Simulation study of biopolymer microspheres shape varying behavior

Roaa Mohammed Munee1, Prof. Nizar Jawad Hadi2, Prof. Ali Al-Zubiedy3
1Al-Mustaqbal University College, 51001 Hillah, Babil, Iraq
2, 3 Collage of materials engineering, Department of Polymers and Petrochemical industries, University of Babylon, Hillah, Iraq
dr.roaamohammed@mustaqbal-college.edu.iq

Abstract Simulation and modeling are very strong tools to design and simulate engineering cases that can be difficult to ably experimentally. In microscale domains, simulation and modeling play a very strong role to maintain results for specific cases that are hard to explain in microfluidic devices experimentally. Microfluidic devices were developed for mixing, separation, drug delivery, and microspheres formation. Drug delivery and microfluidic devices and modeling have a tight relationship that can solve and discuss the behavior of microspheres under variable formation process conditions. The main goal of this research is to discover the microspheres formation behavior under different flow rates. Experimentally, starch microspheres were formed with a different shape ranging from oval to spherical shape. This difference in shape was the main goal to study in this paper. To understand the shape changing, a numerical simulation study has been introduced using (ANSYS workbench 16.1) program, to simulate and study the microspheres formation process and the effect of flow rate varying on microspheres formation.

Key words: Rheology, simulation, potato starch, microcapillary.

1. Introduction

Microspheres and microparticles are polymer particles produced on a micron scale, capable of releasing a preloaded drug that has been incorporated into a central reservoir [1]. Biodegradable polymer microspheres are one of the most common types and hold several advantages including encapsulation for many types of drugs such as small molecules, proteins, and nucleic acids and are easily administered through a syringe needle [2].

The most commonly employed method of producing drug-loaded microspheres is the use of a water-oil-water emulsion (w/o/w) to entrap the protein. Initially, the growth factor is dissolved in the water phase, and the polymer is dissolved in the oil phase (normally an organic solvent such as methylene chloride). The final water phase is the vehicle used to disperse this emulsion by using homogenization or sonication. The solvent is then removed by evaporation, and microspheres are formed, which can be harvested by filtration or centrifugation [3]. These spheres can then be incorporated into a porous synthetic scaffold or water-based hydrogel, which provides structural support and further control release (e.g., via diffusion through pores in the matrix)[4]. Microfluidic devices used in fabrication of both nanoparticles and encapsulation structures. In these processes, the active compounds are driven to the area of adsorption by a carrier enclosed in matrix or core–shell configuration[5]. The carrier can be inorganic (polylactic acid [PLA][2] and poly(lactic-co-glycolic acid)[PLGA][6] or organic (chitosan[7]; hydrogelator [8]; silk protein [9], pectin [10]; hydrazide- and aldehyde-functionalized carbohydrates [11]; dextran hydroxyethyl methacrylate [12]; and starch[13]. For many years microfluidics had been used in biology [14] in the form of microsphere because of the very small amounts of materials used as well as to quality and accuracy in size of microspheres [15]. The flow focusing devise is very popular in microfluidics because it able to deliver bubbles at frequencies exceeding 10⁴ bubbles per second[16]. Microfluidic flow focusing device gain many applications such as studying the production of micrometer-sized droplets using many methods such as control of the flow rates of the two phases[17]. Mainly, microfluidic devises contain three main parts, syringe pumps to deliver both continuous and dispersed phases, a microfluidic chip usually made of polymers or glass, and collector[18].
Microfluidics own the potential to change the preformed way modern biopolymers. Microfluidic devices have the ability to work with smaller volumes of reagents, short reaction time, and the possibility of multiple operations[19]. Flow control is very important in many of the microfluidic systems for use in biochemistry analysis, drug delivery, and so on. Such systems use microchannel to promote efficient mixing without the use of any external means[20]. To locate the properties of fluid flow inside the microcapillary, boundary conditions must be identified first, such as the velocity of flow (flow rate) that has many boundary conditions like no slip and slip; the shear stress at a specific of any system; temperature; and, pressure[21]. The relation between microfluidics and rheology and flow and numerical solution in circular capillaries is very related, since the modeling and simulation process can solve a wide range of experimental cases numerically[22]. The current paper deals with solving the shape changing of microspheres with flow rate change numerically. By simulating the microspheres formation process and detect the formation mechanism from beginning. This way helps to show the parameters effect on the microspheres shape variations and the cause behind it. Besides, the basic contribution to the present study which is different from the previous researches is that this paper solved the shape variation of the microspheres produced in microfluidic capillary device.

2. Materials
Iraqi sweet potato starch, polyvinyl alcohol (PVA) (Mw 1 24 000 Da) – purchased from Sigma Aldrich (New Delhi, India), sodium alginate – purchased from (Central drug house (P) Ltd. New Delhi, India), tween80 – purchased from (Chemical point, Germany), medical glycerol and de-ionized water.

3. Experimental part
Microspheres were produced experimentally with water in oil dispersion using a glass microfluidic device with different flow rates that explained in detail in previous papers[23][24] (Figure 1).

4. Numerical and Modeling Part
Three assumptions were introduced to simulate the change in shape as flow rate varying, Transient laminar flow, Microspheres break up dependent on the flow rate of the dispersed phase and Continuous and dispersed phases dependent on non-Newtonian power-law model. The geometry was sketched in a 2D microcapillary. The dimensions of the microcapillary were similar to the original capillary used experimentally[23]. Two inlets and one outlet were drawn, beside the flow focusing region. Face sizing was used with size elements of (300 μm), Inflation was used to define the shear thought walls, these settings make the number of nodes (9507) and the number of elements (9021), (Figure 2).
The simulations were held using the experimental properties of both continuous phase, Poly (vinyl alcohol) PVA; and dispersed phase Starch+Sodium alginate SA (Table 1).

|                | Density g/cm³ | Contact angle | Viscosity cP | Surface tension mN/m |
|----------------|---------------|---------------|--------------|----------------------|
| **PVA**        | 1.007         | 92°           | 5.37         | 27.65                |
| **Starch + SA**| 0.998         | 102°          | 7.05         | 21.9                 |

The analysis was performed using (ANSYS 16.1) simulation program, using geometry with shape and dimensions that matched with the geometry used in the experimental part [23]. Owing to the importance of graphical representation of result which allows the designer to obtain the breakup mechanism of the microsphere, this paper provides a number of these graphs representing two or more parameter relations or illustrating more than one curve within the same case. The numerical results showed an excellent agreement with the experimental results [23], the graphical performance of results help also in making comparisons between numerical and experimental methods. Besides this, the numerical results explain the reasons that microspheres deform at high flow rates and take a regular spherical shape at lower flow rates. Furthermore, a simulation of the microsphere formation with flow rates that differs from experimental to configure this mechanism with a wide range of flow rate that is hard to identify experimentally.

5. Results and discussion

5.1 Breakup behavior:

The analysis of the microspheres formation process was performed using 2D, the multiphase, laminar, transient volume of the fluid model (VOF). The numerical results of microspheres formation at flow rates were similar to the experimental results, (Figure 4). These results were performed at the same material properties that were adjusted from experimental tests. The only changeable parameter was the flow rate, which was used to identify and track the best flow rate that helps to formed microspheres without deformation.

First, many terms need to be clarified as dealing with microfluidic devices. Turbulent flows refer to unstable and not observed laminar flow. Turbulent flows are always unsteady and rotational, but unsteady flows and rotational flows are not necessarily turbulent. Chaotic flows imply flows for which streamlines separate from each other exponentially as a function of time. Such streamlined separation is observed in turbulent flows, but Chaotic flows need not be turbulent [25]. However, the existence of rapid microspheres breakup and mixing in microfluidic devices at low Reynolds number creates turbulence flow called (elastic turbulence). Polymers with large elasticity (large relaxation time) can be stretched by a weak primary shear flow generated by the surface tension of these polymers. This action causes elastic instabilities, which results in
irregular secondary flow (Chaotic flow). The flow stretches further the polymer molecules, make the laminar flow more unstable, and then elastic turbulence can be reached [26].

Since the literature reports show that the $Re$ for the transition from laminar to turbulent in microfluidic channels might have a different behavior as compared to that predicted for the regular theory of fluids [19], since the $Re$ was lower than 2, (Figure 3), the flow can be considered as (elastic turbulence) that creates the Chaotic flows, in which will be used to explain the rotational flow near the breakup area. For this reason, the following terms will be used to identify and explain the flow behavior of both continuous and dispersed phases. The first term is the *unsteady* and *steady* flow to denote whether a flow rate of both phases is affecting the microspheres morphology; the second term is rotational or (Chaotic) flow to denote whether the magnitude of the vortices or the rotational flow is affecting the microspheres breakup zone causing its deformation.

The numerical results at a flow rate (0.00062) cm$^3$/sec, (Figure 4), show the microsphere was deformed severely in the experimental results. This effect is caused by the very high flow rate of dispersed phase that creates troubled flow (Chaotic flow) as contact by the streamline of continuous phase flow. For this reason, the microspheres at a high flow rate were deformed and crushed because the microspheres were not having enough dripping time to form a microsphere and accumulate as a sphere, (Figure 4). At flow rate (0.00059) cm$^3$/sec, the microspheres start to take the oval shape, where one end is slightly thicker than the other, with the assistance of starch surface tension, the microsphere takes an uniform breakup zone causing this shape, (Figure 4). According to the contouring of volume fraction, the microspheres start to take a regular oval shape as flow rate decreased typically (0.00056) cm$^3$/sec. As Figure 4 shows, the chaotic flow becomes less troubled, but it was not enough to accumulate the spherical shape of microspheres causing a more regular oval shape of the microspheres.

At flow rate (0.00054) cm$^3$/sec, the contouring of volume fraction shows that the shape of microspheres starts to take a more regular shape, where the shell becomes more regular in thickness. The Chaotic flow was steadier with lower rotational flow making the breakup zone owing to the semispherical shape. The mechanism of breakup at flow rates (0.00062-0.00054) cm$^3$/sec causes a non-uniform breakup zone making the shell weaker and creating a membrane that oozes starch. Typically, this behavior is caused by the surface tension of microspheres that tend to attach to the flow source of the dispersed phase creating chaotic flow circulations. The volume fraction contour at a flow rate (0.00051) cm$^3$/sec, shows that the microsphere starts to take a spherical shape with even shell thickness. These results strongly agreed the experimental results. It can be seen clearly that the chaotic flow circulations become less turbulence allowing the microspheres to accumulate to spherical shape. At flow rate (0.00048 – 0.00034) cm$^3$/sec, the contour of volume fraction shows a regular shell with a circular shape which very similar to the shape of microspheres formed at this flow rate experimentally. The microspheres separation was steady with low chaotic flow circulations; this behavior was caused by the low flow rate that allows the microspheres to drip slowly giving them enough time to form spherical shapes with regular shell thickness. The Chaotic flow circulations become very

![Figure 3 The effect of Velocity on Reynolds number](image_url)
smooth and steadier as the flow rate decreased. It can be seen clearly that the chaotic flow circulations become less as the flow rate decreased giving the tendency of microspheres to form a spherical shape. Lower flow rate (0.00031) cm³/sec, Figure 4, showed the deformation region of the microspheres formed at this flow rate, that causes oozing behavior of the microspheres resulted from the very low flow rate. This may cause by the very low dripping time, where the mass flow rate was not enough to form a complete microsphere, causing the microsphere deformation due to oozing core. Furthermore, a simulation of flow rate lower than (0.00031) cm³/sec, and greater than (0.00062) cm³/sec was performed. At a very low flow rate, (0.00027) cm³/sec, no microspheres were formed, where the volume fraction contour didn’t show any microsphere formed, this behavior was caused by the very low mass passing through the dispersed phase inlet. While, simulation of very high flow rate (0.00065) cm³/sec showed severe deformation of microsphere resulted from high.

Figure 4 Microsphere behavior at different flow rates where; (top) numerical result, (bottom) experimental result processed using ImageJ software, for each group.
5.2 Velocity profile and flow rate relation

The behavior of microspheres formation and breakup mechanism were tracked using the velocity profiles, Figure 7. The velocity profiles are plotted at regular intervals from the needle tip to the capillary outlet beginning. The fully-developed flow condition was achieved at every case of flow rate. The fully developed flow exist when the viscous effects of the polymer due to the shear stress between the particles of fluid and pipe wall originate a fully developed velocity profile. This case occurred when the fluid travel through a straight capillary. Also, the fully developed flow velocity will be at its fastest at the centerline of the microcapillary (Equation 1).

\[
U = -\frac{R^2 \frac{dP}{dz}}{8\mu}
\]  \hspace{1cm} (1)

On the other hand, the walls velocity of the capillary was zero. As a result, fluid velocity should be distinguished as an average velocity [27]. Basically, the length of entrance needed for a fully developed velocity profile can be calculated using Langhaar distance \((Le)\) [27] [28],

\[
Le = 0.058 \times Re \times L
\] \hspace{1cm} (2)

Where \(L\) is the characteristic length of the channel. The characteristic length of the continuous phase equals (36 mm) and the Reynolds number equals (~1.1) so that the distance needed to fully developed velocity profile is (2.2068 mm). From (Figure 6) it can be seen clearly that the velocity profile of flow of the continuous phase interface in the middle of the channel is inevitably the same along the channel.

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Figure 5: Simulated microspheres contour at, (a) very low flow rate (0.00027) cm\(^3\)/sec, (b) very high flow rate (0.00065) cm\(^3\)/sec
Figure 6 Fully developed velocity profile contour

For this reason, it is reasonable to assume that there is no slip on the microcapillary walls. In each figure of velocity profiles, the x-axis represents the flow in the y-direction and the y-axis represents the function of the velocity profile. For the x-axis, (0) corresponds to the needle tip, and (1.00) corresponds to the beginning of the tip of the capillary outlet and the flow direction is from top to bottom. For each case and from the comparison of the velocity profiles, Figure 7, can reveal that the velocity profiles intensity increase with flow rate decreasing, this behavior can be explained by regarding decrease in the mass flow rate of the dispersed phase. In other words, the force of the continuous phase as hitting the dispersed phase was low, making the velocity lower as the flow rate increases.

6 Dimensionless numbers

The flow type was examined with the assistance of Reynolds number, using the data of velocity exported numerically. Reynolds number was calculated for each flow rate. It was found that the Reynolds number did not exceed (1.2), (Figure 8a), which leads to conclude a laminar flow type inside the microcapillary [29]. But, in this research the chaotic flow plays an important role with flow rate assisting to change the
Reynolds number support the previous results, where at low flow rates (0.00031, 0.00034) cm³/sec, Reynolds number starts from zero followed by flow rate (0.00037) cm³/sec. Since the relation between the velocity of flow and dynamic viscosity is odd (Equation 3), the effecting parameter is dynamic viscosity. The dynamic viscosity at low mass flow rates was responsible for the stretching phenomenon at the breakup zone, creating unstable flow leading to a chaotic flow.

\[ Re = \frac{vL}{\mu} \]  
(3)

Where \( v \) is the velocity of the flow, \( L \) is the characteristic length of the geometry[30].

Figure 8 The effect of Velocity on; (a) Reynolds number, (b) Capillary number

The capillary number was also calculated depending on numerical data, (Figure 8b), the behavior was linear and lower than 3x10⁻³, so that the interfacial forces between the two phases was enough to microsphere formation [31]. Furthermore, decreasing capillary number will restrict microspheres formation as a result of increasing velocity which prevents the microspheres accumulation process [32].

\[ Ca = \frac{\eta_c u_c}{\sigma} \]  
(4)

Where:
\( \eta_c \) = the viscosity of the continuous phase [Pa-s],
\( u_c \) = the average inlet velocity [m/s],
\( \sigma \) = the interfacial tension between the immiscible phases [N/m][31].

Capillary number \( Ca \) take a steady behavior at different flow rates except at the highest flow rate (0.00062) cm³/sec, (Figure 8b), the capillary number was shafted as compared to other flow rates, this may cause by the destruction of microspheres at this high flow rates leading to this efficient change in dynamic viscosity and flow velocity and as a result the change in capillary number, (Equation 4). These results agreed to Liu H. et al., [32], the microspheres were breakup at high flow rates leading to a decrease in the capillary number.
7 Conclusion

The numerical results showed an excellent agreement with experimental results. The microspheres formation process and the breakup mechanism contours were very similar to the breakup mechanism in experimental work. At high flow rates typically (0.00062) cm$^3$/sec, microspheres deform and breakup leaving an empty shell caused by the high elastic turbulence. At a flow rate (0.00059-0.00054) cm$^3$/sec, the microspheres take an oval shape with non-uniform shell thickness the elastic turbulence begin to stabilize. Decreasing flow rates (0.00051-0.00031) cm$^3$/sec makes the microsphere form a spherical shape where the elastic turbulence was much stable. Using numerical results, a flow rate lower than (0.00031) cm$^3$/sec didn’t show any microspheres formation. Flow rates higher than (0.00062) cm$^3$/sec showed a severe deformation and breakup of microspheres.

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Data Availability

Additional data available within the following articles [23, 24].

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