A Multiphysics Model for Microparticle Transport through Hypodermic Needles

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Introduction

Emergence of microencapsulated-based drug delivery systems in recent years has paved the way for controlled delivery of a wide range of therapeutic agents. A controlled release profile can not only improve the therapeutic efficacy, but also reduce toxicity. The prevalent technique for injection of microencapsulated pharmaceutical products into the body is through hypodermic needles. However, conventional design of commercial syringes/needles might not be optimized for delivery of microparticle solutions. Injection of highly concentrated microparticle solutions could be difficult as particles could be entrapped in the syringe or needle (Figure 1) and not be fully delivered to the patient. This could hamper the effectiveness of the therapy and increase costs associated with drug waste and elevate risk of needle re-use.

Figure 1. An example of unsuccessful transfer of particles (white) during injection with a hypodermic needle

To better understand different design parameters affecting efficiency of syringes in delivery of microparticles, we have developed a multiphysics model using COMSOL Multiphysics ® V 5.3. The model couples two modules, namely, computational fluid dynamics (CFD), and particle tracing. The first module models flow of the injection solution through the syringe, also provides velocity field and pressure distribution for subsequent particle transport simulations. Next, particle tracing is considered to model transport of polymeric microparticles throughout syringe-needle. To quantify the efficacy of each design, we have quantified the number of microparticles successfully reached to the needle outlet, as the metric for delivery efficacy. Effect of a wide range of design parameters such as length and diameter of the syringe, density and size of the particles as well as overall pattern of the syringe tip are studied. Results of this study can aid in design and manufacturing of syringe/needle systems optimized for delivery of microparticles and injectable biomaterials.

Method

A 2D parametric model depicted in Figure 2 was considered as a model medical syringe attached to a hypodermic needle. Effect of different geometrical parameters were then evaluated about efficacy in delivery of microparticles to the needle outlet. The considered boundary conditions were based on a pressure-driven Poiseuille flow to mimic the pressure generated at plunger through the course of injection. Inlet velocity of 10 mm/s was considered in addition to atmospheric pressure at the needle outlet. Injection solution was considered as a model Newtonian fluid with density of 1000 kg/m3 and viscosity of 0.01 Pa.s. Flow of the injection solution was considered steady-state and stationary and the resulting velocity field and pressure distribution were incorporated into the particle tracing as the initial condition. Simulations lasted to the time it would take the plunger to take a full course to displace through the entire barrel length (L in Figure 2). Two forces, including viscous drag forces and gravity were considered to model transport of particles. Syringe wall was assumed sticky, while the needle outlet had freezing properties. The number of particles frozen at the needle outlet was calculated as the number of particles transferred successfully at the end of each simulation. The barrel was initially loaded with 5000 spherical particles with density of 2200 Kg/m^3 distributed uniformly throughout the distance L. The mesh was considered physically-controlled with medium size as shown in Figure 2.

Excerpt from the Proceedings of the 2019 COMSOL Conference in Boston

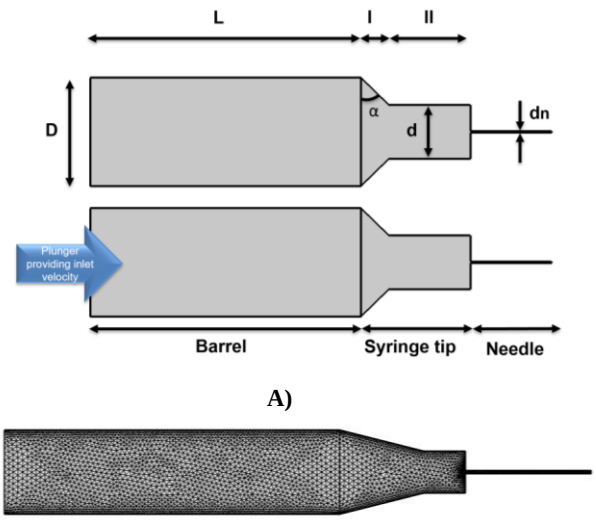


Figure 2. A) Parametric model of a medical syringe attached to a hypodermic needle used in the current study. B) Meshed geometry of a model syringe-needle used in simulations

Governing Equations

Fluid velocity filed and pressure distribution was obtained using CFD module based on Navier-Stokes and continuity equations as [1]:

$$\rho\frac{\partial \bar{u}}{\partial t} = -\bar{\nabla}p + \mu\bar{\nabla}^2 u + \rho\bar{g} \quad (1)$$

$$\rho \cdot \nabla\bar{u} = 0 \quad (2)$$

where ρ is fluid density, ū is fluid velocity vector, μ is fluid viscosity, t represents time, g refers to gravitational acceleration, and p is pressure. After, obtaining the velocity and pressure throughout the syringe under a Newtonian, Laminar, stationary flow, particle tracing module is employed. The following equations were used to model transport of particles in the syringe:

$$\frac{d(m_p\bar{v})}{dt} = \bar{F}_D + \bar{F}_G + \bar{F}_{Ext} \quad (3)$$

where m_p is the mass, and $\bar{v}$ is the velocity vector of a particle, respectively. The right-hand side in Eq. 3 corresponds to the total forces exerted on a solid particle, including drag force, gravity, and external forces, denoted by $\bar{F}_D$, $\bar{F}_G$, and $\bar{F}_{Ext}$, respectively. The drag force is calculated as:

$$\bar{F}_D = (\frac{1}{T_p})m_p(\bar{u} - \bar{v}) \quad (4)$$

In which, T_p represents particle velocity response time. No external forces were considered in this study and the drag force was calculated based on Stokes equation.

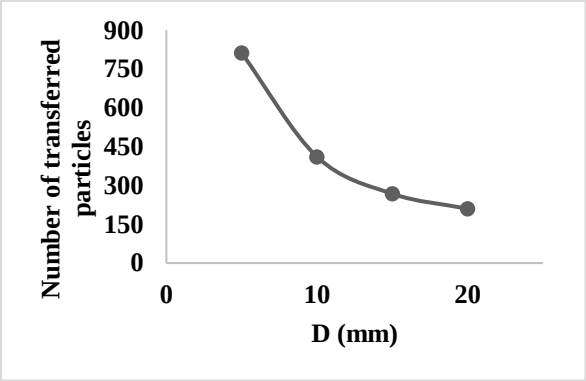
Simulation Results

In the following simulations, only one geometrical parameter changed while the other were set based on a default design provided in Table 1.

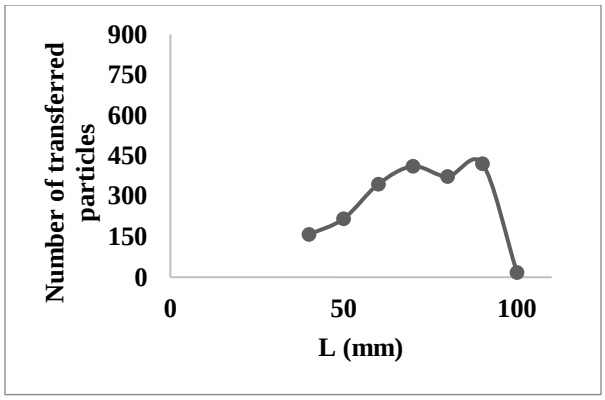
Table 1: Values used in the default syringe-needle design

Parameter	Value
D	10 mm
d	5 mm
d_n	0.4 mm
L	70 mm
l	5 mm
ll	5 mm
α	30°
Initial number of particles in the syringe	5000
Particle density	2200 kg/m^3
Particle diameter	10 μm

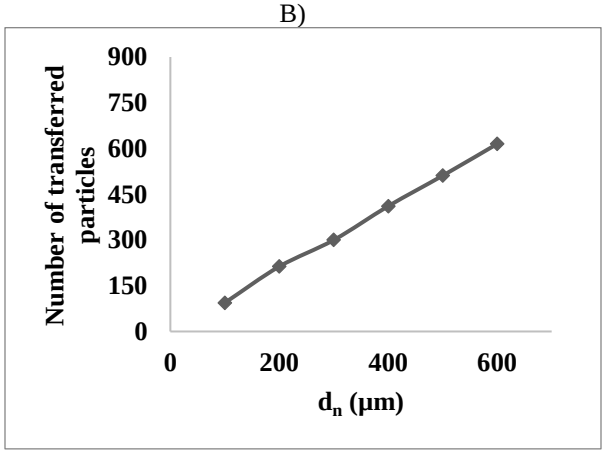
In this regard, Figure 3 demonstrates the effect of various geometrical parameters on the number of particles transported successfully to the needle outlet.



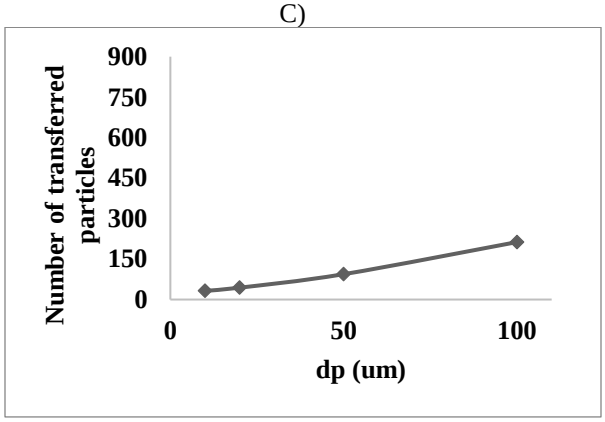
A)


Number of transferred particles
900
750
600
450
300
150
0
0
50
100
L (mm)

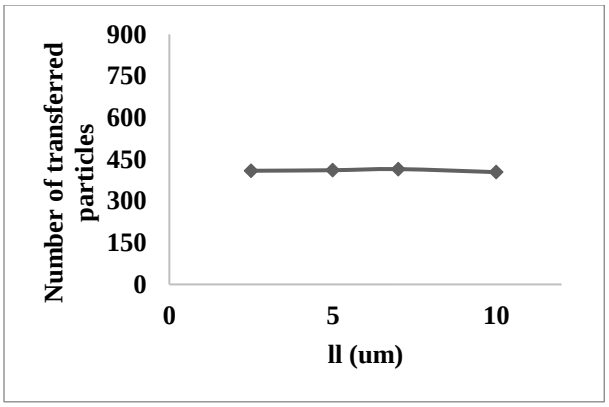
B)


Number of transferred particles
900
750
600
450
300
150
0
0
200
400
600
dn (µm)

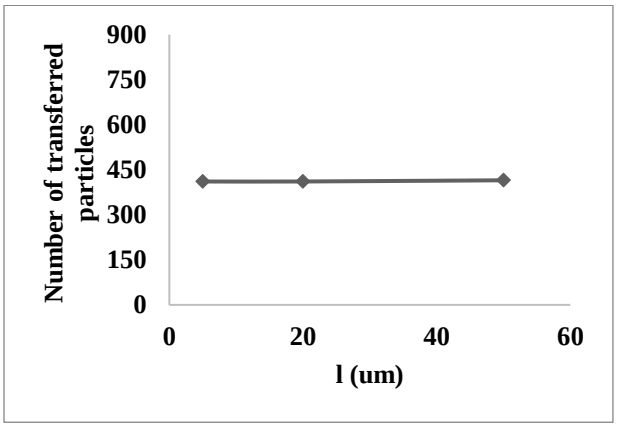
C)


Number of transferred particles
900
750
600
450
300
150
0
0
50
100
dp (um)

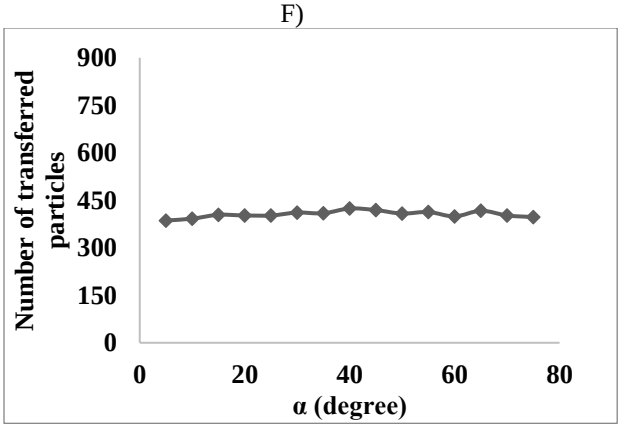
D)


Number of transferred particles
900
750
600
450
300
150
0
0
5
10
ll (um)

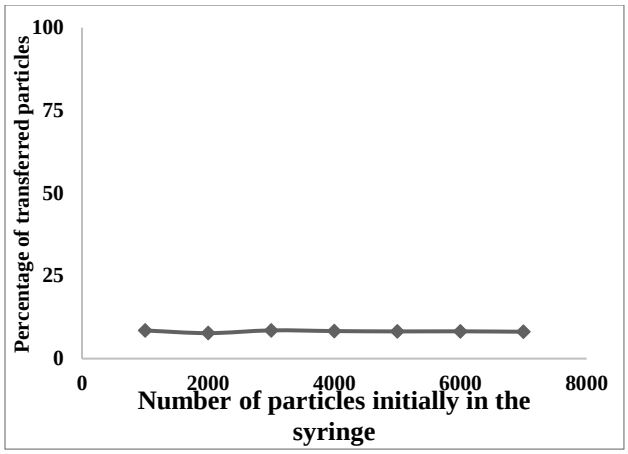
E)


Number of transferred particles
900
750
600
450
300
150
0
0
20
40
60
l (um)

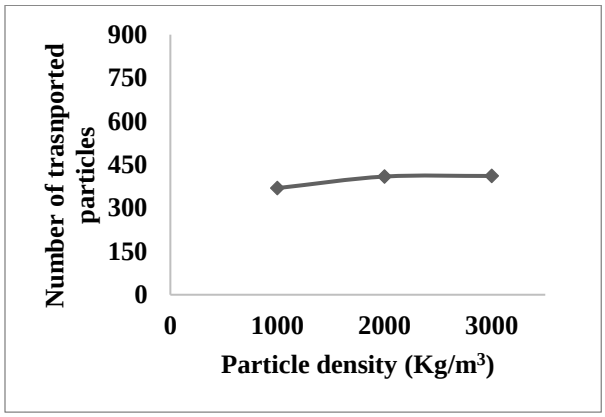
F)


Number of transferred particles
900
750
600
450
300
150
0
0
20
40
60
80
α (degree)

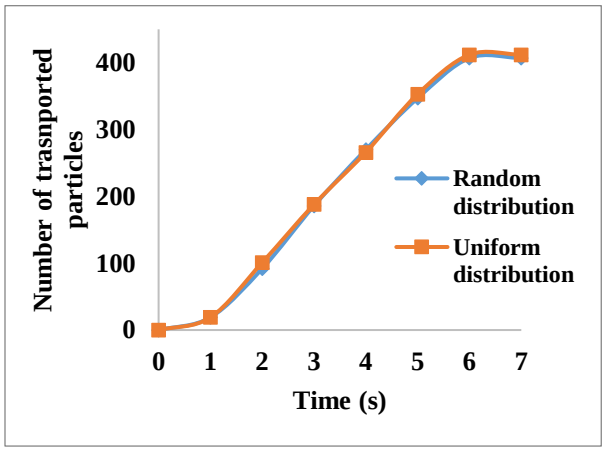
G)



H)



I)

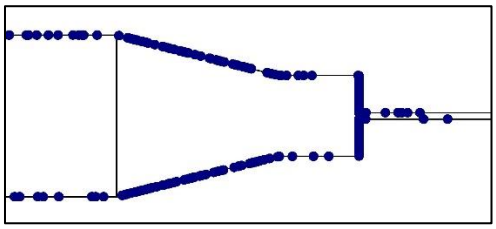


J)

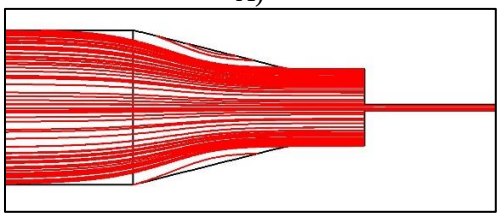
Figure 3. A-I) Effect of different parameters on the number of particles successfully transported to the needle outlet equivalent to particles that could be delivered to the patient during injection. J) comparison between transport of delivered particles either distributed randomly or uniformly in the syringe.

As observed, only a certain fraction (approximately between 2-20%) was transported successfully to the needle outlet. Not all the parameters were found equally important. For example, parameter α, l, and ll did not significantly impact transport of particles. Conversely, needle diameter, and particle size appeared as two major factors. The number of particles initially loaded in the syringe also did not have a major effect. This could be because of highly laminar nature of the flow. Two crucial design parameters were found to be diameter and length of the syringe. It was observed that only a specific range of L (70-80 mm) could provide optimum particle delivery. Increase in particle delivery as a result of decreased D could be attributed to higher velocity magnitudes under the same inlet flow as a result of decreased syringe diameter. Thus, potentially providing more drag force on the particles. Additionally, a linear relationship was observed between needle size and the number of transported particles. Increasing particle size also significantly decreased particle delivery. Particle density was not found as a significant factor within the range studied. In terms of initial distribution of particles, both uniformly distributed particles, and randomly distributed particles had a similar trend of transport toward the needle outlet shown in Figure 2-J.

These results suggest particle size, length and diameter of the syringe, and needle size could be four major components in design of syringe-needle systems. Furthermore, as depicted in Figure 4, most of the particles accumulated in the walls in the transition area from syringe to needle considered as sticky walls in this study. Most notably, they accumulated in the areas with diverging streamlines (depicted in Fig. 4) with elevated pressure and lower velocity magnitude. This potentially suggests syringe designs that better mimic the pattern of flow streamlines could provide higher particle delivery.



A)



B)

Figure 4. A) Accumulation of particles on the sticky walls, B) pattern of streamlines on the corresponding design in A.

Discussion

This numerical study highlights the power of COMSOL Multiphyscis ® in preliminary design and optimization of biomedical systems. Although finite element approaches have been widely used in design optimization in micro- and macroscales [2-6], more studies are required to address optimization of biomedical systems that directly interact with human body such as engineered drug delivery scaffolds, microneedles, or hypodermic needles [7-8]. Hypodermic needles are widely used over the world, and as such, optimization with the aim of improving particle delivery could be of high importance. In this study, unique feature of COMOSL Multiphysics ® enabled coupling of two different physics, namely, CFD, and particle transport. Results of this study pointed out that not all the design parameters in medical syringes are equivalently important and certain parameters should be taken more seriously such as length and diameter of the syringe. Also designs that could minimize stagnation area in transition region from syringe to needle could potentially provide better delivery performance. Using these simulations, we also demonstrated that conventional syringe-needle systems are not optimized for delivery of microencapsulated therapeutic products. This could highlight the importance of designing customized needles for delivery of large injectable scaffolds and microparticles.

Conclusions

This study demonstrated a novel application of COMOSL Multiphsyics ® for modeling transport of microparticles in a medical syringe attached to a hypodermic needle. We investigated the effect of several parameters related to geometry of the system and particle properties. Certain parameters were found more dominant such as size of the particles and the needle. Future studies could be directed toward experimental studies and more complicated two-phase, or shear-thinning solutions. Results of this study could have applications in initial steps of design and manufacturing of novel medical syringes tailor-made for advanced drug delivery purposes based on microencapsulation.

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Acknowledgements

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