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Abstract: In this study, in-vitro experiments were performed to investigate the drug release from a single strut of a drug-eluting stent with respect to the systolic-diastolic flow and the continuous flow. Regarding, a test bench comprising a single strut and agarose gel as an arterial wall model was designed. The model chosen represents a large-scaled strut of a stent, to limit the effect of the geometrical shape of the stents on the drug release results. The comparison is carried out between two continuous flow rates and a systolic-diastolic flow pattern varying between these two flow rates, with a frequency of 70 beats per minute. The stent model is a polylactic-co-glycolic acid film (50:50) loaded with 10% diclofenac sodium. A compartment of agarose gel (1%) and a phosphate-buffered saline solution at 37°C are employed to mimic the arterial wall and the blood, respectively. Our results show the importance of flow type on the drug release from the stent and distribution of drug in the hydrogel, such that the pulsatility promotes an increase in the quantity of drug absorbed into the hydrogel.

Keywords: Systolic-diastolic flow, Continuous flow, Drug release, Agarose hydrogel

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death in developed countries including hypertension, coronary heart disease (CHD), stroke, and lower extremity arterial disease (LEAD) (Bink et al. 2019; Hu et al. 2018). The most common cause of CVD is atherosclerosis which is caused by a local aggregation of blood and blood products, complex carbohydrates, lipids, and calcium deposits in large and medium-sized arteries, accompanied by modifications in the artery (Ferreira et al. 2018). The treatment applied over recent years is using drug-eluting stents (DESs), which are still in development. In this regard, many experimental tests have been done in vitro, ex vivo, or in vivo. Having trustworthy test results need a reliable test setup with consistent test conditions, which simulates the real condition (Stein et al. 2018). As an important example over the last few decades, hemodynamics for diseased arteries has been extensively investigated (Fan et al. 2021; Wong et al. 2020) and the effect of the continuous flow on the release of the drug is not hidden anymore (Bernad et al. 2021). In most in vitro studies, the continuous flow was performed for analyzing the release profile from drug-eluting stents. Some studies have shown experimentally or numerically the effect of the different flow rates on the drug release at the continuous state (Wang et al. 2021). Seidlitz et al. (Seidlitz et al. 2011) studied the effect of different flow rates, 35 and 4 ml/min, in continuous and stationary flow for two different types of drugs, fluorescein sodium and triamterene. They showed that the release and distribution of hydrophilic fluorescein sodium were prone to change with flow rate. On the other hand, triamterene release was not influenced by the flow rate. This dissimilar response of the two model compounds to the variation of the flow rate emphasizes the need for a case-by-case examination of different compositions of drug carriers.

To characterize the influence of the luminal flow on drug diffusion in the arterial wall, it is important to consider many aspects associated with blood flow. Systolic-diastolic blood flow pattern induced by the cardiac pulse produces a complex flow nature (Sood et al. 2018). The pulsatile nature of blood flow in arteries consists of a steady component and its oscillating harmonics consist of amplitude and frequency. It is a time-dependent behavior in which its pattern depends on geometry, Reynolds number, arterial

wall compliance, and non-Newtonian viscosity of the blood. However, the mechanisms that regulate the drug release in the pulsatile flow remain an unanswered question.

Ku et al. (Ku and Giddens 1983) have compared the behavior of the continuous flow and pulsatile flow in the bifurcation without considering drug transport. Their results showed that the pulsatile flow had a different character of flow, especially at the bifurcations. Whereas the steady flow showed a fixed separation of the flow, without any turbulence and wall shear stress which is rather constant during the time. In a study by O'Brien et al. (O'Brien C, Kolachalama V 2013) the effect of pulsatile flow on drug release is investigated. The results demonstrated considerable sensitivity to the spatial pattern of drug distribution when pulsatile flow amplitude was changed, but less sensitivite to the impact on drug absorption. In the literature, numerical and experimental studies on the significant influence of the Reynolds number on drug release have been conducted (Mandal and Mandal 2018; O'Brien C, Kolachalama V 2013; Saha and Mandal 2018). Such that, two times reduction in the Reynolds number has been accompanied by a 28.8% increase in the hydrogel's total drug uptake (O'Brien C, Kolachalama V 2013). Additionally, the numerical analysis showed an increase in the drug release in the lumen by enhancing this number (Saha and Mandal 2018).

To our best knowledge, there is a lack of experimental studies on the effect of the pulsatile flow on the drug release from a strut of a drug-eluting stent. This research investigates the effect of pulsatile and continuous flow on drug release in the lumen and hydrogel. Two different steady-state flow rates related to the systolic and diastolic values, and the pulsatile flow varying between these values are considered.

2. Materials and Methods

2.1. Materials

Polylactic-co-glycolic acid (PLGA), with a molar ratio of 50-50 (D,L-lactic to glycolic acid), M_W (molecular weight) = 38000-54000 g/mol, was used as a drug carrier. Diclofenac Sodium (DS), with water solubility of 2.37 mg/l at 25 °C and molecular weight of 318.13 g/mol, was used as an active substance model. Ethyl acetate was used as the solvent of the PLGA. Phosphate buffered saline (PBS) and molecular biology grade agarose were used as blood flow and the artificial tissue simulator, respectively. All the mentioned components were purchased from Sigma Aldrich.

2.2. Sample preparation

For each set of films 20% w/v polymer to the solvent (ethyl acetate), was prepared with 10 wt.% diclofenac sodium, which means for 1 g of PLGA, 0.1 g drug was added. The solution was agitated by a magnetic stirrer at 600 rpm for about 1 hour at 40 °C. The method of casting in the Teflon-coated mold (Abbasnezhad et al. 2020), was used for sample preparation. The procedure was followed by drying the samples at room temperature for 24 hours. Finally, the mold was placed in the vacuum oven at the temperature of 40 °C for 24 h. The samples were cut in rectangular form with dimensions of 0.3×5×30 mm^3. This geometry was chosen to limit the effect of the geometrical shape of the stents on the drug release results, representing a strut of a stent with a scale factor of 40.

2.3. Hydrogel preparation

Depending on the setup environmental conditions to analyze the drug released from the stents, some properties of the hydrogels such as mechanical properties, degradation, and swelling are among the selection factors. The choice of agarose in this study is motivated by its long-term stability, its mechanical properties, and the close value of the diffusion coefficient to that of the arterial tissue (Semmling et al. 2013; Tzafriri et al. 2012). The agarose hydrogel was prepared at 1% (w/w) concentration to simulate the vessel wall, where for 0.1 g of agarose powder 10 ml PBS was used. The agarose was dissolved in water

heated to 100 °C and stirred on a magnetic stirrer until optically clear solutions were obtained. During this period, the container was tightly closed to avoid evaporation and change in concentration. Later, the temperature was lowered to 60 °C. After that, the samples were poured into the chambers considered for the hydrogel, and then they were cooled until gelation.

2.3.1 Calculation of the diffusion coefficient of hydrogel

The permeability of the agarose gel is experimentally evaluated under the static flow condition. For this, a volume of (4 ml) 1% weight/volume (w/v) agarose was prepared (the same procedure that was used for the hydrogel preparation). Next, it was poured into a syringe of 12 ml capacity, which was cut at the needle side (shown in Figure 1). After the gelation of the agarose in the syringe, the remaining volume of the syringe is filled with a solution containing a precise dose of the drug (50 mg of DS per 1 ml PBS solution). These syringes are withdrawn at three various times and each time the undiffused solution is emptied. Next, the drug-soaked hydrogel is cut into slices of 4 mm thickness so that they are used to quantify, by the UV-Vis technique, the amount of drugs that they contain.

Then the value of the diffusion coefficient was calculated by using the below equation. The value obtained in this regard was about 1.12×10^{-4} mm^2/s. $\frac{C(x,t)}{C_0} = erfc(\frac{x}{2\sqrt{Dt}})$ Eq. 1

here $C(x,t)$ is the concentration of the drug diffused in the gel at distance of x at time t, $C_0$is the initial concentration of the drug in the solution.

2.4. Release test bench

For the drug release, a closed-loop test bench was designed. The components are depicted in Figure 2. The samples were placed in the test chamber (1). The temperature of the fluid in the system was heated with an electric resistance (2) to be always in the range of 37±0.5 °C. To drive the impeller of the centrifugal pump (3), a direct current motor, a Maxon EC-4-pole motor was used (4). It is connected to an ESCON-Maxon servo controller (5). This controller is linked to a National Instruments acquisition card (NI USB-6008) (6). This card, controlled by LabView, generates the commands of the pulsed wave patterns and the number of pulses per minute conveyed to the servo controller. Figure 3 shows the chosen waveform, which is of the carotid artery. Additionally, the acquisition card collects information from the sensors. Flowmeters of FT-110 Series–TurboFlow (7), a pressure sensor (8) of the type JUMO MIDAS SI, and a Class A PT100 resistive probe (9) for monitoring the temperature, as the sensors, in this study were used. A reservoir (10) and a magnetic-drive pump (11), for containing and damping the fluid, were implemented in the system. By-pass (12), valves (13) and distributers (14) were the additional elements in the system to control the flow.

2.5. In vitro drug release procedure and associated measurement

UV–Vis spectrophotometry lambda 35 was used to determine the concentration of Diclofenac sodium released in 1L of PBS solution and diffused into the agarose hydrogel after determined time points. The hydrogel was placed in a compartment (with the dimensions of 130 × 30 × 1 mm^3) situated in the bottom wall of the test chamber; then the polymeric samples were placed on the hydrogel (Figure 4). The polymeric samples were fixed with small clips on the surface of the agarose hydrogel, in order not to move with the flow.

At each time step, the polymeric sample was removed. Then the agarose hydrogel was collected from the compartment for analysis, and it was replaced with the new one, prepared beforehand. Next, the polymeric sample was carefully placed on the new hydrogel to continue the test. At the same time steps,

4 ml of the PBS solution was sampled from the reservoir for studying the drug release in the PBS medium. The statistical analysis is related to the number of tests performed (n=3) that is expressed as mean ± standard deviation in the release curves. To calculate the cumulative drug release, the total amount of DS loaded on the PLGA polymer was also measured after degrading completely the polymer film in ultrasound at high temperature. To establish the calibration curve of measurements, known concentrations of DS in PBS and agarose hydrogel (1%) were measured. The following calibration equations were found with the correlation coefficient of $R^2 = 0.99$ (shown in Figure 5).

This comparison of the released results is performed for two steady-state flows at 7.5 and 15 ml/s (corresponding respectively to the pressures of 75 and 112 mmHg), and the pulsed flow that varies between these values (shown in Figure 3) at 70 heartbeats per minute. These values were chosen from the literature representing the waveform of the blood flow in the carotid (Sood et al. 2018; Yao et al. 2015).

3. Results and discussion

3.1. In vitro drug release at the continuous steady and unsteady flow

Figure 6 (a), and (b) show the results of DS release from the PLGA samples into the PBS medium and the hydrogel compartment. Comparing these two figures indicate that, in all cases, there is much more quantity released in the PBS than in the hydrogel. It is in a 1 to 10 ratio. Figure 6 (a) shows that by increasing the flow rate from 7.5 to 15 ml/s the drug release rate in the PBS is increased at certain time points. For example, after 12 h of release, for the flow rate of 15 ml/s about 55% of the drug is released whereas for 7.5 ml/s about 46% of the drug is released. However, this difference is not much notable at the other time points. It is noteworthy that also in these cases the release curves are following the same tendency. Besides comparing the drug release results, in the steady-state (flow rates: 7.5 and 15 ml/s) with the pulsed flow, one can note a meaningful difference in the release rates. In the case of pulsed flow, the release rate is much higher than in the steady flow, especially in the second period of the release after the burst phenomenon. As an example, at 30 h of release in the steady state about 70% of the drug is released, whereas in the pulsatile flow about 80% of the drug is released. Nevertheless, the results show that for all the flow rates, approximately 90% of the drug is released into the PBS at the time of 192 h. Figure 6 (b) shows the drug concentration penetrated the hydrogel in accordance with the release time. The controlling mechanism of the drug transport into the hydrogel is diffusion (Khodadadi Yazdi et al. 2020). At first, the existence of high drug concentration gradients explains the rapid growth of the curves. At steady-state, for two different flow rates of 7.5 ml/s and 15 ml/s, the amount of the drug diffused into the hydrogel is rather within the same range. In contrast, the results for the pulsed flow show that the amount of drug diffused into the hydrogel is higher than in the steady cases. This variance is almost notable in the time points between 30 and 60 h with a difference of 1-1.5% release.

To analyze these results more deeply, the microstructure of the samples has been observed under a Scanning Electron Microscopy (SEM).

Figure 7 shows the SEM micrographs of the PLGA samples with 10% of DS (a) before, and after 48 hours of release test at (b) the steady flow of 7.5 ml/s and (b) unsteady flow. The figures are captured from the luminal side of the polymer layer. By comparing these figures, one can note in both situations (steady and unsteady), the creation of pores and the wrinkling of the polymer during the release. Thus, it denotes the presence of the swelling and diffusion mechanisms in both cases. Depending on the other environmental conditions such as pressure or the contribution of other mechanisms such as erosion, the pores can blast and make the polymer surface more porous and suitable for drug release. It is evident that diffusion is affected by the swelling phenomenon; its rate increases by increasing the space between the polymer chains and the free volume in the polymer. Contrarily, the enlargement of the polymeric samples due to

the swelling, increases the migration distance for the release of the drug (Scheler 2014). Another mechanism contributing to the drug release from the PLGA polymeric films is the mechanism of degradation/erosion which results in the cleavage of polymer chains and can help the drug release.

From the mechanistic standpoint, it is notable that by increasing the flow rate, the thickness of the hydrodynamic and mass boundary layers is getting smaller (Kleinstreuer 2018). Figure 8 shows a demonstration of this conception. Moreover, in a review article by Rana et al. (Rana and Neeves 2016), it is mentioned that by increasing the velocity, a thin boundary layer near the bottom layer of an arterial wall, is constructed which results in a great Peclet number and therefore results in higher convective flux than diffusive flux. Also, this fact can lead to the weakening of the mechanical behavior of the polymer and an increase in the rate of erosion (Abbasnezhad et al. 2021). Our experimental results are in agreement with the numerical study by Chen et al. (Chen et al. 2015), concerning the steady case at the flow rates of 7.5 and 15 ml/s. Regarding this, a high value of Re number in steady-state conditions causes an enhanced drug release rate in polymer and a lower drug concentration in tissue.

The former discussion is consistent with the obtained results, which indicates that on the lumen side, by increasing the flow rate, convective flux is larger near the sample surface. This causes higher concentration gradients of the drug between the polymer sample and the fluid, leading to higher diffusive flux. Consequently, for the steady-state cases, increasing the flow rate, increases the diffusion of the drug through the polymer, resulting in more drug release from the polymeric samples. One can note that the drug release from the polymeric films in the case of unsteady pulsed flow compared to the steady case is also higher. This is an effect of the flow pulsatility on the enhancement of the drug transfer as already noted in a study by Chabi et al. (Chabi 2017). It is noteworthy that the analysis of the boundary layer in the case of pulsed flow is not as easy. However, it can be explained by other conceptions. For example, in a study by Ku (Ku 1997) on the blood flow in the arteries, it is mentioned that pulsatility creates a periodic generation of turbulence. It reaches the maximum during the deceleration of systole and the minimum during the upstroke of systole, where time and frequency are the reasons for this transition to turbulence. Moreover, it is shown in (Kleinstreuer 2018) that increasing the turbulence in the flow, increases the convective flux. These observations confirm our mass transfer results, where, in the unsteady case due to the creation of turbulence the mass transfer is higher compared to the steady case. Furthermore, in another study by O'Brien et al. (O'Brien C, Kolachalama V 2013) they demonstrated that the drug deposition in the recirculation zone is shown to be dependent on the pulsed flow at various Womersley numbers. It was observed that decreasing the Womersley number results in longer recirculation, confirming our experimental results by indicating that the drug concentration is impacted by the flow recirculation zone. Therefore, the disturbance of the velocity profile in the pulsed case and the generation of the potential more vorticity is believed to be the cause of the increased release rate in the hydrogel and PBS.

4. Study limitations:

Some of the limitations of this study are as follows: the complication of considering the biological reactions, response of the cells to the foreign substances, and the inflammatory reactions, which is complicated to be considered in the in vitro case; considering the filtration aspect in closed-loop systems. Moreover, malpositioning the DES can also have a significant impact on the outcomes of the release.

5. Conclusions

In this study, a system capable of simulating both lumen and arterial tissue was developed. In this regard, the blood flow, continuous or pulsatile, is reproduced via a pumping system. The arterial medium is mimicked using a specific agarose compartment. The results showed the impact of the flow

pulsatility, especially at some periods of diffusion in the hydrogel on the release kinetics. This expresses the usefulness of considering the pulsatility for a realistic simulation of drug release.

Abbasnezhad, N., Shirinbayan, M., Tcharkhtchi, A., and Bakir, F. (2020). "In vitro study of drug release from various loaded polyurethane samples and subjected to different non-pulsed flow rates." *Journal of Drug Delivery Science and Technology*, Elsevier, 55(December 2019), 101500.

Abbasnezhad, N., Zirak, N., Shirinbayan, M., Tcharkhtchi, A., and Bakir, F. (2021). "On the importance of physical and mechanical properties of PLGA films during drug release." *Journal of Drug Delivery Science and Technology*, 102446.

Bernad, S. I., Craciunescu, I., Sandhu, G. S., Dragomir-Daescu, D., Tombacz, E., Vekas, L., and Turcu, R. (2021). "Fluid targeted delivery of functionalized magnetoresponsive nanocomposite particles to a ferromagnetic stent." *Journal of Magnetism and Magnetic Materials*, 519, 167489.

Bink, N., Mohan, V. B., and Fakirov, S. (2019). "Recent advances in plastic stents: a comprehensive review." *International Journal of Polymeric Materials and Polymeric Biomaterials*, Taylor & Francis, 0(0), 1–22.

Chabi, F. (2017). "Etude numérique et expérimentale du transfert de masse , par advection et diffusion en écoulement pulsé , sur des stents actifs . Fatiha Chabi To cite this version : HAL Id : tel-01512747."

Chen, Y., Xiong, Y., Jiang, W., Yan, F., Guo, M., Wang, Q., and Fan, Y. (2015). "Numerical simulation on the effects of drug eluting stents at different Reynolds numbers on hemodynamic and drug concentration distribution." *Biomedical engineering online*, 14 Suppl 1(Suppl 1), S16.

Fan, Z., Liu, X., Zhang, Y., Zhang, N., Ye, X., and Deng, X. (2021). "Hemodynamic Impact of Stenting on Carotid Bifurcation: A Potential Role of the Stented Segment and External Carotid Artery." *Computational and Mathematical Methods in Medicine*, (G. Pontrelli, ed.), Hindawi, 2021, 7604532.

Ferreira, J. A., Gonçalves, L., Naghipoor, J., de Oliveira, P., and Rabczuk, T. (2018). "The effect of plaque eccentricity on blood hemodynamics and drug release in a stented artery." *Medical engineering & physics*, England, 60, 47–60.

Hu, T., Yang, C., Lin, S., Yu, Q., and Wang, G. (2018). "Biodegradable stents for coronary artery disease treatment: Recent advances and future perspectives." *Materials Science and Engineering C*, Elsevier, 91(April), 163–178.

Khodadadi Yazdi, M., Taghizadeh, A., Taghizadeh, M., Stadler, F. J., Farokhi, M., Mottaghitalab, F., Zarrintaj, P., Ramsey, J. D., Seidi, F., Saeb, M. R., and Mozafari, M. (2020). "Agarose-based biomaterials for advanced drug delivery." *Journal of controlled release : official journal of the Controlled Release Society*, Netherlands, 326, 523–543.

Kleinstreuer, C. (2018). *Modern fluid dynamics*. Springer.

Ku, D. N. (1997). "Blood flow in arteries." *Annual Review of Fluid Mechanics*, 29, 399–434.

Ku, D. N., and Giddens, D. P. (1983). "Pulsatile flow in a model carotid bifurcation." *Arteriosclerosis*, 3(1), 31–39.

Mandal, A. P., and Mandal, P. K. (2018). "Distribution and retention of drug through an idealised atherosclerotic plaque eluted from a half-embedded stent." *International Journal of Dynamics and Control*, Springer Berlin Heidelberg, 6(3), 1183–1193.

O'Brien C, Kolachalama V, B. T. (2013). "Impact of flow pulsatility on arterial drug distribution in stent-based therapy." *J Control Release*, 23(1), 1–7.

Rana, K., and Neeves, K. B. (2016). "Blood flow and mass transfer regulation of coagulation." *Blood Reviews*, Elsevier Ltd, 30(5), 357–368.

Saha, R., and Mandal, P. K. (2018). "Effect of flow pulsatility and time-dependent release kinetics on stent-based delivery through atherosclerotic plaque." *International Journal of Dynamics and Control*, Springer Berlin Heidelberg, 6(1).

Scheler, S. (2014). "The polymer free volume as a controlling factor for drug release from poly(lactide-co-glycolide) microspheres." *Journal of Applied Polymer Science*, 131(1), 1–13.

Seidlitz, A., Nagel, S., Semmling, B., Grabow, N., Sternberg, K., and Weitschies, W. (2011). "Biorelevant dissolution testing of drug-eluting stents: Experiences with a modified flow-through cell setup." *Dissolution Technologies*, 18(4), 26–35.

Semmling, B., Nagel, S., Sternberg, K., Weitschies, W., and Seidlitz, A. (2013). "Development of Hydrophobized Alginate Hydrogels for the Vessel-Simulating Flow-Through Cell and Their Usage for Biorelevant Drug-Eluting Stent Testing." *AAPS PharmSciTech*, 14(3), 1209–1218.

Sood, T., Roy, S., and Pathak, M. (2018). "Effect of pulse rate variation on blood flow through axisymmetric and asymmetric stenotic artery models." *Mathematical Biosciences*, Elsevier Inc., 298, 1–18.

Stein, S., Auel, T., Kempin, W., Bogdahn, M., Weitschies, W., and Seidlitz, A. (2018). "Influence of the test method on in vitro drug release from intravitreal model implants containing dexamethasone or fluorescein sodium in poly (D,L-lactide-co-glycolide) or polycaprolactone." *European Journal of Pharmaceutics and Biopharmaceutics*, Elsevier, 127(November 2017), 270–278.

Tzafriri, A. R., Groothuis, A., Price, G. S., and Edelman, E. R. (2012). "Stent elution rate determines drug deposition and receptor-mediated effects." *Journal of Controlled Release*, Elsevier B.V., 161(3), 918–926.

Wang, J., Kural, M. H., Wu, J., Leiby, K. L., Mishra, V., Lysyy, T., Li, G., Luo, J., Greaney, A., Tellides, G., Qyang, Y., Huang, N., and Niklason, L. E. (2021). "An ex vivo physiologic and hyperplastic vessel culture model to study intra-arterial stent therapies." *Biomaterials*, 275, 120911.

Wong, K. K. L., Wu, J., Liu, G., Huang, W., and Ghista, D. N. (2020). "Coronary arteries hemodynamics: effect of arterial geometry on hemodynamic parameters causing atherosclerosis." *Medical & Biological Engineering & Computing*, 58(8), 1831–1843.

Yao, Y., Hao, L., Geng, N., Jin, Y., Du, S., and Xu, L. (2015). "Estimation of carotid artery pressure waveform by transfer function and radial pressure waveform." *Proceedings of the World Congress on Intelligent Control and Automation (WCICA)*, 2015-March(March), 6090–6093.

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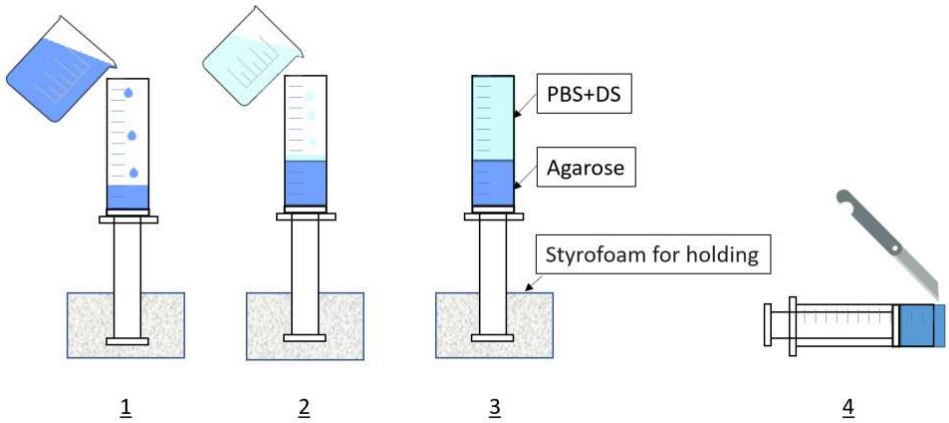

Figure 1. Procedure to measure the diffusion coefficient of the drug in gel

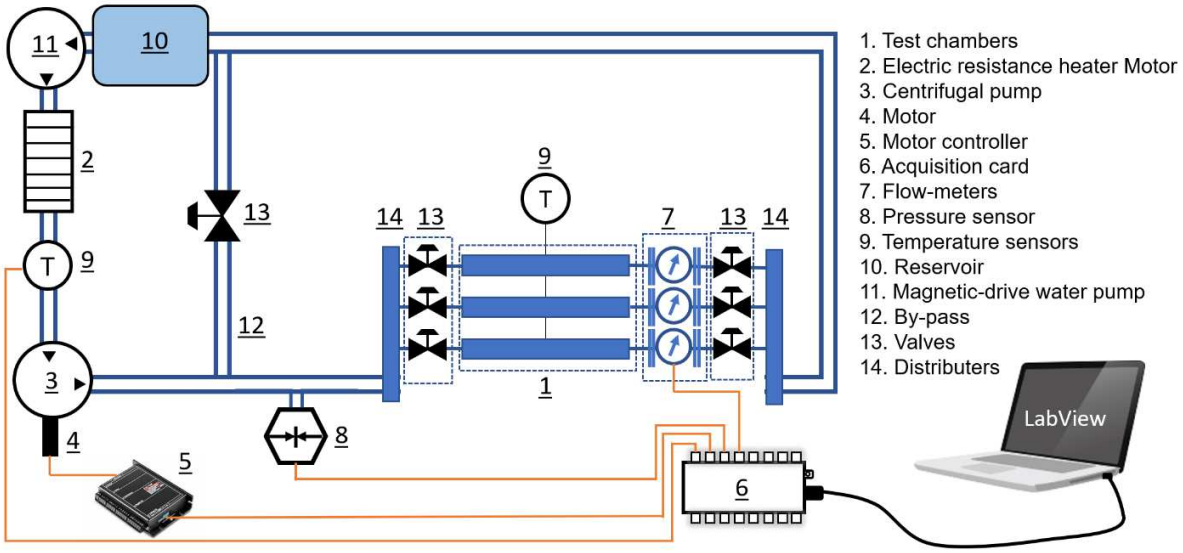

Figure 2. Schematic of the test bench

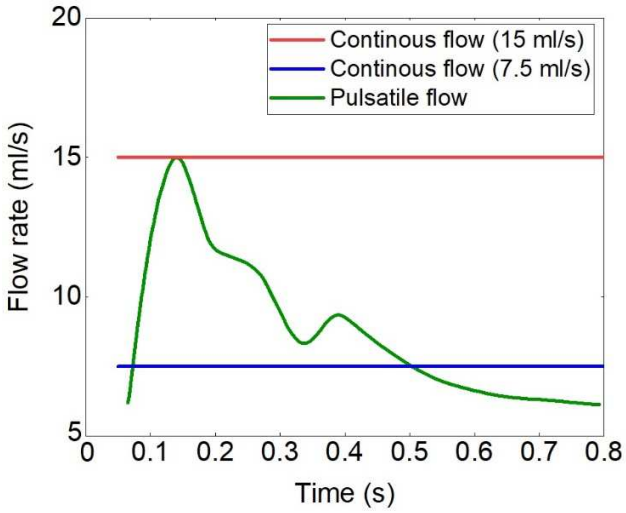

Figure 3. Flow rates related to the three patterns of the flow performed in this study

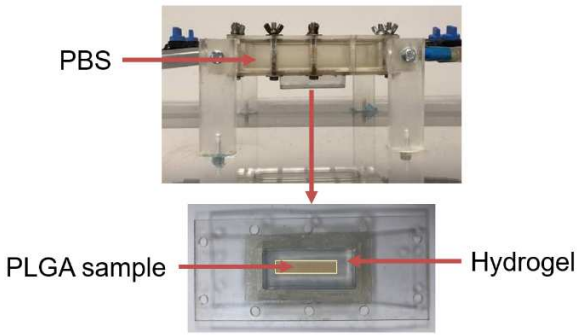

Figure 4. The compartment containing the hydrogel and the polymeric samples

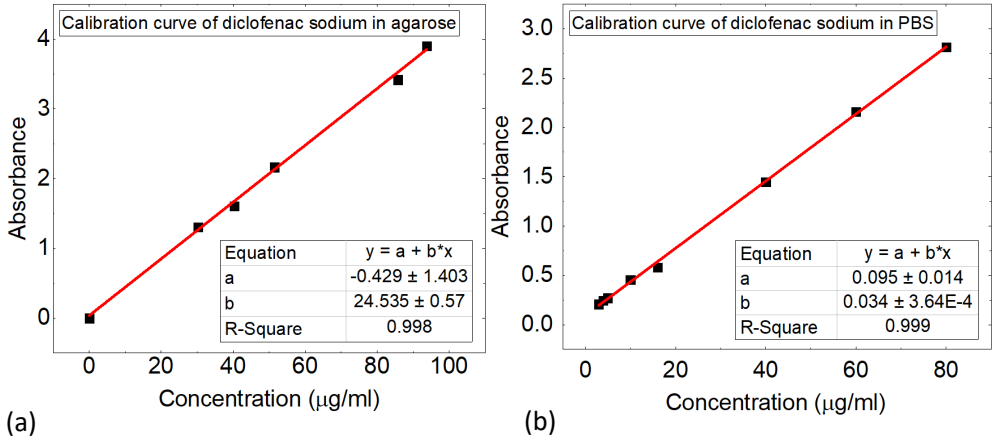

Figure 5. Calibration curves obtained for the diclofenac sodium in (a) hydrogel agarose and (b) PBS

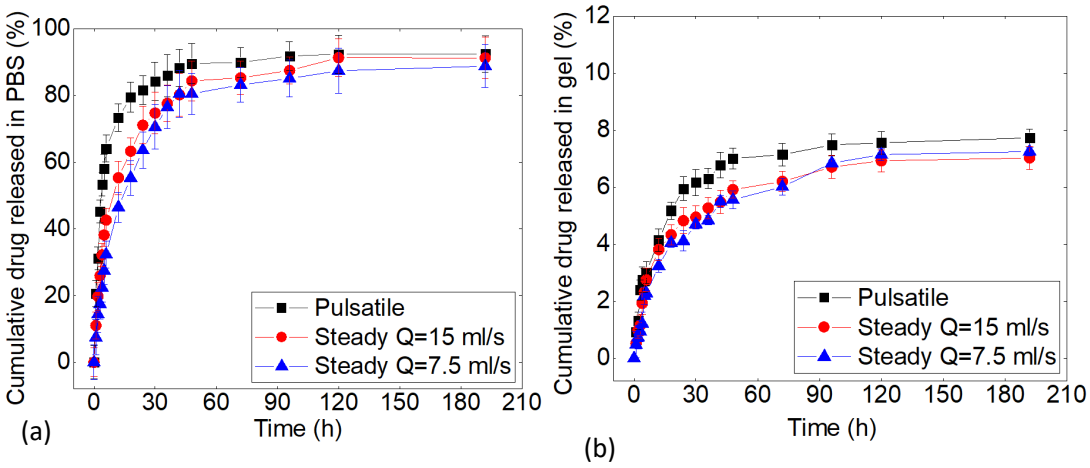

Figure 6. Drug release from the PLGA films with 10% DS at different flow rates in (a) PBS and (b) hydrogel

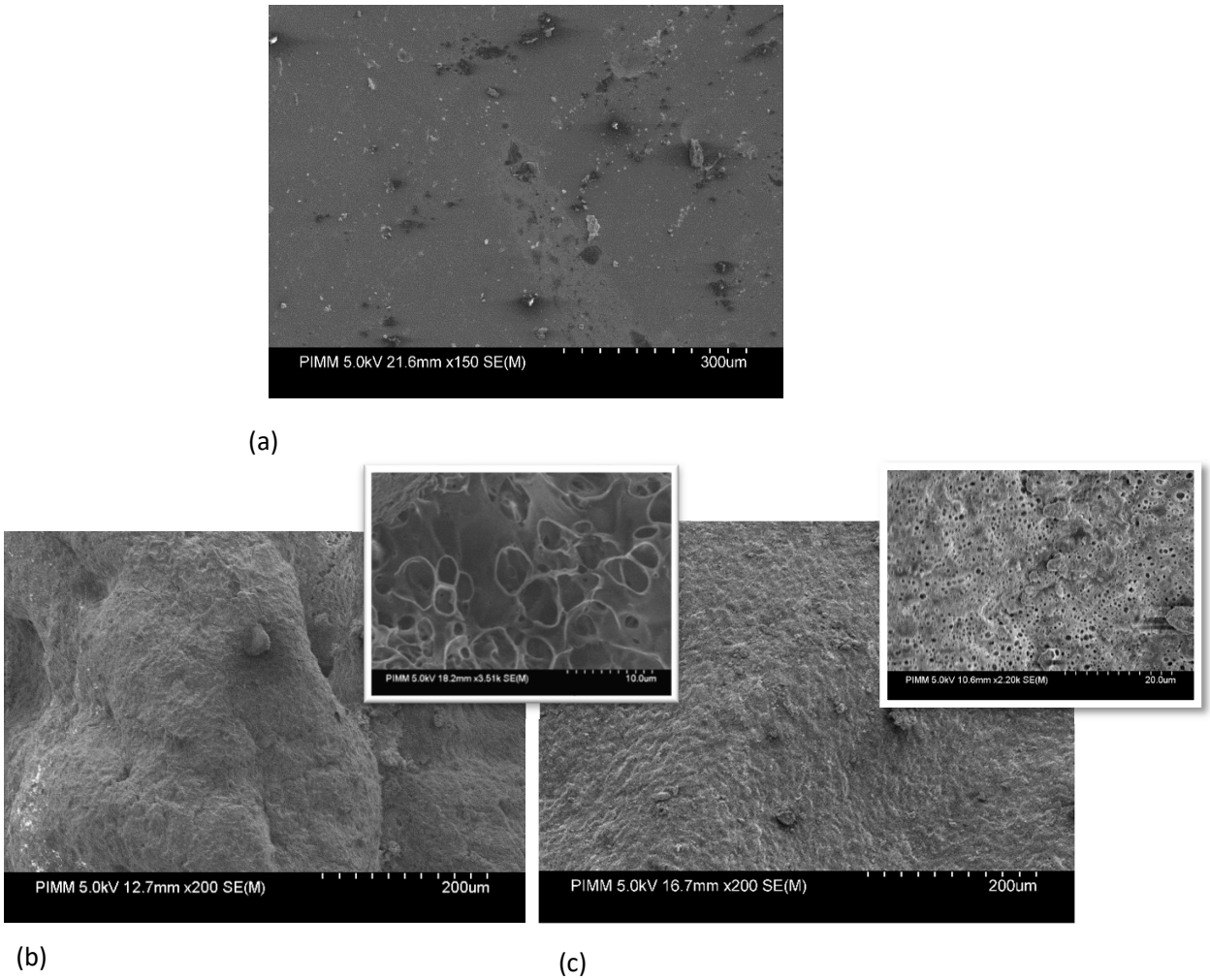

Figure 7. SEM micrographs of PLGA-10%DS samples from the side, contacted with the fluid at (a) t=0; and after 48h at the (b) steady flow with the flow rate of 7.5 ml/s and (b) pulsatile flow, at different magnifications

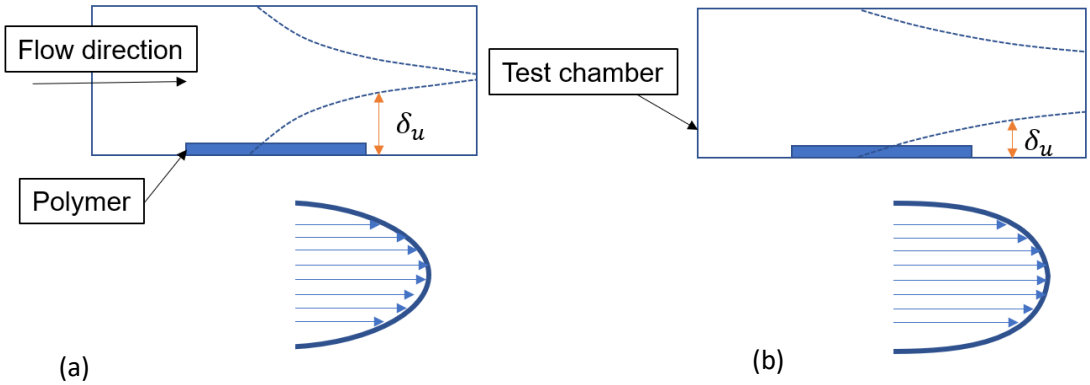

Figure 8. Schematic representing the thickness of boundary layers created at two different flow rates, (a) is for the case with a higher flow rate than (b), δ_u represents the thickness of the mass boundary layer