

Modelling and simulation of the hydrodynamics and mixing profiles in the human proximal colon using Discrete Multiphysics

M. Schütt^{a,*}, K. Stamatopoulos^a, M.J.H. Simmons^a, H.K. Batchelor^b, A. Alexiadis^a

^a School of Chemical Engineering, University of Birmingham, Birmingham, Edgbaston, Birmingham, B15 2TT United Kingdom

^b College of Medical and Dental Sciences, University of Birmingham, Birmingham, Edgbaston, Birmingham, B15 2TT United Kingdom

Abstract

The proximal part of the colon offers opportunities to prolong the absorption window following oral administration of a drug. In this work, we used computer simulations to understand how the hydrodynamics in the proximal colon might affect the release from dosage forms designed to target the colon. For this purpose, we developed and compared three different models: a completely-filled colon, a partially-filled colon and a partially-filled colon with a gaseous phase present (gas-liquid model).

The highest velocities of the liquid were found in the completely-filled model, which also shows the best mixing profile, defined by the distribution of tracking particles over time. No significant differences with regard to the mixing and velocity profiles were found between the partially-filled model and the gas-liquid model. The fastest transit time of an undissolved tablet was found in the completely-filled model. The velocities of the liquid in the gas-liquid model are slightly higher along the colon than in the partially-filled model. The filling level has an impact on the existing shear forces and shear rates, which are decisive factors in the development of new drugs and formulations.

Keywords

Mathematical modelling, Peristalsis, Smoothed Particle Hydrodynamics (SPH), Fluid dynamics, Large intestine, Colon, Proximal colon, Fluid-structure interactions, Drug delivery

* Corresponding author:
E-mail: mxs1275@bham.ac.uk (M. Schütt)

1. Introduction

Whilst a significant amount of research has already been carried out on drug delivery in the gastro intestinal (GI) tract (e.g. [1]), the colon has received less attention [2]. For colonic delivery, dosage forms generally target the ascending colon due to its less variable transit times (measured with radiotelemetry capsule), and higher volumes of less viscous fluids available compared to the transverse and descending parts of the colon [3],[4],[5].

Peristaltic muscle contractions in the colon causes motion of the intestinal content resulting in tangential and perpendicular forces that act as shear and normal stresses on the surface of a dosage form (e.g. tablet) [6]. Modified release dosage forms are formulated to be slowly eroding or swelling matrix systems where the rate of drug release is controlled by fluid ingress/erosion of the tablet thus the hydrodynamic environment will influence their rate of drug release [7],[8],[9].

The study of the fluid dynamics and fluid mechanics of the proximal colon, therefore, is paramount to understand the disintegration/erosion of dosage forms as well as the dissolution and diffusion of the released drug. In this regard, computational fluid dynamics has been proven as a valuable investigation tool (e.g. [10],[11],[12]) since it can achieve a level of detail that it is not possible by direct visualization of the actual human colon. However, with one exception [10], all computational studies performed so far (e.g. [11],[12]) refer to a colon completely filled with liquid, whereas, most of the time, the colon is only partially filled with liquid/solid material [13]. Some studies found a freely mobile liquid volume from 0 to 49 mL in the entire colon, whereby most of the free liquid was found in the ascending colon [14],[13]. Gases are also present in the colon due to swallowed air, blood gases diffusion through the intestinal membrane, and bacterial fermentation [15],[16],[17]. The volume of gases in the proximal colon can be significant: one study [18], for instance, measured about 90 % gas and 10 % liquid/solid material. However, to the best of our knowledge, so far no modelling work, has account for the presence of gasses in the colon.

In this paper, we used an approach similar to Alexiadis et al. [10] applied to three models describing and comparing the hydrodynamics in a completely-filled colon (liquid), a partially-filled colon (liquid) and a multiphase (gas + liquid) partially-filled colon. The intestinal content is propelled by a peristaltic wave. The hydrodynamic results are used to evaluate the affects they have on different dosage forms and to visualise how an undissolved dosage form (tablet) will behave in the different models.

2. Methodology

2.1. Modelling approach

The simulations in this study are based on Discrete Multiphysics (DMP), a modelling technique also used in Alexiadis et al. 0,[19],[20] and Ariane et al. [21],[22],[23],[24]. DMP is based on coupling various particle-based modelling techniques such as Smoothed Particle Hydrodynamics (SPH), Lattice Spring Model (LSM), and the Discrete Element Method (DEM). Theoretical insights on DMP are discussed in Alexiadis et al. 0,[19]. In this study, the model accounts only for SPH and LSM. For a detailed description of the SPH method and the Lattice Spring Model (LSM), the reader can refer to [25] and [26],[27],[28] respectively.

2.2. Model geometry

In our 3D model, we investigated the proximal colon of an adult human. The geometry used is a cylindrical body with a total length of 60 cm, a diameter of 5 cm and open ends. Periodic boundary conditions were used at each end, which means that the fluid exiting the tube on one side re-enters from the other one; this is to mimic the real-world situation of continuous transit through the colon.

The modelling of the peristaltic wave and the colonic motility is described in 2.4.

Discrete Multiphysics is based on coupling various particle-based modelling techniques. In this study, SPH is used for the fluids (both liquid and gas) and LSM for the elastic membrane of the colon. For the recording of the manometric data, we used in the model stationary SPH particles that mimic the presence of a real physical probe, to accurately replicate data obtained *in vivo*. In fact, in *in vivo* studies, manometric data are recorded using fibre-optic catheter with sensors spaced at 1 cm [29] or water-perfused (WP) catheters with pressure sensors spaced every 10 cm [30].

In Fig. 1 (a) and (b), a schematic sketch of the model, including the probe, is shown. More details are given in Table 1 and Table 2.

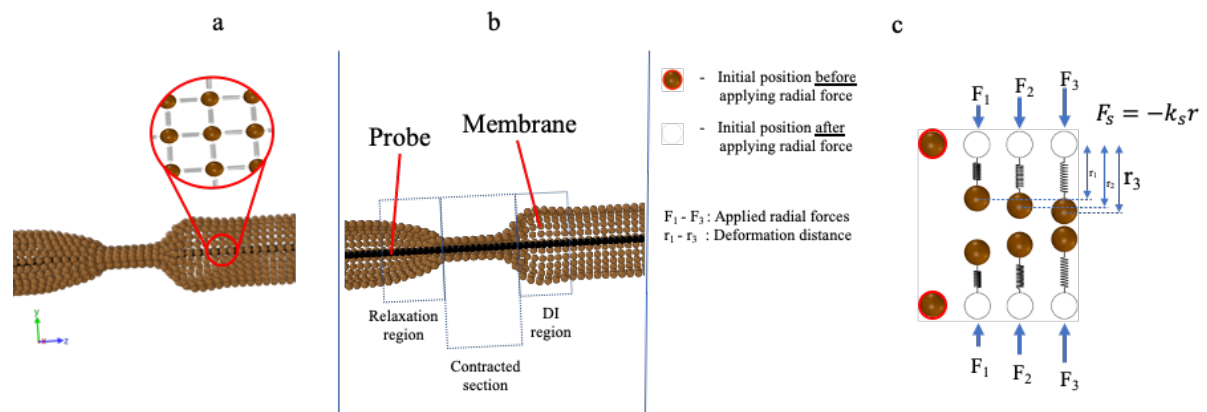


Fig. 1. (a) and (b): 3D sketch of the flexible membrane, showing the contraction and expansion of the wall. The particles representing the membrane are connected by a network of springs. The probe (catheter) for pressure measurements is represented as black, stationary particles. (c) 2D Illustration of the elastic membrane with tethered springs at equilibrium state as well as after the application of three different radial forces (see Table 2 for details)

2.3. Model and simulation parameters

In our model, the membrane is built of 2,500 LSM particles spaced of 6.28×10^{-3} m and its particles are anchored to their initial position with a Hookean force (Fig. 1 (c)). The structure and hence the number of membrane particles is a compromise between complexity and performance (i.e. computational resources and run time) of the model. The number of SPH particles representing the fluid varies due to the different filling levels from model to model as shown in Table 2. According to Diakidou et al. [18], the volume of liquid/solid material in the ascending colon is about 10 %. Standardised dissolution tests are performed with a liquid volume of about 900 mL [31]. This corresponds to a filling of the proximal colon of about 80 %. As a compromise between the results of the study and dissolution tests currently performed, we have chosen a filling level of 40 % fluid for the partially-filled model (Table 2).

The number of fluid particles used in the particular models is the result of several simulations performed with different resolutions. Between these simulations we compared the velocity fields obtained for the completely-filled colon and selected the simulation with approximately 30,000 fluid particle as the best compromise between accuracy and shorter computational times.

The probe records the pressure along the tube every 2.5 cm. This distance was chosen to get a reasonable pressure profile for the comparison of our model with experimental data.

In our model, we used a liquid inside the colon with a similar viscosity to the fluids used for *in vitro* studies in the literature, see [Table 1](#) [32]. Although in the real case the fluid is likely to be non-Newtonian, in this work, for simplicity, it is assumed Newtonian.

For the evaluation of the influence of a gaseous phase we used the partially-filled model and added SPH particles, representing the gas. The pressure of the gaseous phase in the colon is not well known. According to Kurbel et al. [16], the total gas pressure due to bubble formation in the colon is at atmospheric pressure or slightly above. In the model, we assume a gauge pressure of 60 Pa. Chemically, the model assumes that the gas phase is comparable to dry air and follows the ideal gas equation of state: technically speaking this is not true, but given the small gauge pressure, we assume that this is an acceptable simplification. Gravitational acceleration in the y -direction is also added to all particles.

For the simulations in this study, we used three different models: a completely-filled colon, a partially-filled colon and a gas-liquid model. The numerical values we used for the different models and simulations are listed in [Table 1](#) and [Table 2](#).

Table 1: Fundamental model parameters used in all simulations: for more details on the physical and mathematical meaning of the simulation parameters h , c_0 , k_b and k_v , the reader is referred to [26],[25],[27],[28].

Parameter	Value
SPH	
Number of SPH membrane particles (1 layer)	2500
Number of SPH probe particles	134
Initial distance among particles Δr	6.28×10^{-3} m
Smoothing length h	9.42×10^{-3} m
Artificial sound of speed c_0	0.1 m s^{-1}
Time-step Δt	5×10^{-4} s
Density (liquid) $\rho_{L,0}$	1030 kg m^{-3}
Density (gas) $\rho_{G,0}$	1.2 kg m^{-3}
Dynamic viscosity (liquid) $\eta_{L,0}$	0.525 mPa s
Dynamic viscosity (gas) $\eta_{G,0}$	$1.84 \times 10^{-5} \text{ Pa s}$
LSM	
Hookian coefficient k_b (membrane)	0.2 J m^{-2}
Viscous damping coefficient k_v (membrane)	$1 \times 10^{-2} \text{ kg s}^{-1}$
Equilibrium distance r_0	6.28×10^{-3} m

Table 2: Specific model parameter for the different models

SPH Parameter	Value
<i>Completely-Filled model</i> (100 % liquid volume)	
Number of SPH liquid particles	29728
Mass of each particle (solid)	3.9×10^{-4} kg
Mass of each particle (liquid)	3.2×10^{-5} kg
Radial contraction force F	1.280×10^{-3} N
<i>Partially-Filled model</i> (40 % liquid volume)	
Number of SPH liquid particles	8142
Mass of each particle (solid)	3.9×10^{-4} kg
Mass of each particle (liquid)	2.42×10^{-5} kg
Radial contraction force F	0.942×10^{-3} N
<i>Partially-Filled with a gaseous phase present</i> (40 % liquid and 60 % gas volume)	
Number of SPH liquid particles	8188
Number of SPH gas particles	627
Mass of each particle (solid)	3.9×10^{-4} kg
Mass of each particle (liquid)	3.9×10^{-5} kg
Mass of each particle (gas)	4.55×10^{-7} kg
Radial contraction force F	0.9677×10^{-3} N

2.4. Colon contraction

The effect of the contraction of the colonic muscles upon the motion of the fluid inside the colon was investigated through the simulations. In humans, there are different patterns (waves), caused by the contraction the circular and the longitudinal muscle layers which form the membrane of the colon. Here, we focus on the High Amplitude Propagating Pressure Wave (HAPW) [33],[34], which transports the digested materials along the colon. The contraction of the circular muscle cells leads to a partial or complete occlusion of the lumen, and therefore creating effective mixing as they propagate. The contraction of the longitudinal muscle leads to a shortening of the length of the colon and has thus minimal mixing and propulsive functions [33]. The actual shape of a peristaltic wave is still unknown and therefore is estimated according to the data available. For simplicity, and the limited influence of the longitudinal muscle, in respect to mixing and propulsion of the intestinal content [33], the contraction itself is modelled as a local contraction/activation of the circular muscle which propagates along the colon. The contraction wave (peristalsis) is modelled according to manometric measurements of HAPWs,

which show a contraction time of about five seconds [35] and a propagation velocity of about one metre per second [36],[30],[33]. The HAPW is the only wave type that always occludes the lumen completely and additionally produces a feature called Descending Inhibition (DI), where the region in front of the bolus actively relaxes [33]. These characteristics were also implemented in the model; the contraction is modelled by applying a radial force to the membrane particles that, in our simulation, is represented by a ring of 25 particles. Each ring represents one circular muscle fibre, which can be activated independently. The numerical value of the radial force is chosen to allow full closure of the intestinal lumen avoiding interpenetration of the membrane and probe computational particles, which would result in sudden and unrealistic pressure peaks. The same HAPW is used in all three models.

2.5. Software

The open source code LAMMPS [37],[38] is used for the numerical calculations. The open source code of OVITO [39] is used for the visualisation and postprocessing of the simulation data.

3. Results and Discussion

3.1. Comparison with manometric data and other studies

To assess the model, we compared our recorded pressures with the pressure profiles from experimental manometric measurements [36]. The absolute pressure is different because our model refers to a shorter section of the colon with periodic boundary conditions.

Therefore, in Fig. 2 we compare the experimental data with the simulations based on relative pressure:

$$p^* = \frac{p}{p_0}, \quad (1)$$

where p is the experimental or simulation pressure (Pa) and p_0 the reference pressure, which is the maximum pressure in the experiment (16,430 Pa) and in the simulation (1,260 Pa).

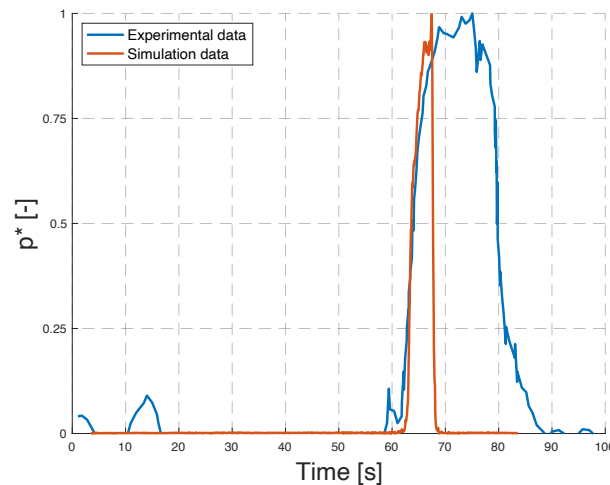


Fig. 2. Comparison between manometric measurements from [36], and simulation data from our completely-filled model.

The pressure peak in the manometric data and in the simulations is similar (Fig. 2). However, it looks like the contraction in the simulation is cut short with respect to the manometric data. In our model, the contracting section (Fig. 1 (b)) is around three times shorter than the real one [36]. This is due to the periodic boundary conditions; in fact, if the contracting section is too large, there would be not enough room for the displaced liquid. However, this difference is only expected to affect the length of the contracting section and not the hydrodynamics in the relaxing region, the DI region (Fig. 3) and along the colon.

Fig. 3 shows an example of a peristaltic contraction travelling in antegrade direction (in our model, from left to right). The higher velocities are in the DI region, directly in front of the peristaltic wave. In this region, we can observe the formation of a vortex under peristaltic flow conditions as also reported by other studies [40],[11].

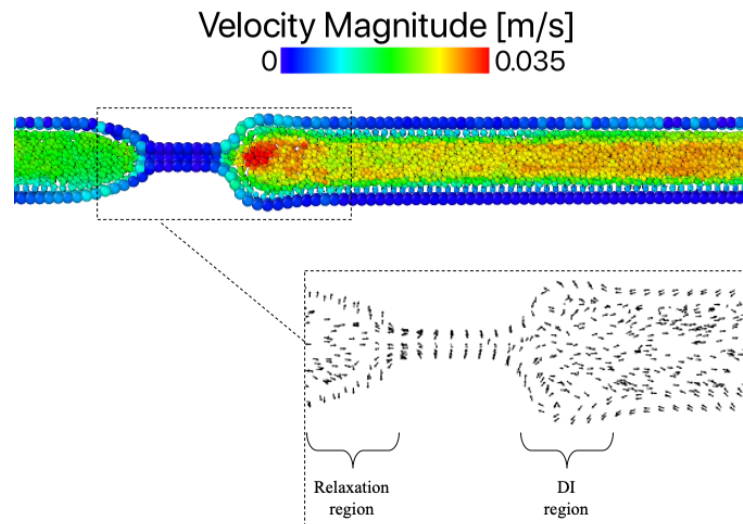


Fig. 3. Representation of a peristaltic wave. In the enlarged section, the formation of a vortex is shown in a vector representation, where the direction of the vectors indicates the flow direction respectively.

3.2. Comparison of completely-filled model with partially -filled model

The magnitude of the applied contraction force is in the partially-filled model smaller than in the completely-filled model to achieve the same pressure measurements. This is due to the fact that fully-contracting a partially-filled colon, in fact, is easier than contracting a completely full colon. The partially-filled model also shows the formation of vortices as presented in Fig. 4.

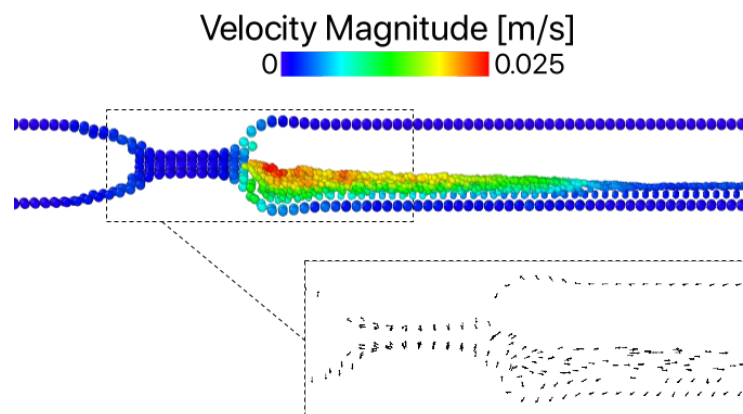


Fig. 4. Representation of a peristaltic wave in the partially-filled model. The enlarged section shows the formation of a vortex in the DI region.

Compared to the completely-filled model the velocities are smaller. As shown in Fig. 5, the velocities of the liquid particles are in both models different. They differ in magnitude as well as in the distribution over time.

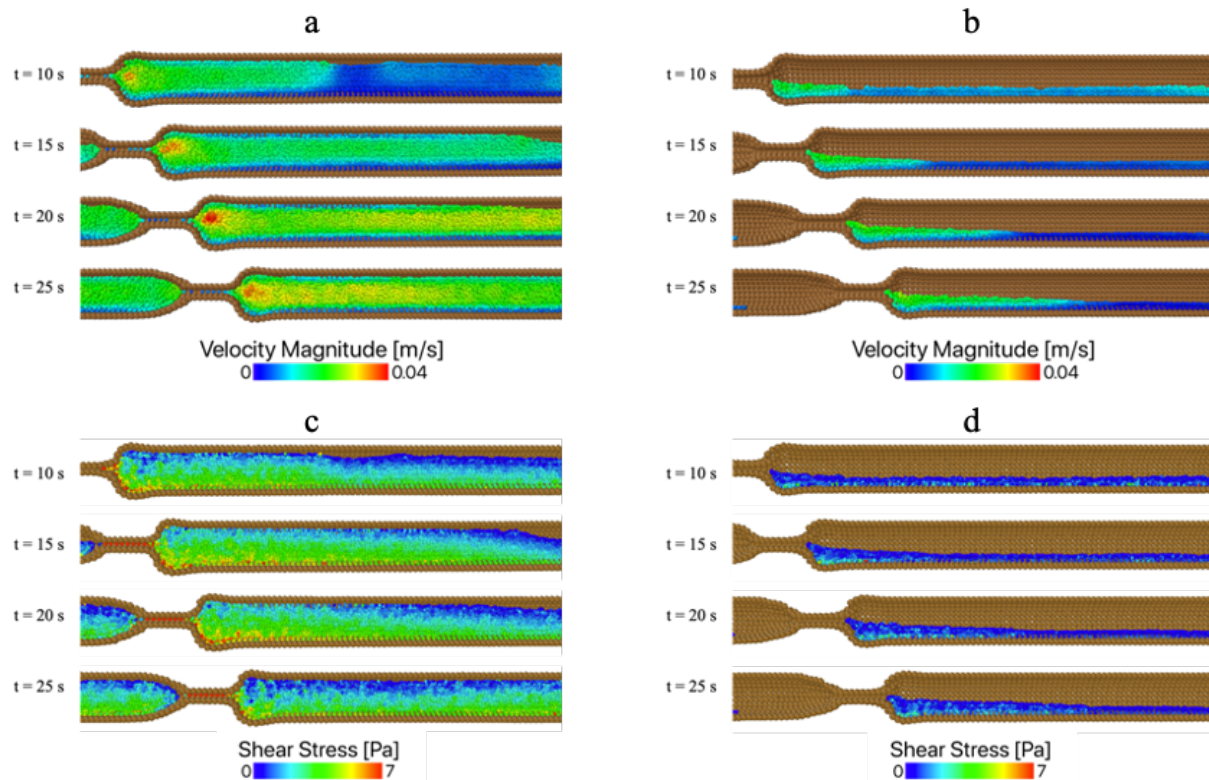


Fig. 5. Comparison of a peristaltic wave with content coloured by the velocity magnitude and shear stress, where (a) and (c) show the completely-filled model and (b) and (d) the partially-filled model.

The highest velocities in the completely-filled model arise in the centre of the tube, while in the partially-filled model the highest velocities occur on liquids free surface. Moreover, the vortex in the completely-filled model (Fig. 5 (a)) is more pronounced than in the partially-filled model (Fig. 5 (b)), which we can trace to the higher velocities found in the DI region.

Also the shear stresses in the completely-filled model (Fig. 5 (c)) are higher than in the partially-filled model (Fig. 5 (d)). In both models, the highest shear stresses are found in the lower part of the DI region where the contraction leads to an active movement of the membrane and pushes the fluid. The shear rates that occur are not presented here because we assumed that the fluid is Newtonian and therefore shear rate and shear stress are proportional.

These results provide insight into the disintegration of a solid dosage form, e.g. tablets and thus the release of drug particles containing the Active Pharmaceutical Ingredient (API). The shear stress is a critical parameter [41] and a higher shear stress acting on the tablet leads to a faster breakage and a corresponding faster release of the API. Once the API has been released the

mixing profile is important for the distribution of the API and thus has a direct influence on the successful treatment.

We analyse mixing in the system by looking at the dispersion of tracking particles with the same properties of the fluid: a passive scalar like the concentration of a dissolving drug will follow the same streamlines of the tracking particles. For this reason, Fig. 6 gives us an idea on how a dissolving drug will mix in the luminal content. To give a visually representation of the difference in the mixing performance of both models, we track the evolution of a group of fluid particles (red particles in Fig. 6).

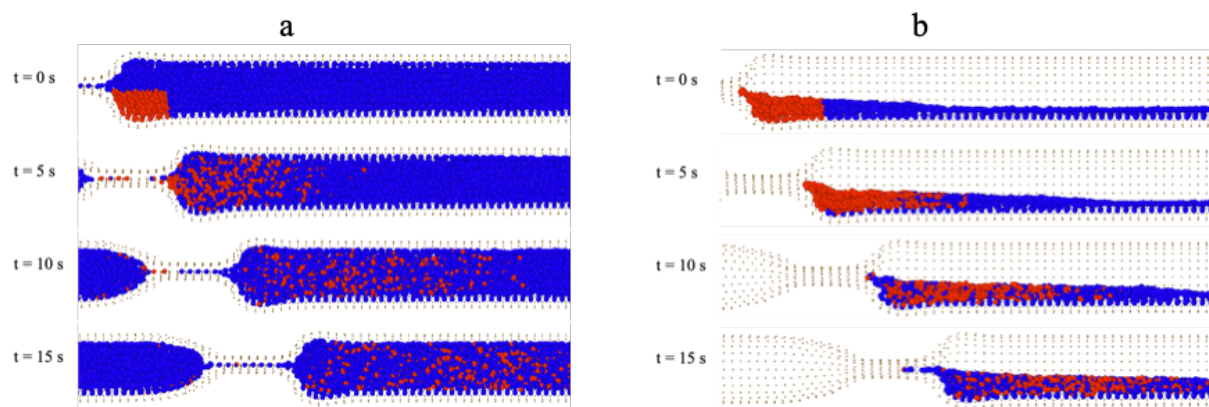


Fig. 6. Mixing profile of (a) completely-filled model and (b) partially-filled model with tracking particles (red coloured) at different time-steps.

The results may be summarised thus:

- After 5 seconds, the distance travelled by the tracking particles is almost identical in both models.
- After 10 seconds, the tracking particles in the completely-filled model cover a distance of about 20% more than in the partially-filled model and the particles in the completely-filled model are more spread out.
- After 15 seconds, in the completely-filled model, the particles are uniformly distributed, while the partially-filled model still shows some patches of higher concentration.

Drugs and medicines are administered in a wide variety of forms as tablets, as capsules, as granulates, as a liquid or as a foam [42],[43]. Some of these forms (e.g. emulsions and suspensions of micro- and nanoparticles in which the API is finely dispersed) are dispersed in the luminal content and, therefore, behave like the tracking particles discussed above.

Studies with a time dependent API release showed an increase in IBD treatment success [44]. A time depending release results in a low but constant API concentration along the colon which

is comparable with the mixing profile of our completely-filled model. The tracking particle are distributed faster along the colon which results in an increased exposure time of API. In Fig. 6, we discussed dosage forms that are finely dispersed in the luminal content.

The opposite scenario occurs when the drug is released slowly like the case of a tablet that is not very soluble in the luminal content. In Fig. 7, we consider the extreme scenario of an insoluble tablet. The tablet is cylindrical with a diameter of 10 mm, a height of 5 mm and neutrally buoyant. Here we look at a tablet with a regular shape that, in reality, will not have such a regular shape because it already passed through the stomach and the small intestine before reaching the colon. Fig. 7 compares the trajectory of the tablet among the completely-filled model, the partially-filled model and the gas-liquid model.

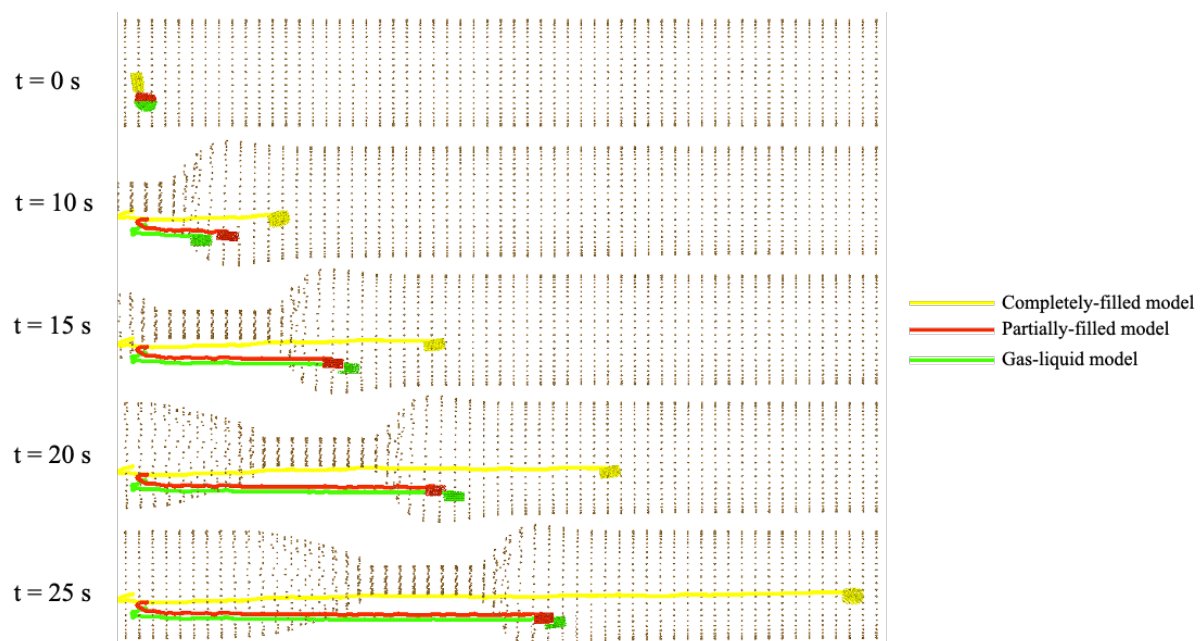


Fig. 7. Visualisation of the time dependent trajectory of a tablet in the different models.

The trajectory of the tablet is recorded from the moment the peristaltic wave begins. In all models, the tablet initially moves slightly to the left before being pushed by the peristaltic wave in the direction of propagation.

In the completely-filled model, the tablet remains its initial position, whereas in the partially-filled model and the gas-liquid model the tablet is pushed by the peristaltic wave (swirl) to the bottom of the colon. The velocity of the tablet in the partially-filled model and the gas-liquid model are approximately equal. At the beginning (10 seconds) the velocity of the tablet in the

partially-filled model is slightly higher than in the gas-liquid model, but this changes between 10 seconds and 15 seconds, so that the distance travelled by the tablet in the gas-liquid model is greater than in the partially-filled model. From 15 seconds on, the velocity of the tablet in the partially-filled model and the gas-liquid model are about the same. The highest tablet velocity was found at all times in the completely-filled model.

As shown in Fig. 5 (c) and (d) the highest existing shear stresses in the completely-filled and the partially-filled model are found in the lower part of the DI region (see Fig. 1 (b)). From Fig. 8 we can obtain that in the completely-filled model the neutrally buoyant tablet does not remain in the region of the highest shear stresses present (Fig. 8 (a)), but rather in the center of the colon where lower shear stress and fewer turbulence occur.

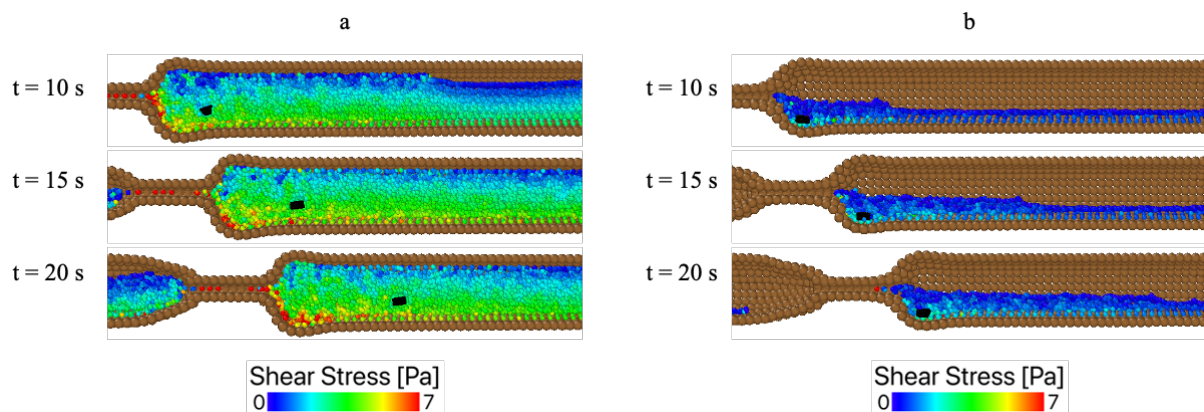


Fig. 8. Visualisation of shear stresses occurring in the fluid and the location of a naturally buoyant tablet (black) in the completely-filled model (a) and the partially-filled model (b).

In the partially-filled model, the tablet is located in the DI region, where the highest velocities (Fig. 5 (b)) and shear stresses (Fig. 8 (b)) are present. For the maximum local shear stress acting on the tablet surface we found 0.24 Pa in the completely-filled model and 5.6 Pa in the partially-filled model. The magnitude of the shear stresses determined corresponds to the values found in other studies, which however focus on the stomach [6],[45].

From the results, we can observe that the forces acting on the tablet and thus responsible for its disintegration depend to a large extent on the location of the tablet in the colon. Although the highest shear stresses occur in the completely-filled model, higher shear stresses act on the surface of a tablet in the partially-filled model.

3.3. Influence of a gaseous phase present

Fig. 9 (a) and (b) shows the particles representing the liquid and gaseous phase, respectively, coloured by the velocity magnitude, caused by a peristaltic wave at different timesteps. **Fig. 9** (c) represents the shear stress occurring in the liquid phase.

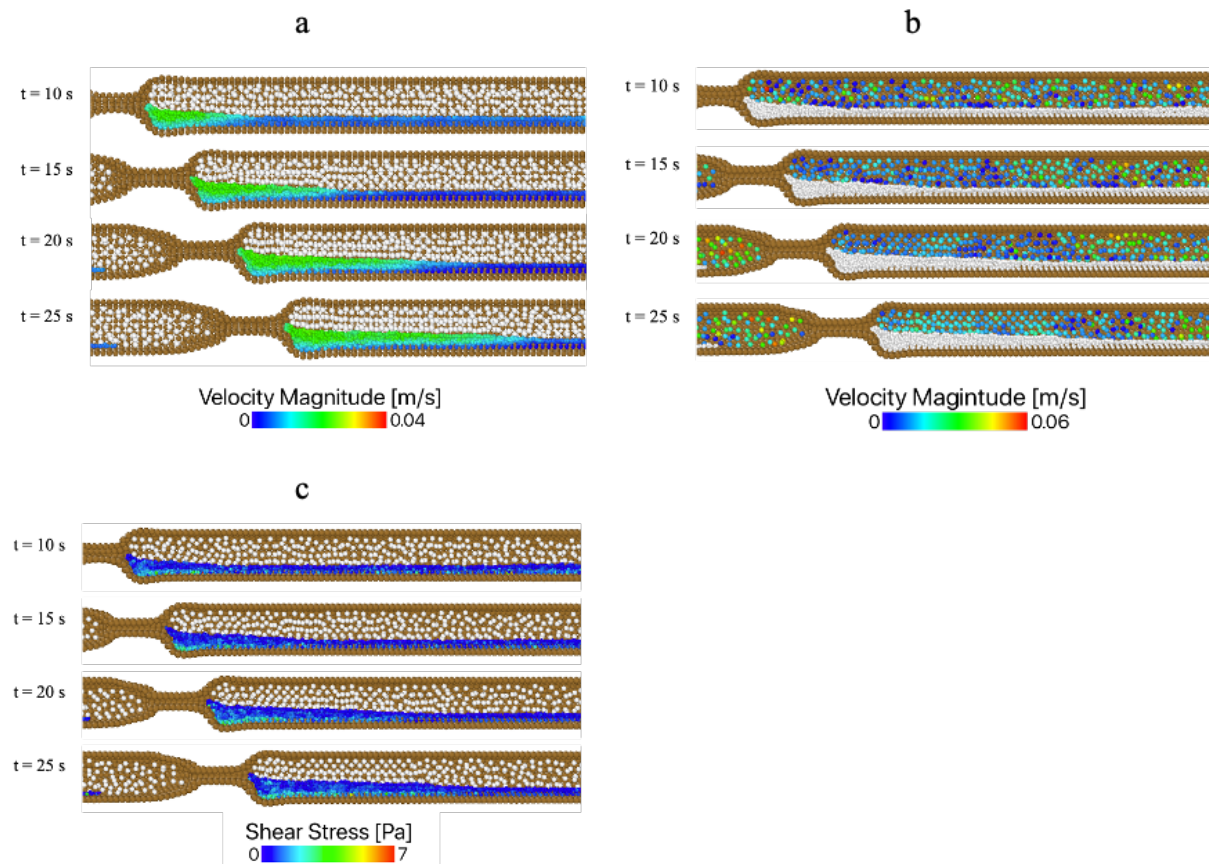


Fig. 9. (a) and (b) Comparison of a peristaltic wave with content coloured by the velocity magnitude in the gas-liquid model. In (a) the velocities of the liquid phase and in (b) the gaseous phase are analysed. (c) Representation of the shear stresses in the liquid phase.

The liquid phase (**Fig. 9** (a)) shows almost the same velocities as seen in the partially-filled model (**Fig. 5** (b)). After 25 seconds the velocity in the gas-liquid model is slightly higher along the colon compared to the model without a gas phase. The velocity magnitude of the gaseous phase (**Fig. 9** (b)) in front of the peristaltic wave stays in the range of the propagation velocity of the peristaltic wave. Except the gas particles entering on the left side again (e.g. at 20 seconds and 25 seconds) show a slightly increased velocity magnitude.

Also the shear stress in the liquid phase (**Fig. 9** (c)) shows almost the same distribution and magnitude as seen in the partially-filled model (**Fig. 5** (d)). As there are no significant

differences, it can be assumed that the gas phase has less or no influence in the shear stresses that occur.

From Fig. 10 (a) it can be seen that the velocity magnitude of the gaseous phase in front of the peristaltic wave is relatively constant and the arrows show a quite linear flow pattern. The gas particles entering on the left-hand side whereas showing higher velocities and swirl.

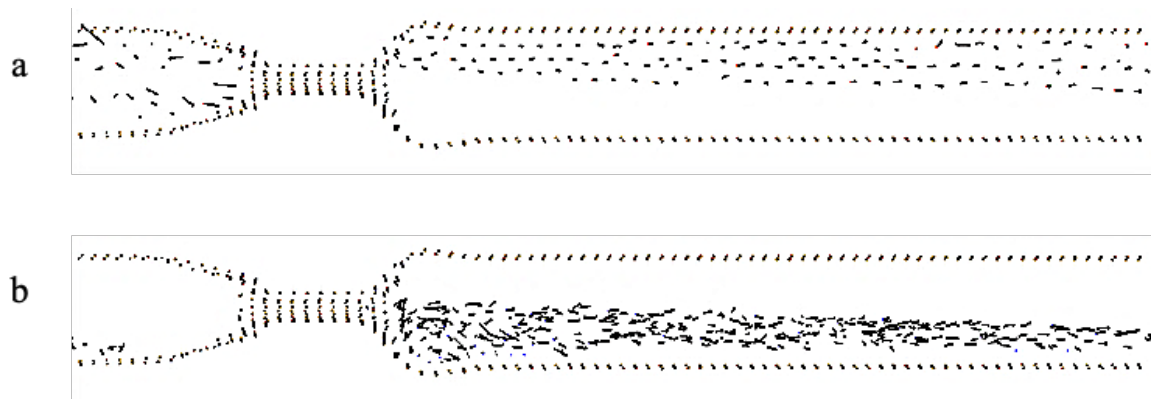


Fig. 10. Vector representation of the (a) gaseous phase and (b) liquid phase in the gas-liquid model, where the length of the vector indicates the velocity.

The liquid phase as shown in Fig. 10 (b) indicates the same flow pattern as in the partially-filled model (Fig. 4) where a vortex is formed in front of the peristaltic wave. With respect to the velocity profile, in our model, the gaseous phase does not influence the liquid flow properties. Also, the mixing profile of the gas-liquid model (Fig. 11), is practically identical to the partially-filled model (Fig. 6 (b)).

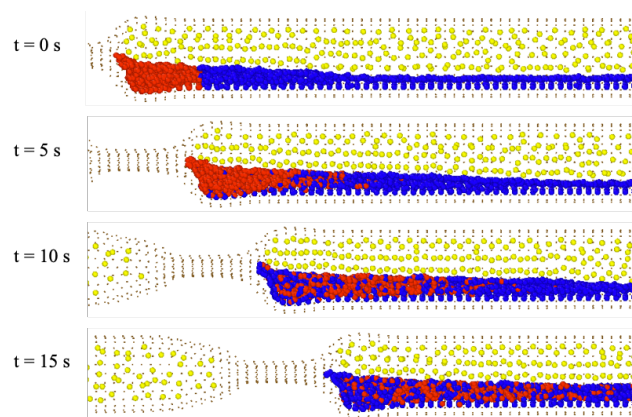


Fig. 11. Mixing profile of gas-liquid model using tracking particles (red coloured) at different time-steps.

3.4. Comparison of the velocity profiles of all three models

The diagrams in Fig. 12 show the axial velocity distribution of the liquid particles along the axial direction at three different time-steps: (a) represents the completely-filled model, (b) the partially-filled model and (c) the gas-liquid model.

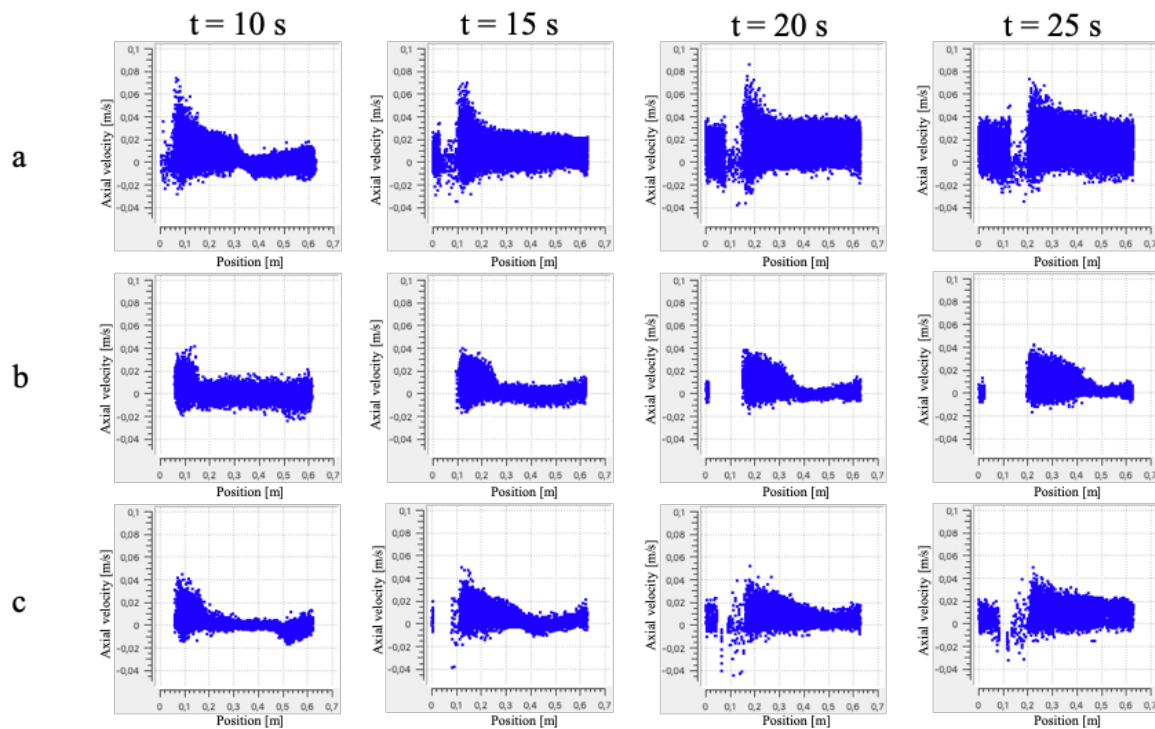


Fig. 12. Graphical representation of the axial velocity along the colon models at different time-steps, where (a) represents the completely-filled model and (b) the partially-filled model and (c) the gas-liquid model

In all models, the highest velocity magnitude (Fig. 5 and Fig. 9) as well as the highest axial velocities are found in the region right in front of the peristaltic contraction in the DI region. If we compare the three models, we can establish that the maximum axial velocity of the particles representing the liquid is in the completely-filled model, which is approximately twice as high as in the other two models. The axial velocity distribution shows in all models a different pattern, whereas the partially-filled model and the gas-liquid model only show a slight difference.

In the completely-filled model the mean axial velocity distribution increases between 10 and 20 seconds by about 40% and stays constant, whereas the axial velocity distribution in partially-filled model remain almost constant. After 25 seconds the gas-liquid model shows a slight increase in the mean axial velocity.

As the reduction of fluid in the colon model by approximately 60 % resulted in a 50 % reduced liquid axial velocity. The addition of another fluid – in this case gas particles – suggests that in

the gas-liquid model the axial velocity of the liquid is slightly higher than in the partially-filled model without gas.

In terms of dosage forms, the velocities in Fig. 12 explain the result of Fig. 6, Fig. 11 and Fig. 7. The completely-filled model, in fact, shows both higher axial velocities and a larger distribution of axial velocities. This is reflected in a faster propagation along the colon of both finely dispersed tracking particles (Fig. 6) and large tablets (Fig. 7), and in the more uniform distribution of particles in Fig. 6 (a) compared to Fig. 6 (b).

4. Conclusion

In this study, we develop three different computational models to describe the peristaltic motion in the colon. These models consider different filling levels as well as the presence of the gaseous phase. We also simulated the mixing of fully dispersed tracking particles and the motion of intact tablets.

Our study investigates how the hydrodynamics are influenced by different filling levels and the presence of the gas phase. The filling level in the colon has an influence on the shear stresses, mixing, concentration and the hydrodynamic profiles, which can be highly relevant for medical research as well as pharmaceutical applications including the design of a modified release dosage form. For the disintegration/erosion of the dosage form and, thus, the release of drug particles, the existing shear forces and shear rates are one of the critical parameters. Conventional *in vitro* dissolution tests for targeted drug delivery predictions are performed under standardised conditions with limited consideration of the environmental motility conditions [31]. Our results show that, the liquid fill volume of the colon plays a crucial role in future models of drug dissolution and drug disintegration. This is true for both the case of solid dosage form (tablet) and fully dispersed form.

The model, therefore, provides a more realistic environment for drug dissolution testing compared to the standardised dissolution tests and apparatuses currently in use [31]. In this study, we focus on the two extreme cases of completely dispersed drugs and insoluble tablets, but the model can be further improved by introducing tablets that gradually disintegrate in the colon lumen [46]. This also affects the reliability of the prediction of *in vivo* performance, which is one of the main focuses in biopharmaceutical research [31]. In fact, computer simulations

may in the near future refine and reduce the number of *in vitro* tests performed or even replace the standardised tools used.

Conflicts of Interest: The authors have declared that no competing interests exist.

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