkan bağlantı cihazındaki nano küre büyüklüğü, aynı akış ve gaz basıncı koşullarıyla bağlantı açısı arttıkça azalmaktadır. Bu çalışmada kullanılan cihazdaki mikro baloncuk oluşumunun gaz basıncına büyük ölçüde bağlı olduğu ve N₂ gaz basıncının 50 kPa'dan daha büyük olduğunda mikro akışkan cihazı ile mikro baloncuk oluşumunun sağlanabildiği görülmüştür.

Anahtar Kelimeler: Mikro Baloncuk Oluşumu, Mikro Akışkan Cihazı, Bağlantı açısı, Gaz Basıncı, Polimer Nano Küre



To my father and mother

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Microfluidics is a technology and science of manipulating and controlling liquids, usually in a range of microliters (10⁻⁶) to picoliters (10⁻¹²), networks of channels with diameters of tens to hundreds of micrometers. This emerging discipline takes its origins in the early 1990s and has shown significant growth since then our time to growing popularity of micro analytical in chemistry techniques and the development of microelectronics technologies [1], the microfluidic devices exhibit such as many advantages compared to the larger reaction devices, less power reagent, increased portability, shorter switching time and more precise control. Microfluidic hardware manufacturing has received significant attention in the last two decades because of its enhanced application in the above areas [2], microfluidics is the science that deals with liquid inside channels of micrometer size. At least one dimension of the channel is in the order of a micrometer or tens of micrometers in order to consider it as microfluidics. Nanometer or nanofluids and so on. Microfluidic can be considered both as a science (study of fluid behavior in small channels) and technology (manufacturing microfluidic devices for applications such as laboratory-based devices) [3], the preparation of polymer nanospheres is currently a prime focus of research due to their broad range of applications, including disease detection and therapy [1], chemical reagents, [2,3], cell/enzyme experiments, targeted therapeutic applications [4-6], Multimodal contrast enhancement [7-10], therapeutic agents such as proteins, genes and drugs [11-15] and controlled delivery [16], Phase separation [17, 18], self-assembly [17- 19-21], spray drying [22], electrohydrodynamic techniques [23-25], emulsion polymerization [21, 26-28], precipitation polymerization [19], and microfluidics [29, 30] are moderately used to prepare

monodisperse polymer nanospheres. However, most of these techniques have limitations such as time consuming, material specific requirements and rare desired narrow size distribution of the forming nanospheres, which is very significant for advanced applications in pharmacy and food industry [29, 31], microfluidics is a widely used system and advanced approach that is currently receiving much attention for the preparation of polymer nanospheres with narrow size distribution from bubble bursting due to its compelling advantages such as easy and effective control of liquid flow and gas pressure and cost effective preparation over the other methods] [32, 33], a number of microfluidic methods with various device geometries for consistently generating continuous bubbles and subsequently polymer nanospheres have been discussed in the literature: T-junctions, coflowing or crossflowing devices and flow-focusing capillaries [34-36], in particular, gas-driven microfluidic systems take advantage of device geometries and narrow capillary size to achieve discrete and independently controllable bubbles leading to polymer nanospheres with various geometries and polydispersity [31,37,38], the aim of this study a remarkable advantage of the combined microfluidic device with different junction angle in addition to transparency, cost efficiency and reusability is the control over the gas pressure and hence ability of continuous monodisperse microbubble formation satisfying criteria for therapeutic application.[Polymethylsilsesquioxane (PMSQ) is a highly desirable polymer that has non-toxicity, high chemical stability and biocompatibility which provide us use of them as a model micro/nanosphere material] [39-41], studies conducted by Ye et al. reported on producing PMSQ microspheres with 28 μm in diameter using a microfluidic method with the mechanism of monodisperse bubble generation. This study, along with digital microscope images of experimental procedures, describes a gas-driven combined microfluidic device with different junction angles for generating independently discrete microbubbles and hence nearly monodisperse polymer nanospheres. This simple technique achieves no waste of any significant volume of the sample, controllable size distribution and easy-going process.

1.2 Organization of the work

This study, along with digital microscope images of experimental procedures, describes a gas-driven combined microfluidic device with different junction angles for generating independently discrete microbubbles and hence nearly monodisperse polymer nanospheres. This simple technique achieves no waste of any significant volume of the sample, controllable size distribution and easy-going process.

This thesis is organized in five chapters.

The following chapter, Chapter 2, denotes the most related works on the “preparation of polymer nanospheres” through preparation from microbubble bursting in a 100 μm capillaries embedded combined microfluidic device based on effects of junction angle and flow rate of liquid solution.

Chapter 3 deals with material and methods of microfluidics devices used in medical, other sector and the general knowledge on preparation of polymer nanospheres. Theoretical approach is explained in detail.

The experimental procedure and newly proposed method is explained in Chapter 4. Procedure for microstructural analysis is also provided in this chapter.

In chapter 5, microscopic analysis and results are discussed according to different experimental cases. And the conclusion gathered forms the work results.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Many researches have been carried out some effects on the effect of microfluidics devices; and the mechanism of polymer nanosphere formation from microbubble generation. This chapter presents a comprehensive up to date literature survey.

2.2 Literatures on Microfluidic Devices

Thorsen, T. & Quake [42], in 1946, 19,000 tubes of air were prepared, and 30 tons were weighed, 200 kW of energy was used. The transistor was invented in Bell Labs in 1947 and continued to replace large vacuum tubes in the circuits, but the communication process remained a problem. Although engineers and technicians can in principle design and form increasingly complex and diverse circuits consisting of hundreds of thousands of transistors, each of the inside of the circuit will be welded by hand, considered to be a low-cost process, requiring manual labour. The addition of more parts to the circuit reduced its reliability, so it made a cold type cold welding circuit useless. Thorsen, T. & Quake Microfluidic chips which are high density and contain a total of plumbing networks with thousands of valves, micro-mechanical pipes and hundreds of channels that can be individually processed. These fluidic devices are similar to integrated electronic circuits fabricated using integration on a wide range. One of the key components of these networks is the fluidic multiplexing, a fusion matrix of dual valve patterns that significantly increases the processing power of the network by dealing with many complex fluids with minimal input through the channels. These integrated microfluidic networks are used to construct a microfluidic analog from a comparison group and a microfluidic memory storage device that is similar to random.

Kilby and Noyce [43], solving the problem of electronic "numbers" By working on the creation and manufacture of all elements outside one of the forms of Germanic conductors at first, the silicon wire Kelby and Noisey work to form circuits consisting of transistors, capacitors, resistors and the corresponding conductors, which will eliminate the collection by hand. The invention and work on the development of transistors in the first stage. Which are made in blocks of conductors, where the lamps that were previously used in the formation of electronic devices have been changed gradually (radio, computer)

Kim, S. M. [44], we have developed many techniques such as optical printing, which in turn we have been able to reduce and integrate thousands of transistors subject to and focused on the chips in the form of conductors, especially silicon. Studies and research led to the initial production of an integrated circuit with the first microprocessor.

Martinez, A. W. [45], the development of microfluidics has been developed at the University of Standard. Work on the development of genetics has begun to stimulate analysis by using a combination of a highly complex mixture of massive molecules, especially DNA and protein. The microfluidic system will analyze and find ways to access the development of this science through the use of 4 techniques taken from microelectronics to silicon and glass because these techniques have been available as well as very sophisticated.

Sen Yang [46], Using the silicon drilling process, which was recently developed for the microelectronics industry, where the first portable microprocessor was manufactured on its silicon chip. This device is called MEMS (Micro Electro Mechanical Systems) some other parts called "Microsystems Technology" or "Micromechanical Devices" have played an active role in pressure sensors and printer. MEMS is a mechanical and electromechanical mini-technology. It has different dimensions of MEMS from one micron, up to several millimeters. MEMS designs include motors, sensors and microelectronics. MEMS can integrate multiple devices into a single chip and is expected to be the most important technological invention in the future. Many scientists and researchers have investigated the use of MEMS in many sciences. There is an urgent need for these areas to control fluid

flow in small channels where they have effectively contributed to microfluidic development. Much research has been done to develop several laboratories on a device to enable the integration of all diagnostic mechanisms in the hospital onto one microfluidic device. At that time all microfluidic devices were made of glass or silicon.

Jo, B. H [47], research based on polymer microelectric channels such as PDMS (PolyDiMethylSiloxane) has seen strong growth. Reducing the cost and time of processing of such devices has allowed a large number of laboratories to work on microfluidic research. To date, there are many researchers working in the field of microfluidic to expand its applications, especially in the field of medicine. The microfluidic device consists of narrow channels cast in a polymer that is interconnected in a flat surface. The most common polymer for a microfluidic device is PDMS. PDMS It is transparent, biologically (very similar to silicon), inexpensive, easy to mold and more interconnected.

Dendukuri [48], there are three laws that govern the formation of droplets when changing the flow rate. They are pressure, drip and jetting. In the pressure laws, both flow rates and number of capillaries are low (CA usually less than 0.01) CA is a number between 10, 3 and 10 in most microfluidic devices. T junction. The sharp collapse is due to the control of surface tension strength and is clearly a low flow flow. , The size of the components becomes smaller when we increase the flow. Relative viscosity becomes dominant when we increase the flow and tensile strength is not sufficient for the sharp disintegration of the elements. This will allow flow to the differentiation stage in the horizontal channel before the shear operation occurs.

Garstecki [49], results of the forces involved in the process of creating droplets. The most important variables affecting the work of the T-junction device are the geometry of the channel, the design and configuration, the working state of the channel type, the properties of the fluids (density, viscosity, surface tension and contact angle) and operating parameters (pressure, flow rate ratio, temperature electric field etc.). To express these variables, some variables that depend on parameters are more dominant than others. The micrometer scale, gravitational effect and inertia can be ignored. Finally, the poetic figure is considered the most important parameter of three droplet formation systems: pressure and drip systems. There are

three dynamic types that correspond to three drip flow systems in the T junction of the microfluidic. When the capillary number is less than 0.01, the shear stress is much smaller than the inertia force. Therefore, the distillation of droplets is controlled by hydrostatic pressure drop through the resulting droplets. In T - junction, where it forms two unbreakable liquids at the input junction and at the main channel. The uninterrupted phase breaks through the main channel and the droplet begins to grow. The pressure mechanism can be described with two conditions. The first condition is that the width of the main channel should be greater than its height and the width of the input channel should be at least half the width of the main channel. . In the experiment, the carrier fluids were castor oil and silicone oil of various viscosity introduced from the horizontal channel of the intersection while the scattered phase (ionized water with clay or without mud) flows through the vertical channel.

Garstecki [49], it is explained in the mechanism of forming droplets and bubbles through the T-junction microfluidic. When the vertebrate is low, cracking is not controlled by shear stress: the initial obtained results support the assertion that the effective contribution to fracture dynamics results from increased pressure drop through the emerging bubble. This decrease is due to the pressure resulting from high resistance to continuous fluid flow in membranes that separate the droplet from the microscope walls when the droplet fills the cross section of the capillary channel. , Based on the volume of droplets and bubbles produced in T devices over time for a set of flow rates and for two non-mating phases, continuous phase viscosity, interstitial tension, and geometric shape. Dimensions of the device.

Jiaming. Zhang [49], many simple, fast and cost-effective methods have been developed to form microfluidic devices, especially for generation and processing of microdroplets and microbubbles. The first work on the microfluidic devices of inexpensive glass material with the collection of glass capillaries, to generate multiple emulsions mono exchange. The design, formation, testing and testing of many different types of devices and results have been demonstrated to have the ability to prepare single-layer and double-layer emulsions Triple layer and multi-element. Second, it is proposed to manufacture a glass-like device to produce microbes, with a smaller nozzle pool collected from the capillary. Single-density

microbanks with diameter ranging from 3.5 to 60 microns were produced at a rate of 40 kHz. There is a law of measurement based on the number of capillaries and the rate of flow of liquid to gas, to the success of the size of the bubble.

Xu et al [50], Working on a comparison with orthogonal flow technology and technology; this technique, which produces cross-flow cracking, produces a set of droplets with a small and narrow range of shape and volume of droplets. The process of building micro fluid flows plays an important role in controlling and controlling liquid flow technology. A microfluidic device is the most commonly used and used to generate droplets through the T junction. The microfluidic device works in one position through a continuous, vertical flowing flow. In the cross where the continuous material is inserted from the horizontal channel and the phase flows through the vertical channel through which the droplets are intersected by shear force. The vertical flow of the flow is in contrast to the cross shearing, which is the process of continuous flow of the perpendicular output and the flow of the spatter from the horizontal outlet.

Wang, K., & Luo, G. S [51], they are used several vertical flow paths at different angles ranging from 30 degrees to 150 degrees between channels from which the added material is applied to control the flow and flow of intermittent liquid gases in microconductors. The gas bubbles are in the form of flows and are fixed in two phases within the channels of microfluidic devices. The flow and flow of these gases and liquids and the size and diameter of the gas bubbles, ranging from 800 to 3100 μm , are dependent entirely on several key factors including flow rates and physical properties of the liquid phase. The angle between the input channels is also impressive Major impact. The angle is connected through the two-stage input channels to the length of the plug into the gas bubble inside the microfluidic device. This correlation allows for the expectation of calculating the gas bubble plug length in the T-fluid microcircuits, which use cross angles ranging from 30 ° to 150 °, and have very useful utility for the controllable setting of gas bubbles.

Samuel K. Sia George M. Whitesides. [52], they have studied microfluidic systems in poly (dimethylsiloxane) (PDMS) for studies and biologics. The most important characteristics of PDMS, which are considered as the appropriate starting points for micro-biological studies, are discussed and techniques are learned through which

PDMS microprocessors are manufactured, and the most important methods of obtaining control through which fluid flow is controlled in microchannels. The most important procedures and biological processes that have already been resized and minimized in the PDMS-based precision immunological devices are separation of proteins and DNA, cell sorting and handling, cell studies in small channels exposed to fluid flow of the fluid, and extensive structural examination.

Ushikubo, F. Y., Birribilli [53], he has produced water emulsions in oil by using microchannels with their forms and geometry in the form of Y- and T-thru by generating a total of single drops. For each composition composition in the microchannel, we have evaluated the most important effect and results of fluid and study interface properties despite practical conditions. The size of the droplets depends entirely on the relative velocity between the continuous and dispersed phases and depends on the viscosity of the relative liquid between the phases. All these variables were associated with the stress of shear between these stages which caused the separation of droplets. In addition, the role of the interstitial forces played a secondary role in the intersection of the Y shape, and there was no effect on the change and formation of the droplets in the T junction microchannels. In the Y connection, there was a large and wide variation in droplet size, the formation of the system and the conditions in which it was operated. At low relative velocity and fluid viscosity, no droplets are created. In contrast, the process in the form of T-junction resulted in less than expected.

Christopher, G. F., & Anna, S. L [54], studied and manipulated the microspheres of Ca-alginate, where a microfluidic chip was used to work on coating and encapsulating small gold nanoparticles. The strategy of working on several factors is based on a hydrodynamic focus on the formation and study of a series and a series of compositions in the self-assembly field, which is called the water emulsions inside the oil (w / o), in a cross or interlocking microchannel. These water emulsifiers, consisting of Na-alginates water, are then cut to a solution of 20% calcium salt for completion and for the achievement of microscopic pellets as image, in an effective and effective manner. Experimental data and studies show that diagonal microseconds ranging from 50 μm to 2000 μm with radically less than 5% variation were generated accurately and successfully. Therefore, the size and diameter of the

gap can be adjusted by adjusting and checking the ratio of the relative sheath / relative flow rate. In addition, it has been applied to nanoparticles and coated with gold, and this process is implemented "Lab on a Chip".

Stone, H. A., Stroock, A. D., & Ajdari, A. [55], it provides a general overview of the flows generated through the use of microdevices, as well as emphasis on electrokinetics, mixing, and flows of many, multiple types and phases. There are many important topics to describe the work and fundamentals of fluid dynamics: the driving forces, engineering and chemical properties of surfaces. Microfluidic devices are used to manipulate fluid and widely, as well as the possibility of finding a lot of uses that are used in many procedures and scientific contexts, including industrial. Often, or often, their design and configuration require an unusual and unusual engineering geometry. The interaction between the most important effects of multiple physical processes, such as pressure gradients and electrical measurements, is usually required. These conditions may lead to very interesting forms and designs of multiple problems as well as well-studied fluid dynamics and some responses by new fluids.

Yang, L., Wang, K., Tan, J., Lu, Y., & Luo, G [56], they have worked on and studied the docking process that gets in the microscope in the confined microchannel. Work has been done on the design and formation of devices and models of microfluidic tri-intersections T with the size and diameter of a different main channel in and out to obtain generating monodispersed microbubble pairs with an air glycerol solution. The direct collision of the microbubble pair was investigated in microfluidic devices. Three of the most important outcomes were the results of collision and collision, including collision or collision, potential collisions, and the failure or failure of integration. All traces obtained in the experiments have been determined through liquid viscosity and the surface velocities measured in two phases on the type and behavior of fusion or docking. Where all the results showed us that the fundamentals of the merger or integration of microbes in the narrow space that was obtained is considered relatively faster or slightly than the open and free space. The increased viscosity of the liquid, as it appears in the results, appears to be a reason for preventing fusion or fusion. At the point of potential manipulations, as such, surface velocity, which is the highest in two phases, can reduce the percentage of fusion or

docking. It has been working on the creation and introduction of two information representing the period in which bubbles occur and the time that takes the discharge of films and so to analyze the methods and behaviors of the convergence of the microscope and also can distinguish the link or linear integration and clearly between the docking area merger or not.

Van Steijn, V., Kleijn, C. R., & Kreutzer, M. T[57], they have been successful in verifying models and experimentally through the study and analysis of the body and formation of gas bubbles, as well as the formation of liquid droplets, in the joints type and form T-Junctions Kmalik with a variety and a variety of forms under the duties and conditions of scientific and model microfluidic We have been able to obtain a suitable closed expression that researchers can use and adopt by means of the size of bubbles and droplets through which the process of formation and construction in the T-Junctions without reverting to the structure. Although the recent and widespread use of microfluidic devices and work to create bubbles and drops, but so far has not been or did not get a suitable expression as there was not even so that the phrase \ sound and physically appropriate for the size and diameter of bubbles and droplets, where It is the key we use in many fields and applications. The theoretical basis is formed to obtain the expression of the three main elements: continuity, geometry, forms, comprehension, and the newly discovered mechanism of action that leads or leads to pressure. This theoretical model shows why it is completely dependent on the size of the bubbles and droplets and is strongly in the form of the T-junction device, and knows how to adjust this shape to achieve the desired size or size. The model, which has been tested in a preliminary and experimental way, has been verified by analyzing and studying the formation and formation of gas bubbles, as well as liquid droplets, in T-junctions with many different types of geometric shapes under different and typical microfluidic conditions on many of the stages.

Skurtys, O., & Aguilera, J. M. [58], they have studied and designed many new micro-micro-structures in which quality, quality, health, and are targeted. The unit size and shape of the geometrical device must be closer to the size of the elements and structural characteristics (From 1 to 100 μm). The most important and one of the possibilities that arise and are emerging are microfluids or devices that are used in

the fields of small quantities of fluids and liquids (from 10⁻⁶ to 10⁻⁹ liters), which have flow and flow in the channels is very small in which the dimension is small where one is less than approximately 1 mm. However, through all these circumstances and the shadow of these events, the resulting and predominant effects are not necessarily those that are present in the most important operations of the normal microscopic unit. The most important cost and material effects are controlled through microfluidic scale through the use of Results and without any dimensions. The most important types of sizes and geometric shapes are declared and reviewed to generate multiple flows and stages in the micro and micro channels, techniques and the most important materials necessary for the construction and construction of sensitive and precise devices, especially or for example printing Lithography and laser, as well as all methods used and used to modify the most important characteristics shown and surface

for micro channels. The gamut of the process of precision devices, high role in micro flow systems, and fluid and fluid flow behavior in micro and micro ducts is discussed. Systems and devices for the generation of emulsifiers and foams, fluid mixing, dispersion and dispersion in nutrition are the future applications of these devices in the field of food processing and analysis.

Chou, H. P., Fu, A. Y., & Quake, S. R. [58], microfluidic device includes pumps that are designed as well as valves and dampers that all oscillate fluids and liquids. In the various devices used in the sorting process, through which the flow of materials is carried out by the pump device along the narrow channel of the flow and through the detection area to reach the junction point. Based on the identity of the material identified in the area through which the detection is performed, where the valve that collects or wastes the waste is located on the branches that meet the flow channel at the intersection site, which in turn leads to either the waste collection center or To the assembly pool area. There may be a damper structure that is connected between the pump and the junction area. The damper reduces the amplitude of the oscillation pressure in the flow channel or flow zone due to the start of the pump operation, which reduces the oscillation in the speed of the material during the sorting mechanism. A microfluidic device can be designed from synthetic rubber, using fine

and fine rubber membranes that are reflected in the flow zone and channel to obtain the function and function of the pump or valve.

2.3 Originality of This Thesis

From the above discussion we can discover that there are some various attempts to amend the “design and material of microfluidics devices”. But most of the attacks were based on the devices of microfluidics for example channels, chambers / wells / cavities, pillars, T- or Y-Junctions and holes. The purpose of the present study is to describe PMSQ nanospheres preparation from microbubble bursting in a 100 μm capillaries embedded combined microfluidic device based on effects of junction angle and flow rate of liquid solution.



CHAPTER 3

MATERIALS AND METHODS

3.1 Introduction

The aim of this chapter is to present brief information on microfluidics devices by construction and manufacturing V- Junction devices, focusing on the types used in medical and chemistry sector.

3.2 Microfluidic Device Theory

Microfluidic devices are tiny circuits that flow fluids instead of electrons. Because they are inexpensive and portable, microfluidic devices are ideal for use in areas where medical resources are scarce. Inertial microfluidic devices represent a new direction in microfluidic device design in which high flow speeds are used to exert nonlinear inertial effects on the fluid and on fluid-suspended particles. While inertial microfluidic devices are finding applications in fields such as fluid mixing, particle filtration, flow cytometer. In this work we will describes PMSQ nanospheres preparation from microbubble bursting in a 100 μm capillaries embedded combined microfluidic device based on effects of junction angle and flow rate of liquid solution. The effects of the junction angle ($\theta=0^\circ$ to 60°) between the liquid and gas channels and the gas pressure ratios (50 to 400 kPa). Microfluidics devices parts can be divided into three categories:

- Microfluidics devices and adapters, which are used to connect fittings of the same or different threading
- Fittings and connectors, which are used to connect, either with rigid or soft tubes, your microfluidic devices or devices to external components such as pumps and reservoirs.
- Pipes and sleeves, which are commonly used to transport small amounts of fluid to devices.

Microfluidics devices theory areas are further elaborated in the sections below:

1. Open the microfluidics system. In the science and research of liquids and fluids of high precision and of the open type, through which the removal of at least one of the system, which will expose the fluid to the air or another problem [59-61], the most important advantages of fluid science The micro-type open has access to flowing fluid for interference, operates on the gas surface, and minimizes it to the extent possible. For the bubble [59-562], another standard for open-type microns is the ability to integrate all open-type systems with fluid flow to the surface, eliminating the need for external injections such as syringe pumps [63], microfluidic [64-67] In addition to all that is stated below, the open type microfluidics work to eliminate the need to glue a lid to devices that are considered harmful to the flow And noodles. One of the most important examples of open-type microfluidics on open channel microfluidics, rail-based microfluidics, micro-type compounds that are paper-based, and others based on threads [79] [63] [68], and the most important defects are evaporation, pollution , And the specified flow rate [69, 70] [61].
2. Continuous flow - microfluidics. The adoption of these modern technologies and technologies on the continuous change in the process of liquid flow through micro-narrow channels. Fluid flow is performed either by external pressure source, mechanical pumps, micro pumps, or through combinations of fine and kinetic processes [71,72]. The flow method in microfluidic is the predominant process because the process of purification is easy and less harmful Problems of protein contamination. Microfluidic devices are suitable for many applications, the most important of which is biochemical, well defined and very simple, as well as certain actions as an example of chemical separation, and are less suitable for many tasks that require high degree of manipulation of the fluid. These systems have closed channels whose range is difficult to expand because the variables control flow and flow that vary along the path of the flow channel, which works on the flow of fluids at any location, which is entirely dependent on the characteristics of the system. Microscopic shapes that are permanently engraved are also considered to be re-designed and configured in a limited manner and have a poor ability to withstand many errors.

3. Microfluidics based on the dropper. Microfluidic, which works in diameter, is a microfluidic sub-section of microfluidic science of continuous flow. Microfluidics that act as droplets are formed on the separate volumes and shapes of liquids and liquids in non-reductive fluxes. In recent times, the interest in microfluidic association has increased dramatically. Microdroplets allow small volumes and shapes of liquid and fluid to be handled well, providing best mixing, packaging, dispersion and sensing, and are compatible with many high-yield experiments. The exploitation of the most important benefits of microfluidics is an understanding and a study to generate droplets [74], to perform different and logical processes [75, 76], such as droplet movement, dispersion of droplets, and the process of merging droplets.
4. Microfluidics digital. Alternatives to the continuous flow ducts with narrow and closed channels above are open to new open equipment, where isolated and discrete droplets are controlled and controlled separately and independently based on the substrate using electrowetting method. After the measurement process, which is completed on microelectronics and digital, it is called the narrow and accurate digital fluid. The use of electrocapillary powers to transfer a total of drops on a previously digital path [70], while the "liquid transistor" also had a brilliant role in this area. Have been marketed. Using isolated droplets and a separate volume unit [74], the function of reducing the function of the microfluidic device can be reduced to a sequential core sequence, and moving one section of the fluid onto the unit of distance. To facilitate digitization. The use of a hierarchical approach based on the cell and its formation and microfluidic design. Therefore, digital microfluidics provides a flexible and scalable platform, as well as a very high capacity to withstand the problems and errors that result.

3.3 Importance of Nanosphere

Nanosphere materials are unique and are important when processed and designed on a very small scale. These specifications and characteristics may be visible, magnetic, electric or other specifications. For example;

- 1- This technique can be used and developed in the design and discovery of certain drugs and drugs (such as drugs used to treat cancer), which can be focused on specific organs, cells or tissues found in the organism's body only,

- 2- It can be added to cement, clothing and various other materials to make it stronger with a lighter weight.
- 3- Its compact size makes it very practical in the electronics industry [79, 80],

Nanosirates are classified according to their number and dimensions and are not in the field of nanometer; the material is divided into four sections:

- 1- Materials dimensional - zero. In the last ten years, scientists have gone a long way in researching these materials. Smaller than 100 nm. Examples of these quantum dots recently entered the transistor industry and solar cells.
- 2- Materials dimensional -one. This material contains one dimension greater than 100 nm. For example nanotubes. Is expected to play an active role in the electronics industry.
- 3- Materials dimensional - two. In the last years, many researchers have turned to studying the design of these nanoparticles, which are in the form of dimensions greater than 100 nanometers. Examples of such particles, nanosphers are used in manufacturing sensors, and nanocontainers [81].
- 4- Materials dimensional - three. Have all dimensions greater than 100 nm. These nanosphers either have some of the (nanoparticles) or some of the properties of nanoscale resulting from their containment of other 2D materials, mono or zero.

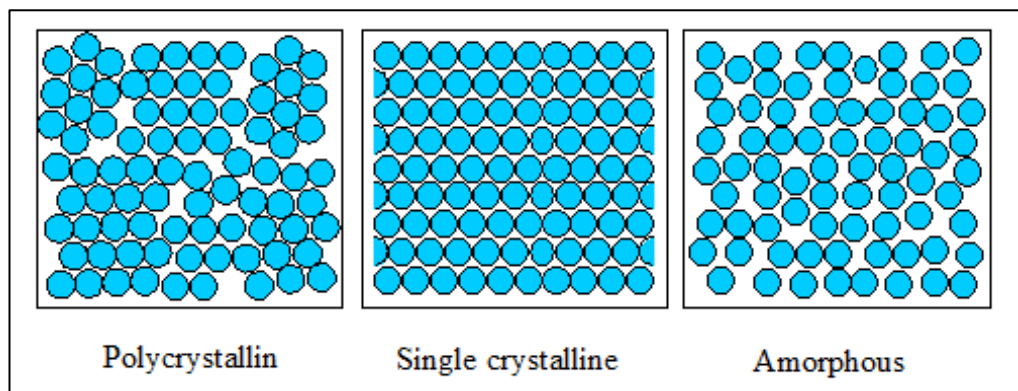


Figure 3.1 Nanosphers types more than one (for atoms randomly).

3.4 Types of Microfluidic Devices

Microfluidic devices are usually composed of a different set of structures to meet the required requirements and microfluidic workings for examples (separation, mixing,

transport and division), respectively [82], in the following, some basic microfluidic designs are listed:

Channels / Holes / T –or Y Junction

1. Chambers / Wells / Cavities.
2. Pillars.

3.5 Microfluidic Devices Application Areas

- 1- Microfluidics for food analysis: There are microfluidic applications in nutrition in both manufacturing and diagnostics. The first phase of microfluidic devices refers to work to develop new microsecond devices such as micro-generators or microfluidic emulsions to improve the performance of bioremediation. Where a comprehensive summary of the physics and methods used for manufacturing and microfluidic fields is given in engineering and food science. A second part of microfluidic fields is involved in food diagnostic devices. In general, microfluidic analyzers are called on traditional analytical systems to reach food safety and quality. The devices used in microfluidic food analysis are widely classified as micro-fiber-based, microfluidic-based construction systems (microfluidic-based microbes and chemical analysis systems). Both types of devices provide an effective analysis for identifying biological molecules and the most important chemical components within the food samples [83].
- 2- Agriculture sector in microfluidics: There is great importance in the food and agricultural industries. Microfluidics treats liquids in channels with small dimensions up to tens of micrometers. Analytical devices can be minimized, cost reduced and response times reduced. There are several analyzes of high productivity and addressing food and agricultural fields. The purpose is to provide a range of information on microfluidic applications and areas in the agro-food sector to overcome constraints imposed by simple techniques. Fluid hydrology contributes to medical diagnosis, biologic analysis, chemical synthesis, drug discovery, gene sequencing, biotechnology and ecology. Recently, the areas and applications of micro-liquids in the food and agricultural industries have increased. Examples of such applications include food safety analysis, animal production and food processing. Microfluidic

basics including manufacturing, design, control and application areas and future trends of microfluidic in agro-food sector. We must focus research efforts and future science on the development of small portable devices with sophisticated modules for fluid processing, modeling and sampling, and electronics identification signals [83].

- 3- Chemistry field in microfluidics devices: The newly developed nanotechnology and electronics industry, especially in the development of parallel optical and parallel optical and chemical capabilities to detect micro-reagents and sensors, have barely benefited from the potential of microfluidic flow processes in chemistry. "So far, we have been scratching the surface only by simulating what is currently in batch mode, but that means that microfluidics we can prepare samples for chemical separation and detection in a different chemical laboratory approach the convergence of micro-fluid technology and electronics industry, particularly in the development of detection systems Visual and electronic parallel
- 4- Medical and environmental in microfluidics device: Microfluidic devices are a renewable science of medical appointment areas that are portable, low-cost and simple to use [85]. These devices have frantic barriers to the process of transferring solutions negatively to channels where biological interactions [86] and environmental testing [88], with hopes of access to areas lacking diagnostic areas and advanced medical field.

3.6 Materials for Microfluidic Devices

- 1- Microfluidic devices are instruments used in the field of microfluidology where a network of narrow and small channels is designed. Due to a variety of access channels and exits, these microfluidic devices allow liquids to pass through different channels of varying diameter, ranging from 5 to 500 micrometers. A narrow network of narrow, narrowly tailored channels (DNA analysis, cell culture, etc.) should be designed. [89] Narrow and precise fluid devices, such as devices with many properties and features, can reduce sample properties and increase automation And the consumption of the detector, and eventually will reduce the time taken for analysis. Applications of these devices also allow in many fields such as medicine, biology, chemistry and physics. Three types of materials are commonly used to form

microfluidic devices: glass, silicon, and polymers [90,91]. Each material has specific physical and chemical characteristics. The selection of materials depends on the requirements and conditions of their use, and the design of the device depending on your budget. Note that there are applications of microfluidic devices.

- 2- Microfluidics devices in silicon: The most important advantages of silicon are advanced thermal conductivity, stable surface and solvent compatibility. Note that no magazines and applications can be performed in optical detection due to visual opacity [92].
- 3- Microfluidics devices in glass: Glass material worked with silicon in the same advantages as previously reported. The specific surface chemistry, high optical transparency and high pressure resistance make it a good and favorite material for many magazines and applications. The glass is also considered compatible, chemically inert, and good with waterproof and allows paint. The main hurdle with this article is still fairly high cost [92, 93].
- 4- Microfluidics devices in polymers: Polymers have recently provided an alternative to glass and silicon because they are stronger, cheaper and faster. Many polymers can be used to form these devices. The fluid flow process in a continuous microfluidic device is the predominant work because it is easy to design and less sensitive to protein contamination problems. Continuous flow devices are suitable for many well-defined and simple biochemical applications and journals, and for certain functions such as the chelates on chemical separation, but they are less suitable for high-flexibility businesses. These narrow and closed channel systems are very difficult to integrate and extend their scope and scope because the differences in the flow domain vary across the flow of the channel, making fluid flow in any location dependent on the characteristics and specifications of the entire system. Structures and microscopic structures that are continuously and permanently adapted have limited vulnerability to error correction [93].

3.7 Characterization of microfluidics device materials

- 1- **Poly (methyl methacrylate) PMMA:** It is a very strong material which is lightweight. The density of 1.17-1.20 g / cm³ is less dense than half the glass. That the strength of their effect is good, often higher than the polystyrene and

glass. , But less than polymers and some types of engineered polymers. PMMA ignites at 460 ° C (860 ° F), which forms carbon dioxide, low molecular weight compounds, water and carbon monoxide, including formaldehyde. PMMA broadcast 92% of visible light (3mm thickness), reflecting about 4% of each surface due to refractive index (1.4905 at 589.3 nm).It analyzes ultraviolet light with wavelengths of less than 300 nm (compared to glass).Some companies add some coating material or)PMMA(to improve the absorption mechanism in the range of 300-400 nm.)PMMA(where the infrared light passes up to 2800 nm, while IR blocks may reach wavelengths to 25,000nm [94.95].

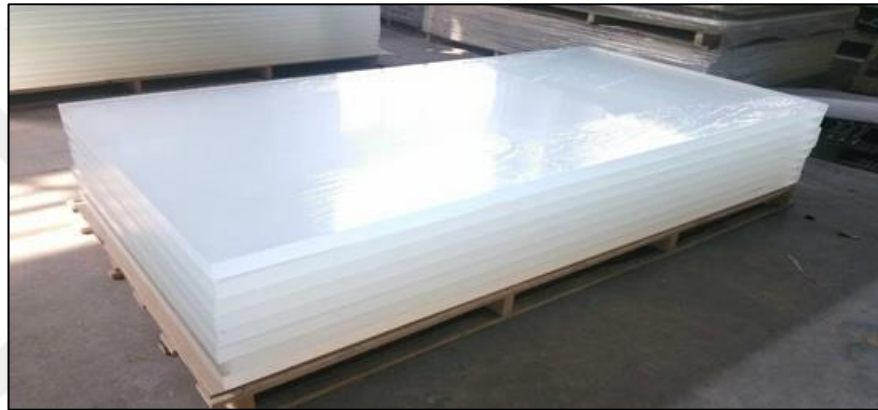


Figure 3.2 Transparent sheet to manufacture microfluidic device

- 2- **High-precision pumps:** There are two ways to provide fluids and waves through microchannels. In the pressure-driven flow, the fluid is pumped through the apparatus by pumps that press positive displacement, such as conventional pumps and syringes. One of the basic laws of fluid mechanics is to compress platelet flow, so this boundary condition prevents sliding. The second is by using a continuous flow of high precision pumps and technology (Harvard PHD 4400, Device) to a VHF device. A scheme that prepares solid polymer polymer solutions called polymer using high-precision pump techniques [96].



Figure 3.3 Pressure fluid by harvard4400, apparatus, Eden Bridge, UK

- 3- Fitting connection:** One of the most important practical research is the design and formation of microfluidic devices in order to achieve a strong image between the device and the acceptable communication. Various groups of micro-fluid systems have been developed for other applications. At this stage of the study we propose a new way to obtain the fluorescent interstitial, which helps to provide a simple interface between the external channels and a microfluidic device must also be compatible with conventional syringes and pumps used to squeeze, and there are three slots inlet and one outlet. All pipe, pipe and pump connections shall be made and connected before inserting materials of the size of the dead. The size of the inbound device shall be mixed [97, 98]. The internal size of the instrument shall be the sum of the withdrawn and dead volumes. If the connection is not obtained with the tube, an additional internal storage partition can be created in the device. To help direct and complete fluid flow in the tube, make sure that all pipes and ducts are ideally and tightly connected at all times as shown in Figure 3.4. Also good to try to match the pipe identifier as much as possible to the channel diameters. [99].
- 4- Fluid connection fitting:** To provide steady and stable heat-contact fluid for proper laboratory analysis it could be have used DIBA Company to have a patent line in wait for Click-N-seal connection links with click-n-seal torque limiting Ultra-fittings made of Polyarithriethricton (PEEK) plastic PEEK plastics. The fittings provide stability even at very high temperatures [100], it also makes it chemically resistant and tolerant of pressures up to 15,000 pounds per square inch. It is fitted with DIBA right torque technology which prevents the fittings from over-or under-stress - causing poor fluid contacts

and leakage treatment - without tools or guesswork. When the correct torque is reached, reusable produces a click the installer can hear and physically prevent tightening after end point. It can be readable as appropriate and reused, and stop at the correct torque every time [101].



Figure 3.4 Microfluidic device fitting connections (DIBA) company

3.8 Nanosphere formation

The available techniques are reviewed and categorized in order to prepare nanoparticles that have biodegradable nanospheres and nanocapsules from pre-formed polymers. Although there is a lot of research and is extensive in this area, few of these are the only research focused on the analysis of the overall results of the preparatory process. There are four techniques classified by their technical and technological advantages and disadvantages: solvent displacement, evaporation of emulsions, salting, and loss of emulsification. The formation of nanoparticles for each technique is described from a physiochemical perspective. The nanospher can be classified into (micelles, nanospheres, nanocapsules and polymersomes). In recent years there has been a growing interest in the use of nanoparticles for applications and drug delivery areas. Nanoparticles are particles, whose diameter ranges from 1 to 1000 nm, and may be worked on, coated, or absorbed. The basic example of these polymers is the polymerization particles in the material. The particle design of the polymer material is an important indicator of efficiency and quality in hollow carbon nanospheres [102]. We have implemented a total and a series of tests. Due to the three-dimensional device is very complex such a typical method of shaping materials design. The diagram can illustrate the main rating on the nanospher. These composite polymers with anhydrous mass can be capable of forming a good array of structures

with different nanoparticles and shapes. These include micelles, nanospheres, nanocapsules, and polymersomes.

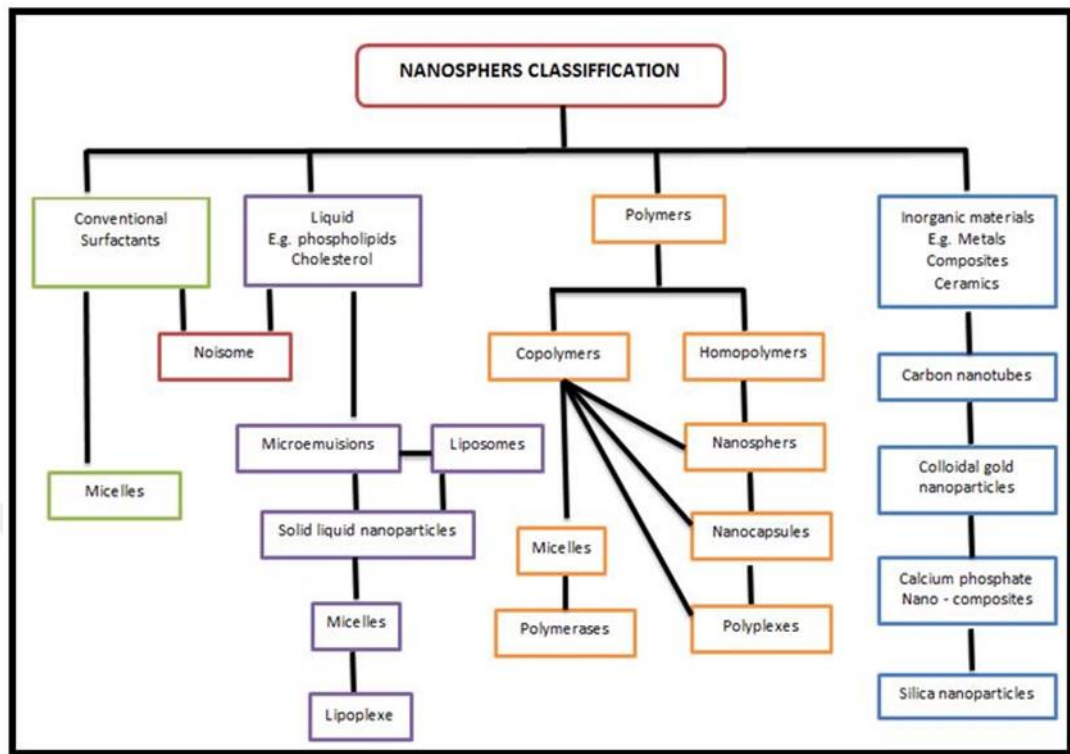


Figure 3.5 Nanospher classification clarify terminology

CHAPTER 4

EXPERIMENTAL SETUP AND RESULTS

4.1 Introduction

This chapter describes the experimental procedure to examine the microfluidics devices with different arms by describes PMSQ nanospheres preparation from microbubble bursting in a 100 μm and 150 μm capillaries embedded combined microfluidic device based on effects of junction angle and flow rate of liquid solution.

4.2 Polymer Solution Viscosity Characteristic

All polymers increase the viscosity of the solvent in which they are dissolved. This increase allows for a convenient way to determine the molecular weight of polymers. Since the viscosity method is not based on strict physical laws, it must be calibrated by known molecular weight standards with narrow molecular weight distributions. Several important viscosity functions are used in viscosity studies an Ostwald's U-tube viscometer was utilized to measure the polymer solution viscosity. To measure the polymer solution surface tension using the standard Wilhelmy's plate method, [103].

4.3 Optical Microscopy Imaging

Utilization of graphene-supporting films and low-voltage scanning transmission electron microscopy (LV-STEM) in scanning electron microscopy (SEM) is shown to be effective for observing nanospheres in microfluidic device. A digital microscoping technology contacted with monitoring to provide all reports and records with analyses all the process in experimental the digital microscope will describes a gas-driven combined microfluidic device with different junction angles for generating independently discrete microbubbles and hence nearly monodisperse polymer

nanospheres will technique achieves no waste of any significant volume of the sample and controllable size distribution.

4.4 The Flow Rate of Polymer Solution

Typically when the velocity is high, the viscosity is low and the size of device is important to change the parameters of the flow rate when it was small or large. In contrast, viscoelastic fluids such as solutions of flexible long-chain polymers have nonlinear mechanical properties and therefore may be expected to behave differently. Here we observe experimentally that the flow of a sufficiently elastic polymer solution can become irregular even at low velocity, high viscosity and in small devices. The fluid motion is excited in a broad range of spatial and temporal scales, and we observe an increase in the flow resistance. The flow rate affects polymer retention. The increase in velocity was accompanied by polymer retention. The polymer was expelled when the flow rate of the polymer was expelled when the flow rate was reduced. The size of the pores was reachable about 19 % of the total follicle volume.

4.5 Droplet Formation of Polymer Solution in Microfluidic

Polymers such as poly (ethylene oxide) (PEO), poly (vinyl alcohol) (PVA), and poly (vinyl pyrrolidone), (PVP). In a series of solutions containing these polymers of various molecular weights, shear viscosity and surface tension were varied. However, these differences can not represent the observed trends in decay behavior. The availability of droplet formation and droplet size was found to be highly dependent on the expansion properties of polymer solutions with apparent viscosity and longer relaxation times. The expansion properties of polymer solutions were effectively measured by our microfluidic system.

4.6 Follow and Monitoring by High Speed Camera and Image J Program

In the experiment, we will use high-speed camera and precision microscope microscope with high-speed video camera and accuracy as soon as work and start experiment. After samples are collected the polymer nanospheres are collected to dry and for 48 hours at ambient temperature (23 ± 2 ° C) placed in the dryer. To prepare them for photography. SEM was used to characterize the size and morphology of the

nanosocial product. Most of the nanospheres were studied using image analysis software (ImageJ 1.51g, licensed from the National Institute of Health, USA). Image J is a public domain program that handles Java-based images developed at the National Institutes of Health. ImageJ is designed with an open architecture that provides scalability through plug-in Java components and recordable macros. Many image processing and analysis problems, through 3D imaging of live 3D imaging, will address radiotherapy. The straight line selection tool will use to drag a line across the measurement bar. Then a scale will be determined. The measured distance will be displayed in pixels. More than one model has been taken to measure diameters and dimensions of the microbubble and nano-polymer for our study.

4.7 Experimental Setup

4.7.1 Microfluidics Devices Accuracy

Process control or quality control is considered a necessary step for the manufacture of high quality hardware and products, which in turn will involve process modelling, prediction, sensing or measurements. In our industry, the variables that can be controlled are often hardware information. However, the final microfluidic device was concerned with other information that could directly affect the performance of the device, for example, critical dimensions, fluid leakage, bond strength, etc. Process control is essential for translating information types, for controlling the accuracy of fluid information and for making high precision and quality devices. The measurements discussed here are essentially those that matter until the end of the success of our experiment. These procedures provide feedback not only for process control, but also for device quality. The measurements used in micro fluid instruments vary widely, due to the size, design and structure of the instrument, as well as the measurement and manufacturing methods. There is no global approach. Measurement methods must be defined according to specific requirements. However, this pilot will attempt to classify measurements of microfluidic devices into a generation of nanoparticles.

4.7.2 Manufacturing of Microfluidics Devices in Different Arms Angle

To construct and manufacture a microfluidics devices with different geometry by used a laser cutter CNC Cutter CMD-1218- Laser to cut a cylindrical with a diameter

of 20 mm and also make either etch a center mark or make a small center. By using a small drill bit(1 mm and 1.5 mm) , drill a pilot hole from three sides and use larger drill bit to follow in the center of drill bit and make a pilot hole with dimension 1/4in-28 UNF in 3 places (1.58 hole diameter) as shown in Figure 4.1 , Figure 4.2 show the final product of microfluidics device.6 When we cut the model and made drilling will using the ¼-28 type and appropriate technique, tap the hole you had been created in all devices with different angle for each inlet and outlet it should be not use oil in steps 1and 2. For lubricate the plastic as unnecessary and difficult to clean. After removing the sample from the subject when manufactured all models, thoroughly clean the microfluidic device to be bonded using a 50-50% mixture of ethanol and water. Place Harvard PHD 4400, Apparatus, Edenbridge, lapped side down, onto the microfluidic device’s surface where the connection is desired. It is essential to center the sample over the hole which receives the fluid or gas from the high precision pumps. We used different Capillaries with inner diameter (1mm and 1.5 mm) and with angles of the tubes: (0, 35, 45 and 60 angles).

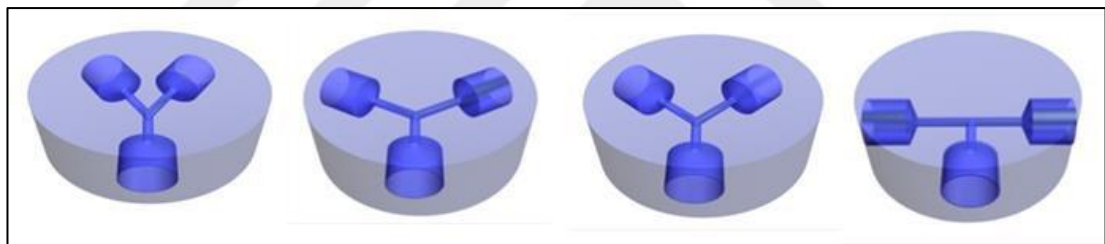


Figure 4.1 Typical sizes inner diameter (100 µm) angles of tubes (0, 35, 45 and 60)

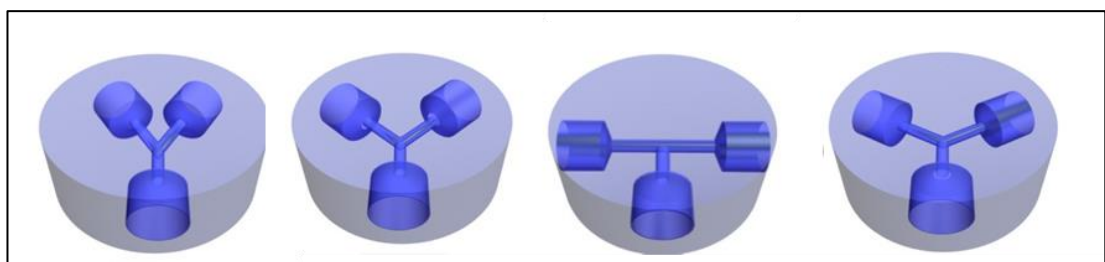


Figure 4.2 Typical sizes inner diameter (150µm) angles of tubes (0, 35,45and 60)

4.7.3 Microfluidic Preparation Mechanism

A combined microfluidic junction device with thin capillaries that is capable of generating polymer nanospheres from bubble bursting was successfully designed. The microfluidic device was fabricated by a CNC technique, and constructed using

polymethylmethacrylate (PMMA) with dimension of 20 mm. The microfluidic device setup is shown in Figure 4.3 where different junction angles (0° , 35° , 45° and 60° respectively) are specified in terms of the central axis. The schematic view of the combined microfluidic devices with different junction angles used are inserted in Figure 4.3. There are two inlets in this design: one for the PMSQ solution flow and the other for the N₂ gas flow. The PMSQ solution flow is supplied into the inlet A with average flow rate. N₂ gas pressure is injected into the inlet B that is located at junction angle relative to the x axis. Both liquid solution and N₂ gas were separately injected inside the microfluidic device for the generation of polymer nanospheres from microbubbles using Teflon-fluorinated ethylene polypropylene (TEP) capillaries with internal and external diameters of 100 μm and 1.6 mm, respectively. Inlet A is connected to high precision pump (Harvard PHD 440, Apparatus, Edenbridge, UK) using TEP capillaries to provide a continuous flow of PMSQ solution (5 wt. %) into the microfluidic device used. Also, Inlet B is connected to the N₂ gas cylinder to feed a controllable N₂ gas flow as an immiscible material into the microfluidic device used for a continuous microbubble stream. Both feeds, polymer solution and N₂ gas, mixed in the centre of the device where the channels of the microfluidic junction meet. Subsequently, generation of microbubbles occurred. These resultant microbubbles are then guided down an exit channel (outlet capillary) placed at the bottom, and bubble clusters are collected at the channel exit. Upon impact with the water in the collector, the microbubble is disrupted and releases the N₂ gas while polymeric material forms nanospheres. Resulting nanospheres were collected in a glass vial filled with distilled water. Optimisation studies were conducted to obtain near-monodisperse microbubbles and polymer nanospheres by varying the junction angle (0° - 60°) and N₂ gas pressure (in the range 50-400 kPa).

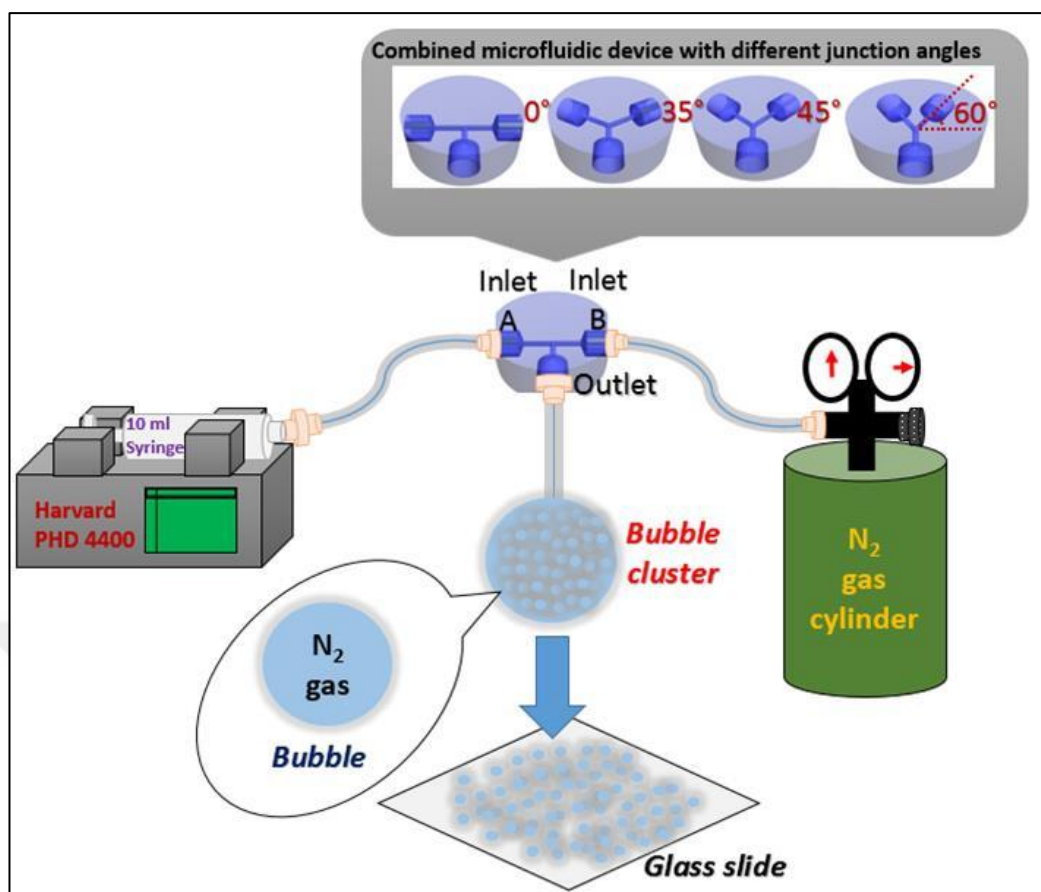


Figure 4.3 Schematic representation of the microfluidic device setup

4.8 Experimental Material Selection

Polymethylsilsesquioxane, PMSQ, (Walker Chemie AG, GmbH, Burghausen, Germany), with an average molecular weight of 7465 g mol⁻¹ was used to prepare the polymer solution that enables formation of the shell layer of the microbubbles. Ethanol (98%, Sigma Aldrich, UK) was used to prepare 5 wt. % PMSQ solution, by dissolving PMSQ with magnetic stirrer in a conical flask for at least 1800~s at the ambient temperature (~23 °C) until the polymer solution apparently fully dissolved. The British oxygen company (UK) supplied nitrogen (N₂) gas that was chosen as an immiscible gas for all the experiments.

4.8.1 Characterization of Polymer Solution

The polymer solution used was characterized to determine its density, viscosity and surface tension. Density values were obtained using a standard 25-ml density bottle (DIN ISO 3507-Gay-Lussac). An Ostwald's U-tube viscometer was utilized to

measure the polymer solution viscosity. A Kruss tensiometer (K9, Kruss GmbH, Germany) was used to measure the polymer solution surface tension using the standard Wilhelmy's plate method. All the measurements, presented in Table 1, were performed at the ambient temperature (~ 23 °C) and relative humidity of 40% after an equipment calibration using ethanol. Ethanol was also used as a cleaning agent in all the experiments.

Table 4.1 Physical Properties of PMSQ Solution

Polymer solution	Density (Kg m ⁻³)	Viscosity (mPa s)	Surface tension (mN m ⁻¹)
5 wt. % Polymethylsilsesquioxane	760 (± 5.0)	1.0 (± 0.10)	21 (± 1.0)

4.9 Results

The results of the different arms angles in microfluidic device cross-section support emphasize that the dominant contribution to the dynamics of disintegration arises from low pressure across an emerging bubble or drop. This decrease in pressure results from high resistance to continuous flow of fluid in the thin films that separate a drop from the walls of the small channel when almost a full drop of the microfluidic device fills this assertion. The volume of droplets and bubbles produced in microfluidic device with different angles is depends on a set of flow rates non-combustible, viscosity of continuous phase, tension between surfaces, engineering dimensions of the device.

4.9.1 Mechanism of Polymer Nanosphere Formation Generate Bubble

In this work, near-monodisperse PMSQ polymer nanospheres from microbubble generation were conceived by a combined microfluidic junction device when a steady continuous stream of bubbles was first attained. Observations shows that a microbubble is generated every 12.3 ms. Two immiscible feeds are infused into the mixing area in order to generate microbubbles and the less dense polymer-ethanol solution encapsulates N₂ gas having much greater dense. This could be due to the fact that the 5 wt.% PMSQ solution surface tension was much higher than N₂ gas

(Table 4.1). Thus, PMSQ is infused into the mixing area and acts as the driving force for encapsulating the N₂ gas.

The generated encapsulated microbubbles stream down through the outlet capillary and were gathered in insoluble media at the channel exit. Upon making contact with an aqueous environment from dense microbubbles becomes evident. Under an optical microscope at a post collection time of approximately 100 s, the resultant microbubbles were around 110 μm in diameter. A cluster of nanospheres are formed on the bubble surface. Upon impact with the water in the collector, the microbubble breaks up much like an explosion to release the N₂ gas, while the PMSQ coating forms polymer nanospheres. The high density of nanospheres on the surface is brought about by the spontaneous bursting of the bubble surface. Evaporation of N₂ gas continuous and the polymer nanospheres shrink and adopt a rough surface. This stage leads to solidification. The mechanism of polymer nanosphere formation from microbubble generation using V-shaped microfluidic junction device is described in a separate paper which has useful schematic diagram showing the evolution of microbubbles during the process of PMSQ nanospheres [103].

4.9.2 Effect of Junction Angle

Junction angle had a crucial impact on the microbubble and nanosphere size, respectively (Figure 4.4). Varying the junction angle between 0° and 60° for the combined microfluidic device used while keeping the others constant (flow rate of PMSQ solution, capillary size and gas pressure) resulted in decreased microbubbles and polymer nanosphere size in this case. Figure 4.4(a) shows the effect of junction angle on the mean microbubble diameter which decreased from 245 μm at 0° to 100 μm at 60°. Incremental changes to the microbubble mean diameter were observed between a junction angle range of 0° - 60°. Furthermore, Figure 4.4(b) highlights the effect of junction angle on the mean polymer nanosphere diameter. A reduction in polymer nanosphere diameter is observed when the junction angle was increased (~700 nm at 0° to ~230 nm at 60°). A steep change in polymer nanosphere size was observed when the junction angle was increased (0° to 60°). Figure 4.5 shows digital (a-d) and SEM (e-h) images of microbubbles and polymer nanospheres generated at junction angles of 0, 35, 45 and 60°, respectively. The digital and SEM images reveal near-monodisperse microbubbles and polymer nanospheres with spherical

morphology as a result of the changes in the junction angles. The resulting near monodisperse microbubbles and polymer nanospheres are observed suggesting that the combined microfluidic junction device used has potential to prepare uniform polymer nanospheres as nearly efficiently as other microfluidic systems, but with larger sphere size.

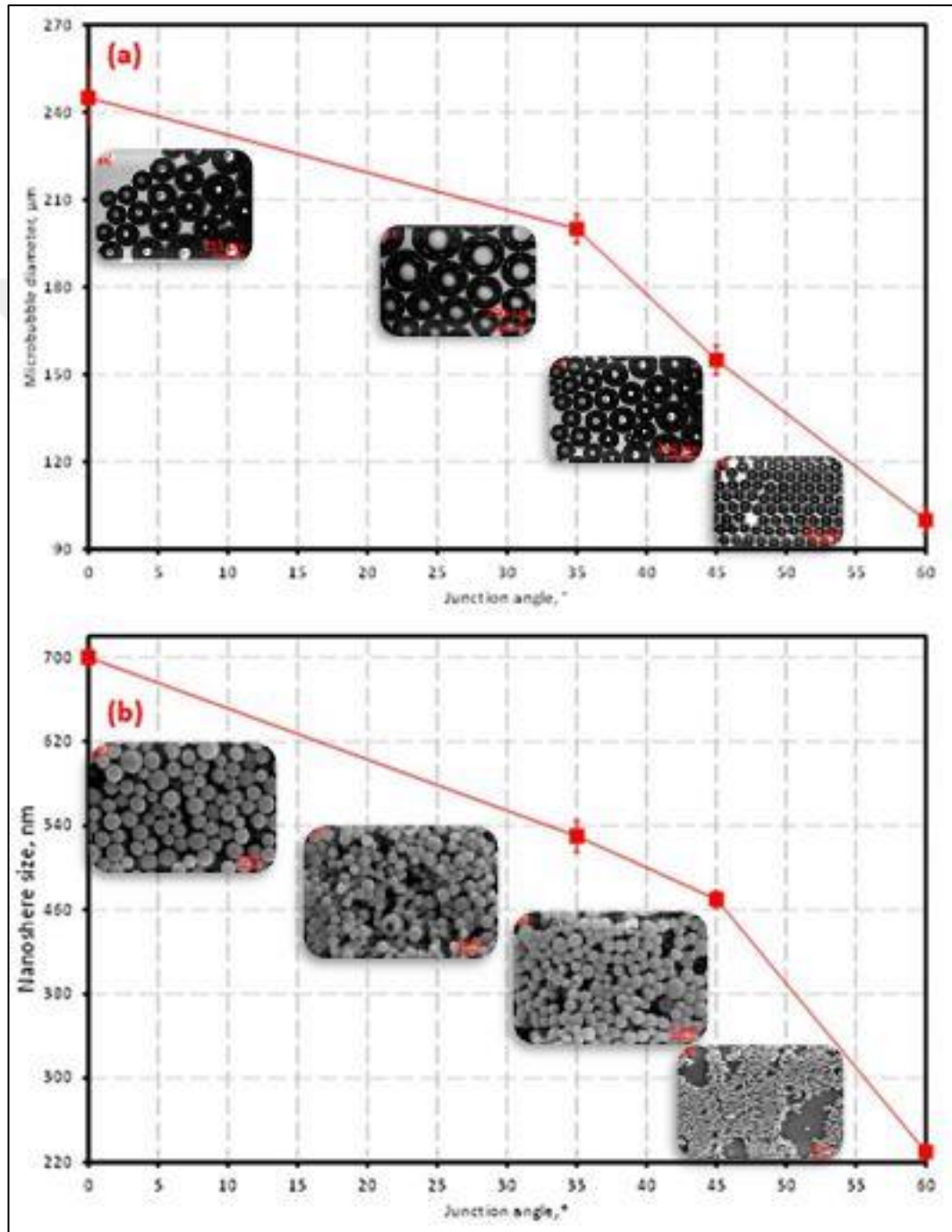


Figure 4.4 Effects of junction angle

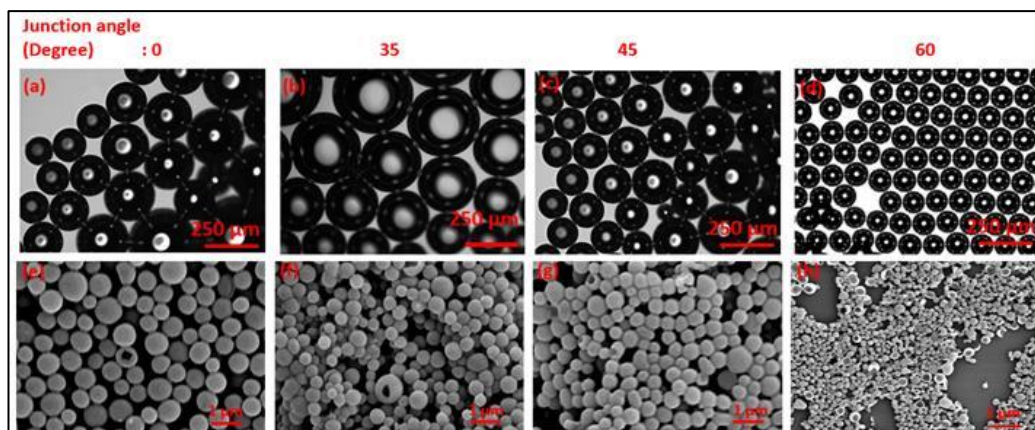


Figure 4.5 (a), (b), (c) and (d) pictures of microbubbles. (e), (f) and (g) SEM images of microbubbles with angle (0, 35, 45 and 60)

4.9.3 Influence of Gas Pressure

The microbubble and polymer nanosphere mean diameter were influenced by the gas pressure (Figure 4.6). The gas pressure supplied was varied from 50 kPa to 400 kPa, while keeping the flow rate of PMSQ solution at $300 \mu\text{l min}^{-1}$ and junction angle at 60° . Figure 4.6(a) shows the effect of gas pressure on the mean microbubble diameter which decreased from $\sim 110 \mu\text{m}$ at 50 kPa to $\sim 90 \mu\text{m}$ at 400 kPa. Figure 4.6(b) also describes an influence of gas pressure on polymer nanosphere size. As shown in Figure 4.6 (b), an increase in the N_2 gas pressure (from 50 kPa to 400 kPa) resulted in a decrease in the mean diameter of polymer nanospheres obtained (from 550 nm to 380 nm). Moreover, this increase of gas pressure affected the polydispersity of the PMSQ nanospheres, decreasing from 30 to 18 %, respectively. Findings are further confirmed by the digital and SEM images, presented in Figure 4.7. As seen in Figure 4.7(a) and (b), the microbubble and polymer nanosphere mean diameter are spherical and near-monodisperse as a result of the changes in the gas pressure. These results indicate that gas pressure applied of the combined microfluidic device used has significant influence not only on microbubble size and also polymer nanosphere size.

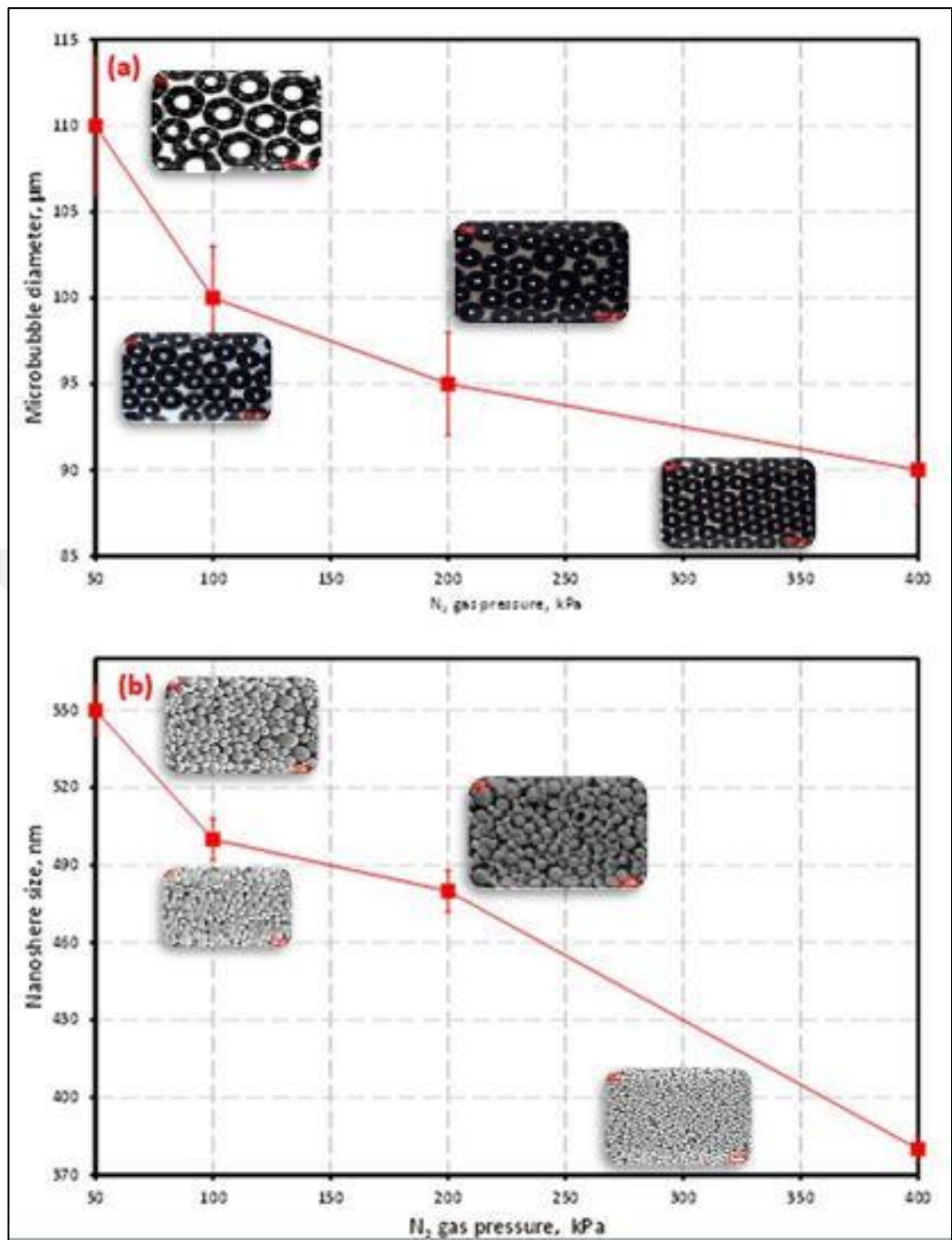


Figure 4.6 Effects of gas pressure on microbubble and nanosphere

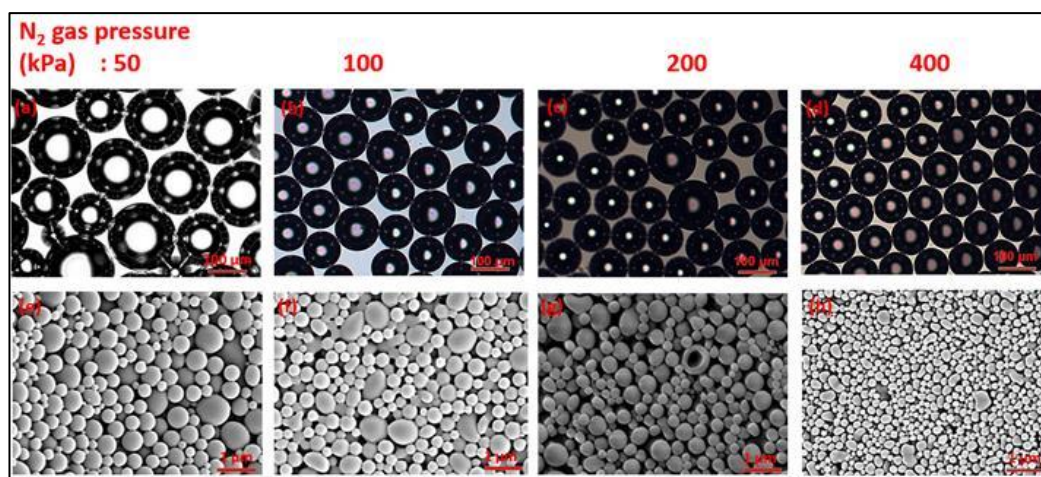


Figure 4.7 (a), (b), (c) and (d) pictures of microbubbles (e),(f) and (g) SEM images of microbubbles angle (60)

4.9.4 Chemical Structure

The composition of the pristine PMSQ powders and the resultant nanospheres were confirmed by FT-IR spectra obtained over the range $400\text{e}4000\text{ cm}^{-1}$ Figure 4.8 Characteristic absorption bands for the C-H vibrations with eCH, -CH₂ and eCH₃ groups at around 2900 cm^{-1} were showed the spectra of pure PMSQ powders used in Figure 4.8 (a). The residual atmospheric carbon dioxide (C-O asymmetrical stretching vibration) could affect to form very low level absorption detected at 2359 cm^{-1} [105]. The absorption bands at 1410 and 1275 cm^{-1} match with the methyl groups (CH₃). Figure 4.8 (b) indicated an absorption band of pristine PMSQ at $\sim 1130\text{ cm}^{-1}$ comparing the spectrum of pure PMSQ powders and the resultant.

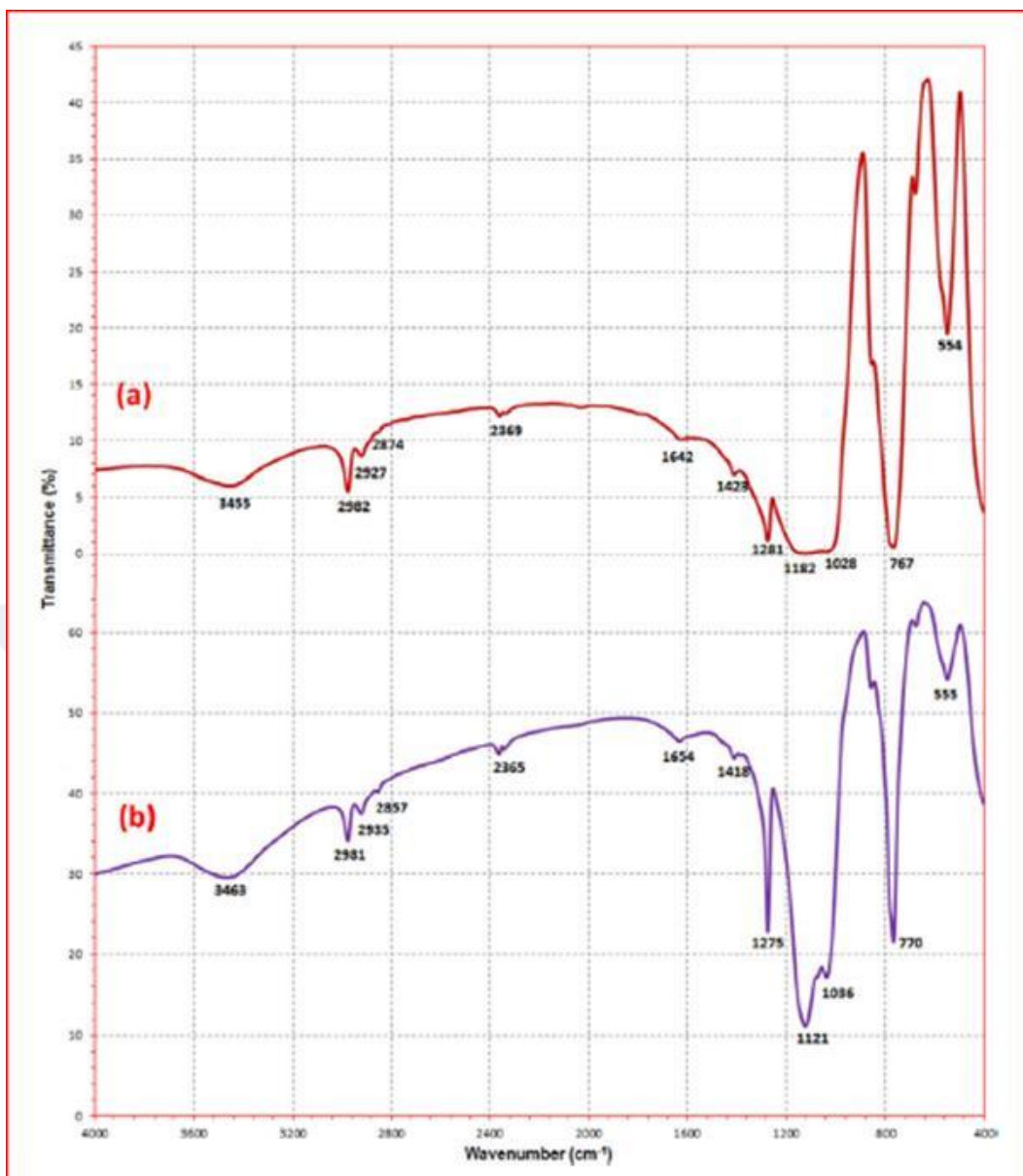


Figure 4.8 (a),(b) FTIR spectra (a) PMSQ powders (b) resultant PMSQ

CHAPTER 5

DISCUSSION AND CONCLUSIONS

5.1 Introduction

A combined microfluidic device with different junction angles for preparing polymer nanospheres from microbubble generation has been successfully used. This microfluidic device system allows the near-monodispersed polymer nanosphere generation from bubble bursting, which enhances stability, while enabling facile therapeutic materials transport as required for efficiency. It has been demonstrated this microfluidic device is simple and applicable to optimization of nanosphere size. Moreover, junction angle and N₂ gas pressure have a significant effect on the microbubble and polymer nanosphere diameter, which could be suitable for some therapeutic applications such as drug delivery. The conclusion given below can divide by this work:

- A microfluidics widely used in the preparation of polymer nanospheres due to the fact that microfluidic technologies offer compelling advantages, including cost-effective preparation and easy and effective control of fluid flow over the other methods.
- Gas pressure applied of the combined microfluidic device used has significant influence not only on microbubble size and also polymer nanosphere size. Influence of gas pressure on polymer nanosphere size. Error bars denote standard deviation of the microbubbles or polymer nanospheres analysed.
- An increase in the N₂ gas pressure (from 50 kPa to 400 kPa) resulted in a decrease in the mean diameter of polymer nanospheres obtained (from 550 nm to 380 nm). Moreover, this increase of gas pressure affected the polydispersity of the PMSQ nanospheres, decreasing from 30 to 18 %, respectively.

- The changes in the junction angles improve that microbubbles and polymer nanospheres are observed suggesting that the combined microfluidic junction device used has potential to prepare uniform polymer nanospheres as nearly efficiently as other microfluidic systems, but with larger sphere size.
- Junction angle had a crucial impact on the microbubble and nanosphere size
- Polymer nanosphere diameter size was observed when the junction angle was increased from (0° to 60°).
- Methods with different device geometries, including (T and V)-junctions, flow focusing devices and co-flow or cross-flow capillaries for generating continuous droplets.
- A microfluidic method has been widely used to prepare discrete and independently controllable droplets leading to polymer nanospheres with various geometries and polydispersity.
- A remarkable effect of junction angle and inlet of gas pressure on the microbubble and polymer nanosphere diameter has been investigated.
- In microfluidics devices Junction microbubble is generated every 12.3 ms.
- The 5 wt.% PMSQ solution surface tension was much higher than N2 gas .
- 100 s approximately it will take for calculation and resultant microbubbles were around 110 μm in diameter.
- Microfluidic device used instead of robot because is a very attractive technology for both research's and industrial since.
- Decreases sample and reagent consumptions.
- Shortens time of experiments and doing so.
- Reduces the overall coast of applications.

5.2 Future Works

- Investigation of dye release profile
- Enhanced surface roughness should be investigated
- Optimizing the process parameters in order to further control the polydispersity of the nanosphere



REFERENCES

- [1] Byrne J.D., Betancourt T., Brannon-Peppas L. (2008). Active targeting schemes for nanoparticle systems in cancer therapeutics. *Advanced drug delivery reviews*. **60**,1615-26.
- [2] Meier W. Polymer nanocapsules. (2000). *Chemical Society Reviews*. **29**, 295-303.
- [3] Yu B., Zhu J., Xue W., Wu Y., Huang X, Lee L.J. (2011). Microfluidic assembly of lipid-based oligonucleotide nanoparticles. *Anticancer research*. **31**, 771-6.
- [4] Fernandez A., Manchanda R., McGoron A.J. (2011). Theranostic applications of nanomaterials in cancer: drug delivery, image-guided therapy, and multifunctional platforms. *Applied biochemistry and biotechnology*. **165**, 1628-51.
- [5] Gao Z., Kennedy A.M., Christensen D.A., Rapoport N.Y. (2008). Drug-loaded nano/microbubbles for combining ultrasonography and targeted chemotherapy. *Ultrasonics*. **48**, 260-70.
- [6] Xu R.X., Xu J.S., Zuo T., Shen R., Huang T.H., Tweedle M.F. (2011). Drug-loaded biodegradable microspheres for image-guided combinatory epigenetic therapy in cells. *Journal of biomedical optics*. **16**, 50-73.
- [7] Kim C., Erpelding T.N., Maslov K., Jankovic L., Akers W.J., Song L. (2010). Handheld array-based photoacoustic probe for guiding needle biopsy of sentinel lymph nodes. *Journal of biomedical optics*. **15**, 046010.
- [8] Pisani E., Tsapis N., Galaz B., Santin M., Berti R., Taulier N., (2008). Perfluorooctyl bromide polymeric capsules as dual contrast agents for ultrasonography and magnetic resonance imaging. *Advanced Functional Materials*. **18**, 2963-71.
- [9] Schneider M., Bussat P., Barrau M.B., Arditi M., Yan F., Hybl E. (1992). Polymeric Microballoons as Ultrasound Contrast Agents: Physical and Ultrasonic Properties Compared with Sonicated Albumin. *Investigative radiology*. **27**, 134-9.

- [10] Xu R.X., Huang J., Xu J.S., Sun D., Hinkle G.H., Martin E.W. (2009). Fabrication of indocyanine green encapsulated biodegradable microbubbles for structural and functional imaging of cancer. *Journal of biomedical optics*. **14**, 034020.
- [11] Bourges J.L., Gautier S.E., Delie F., Bejjani R.A., Jeanny J.C., Gurny R. (2003). Ocular drug delivery targeting the retina and retinal pigment epithelium using polylactide nanoparticles. *Investigative ophthalmology & visual science*. **44**, 3562-9.
- [12] Capretto L., Cheng W., Carugo D., Katsamenis O.L., Hill M., Zhang X. (2012). Mechanism of co-nanoprecipitation of organic actives and block copolymers in a microfluidic environment. *Nanotechnology*. **23**, 375602.
- [13] De Jalón E.G., Blanco Prieto M., Ygartua P., Santoyo S. (2001). PLGA microparticles: possible vehicles for topical drug delivery. *International journal of pharmaceutics*. **226**, 181-4.
- [14] Hall J.B., Dobrovolskaia M.A., Patri A.K., McNeil S.E. (2007). Characterization of nanoparticles for therapeutics.
- [15] Mundargi R.C., Babu V.R., Rangaswamy V., Patel P., Aminabhavi T.M. (2008). Nano/micro technologies for delivering macromolecular therapeutics using poly (D, L-lactide-co-glycolide) and its derivatives. *Journal of Controlled Release*. **125**, 193-209.
- [16] Zhang L., Huang J., Si T., Xu R.X. (2012). Coaxial electrospray of microparticles and nanoparticles for biomedical applications. *Expert review of medical devices*. **9**, 595-612.
- [17] Chan E.M., Alivisatos A.P., Mathies R.A. (2005). High-temperature microfluidic synthesis of CdSe nanocrystals in nanoliter droplets. *Journal of the American Chemical Society*. **127**, 13854-61.
- [18] Chang M.W., Stride E., Edirisinghe M. (2010). A new method for the preparation of monoporous hollow microspheres. *Langmuir*. **26**, 5115-21.
- [19] Nie Z., Li W., Seo M., Xu S., Kumacheva E. (2006). Janus and ternary particles generated by microfluidic synthesis: design, synthesis, and self-assembly. *Journal of the American Chemical Society*. **128**, 9408-12.
- [20] Cui W., Lu X., Cui K., Wu J., Wei Y., Lu Q. (2011). Photosensitive nanoparticles of chitosan complex for controlled release of dye molecules. *Nanotechnology*. **22**, 065702.

- [21] Shestopalov I., Tice J.D., Ismagilov R.F. (2004). Multi-step synthesis of nanoparticles performed on millisecond time scale in a microfluidic droplet-based system. *Lab on a Chip*. **4**, 316-21.
- [22] Vehring R. (2008). Pharmaceutical particle engineering via spray drying. *Pharmaceutical research*. **25**, 999-1022.
- [23] Eltayeb M., Stride E., Edirisinghe M., Harker A. (2016). Electrospayed nanoparticle delivery system for controlled release. *Materials Science and Engineering*. **66**, 13-46.
- [24] Jayasinghe S., Edirisinghe M., Wang D. (2004). Controlled deposition of nanoparticle clusters by electrohydrodynamic atomization. *Nanotechnology*. **15**, 15-19.
- [25] Nangrejo M., Ahmad Z., Stride E., Edirisinghe M., Colombo P. (2008). Preparation of polymeric and ceramic porous capsules by a novel electrohydrodynamic process. *Pharmaceutical development and technology*. **13**, 25-32.
- [26] Jahn A., Reiner J.E., Vreeland W.N., DeVoe D.L., Locascio L.E., Gaitan M. (2008). Preparation of nanoparticles by continuous-flow microfluidics. *Journal of Nanoparticle Research*. **10**, 25-34.
- [27] Liu P, Liu G, Zhang W, Jiang F. (2009). Crosslinked polymeric nanocapsules with controllable structure via a 'self-templating' approach. *Nanotechnology*. **21**, 015603.
- [28] Song H., Chen D.L., Ismagilov R.F. (2006). Reactions in droplets in microfluidic channels. *Angewandte chemie international edition*. **45**, 36-56.
- [29] Jiang X, Zhang Y, Edirisinghe M, Parhizkar M. (2016). Combining microfluidic devices with coarse capillaries to reduce the size of monodisperse microbubbles. *RSC Advances*. **6**, 68-77.
- [30] Sun J, Xianyu Y, Li M, Liu W, Zhang L, Liu D, (2013). A microfluidic origami chip for synthesis of functionalized polymeric nanoparticles. *Nanoscale*. **5**, 52-62.
- [31] Vauthier C, Bouchemal K. (2009). Methods for the preparation and manufacture of polymeric nanoparticles. *Pharmaceutical research*. **26**, 25-58.
- [32] McEwan C, Kamila S, Owen J, Nesbitt H, Callan B, Borden M. (2016). Combined sonodynamic and antimetabolite therapy for the improved treatment

of pancreatic cancer using oxygen loaded microbubbles as a delivery vehicle. *Biomaterials*. **80**, 20-32.

- [33] Kucuk I. (2015). Polymer nanospheres formed by a microfluidic technique with Evans blue dye. *Polymers for Advanced Technologies*. Doi: 10.1002/pat.3641.
- [34] Park JI, Saffari A, Kumar S, Günther A, Kumacheva E. (2010). Microfluidic synthesis of polymer and inorganic particulate materials. *Annual Review of Materials Research*. **40**, 15-43.
- [35] Khoshmanesh K, Almansouri A, Albloushi H, Yi P, Soffe R, Kalantar-Zadeh K. (2015). A multi-functional bubble-based microfluidic system. *Scientific reports*, **5**.
- [36] Heath GR, Abou-Saleh RH, Peyman SA, Johnson BR, Connell SD, Evans SD. (2014). Self-assembly of actin scaffolds on lipid microbubbles. *Soft matter*, **10**, 694-700.
- [37] Solaro R, Chiellini F, Battisti A. (2010). Targeted delivery of protein drugs by nanocarriers. *Materials*, **3**, 28-80.
- [38] Qiu LY, Bae YH. (2006). Polymer architecture and drug delivery. *Pharmaceutical research*. **23**, 1-30.
- [39] Ahmad Z, Stride E, Edirisinghe M. (2009). Novel preparation of transdermal drug-delivery patches and functional wound healing materials. *Journal of drug targeting*. **17**, 724-9.
- [40] Vitale A, Quaglio M, Turri S, Cocuzza M, Bongiovanni R. (2013). Siloxane photopolymer to replace polydimethylsiloxane in microfluidic devices for polymerase chain reaction. *Polymers for Advanced Technologies*. **24**, 68-74.
- [41] Enayati M, Ahmad Z, Stride E, Edirisinghe M. (2010). One-step electrohydrodynamic production of drug-loaded micro- and nanoparticles. *Journal of the Royal Society Interface*. **7**, 67-75.
- [42] Thorsen, T., Maerkl, S. J., Quake, S. R. (2002). Microfluidic large-scale integration. *Science*. **298**, 580-584.
- [43] Saxena, A. N. (2007). Monolithic Concept and the Inventions of Integrated Circuits by Kilby and Noyce. In *Tech. Proc. Nano Science and Technology Inst. Ann. Conf.* **3**, 460-474.
- [44] Kim, S. M., Lee, B., Yoon, H., Suh, K. Y. (2013). Stimuli-responsive hydrogel patterns for smart microfluidics and microarrays. *Analyst*. **138**, 6230-6242.

- [45] Martinez, A. W., Phillips, S. T., Whitesides, G. M., Carrilho, E. (2009). Diagnostics for the developing world: microfluidic paper-based analytical devices.
- [46] Grayson, A. C. R., Shawgo, R. S., Johnson, A. M., Flynn, N. T., Li, Y., Cima, M. J., Langer, R. (2004). A BioMEMS review: MEMS technology for physiologically integrated devices. *Proceedings of the IEEE*. **92**, 6-21.
- [47] Jo, B. H., Van Lerberghe, L. M., Motsegood, K. M., Beebe, D. J. (2000). Three-dimensional micro-channel fabrication in polydimethylsiloxane (PDMS) elastomer. *Journal of microelectromechanical systems*. **9**, 76-81.
- [48] Dendukuri, D., Pregibon, D. C., Collins, J., Hatton, T. A., Doyle, P. S. (2006). Continuous-flow lithography for high-throughput microparticle synthesis. *Nature materials*. **5**, 365-374.
- [49] Garstecki, P., Fuerstman, M. J., Stone, H. A., Whitesides, G. M. (2006). Formation of droplets and bubbles in a microfluidic T-junction-scaling and mechanism of break-up. *Lab on a Chip*. **6**, 437-446.
- [50] H. A. (2008). Emulsification in a microfluidic flow-focusing device: effect of the viscosities of the liquids. *Microfluidics and Nanofluidics*. **5**, 585-594.
- [51] Tan, J., Li, S. W., Wang, K., Luo, G. S. (2009). Gas-liquid flow in T-junction microfluidic devices with a new perpendicular rupturing flow route. *Chemical Engineering Journal*. **146**(3), 428-433.
- [52] Sia, S. K., Whitesides, G. M. (2003). Microfluidic devices fabricated in poly (dimethylsiloxane) for biological studies. *Electrophoresis*. **24**(21), 3563-3576.
- [53] Ushikubo, F. Y., Birribilli, F. S., Oliveira, D. R. B., Cunha, R. L. (2014). Y- and T-junction microfluidic devices: effect of fluids and interface properties and operating conditions. *Microfluidics and nanofluidics*. **17**(4), 711-720.
- [54] Christopher, G. F., Anna, S. L. (2007). Microfluidic methods for generating continuous droplet streams. *Journal of Physics D: Applied Physics*. **40**(19), R319.
- [55] Stone, H. A., Stroock, A. D., Ajdari, A. (2004). Engineering flows in small devices: microfluidics toward a lab-on-a-chip. *Annu. Rev. Fluid Mech.* **36**, 381-411.
- [56] Yang, L., Wang, K., Tan, J., Lu, Y., Luo, G. (2012). Experimental study of microbubble coalescence in a T-junction microfluidic device. *Microfluidics and nanofluidics*. **12**(5), 715-722.

- [57] Van Steijn, V., Kleijn, C. R., Kreutzer, M. T. (2010). Predictive model for the size of bubbles and droplets created in microfluidic T-junctions. *Lab on a Chip*. **10**(19), 2513-2518.
- [58] Skurtys, O., Aguilera, J. M. (2008). Applications of microfluidic devices in food engineering. *Food Biophysics*. **3**(1), 1-15.
- [59] Chou, H. P., Fu, A. Y., Quake, S. R. (2007). U.S. Patent No. 7,258,774. Washington, DC: U.S. Patent and Trademark Office.
- [60] Berthier, J., Brakke, K.A., Berthier, E. (2016). Open Microfluidics. doi:10.1002/9781118720936.
- [61] Pfohl, T., Mugele, F., Seemann, R., Herminghaus, S. (2003). Trends in Microfluidics with Complex Fluids. *ChemPhysChem*. **4**(12), 1291–1298.
- [62] Kaigala, Govind V., Lovchik, Robert D., Delamarche, E. (2012-10-30). Microfluidics in the "Open Space" for Performing Localized Chemistry on Biological Interfaces. *Angewandte Chemie International Edition*. **51**(45), 11224–11240.
- [63] Li, C., Boban, M., Tuteja, A. (2017). Open-channel, water-in-oil emulsification in paper-based microfluidic devices. *Lab on a Chip*. **17**(8), 1436–1441.
- [64] Casavant, B. P., Berthier, E., Theberge, A. B., Berthier, J., Montanez-Sauri, S. I., Bischel, L. L., Brakke, K., Hedman, C. J., Bushman, W. (2013). Suspended microfluidics. *Proceedings of the National Academy of Sciences*. **110**(25), 10111–10116.
- [65] Guckenberger, David J., de Groot, Theodorus E., Wan, Alwin M. D., Beebe, David J., Young, Edmond W. K. (2015). Micromilling: a method for ultra-rapid prototyping of plastic microfluidic devices. *Lab on a Chip*. **15**(11), 2364-2378.
- [66] Truckenmussmlsler, R., Rummler, Z., Schaller, T., Schomburg, W.K. (2002). Low-cost thermoforming of micro fluidic analysis chips. *Journal of Micromechanics and Microengineering*. **12**(4), 375-379.
- [67] Mazutis, L., Gilbert, J., Ung, W. L., Weitz, D. A., Griffiths, A. D., Heyman, J. A. (2013). Single-cell analysis and sorting using droplet-based microfluidics. *Nature protocols*. **8**(5), 870.
- [68] Pamme, N. (2007). Continuous flow separations in microfluidic devices. *Lab on a Chip*, **7**(12), 1644-1659.

- [69] Dendukuri, D., Pregibon, D. C., Collins, J., Hatton, T. A., Doyle, P. S. (2006). Continuous-flow lithography for high-throughput microparticle synthesis. *Nature materials*. **5**(5), 365.
- [70] Seemann, R., Brinkmann, M., Pfohl, T., Herminghaus, S. (2011). Droplet based microfluidics. *Reports on progress in physics*. **75**(1), 016601.
- [71] Jeon, Jessie S., Chung, S., Kamm, Roger D., Charest, Joseph L. (2010). Hot embossing for fabrication of a microfluidic 3D cell culture platform. *Biomedical Microdevices*. **13**(2), 325-333.
- [72] Young, Edmond W. K., Berthier, E., Guckenberger, David J., Sackmann, E., Lamers, C., Meyvantsson, I., Huttenlocher, A., Beebe, David J. (2011). Rapid Prototyping of Arrayed Microfluidic Systems in Polystyrene for Cell-Based Assays. *Analytical Chemistry*. **83**(4), 1408-1417.
- [73] Bouaidat, S., Hansen, O., Bruus, H., Berendsen, C., Bau-Madsen, Niels Ki, Thomsen, Pi, Wolff, A., Jonsmann, J. (2005). Surface-directed capillary system; theory, experiments and applications. *Lab on a Chip*. **5**(8), 827.
- [74] Kachel, S., Zhou, Y., Scharfer, P., Vrančić, C., Petrich, W., Schabel, W. (2014). Evaporation from open microchannel grooves. *Lab Chip*. **14**(4), 771–778.
- [75] Mazutis, L., Gilbert, J., Ung, W. L., Weitz, D. A., Griffiths, A. D., Heyman, J. A. (2013). Single-cell analysis and sorting using droplet-based microfluidics. *Nature protocols*. **8**(5), 870.
- [76] Seemann, R., Brinkmann, M., Pfohl, T., Herminghaus, S. (2011). Droplet based microfluidics. *Reports on progress in physics*. **75**(1), 016601.
- [77] Higashi, K., Ogawa, M., Fujimoto, K., Onoe, H., Miki, N. (2017). Hollow Hydrogel Microfiber Encapsulating Microorganisms for Mass-Cultivation in Open Systems. *Micromachines*. **8**(6), 176.
- [78] Chang, H.C., Yeo, Leslie (2009). Electrokinetically Driven Microfluidics and Nanofluidics. *Cambridge University Press*.
- [79] Fluid transistor Archived July 8, 2011, at the Wayback Machine.
- [80] Churchman, A. (2018). Data associated with 'Combined flow-focus and self-assembly routes for the formation of lipid stabilized oil-shelled microbubbles'. University of Leeds.
- [81] Chokkalingam, V., Herminghaus, S., Seemann, R. (2008). Self-synchronizing Pairwise Production of Monodisperse Droplets by Microfluidic Step

- Emulsification. *Applied Physics Letters*. **93**, 254101. Bibcode: ApPhL.93y4101C.
- [82] Joshi, M., Adak, B., Butola, B. S. (2018). Polyurethane nanocomposite based gas barrier films, membranes and coatings. A review on synthesis, characterization and potential applications. *Progress in Materials Science*.
- [83] Shafritz, J. M., Borick, C., Russell, E. W., Hyde, A. C. (2016). *Introducing public administration*. Routledge.
- [84] Sozer, N., Kokini, J. L. (2009). Nanotechnology and its applications in the food sector. *Trends in biotechnology*. **27**(2), 82-89.
- [85] Whitesides, G. M. (2005). Nanoscience, nanotechnology, and chemistry. *Small*. **1**(2), 172-179.
- [86] Berthier, J., Brakke, Kenneth A., Berthier, E. (2016). *Open Microfluidics*. John Wiley & Sons. 229–256.
- [87] Galindo, R., Francisco J., (2017). *Complex Fluid-Flows in Microfluidics*. Springer.
- [88] Martinez, Andres W., Phillips, Scott T., Butte, Manish J., Whitesides, George M. (2007). Patterned paper as a platform for inexpensive, low-volume, portable bioassays. *Angewandte Chemie International Edition*. **46**(8), 1318-1320.
- [89] San Park, T., Yoon, J. Y. (2015). Smartphone detection of Escherichia coli from field water samples on paper microfluidics. *IEEE Sensors Journal*. **15**(3), 1902-1907.
- [90] Pritchard, G. (1994). *Anti-corrosion polymers: PEEK, PEKK and other polyaryls* iSmithers Rapra Publishing. **80**.
- [91] Stone, H. A., Stroock, A. D., Ajdari, A. (2004). Engineering flows in small devices: microfluidics toward a lab-on-a-chip. *Annu. Rev. Fluid Mech.* **36**, 381-411.
- [92] Stone, H. A., Stroock, A. D., Ajdari, A. (2004). Engineering flows in small devices: microfluidics toward a lab-on-a-chip. *Annu. Rev. Fluid Mech.* **36**, 381-411.
- [93] Happel, J., Brenner, H. (2012). *Low Reynolds number hydrodynamics: with special applications to particulate media*. Springer Science & Business Media. **1**.
- [94] Connor, E. M., Sperling, R. S., Gelber, R., Kiselev, P., Scott, G., O'sullivan, M. J., Jimenez, E. (1994). Reduction of maternal-infant transmission of human

- immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine*. **331**(18), 1173-1180.
- [95] Pritchard, G. (1994). Anti-corrosion polymers: PEEK, PEKK and other polyaryls. *iSmithers Rapra Publishing*. **80**.
- [96] Subodh K., Shahi, A.S. (2011). Effect of heat input on the microstructure and mechanical properties of gas tungsten arc welded AISI 304 stainless steel joints. *Materials and Design*. **32**, 3617–3623.
- [97] Weiss, M., Gerber, S., Fuchslin, R. M., Neff, T. A. (2004). Accurate continuous drug delivery at low infusion rate with a novel microvolumetric infusion pump (MVIP): pump design, evaluation and comparison to the current standard. *Anaesthesia*, **59**(11), 1133-1137.
- [98] Lyon, G. T. (1953). U.S. Patent No. 2,661,225. Washington, DC: U.S. Patent and Trademark Office.
- [99] Hawkins Jr, I. F., Caridi, J. G., Klioze, S. D., Mladinich, C. R. (2001). Modified plastic bag system with O-ring fitting connection for carbon dioxide angiography. *American Journal of Roentgenology*. **176**(1), 229-232.
- [100] Diba, K. T. (1985). U.S. Patent No. 4,498,822. Washington, DC: U.S. Patent and Trademark Office.
- [101] Ohlson, J. F. (1969). U.S. Patent No. 3,425,314. Washington, DC: U.S. Patent and Trademark Office.
- [102] V. Vapnik, *The Nature of Statistical Learning Theory*, Springer-Verlag, New York, 1995.
- [103] Groisman, A., Steinberg, V. (2000). Elastic turbulence in a polymer solution flow. *Nature*. **405**(6782), 53-55.
- [104] Kucuk I. (2015). Polymer nanospheres formed by a microfluidic technique with Evans blue dye. *Polymers for Advanced Technologies*. Doi: 10.1002/pat.3641.
- [105] Chang M. W., Stride E., Edirisinghe M. (2010). A new method for the preparation of monoporous hollow microspheres. *Langmuir*. **26**, 5115-5121.