Computational Approaches for Investigating different shapes of nanoparticles-based drug delivery

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Abstract: In recent years, the interest in materials innovation and nanotechnology for drug delivery has increased, with the design and synthesis of such systems playing an important role in the fields of medicine and health care besides supporting the development of the drug delivery. This study aims to simulate different shapes of nanoparticles-based drug delivery system using COMSOL Multiphysics® fluid flow module (Laminar two-phase flow moving mesh) in order to examine and investigate the effects of nanoparticle shape as drug delivery systems on the concentration of a water-soluble drug and on the contact angle between the droplet and both of the capillary and membrane during traveling on a permeable membrane to give a deep understanding of nanocarrier design that has the capability to achieve the desired medication results. The main finding of this study showed that the drug delivery system with multiply twinned shape was the best one amongst other shapes as it showed the highest drug concentration, as well as the greatest amount of delivered moles with 80.50×10^{-12} (mol) while the oval shape was the lowest one. We can conclude that using of COMSOL Multiphysics software is a useful integrated platform in the design and simulate a wide range of medical applications such as in drug delivery applications and quite achieves the desired outcomes with degree come close to reality.

Keywords: Computational, Drug Delivery, nanoparticles Shapes, Drug Concentration

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1. Introduction

So far, many improvements and improvements have been made in drug delivery systems using nanoparticles through the development of different dosage forms [1, 2]. The nanoparticles, which range in size from 1-100 nanometers, defined as the structures of ultra-dispersible solid particles [3]. Indeed, due to nanoparticles' small size and their high surface area ratio, it acts as the most promising techniques in the medical field applications in general and in the vectors for the joint delivery of multiple drugs in particular [4]. Over the years, the organism's response to various therapeutic drugs has been a major challenge for doctors, pharmacists, and scientists. In the past few decades, targeting and delivering of the drug techniques have started to evolve rapidly and became leading in the pharmaceutical research activities [5]. These systems are distinguished by delivering the drug at the desired time and to the specific place [6]. In addition,

controlling both of the drug releases besides the therapeutic agents [7]. Furthermore, a greater revolution is expected in the targeted drug delivery systems area in the near future [8]. Applying targeted drug delivery systems can facilitate to maintain of both the active agent and the drug effect which in turn can improve and achieve the optimal compliance of the patient and thus reduce the side and toxic effects of these medications [9-11]. To demonstrate, knowing and studying the relationship that fastens together both the concentration of drugs and the patient's body response to these medications will contribute greatly to understanding the basics of these medications and its main principles of action, thus apply the pharmacological principles to actual patient situations [12, 13].

Existing researches on drug delivery systems can be limited to four categories: Targeting strategies, delivery vehicles, delivery methods…etc. The medicines different kinds that can be delivered to the patient's body in order to release and administrate the active agent can be done in many ways, such as injection systems, ointments, pills, fumigation, and other available methods. The design and synthesis of these delivery systems require a great deal of accuracy to achieve the maximum possible efficiency of the drug, by illustrating the drug release location, time, amount and concentration [14, 15]. A group of researchers [16] has used calcium phosphate particles to study the relationship between both the shape and size of particles in the delivery of antibiotics by testing their antibacterial activity. They found that the morphology of these particles plays a big role in loading and releasing drugs, which contributes to achieving optimal treatment. Other researchers [17, 18] have studied the performance of the drug carrier and the effects that occur on it as a result of controlling the shape and size of particles. These studies have concluded that this control has a direct effect on both the biological distribution of tissues and internal absorption.

Indeed, despite studies conducted to investigate these properties, there is no comprehensive study that examines or accurately described the role of the different nanoparticles shape effect in the drug concentration, often due to the lack of optimal and easy ways to control the shape of the particles. This is what this study seeks to solve by modeling different nano-shapes as (sphere, cylinder, rod, oval, disc, multiply twinned and star) to study its shape effect on the concentration of a water-soluble drug. In fact, modeling and simulation processes/software can be a great and helpful tool that provides and allows simulation and modeling of different forms of nanoparticles and studying the effect of this shape on drug concentration at a specific time. Which effectively contributes to choosing the appropriate form of the drug for the manufacturing process. Also, this can ensure an appropriate drug delivery, dose, concentration and medication to the patient, which is the most important key to achieve optimal treatment.

2. Materials and Methods

2.1 Drug Delivery Systems Simulation

The Nanoparticle-laden droplets of liquid crystals for water-soluble drug were modeled using COMSOL Multiphysics® fluid flow module (Laminar two-phase flow moving mesh) to simulate the operation of drug delivery systems as illustrated in (Figure 1) over time ranges between (0,0.5,10) in different forms such as (cylinder, disk, multiply twinned, sphere, rod, oval and star) within a capillary tube to study the variable concentrations provided by the drug depending on the shape as well as the changes of sessile droplet contact angle with capillary and membrane.

Moreover, the drug delivery system modeled with the principle of providing different concentrations of a drug that is soluble in the aqueous medium, and the drop of the drug which is mixed with a fixed volume of water and dissolves in it after the drop moves with a constant speed to the bottom of the capillary tube with (width= 0.05 mm and height= 1.5 mm) and passes the permeable membrane that forms part of the capillary wall and the permeable capillary part is represented by a function applied to the boundary condition where it cannot be seen as part of the geometric shape. As well as, separated the concentrated drug solution from the inner capillary portion. Taken into account that, the delivery process occurs with a constant flux of the drug on the capillary wall throughout the duration of the drug's contact with the capillary wall and the final drug concentration inside the drop can be adjusted by changing the velocity of the droplet between 0.1 and 1 mm/s.

As shown in (Figure 2) the droplet located near the top between (z=6, z=8 mm) of the capillary geometry and in order to help the model mesh a horizontal line was included across the capillary. The modeling parameters values were listed in (Table 1).

Table 1: The modeling parameters values.

Parameter	Value
Liquid water density in droplet	1000 kg/m³
Liquid water viscosity in droplet	10^{-3} Pa·s
Air density in capillary rest	1.25 kg/m³
Air viscosity in capillary rest	2×10^{-5} Pa·s
Water air surface tension coefficient	70 mN/m
The contact angle between droplet and capillary wall	135°
The contact angle between droplet and membrane	157.5°
Drug flux	1×10^{-3} mol/(m²·s)
Drug diffusion coefficient	5×10^{-9} m²/s
Droplet velocity (u0)	0.001 m/s

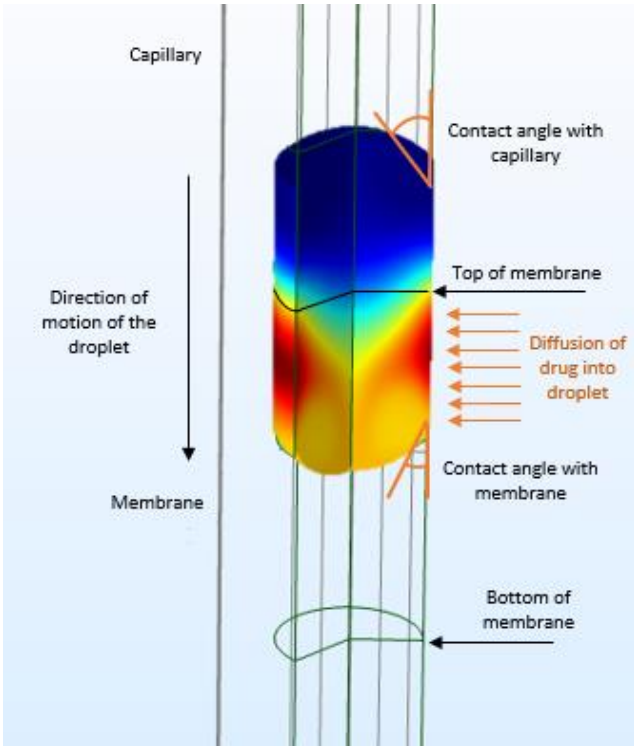

Figure 1: The drug delivery device operating principle diagram.

The seven models were designed using two-dimensional symmetrical geometry as shown in (Figure 2). after building the geometry both the "Laminar Two-Phase Flow, Moving Mesh" and "Chemical Species Transport" models were selected to add the model physics such as fluid Interface, diluted species interface, transport properties, velocity, and diffusion. Then, the model materials have been set as new material with specific properties as illustrated in (Table 2). The mesh was chosen to be free quad mesh and the study was solved at the time-dependent domain.

Table 2: The materials properties of the model.

Property	Variable	Value	Unit	Property group
Capillary Density	rho	1.25	kg/m³	Basic
Capillary Dynamic viscosity	mu	2e-5	Pa·s	Basic
Droplet Density	rho	1000	kg/m³	Basic
Droplet Dynamic viscosity	mu	1e-3	Pa·s	Basic

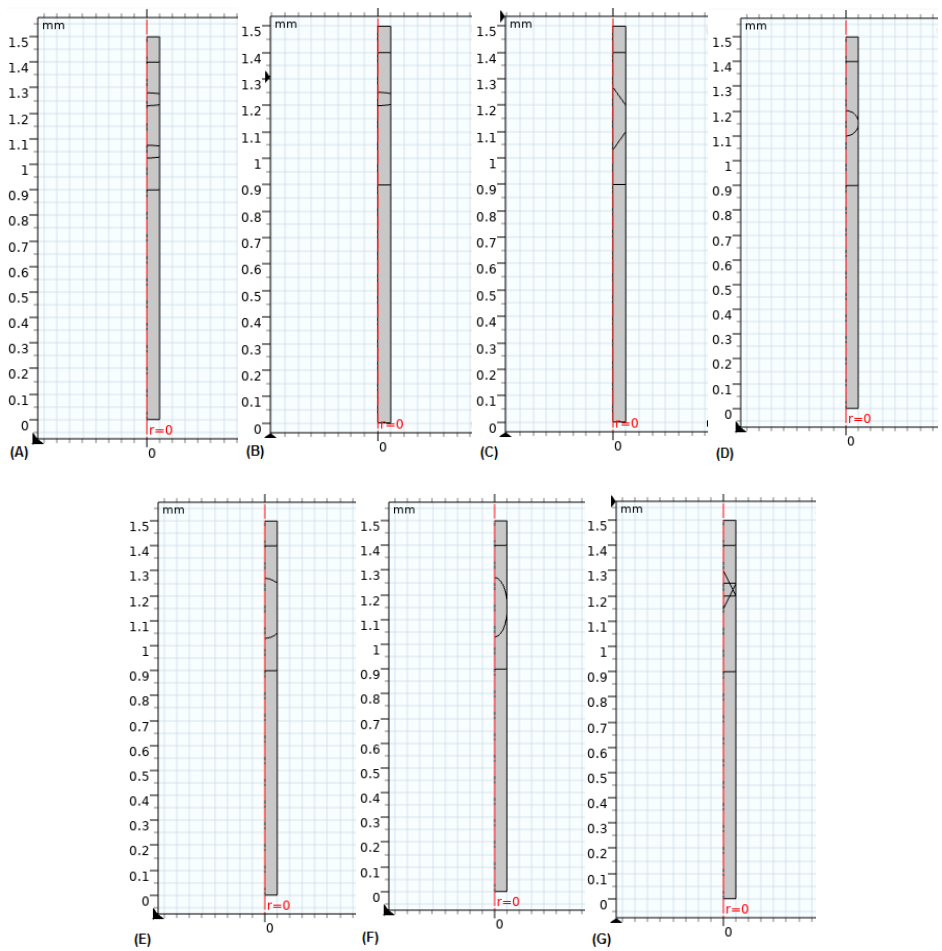

Figure 2: Axisymmetric model for A) Cylinder, B) Disk, C) Multiply Twinned, D) Sphere, E) Rod, F) Oval and G) Star geometrie

3. Results and Discussion

At the beginning of the 0 s, the water-drop is fixed at the upper part of the capillary tube and after the droplet is released it is moved to the bottom of the capillary tube it is accelerated at a constant speed before getting in touch with the permeable membrane. The drug is dispersed in water with a diffusion coefficient = 5×10-9 m2/s. The final concentration of the drug is obtained inside the drop when its surface is exposed to the membrane with a velocity between 0.1 and 1 mm / s.

The color contrast in the droplet represents the drug concentration, the blue color represents the zero or lowest concentration, while red color represents the highest concentration. As shown in (Figure 3) and by comparing the shape effect on the drug concentration, it's clear that the twinned shape has the highest concentration as there is no blue color appeared and the drug at the middle is higher than at the top and bottom of the twinned droplet. The next shape with good concentration was the disk as the drug concentration represented about 90% of the total shape. The cylinder droplet concentrates the drug at the middle and bottom as the red and orange colors represented about 70% of the total shape.

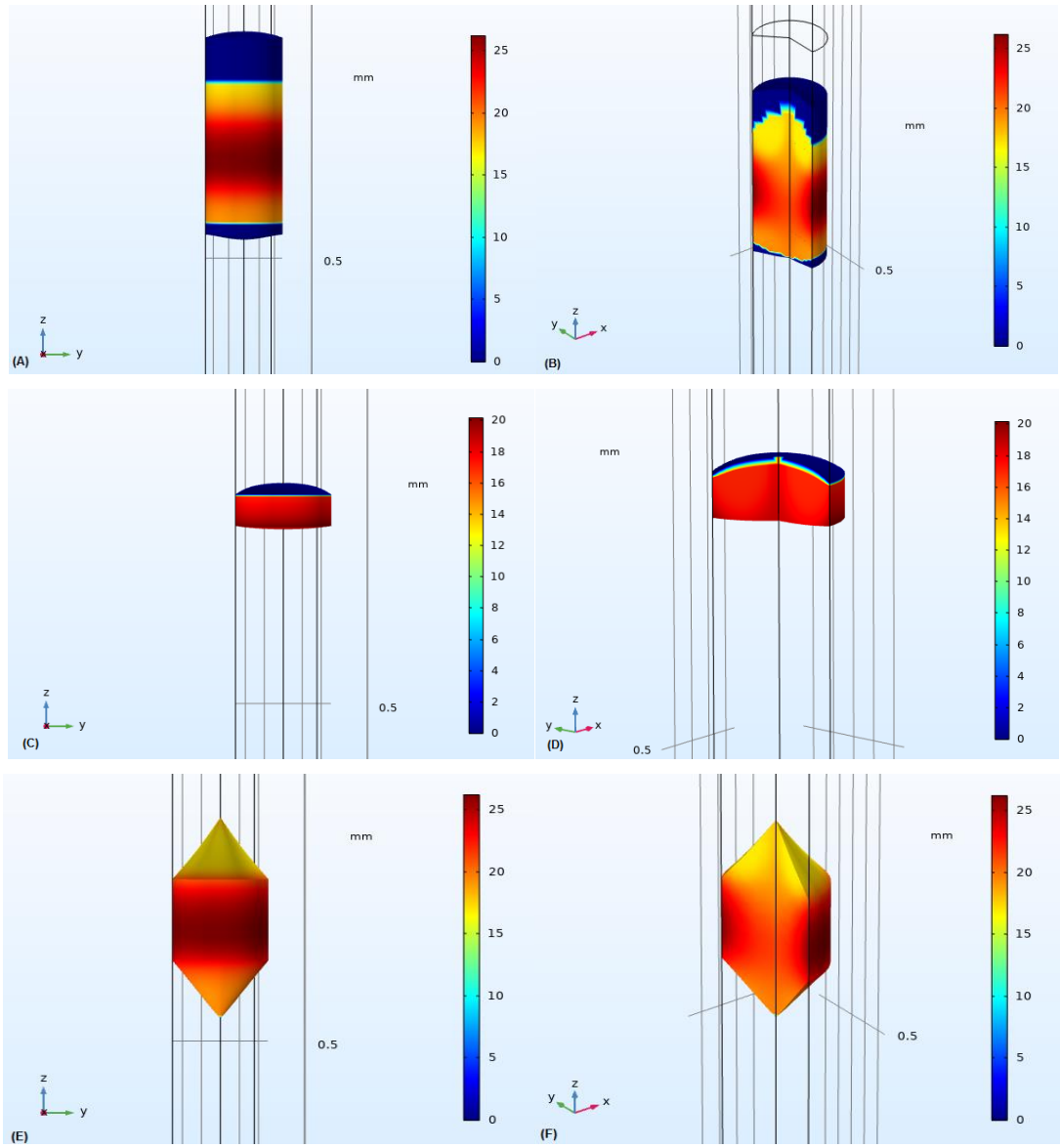

Figure 3: The drug concentration distribution in the droplet with 0.25 mm/s speed as it travels across the permeable membrane edge. (A, B) Cylinder (C, D) Disk (E, F) Twinned geometries in z-y axis and 3d domain respectively.

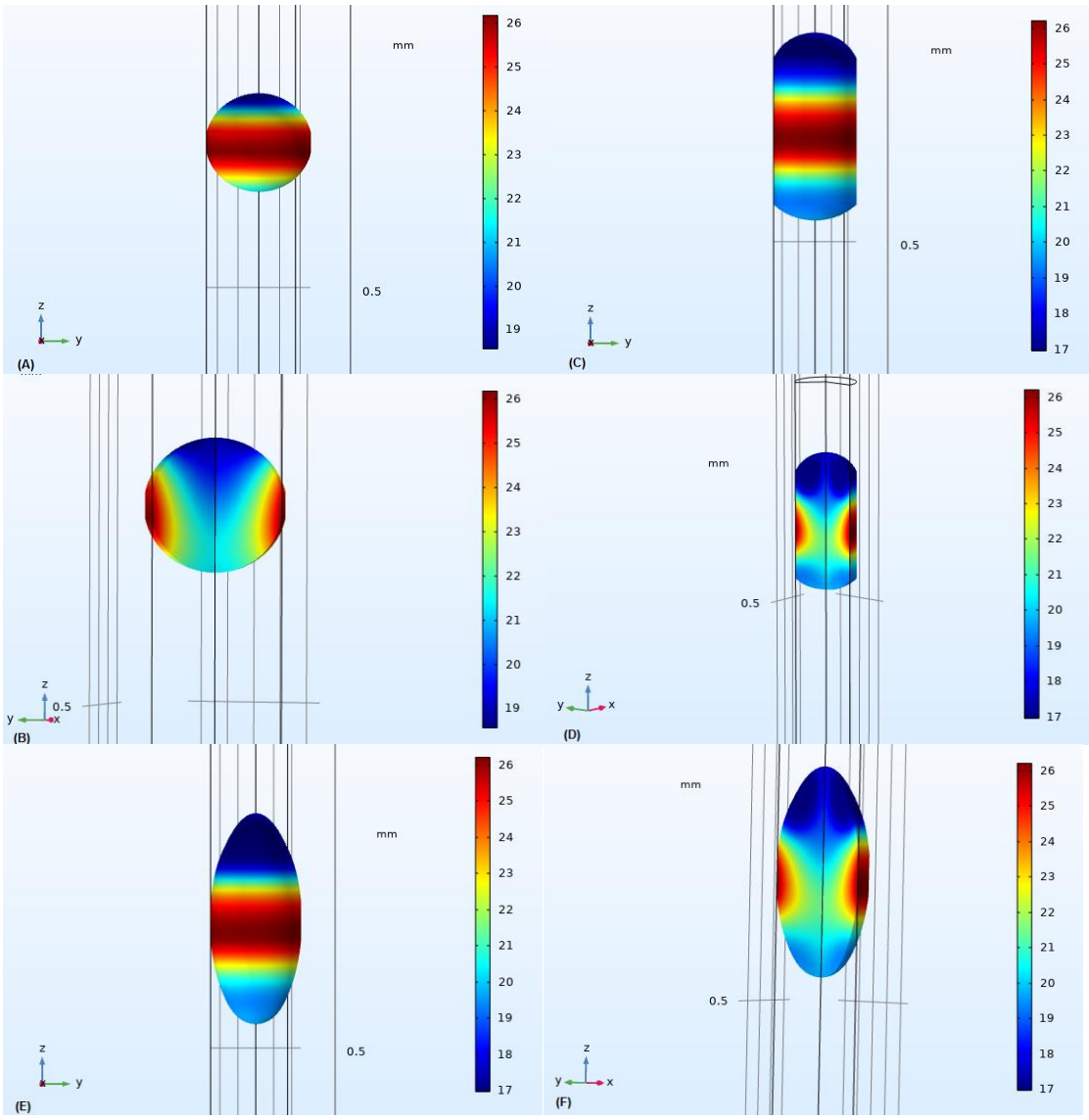

Figure 4: The drug concentration distribution in the droplet with 0.25 mm/s speed as it travels across the permeable membrane edge. (A, B) Sphere (C, D) Rod (E, F) Oval geometries in z-y axis and 3d domain respectively.

The drug delivery carriers became one of the important applications in treating various diseases type and this application will increase over the upcoming years. So, the design and shape of the carriers contribute to the delivery and diffusion of the drug to the desired place in a specific time. In Figure 4 the drug concentration for the sphere, rod, and oval shapes is restricted in the middle of the carrier but when the shape becomes small with curved edges such as the sphere the drug is restricted in about 90% of the total shape. As seen in (Figure 5) in the star shape of the drug concentration limited in the star core of the red color. While the five-pointed star with blue color does not contain any drug inside it and this type of drug carriers may suitable for the medicine that doesn't need an immediate release when contacting with water.

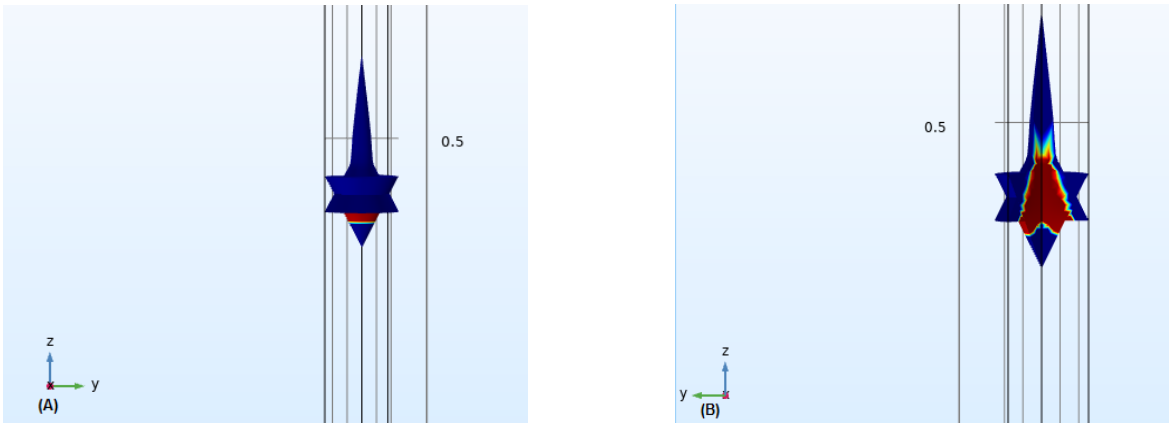

Figure 5: The drug concentration distribution in the droplet with 0.25 mm/s speed as it travels across the permeable membrane edge for the star shape (A, B).

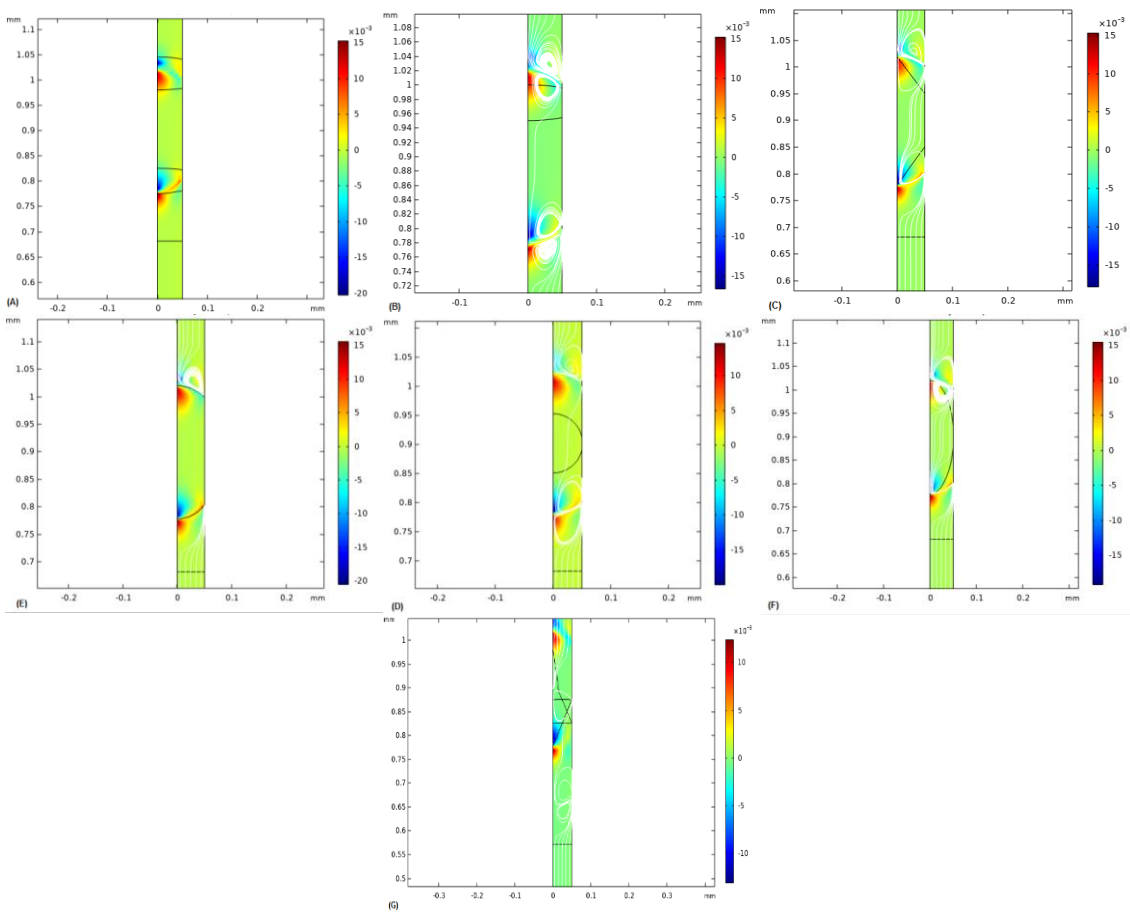

Figure 6: The velocity flow around the droplet with 0.25 mm/s as it travels across the edge of the permeable membrane. A) Cylinder, B) Disk, C) Multiply Twinned, D) Sphere, E) Rod, F) Oval and G) Star geometries.

Figure 6 shows the drop velocity profile for all shapes (cylinder, disk, multiply twinned, sphere, rod, oval and star) at 1.5 seconds in simulation. We examined the flow velocity of the flow field surrounding the drop of water as it passes through the permeable membrane which moves at 0.25 mm/s and the concentration of the droplet as the drug spreads in the water. However, the flow must re-distribute itself from the Poiseuille flow profile and away from the droplet surface until it reaches a constant velocity flow.

To demonstrate, the constant velocity across the capillaries causes a large redistribution of the flow field, that is why the flow pattern around the interface is complex. As seen in (Figure 6) at both z = 1 and 8 mm the change in the contact angle is evident between the edge of the capillaries and the droplet surface when it passes through it. The velocity profile corresponds to the Poiseuille flow, where the vortices and nonuniformities are present. Note that, the steady Hagen-Poiseuille Flow is a physical law that demonstrates and measures the pressure drop in a Newtonian liquid so that it is not compressible in a laminar flow that flows through a long cylindrical tube of a fixed cross-section [19].

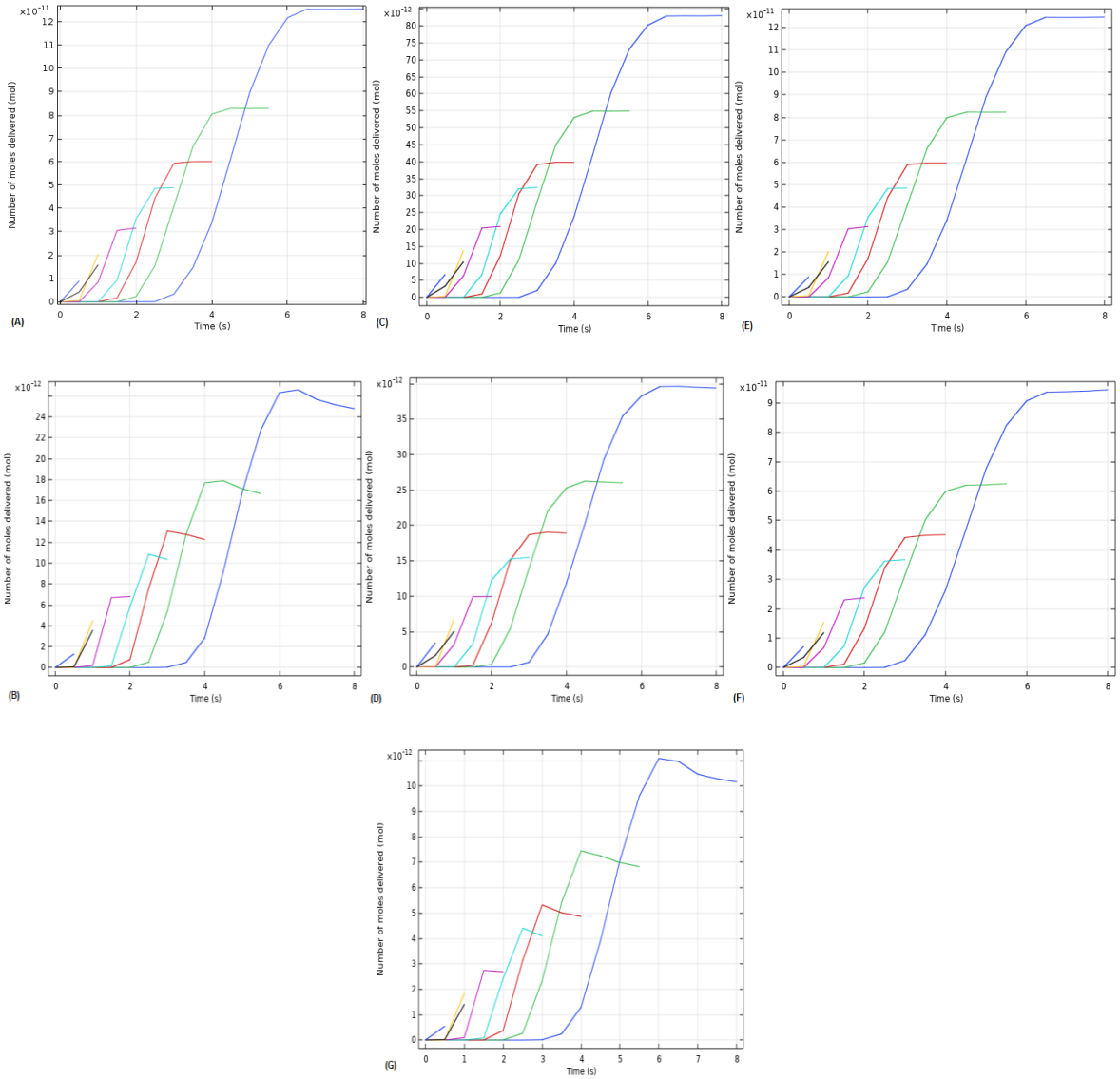

Figure 7: Total drug dose and the concentration profile in the droplet as a function of time when moving at 0.1 mm/s. A) Cylinder, B) Disk, C) Multiply Twinned, D) Sphere, E) Rod, F) Oval and G) Star geometries.

The drug concentration profile and the total amount that diffused inside the droplet for all mentioned shapes previously were analyzed as a function of time when the droplet crossing at 0.1 mm/s.

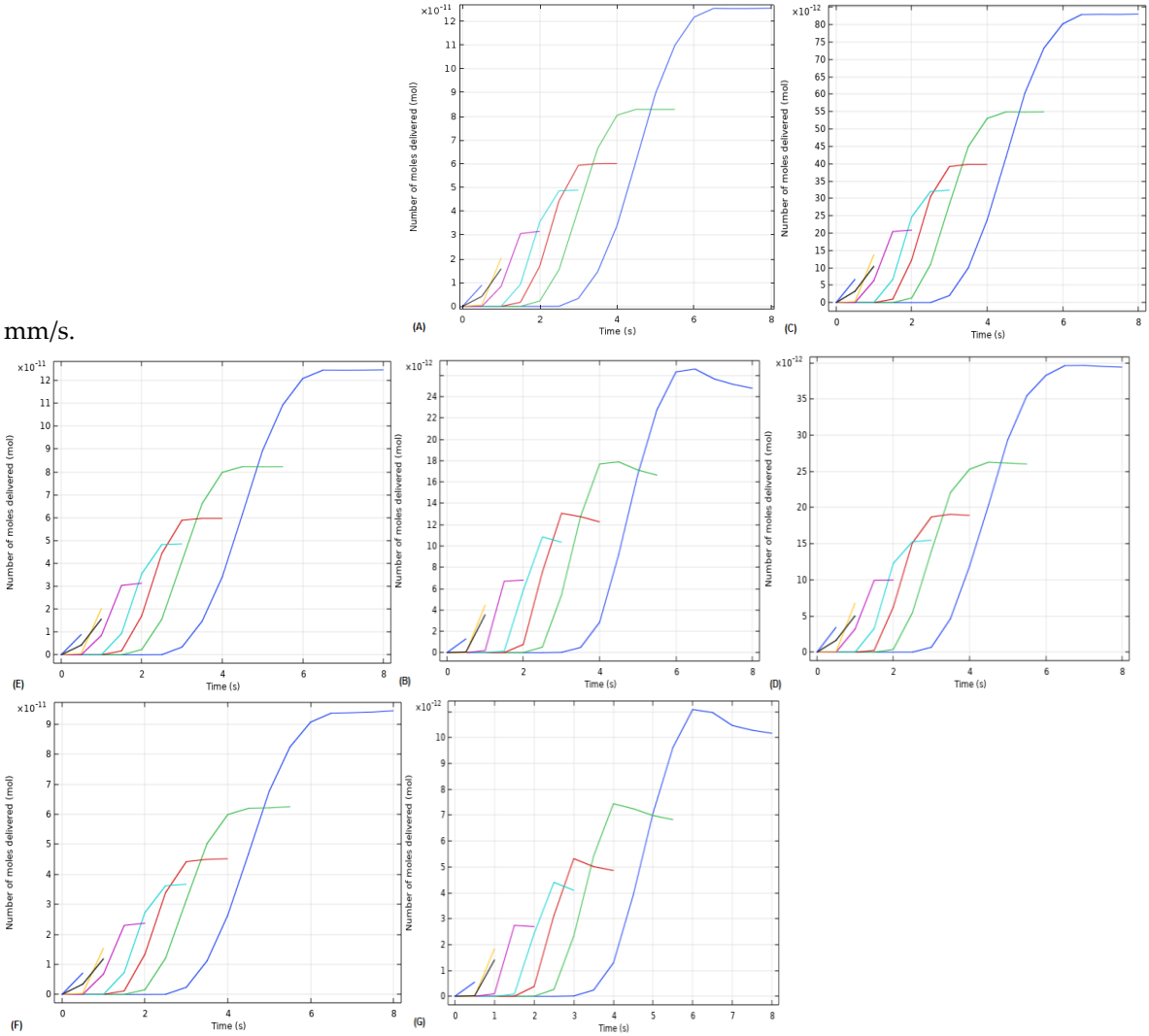

Figure 7 shows that the concentration of the drug increases continuously between 3 and 6 seconds, as it increases in the form of the letter "S", as the amount of the dissolved drug increases and the surface of the drop is taken to the capillary membrane and the curve in blue represents the total amount of the drug. When comparing the number of moles delivered in (cylinder, disk, multiply twinned, sphere, rod, oval and star) geometries we found it 12.89×10^{-11}, 25×10^{-12}, 80.50×10^{-12}, 36×10^{-12}, 12.50×10^{-11}, 9.50×10^{-11}, and 11×10^{-12} respectively. So, it is clear that the multiply twinned has the greatest amount of moles with 80.50×10^{-12} (mol) which means it the best shape for drug delivery carriers among other shapes.

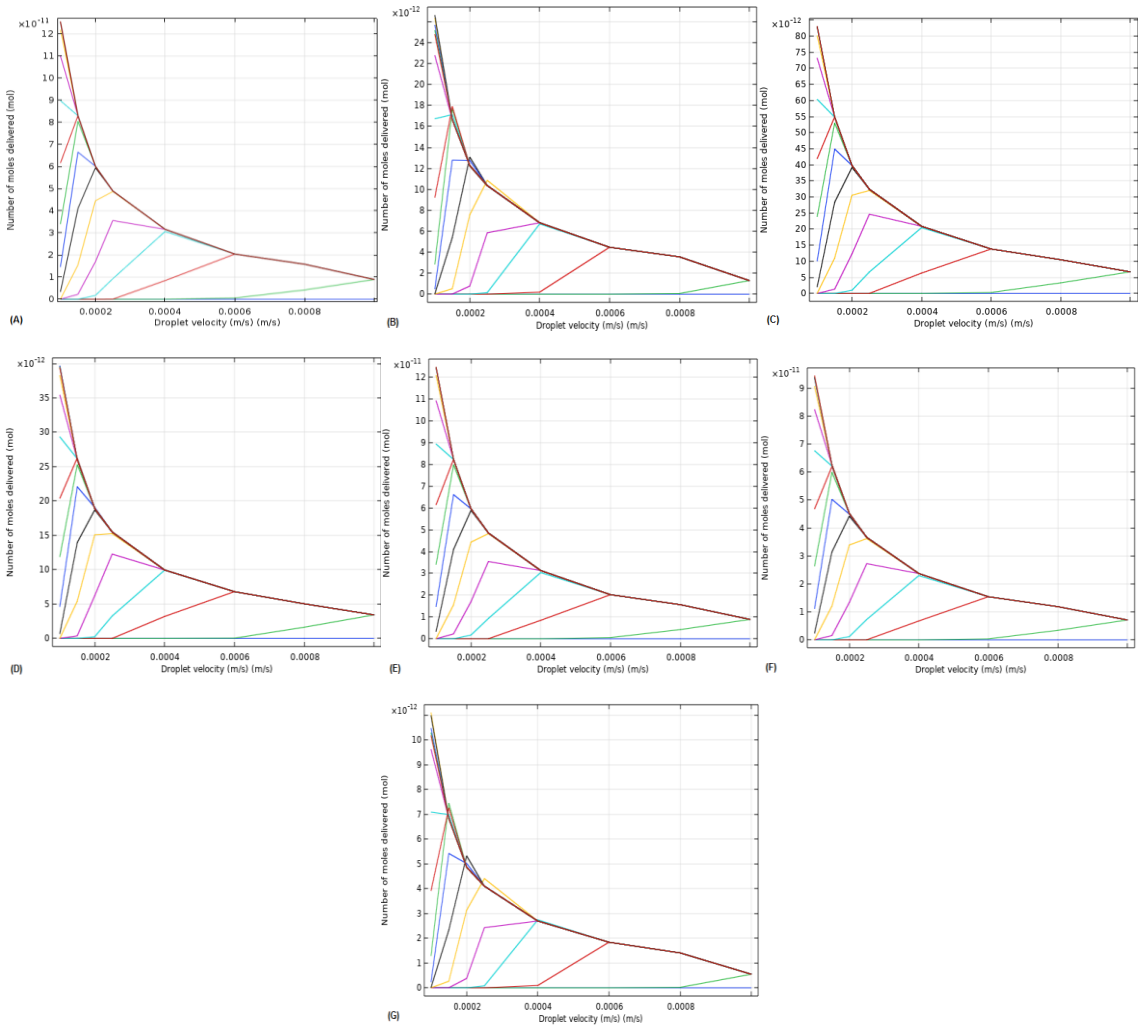

Figure 8: The number of delivered moles and the velocity of the droplet. A) Cylinder, B) Disk, C) Multiply Twinned, D) Sphere, E) Rod, F) Oval and G) Star geometries.

Through simulation, it is easy to manage the concentration of the required drug dose inside both the droplet and the body, where it can be controlled and find both optimum speed and time. By changing the full time, the drug remains inside the membrane, the amount of drug spread in the drop can be changed, thereby achieving optimal compliance with the drug as the system that we simulated can be described as accurate and enables the exact dose to be determined, reaching picomole. As shown in (Figure 8) which explains the relationship between the total number of moles delivered in the droplet and its speed, which have been proven to be inversely proportional. The more moles that are delivered, the lower the speed of the drop. The number of delivered moles and the speed of the droplet were listed in (Table 3) for cylinder, disk, multiply twinned, sphere, rod, oval and star) geometries.

As illustrated in (Table 3) the number of delivered moles decayed as the velocity of the droplet increased and in the 0 (m/s) for all shapes was the maximum amount of moles with the greatest amount for the Multiply Twinned with 85 x10^{-12} and the lowest amount for the oval with 9.5 x10^{-11}.

Table 3: The number of delivered moles and the velocity of the droplet.

	Dreg Delivery Shape						
Droplet Velocity (m/s)	**Cylinder (x10-11)**	**Disk (x10-12)**	**Multiply Twinned (x10-12)**	**Sphere (x10-12)**	**Rod (x10-11)**	**Oval (x10-11)**	**Star (x10-12)**

0	**12.9**	**25.5**	**85**	**40**	**12.5**	**9.5**	**11**
0.0002	**6**	**12.1**	**40**	**19**	**6**	**4.5**	**5**
0.0004	**3.1**	**7**	**20**	**10**	**3.1**	**2.4**	**2.8**
0.0006	**2**	**4.1**	**14**	**8**	**2**	**1.5**	**1.9**
0.0008	**1.5**	**3.9**	**10**	**5**	**1.5**	**1.1**	**1.5**
0.001	**1**	**1.8**	**6**	**4**	**0.9**	**0.8**	**0.5**

Overall, these results go beyond previous reports, showing that the morphology and design of the nanoparticles as drug delivery systems play a big role in drug loading, the number of delivered moles, soluble drug concentration and the drug release process.

4. Conclusions

One of the most important practices required to administrate drugs locally and not systematically depends mainly on the good manufacturing of pharmaceutical products. For this reason, drug delivery systems came to address the problems and shortages of traditional methods, which contributed significantly to reducing side effects and drug toxicity while increasing and enhancing the effectiveness of treatment. This study adds and provides a clearer understanding of the effect of the geometrical shapes of nanoparticles for drug delivery and the drug concentration, which effectively contributes to the pre-selection of the drug delivery engineering according to the required concentration.

Furthermore, with the development of technology, there is an increase in the simulation programs like the COMSOL Multiphysics software, which have contributed to simulating and modeling many systems in various fields, especially in the medical field, such as modeling and simulating the way medication is delivered and how our bodies respond to it and correspondingly these programs are able to revolutionize the world of medicine, which reduces the cost, effort and shortages of laboratories to conduct experiments.

Finally, as there is a growing need to find optimal and new ways to deliver the drug safely and effectively, further research is needed on ways to deliver the targeted drug together and with the advances in technology which enable more research conductions possibilities and facilitate methods of studying how the disease developed and the ways in which the disease responds to the drug.

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