Simulation of dissolution of matter and flow in restricted geometries

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Abstract

In this work a finite element model (FEM) characterizing the dissolution behavior of a solid state form in a flow cell geometry, is presented. The FEM method facilitates the possibility of simulating the spatially resolved concentrations of dissolved drug within the flow cell geometry. Furthermore, this method provides the possibility of calculating the dissolution rate by mathematical evaluation of the mass transport flux over the solid-solution interface. Verification of the FEM method can be performed experimentally by collecting and analyzing the effluent from the flow cell. Such an approach enables the comparison of the experimentally obtained dissolution rate with the FEM calculated dissolution rate.

Introduction

Numerical analysis has been utilized for several decades[1] for solving problems where conventional analytical equations fail due to e.g. complex geometry of the dissolution vessel[2]. Furthermore, numerical analysis enables the visualization of the formed concentration gradients that persist during dissolution testing. Numerical analysis utilizing finite element modeling (FEM) can thus aid in elucidating the dissolution process that is occurring in highly complex geometries.

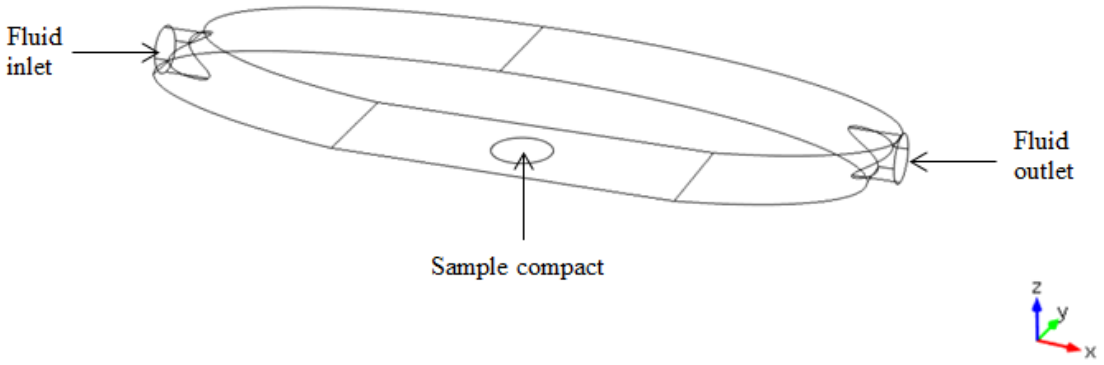
Experimental section

The FEM method was implemented using Comsol Multiphysics version 4.2a on a conventional Hewlett Packard ProBook 6550b laptop with a 2.4 GHz CPU processor and 4 GB RAM running on a 64-bit operating system.

Results and discussion

The flow cell consists of a fluid inlet, a fluid outlet, a sample compact and wall boundaries (Figure 1,a). A mixed mesh was applied to the flow cell geometry with 511.275 mesh elements with the highest mesh density closer to the sample compact (Figure 1, b).

a)



b)

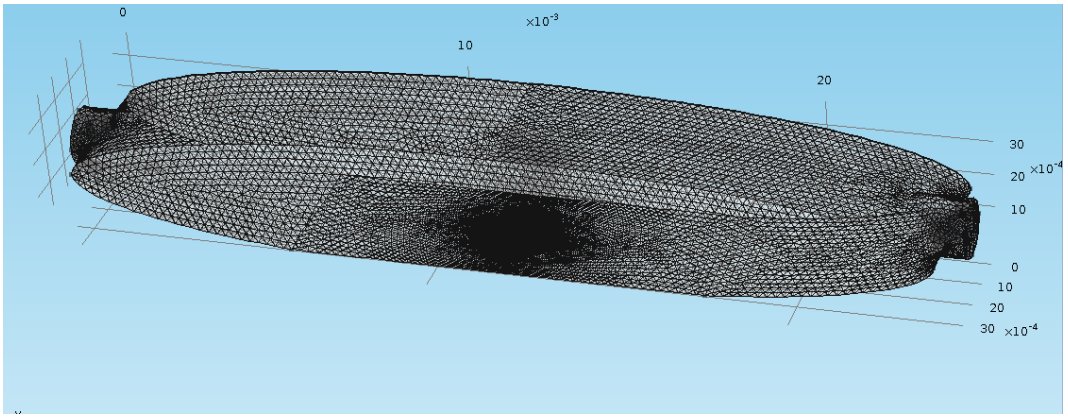


Figure 1 (a) Schematic representation of the flow cell. (b) Meshed inner geometry of the flow cell. The mesh density is increased at the sample compact boundary.

The flow profile within the cell was solved using the FEM method (Figure 2). The maximum flow velocity in each cross section of the flow cell is, as expected, inversely proportional to the cross sectional area and situated in the center of the cross section.

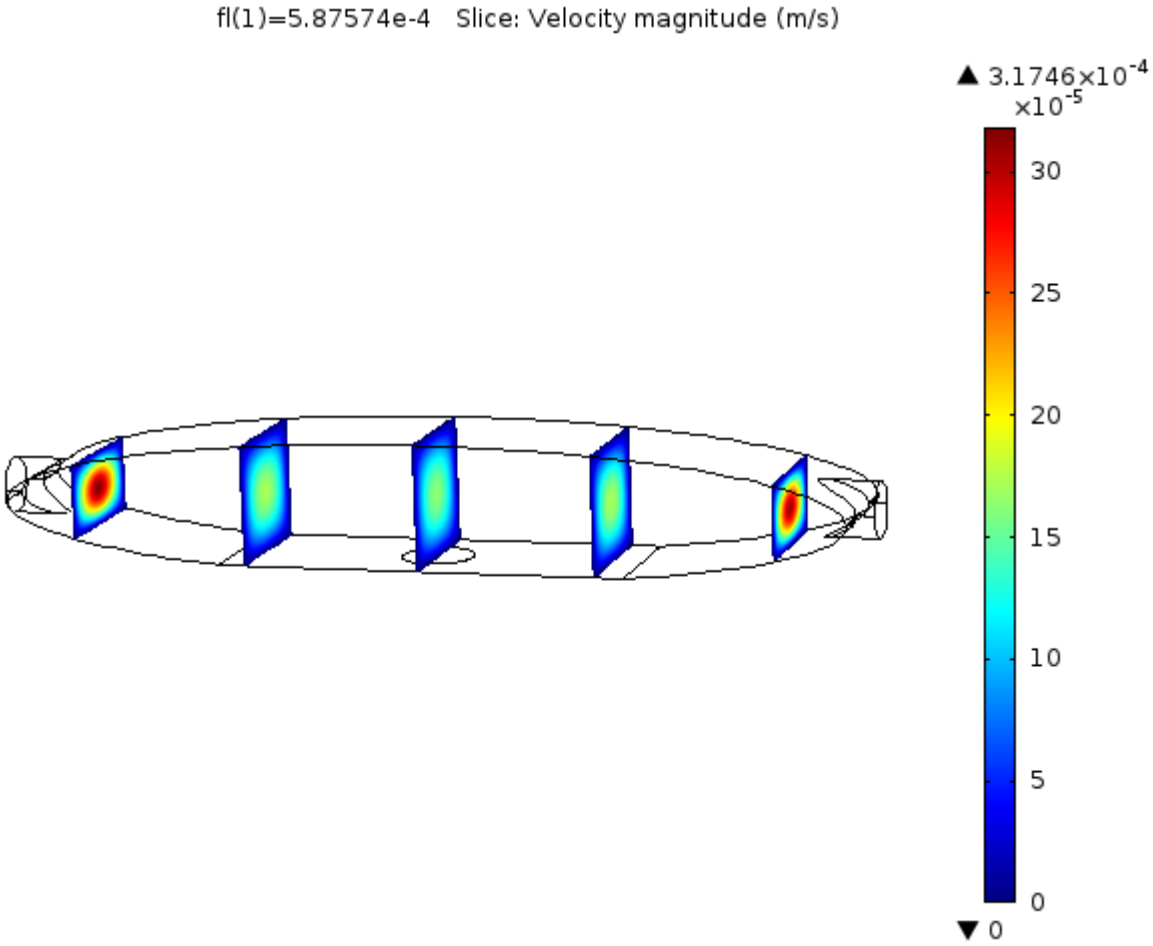


Figure 2. Simulation of flow profile within the flow cell.

Dissolution was simulated by coupling of the laminar flow problem and the mass transport problem. The following boundary conditions were utilized on the geometry (Figure 1, a):

Fluid inlet	$u = u_0$, $c = 0$
Fluid outlet	$p_0 = 0$
Sample boundary	$c = c_{sat}$

In which u_0 is the flow velocity at the inlet boundary (m/s), u is the flow velocity at an arbitrary point within the geometry, c is the concentration of solute (mol/m^3) within the bulk, p_0 is the pressure at the fluid outlet (Pa), and c_{sat} is the saturation concentration. The FEM is solving a partial differential equation for the flow problem (1) and thus obtains an approximate solution for the flow profile. This flow profile is subsequently coupled to the mass balance equation (2).

$$p\nabla \cdot u = 0 \qquad (1)$$

$$u \cdot \nabla c = \nabla \cdot (D \nabla c) \qquad (2)$$

In which p denotes the density (kg/m^3), u is the velocity (m/s), c is the concentration of solute (mol/m^3) and D is the diffusion coefficient (m^2/s).

The visualization of the solute concentration gradients within the flow cell can be obtained by the construction of an isosurface plot (Figure 3). The shape of the isosurface is dependent on the three input variables; the flow rate of the solvent, the solubility of the compound and the diffusion rate of the compound.

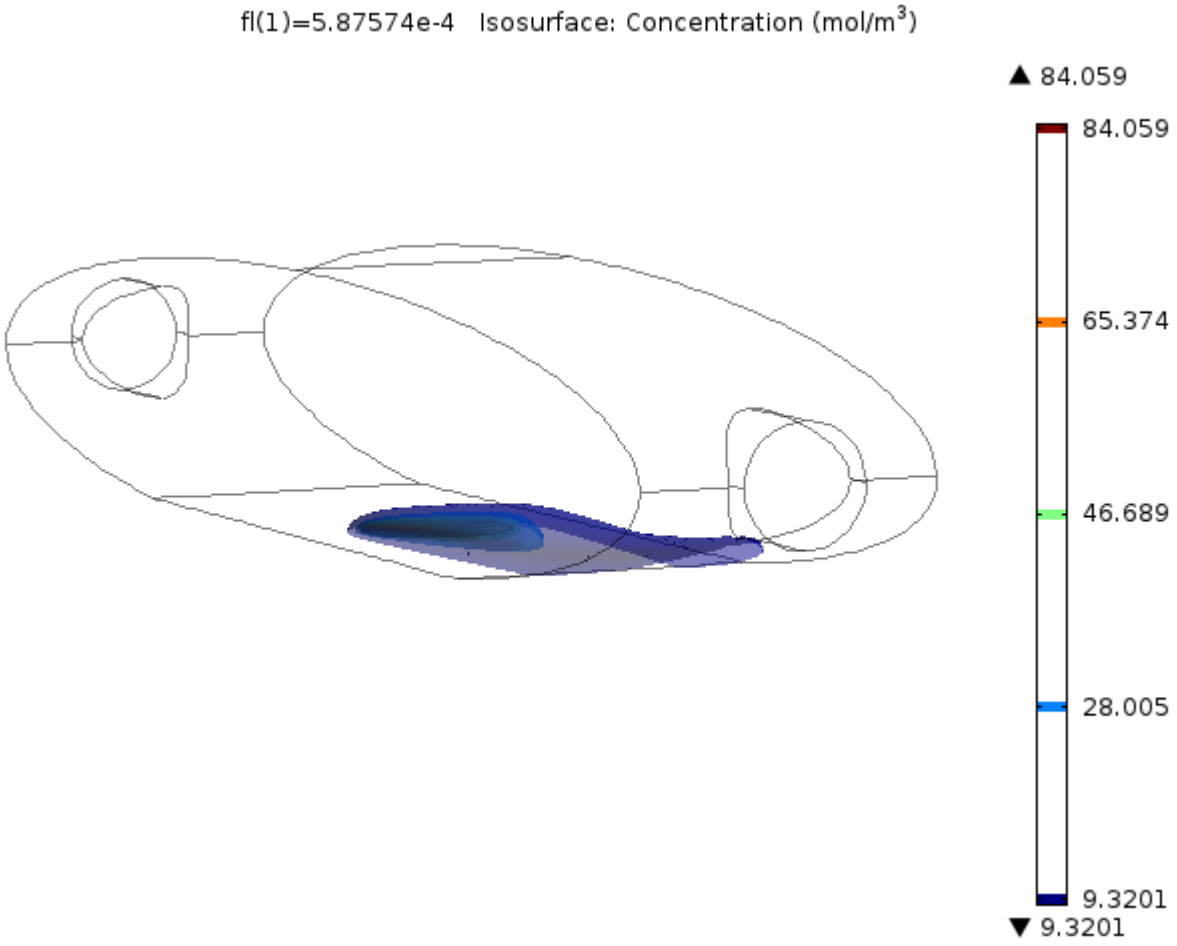


Figure 3. Isosurface of solute concentrations within the flow cell.

A direct comparison between the FEM simulation and the dissolution rate data obtained from effluent sampling was subsequently performed. The preliminary data indicate that the FEM simulation is capable of obtaining quite satisfactory approximations of the obtained experimental dissolution data from sampling of the effluent.

The FEM method has therefore been demonstrated to be capable of calculating the spatial concentration distributions and dissolution rates of a given compound with only the need for *a priori* knowledge of the flow rate, solubility of the compound and diffusion rate of the compound.

It is suggested that the model could be extended to more complex dissolution media, eg. micelle containing media. In this case the micellar diffusivity also has to be taken into account, as well as the compounds solubility in this media. Dissolution of more complex compounds exhibiting for instance solvent mediated recrystallization would also be possible to analyze using the FEM method. For such a recrystallizing compound it would be needed to know a priori the recrystallization kinetics and the solubility of the different solid state forms. A time dependent FEM method could subsequently be capable of calculating the dissolution rate of the recrystallizing compound over time.

Conclusion

The FEM approach facilitated the visualization of concentration gradients within the flow cell. Thus, the FEM method provides new possibilities for the investigation of dissolution processes in complex geometries and encompasses the capability to visualize various phenomena related to the dissolution mechanisms. This platform could in future also be suitable for studying more complex dissolution phenomena where micelles are present in the solvent phase. Future simulations supported by dissolution studies will also explore compounds that exhibit solvent mediated recrystallization.

References

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2. Kaunisto, E.; Nilsson, B.; Axelsson, A. Drug dissolution rate measurements - evaluation of the rotating disc method. *Pharmaceutical Development and Technology* **2009**, *14*, 400-408.