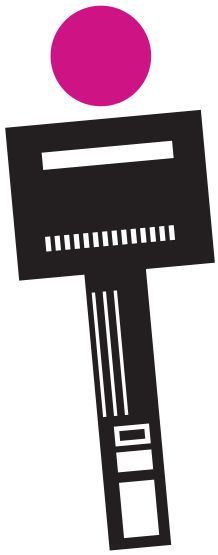

RAM ROBOTICS AND MECHATRONICS

Development of a Myocardial Perfusion Tube Phantom: Analysis of Tissue perfusion by contrast kinetics

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Abstract

Background

Cardiovascular Disease is the most common cause of death worldwide. An important subclass is Coronary Artery Disease (CAD) which causes angina and myocardial infarction. Myocardial Perfusion Imaging (MPI) plays a major role in diagnosing CAD. Although MPI is of crucial importance, validation and standardization of the available methods is still limited. Our previous study has developed myocardial perfusion phantom to evaluate the multimodal quantitative MPI. Though their analysis results of Arterial Input function were good yet, the retention time of the tracer was shorter in phantom on comparison with the retention time of the tracer.

Aim

The main purpose of this study is to resemble the physiological tissue perfusions by contrast kinetics. Thus, our project aims to prolong the residence time of the contrast agent (CA) in the systems (Myocardial Perfusion Tube Phantom and Pharmacokinetic (PK) Compartment models).

Methods

Based on a novel 3D printed myocardial perfusion phantom (prototype 1) that was developed earlier, we investigated three concepts which we name them as “Myocardial Perfusion Tube phantoms”, to prolong the residence time of the CA. These are incorporated later into the arc shaped myocardial segments of the latest version of the 3D printed myocardial perfusion phantom (prototype 2) and include the following designs: (1) Basic tube phantom (BTP); (2) Membrane module filled tube phantom (20 Twisted type with 20 membrane modules or fibres (20TMMTP) and 10 Normal type with 10 fibres (10NMMTP)); (3) Mixed tube phantoms (MTP).This report comprises three different types of studies. Prior to these Studies, various types of designs of the tube phantoms were proposed and designed using the Solid Works Software. Study 1 describes the development and the testing of the myocardial perfusion tube phantoms. To determine the residence time of the CA in different types of tube phantoms, Iodine-based CA was injected into the flow setup by varying several parameters like the flow rate and the dosages of the CA. The distribution of the CA inside the different types of tube phantoms were observed by taking an average of the pixel values in the region of interest (along y-axis) and plotting it over time (along x-axis). This plotted curve is known as Time Intensity Curves (TICs). Study 2 involves the simulation of the pharmacokinetic (PK) compartmental models and the goal is to identify the suitable model which could imitate the drug kinetics in myocardial segments. This was done by varying the dosages of the drug (CA) inside the different types of compartmental models. The concentration of the drug (along y-axis) is plotted over time (along x-axis) and this graph is named as Time Concentration Curves (TCCs). The TCCs, which was obtained through this study helped us to visualize the drug distribution within the compartments. The comparison of both the experimental results (TICs) and the simulation results (TCCs) that was obtained by varying the dosages (3ml, 5ml, 7ml) was investigated in Study 3. The final obtained results from study 3 are compared with the results of the previous study (Prototype 1).

Results

In Study 1, 20TMMTP showed longer residence time of CA compared to all the other types of tube phantoms. Reproducibility experiments which was conducted for the BTP and MTP showed good reproducibility. Study 2 simulation results showed that the two-compartment PK model have longer residence time of the drug (CA) on compared to the one-compartment model. The Time Concentration curves (TCCs) which were obtained using two-compartment model through this study helped us to conclude that, The higher the concentration of the drug in the tissue, greater the residence time of the drug. Study 3 results supported Study 1 results (Experimental results by Varying the dosages of the drug (CA)), by comparing them with the Study 2 interpretations (Simulation results). At last, these results were compared with the previous study (prototype 1) and it was observed that the 20TMMTP, MTP and Two-compartment PK model showed longer residence time of CA/drug and closely resembles the patient Time Activity Curves (TACs).

Conclusion

We have designed and developed different types of myocardial perfusion tube phantoms that allows reproducible and efficient simulations of the myocardial perfusion. Overall, we have successfully resembled the physiological tissue perfusions by contrast kinetics to a greater extent.

Preface

As a part of my master's programme in Biomedical Engineering at University of Twente, I chose to do my Master thesis graduation assignment with RAM group in collaboration with M3I group at University of Twente.

This report is about the topic "Development of a myocardial perfusion tube phantom: Analysis of the Tissue perfusion by contrast kinetics". The thesis is carried out in the form of the project. This project started on Wednesday 11th of December 2019 and concludes on 24th August 2020.

The project is carried out under the chair of Robotics and Mechatronics (RAM) of the University of Twente. It is supervised by Prof.dr.ir. C.H. (Kees) Slump. Daily supervision is carried out by M.E. (Marije) Kamphuis, MSc. In addition, dr.ir. B.E. (Berend) Westerhof is the part of the assessment committee as an external member.

Acknowledgements

First, I would like to thank Marije Kamphuis, Kees Slump and Berend Westerhof for their great supervision and for their kind support throughout the project. I was given full freedom to suggest new ideas, and to share insights about this project and to perform this project on my own. This helped me to manage my work and complete this project on time.

Additionally, I would like to thank Henny Kuipers, Sander Smits, Iska Achterhuis, for their technical support during the initial development phase and Lennart van de Velde, for sharing and supporting us with his knowledge on Computational Fluid Dynamics (CFD) in Solidworks. I also would like to thank Jacqueline Verschoor and Jaap Greve for their wonderful help before, during and after the experiments at the ZGT (Ziekenhuisgroep Twente), Hengelo and at the Techmed Centre, Enschede respectively, and all others those who were involved in organizing and arranging these experiments.

Adharshna Saravanan,

Enschede, Monday 24th August 2020

List of Abbreviations

ATP	Adsorption Tube Phantom
BAT	Bolus Arrival Time
BTP	Basic Tube Phantom
CA	Contrast Agent
CAD	Coronary Artery Disease
CT	Computed Tomography
CVD	Cardiovascular Diseases
CFD	Computational Fluid Dynamics
EV	Extravenous
IV	Intravenous
MPI	Myocardial Perfusion Imaging
MMTP	Membrane module filled tube phantom
MRI	Magnetic resonance imaging
MR	Magnetic resonance
MTP	Mixed Tube Phantom
ODEs	Ordinary Differential Equations
PASL	Pulsed Arterial Spin Labelling
PES	Polyethersulphone
PET	Positron Emission tomography
PP	Polypropylene
PK	Pharmacokinetic
PMMA	Polymethyl methacrylate
SPECT	Single Photon Emission Computer Tomography
TACs	Time Activity Curves
TCCs	Time Concentration Curves
TICs	Time Intensity Curves
TTP	Time to peak
US	Ultrasound
WHO	World Health Organization

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Chapter 1: Introduction

Background

Cardiovascular disease (CVD) is the most prevalent cause of death worldwide. Every year, the death rate of people who suffer from CVD is greater than any other cause [1]. According to WHO, approximately 18 million of people have died as of 2016, because of CVDs, constituting 31 percent of mortality across the world [2]. Leeder et al. [3], predicted that the mortality of CVDs was expected to reach approximately 5 million in 2020. An important subclass of CVD is Coronary Artery Disease (CAD), also known as coronary heart disease, ischemic heart disease or simply heart disease, which causes angina and myocardial infarction. Other CVDs involve heart failure, stroke, cardiomyopathy etc [5].

CAD is the major cause of CVD deaths worldwide, accounting for about 7 million deaths each year [40]. In the Netherlands, the percentage of deaths caused due to CAD is amounted to 14.73% of the total deaths [4]. CAD is a condition in which the plaque build-up occurs inside the coronary arteries which causes the blood flow to be restricted to the myocardial tissue [6]. The patients with CAD, who are at high risk need early diagnosis and management at appropriate times. If it is not done at the right time, the situation of the patient could get worse, eventually leading to death. Thus, diagnosing CAD early and well-informed clinical decision-making is crucial.

Myocardial perfusion imaging (MPI) acts as a key role in diagnosing CAD [7]. There are two types of imaging modalities that are available for diagnosing CAD, namely: (1) Invasive imaging modalities; (2) Non-invasive imaging modalities. Recently, Non-invasive imaging modalities like MPI have proven their reliability [8][9]. While diagnosing CAD, identifying the myocardial perfusion abnormalities are the initial challenges that might arise and to diagnose early asymptomatic CAD, non-invasive tests like MPI tests are highly preferred [10]. For estimating CAD, Invasive coronary angiography is the gold standard [11]. However, the high-risk patients, who were referred for coronary angiography are found to have no significant obstructive coronary disease. There is evidence that the combination of intervention against cardiovascular risk factors and the early detection of the myocardial perfusion abnormalities may restore myocardial perfusion [12]. Moreover, combination of anatomical and perfusion-based imaging perhaps a good solution for diagnosing CAD, even for the patients who are at high risk [13].

Myocardial Perfusion Imaging (MPI) is the most important imaging technique for diagnosing, assessing, and for providing treatment to the patient with suspected CAD [14]. Before performing MPI test, the contrast agent is injected in the form of Intravenous (IV) bolus administration into the patient's veins and this contrast agent flows along with the blood and gets circulated throughout the heart muscle. The distribution of the contrast agent over the certain region of the myocardial tissue has been captured in the form of images from a dynamic scan using two imaging techniques for MPI: Single Photon emission computed tomography (SPECT) and Positron emission tomography (PET). These captured sequences of images are recorded over time as shown in figure 1. The average of the pixels in the region of interest are taken and it is plotted as intensities on y-axis and time across x-axis and this obtained curve is known as Time Intensity Curves (TICs). A myocardial perfusion scan uses radioactive material called a radioactive tracer. In medical imaging, Time Activity Curves (TACs) are obtained by plotting the activity of the tracer over time. The concentration of the radioactive tracer is displayed within the region of interest in an image measured over time from a dynamic scan. In a few imaging techniques like Fluoroscopy, the contrast agents like barium or Iodine are often used. The area under the time concentration curves (TCCs) shows the effective systemic circulation of the contrast agent and also the elimination of the contrast agent from the body.

In patients with a healthy heart, the uptake of the contrast agent or the tracer inside the myocardial tissues are normal and gets equally distributed. If there is a less uptake of the contrast agent or tracer over a certain region, then it means that the specific region of the heart muscle is affected and has less supply of oxygen. Additionally, these TICS/TACS/TCCS are used to identify the perfusion defects in the heart muscle. The uptake of the contrast agent is recorded over time. The anatomical features of the heart like the coronary arteries are not seen using MPI, yet from the data obtained, physicians can easily identify the certainty of CAD.

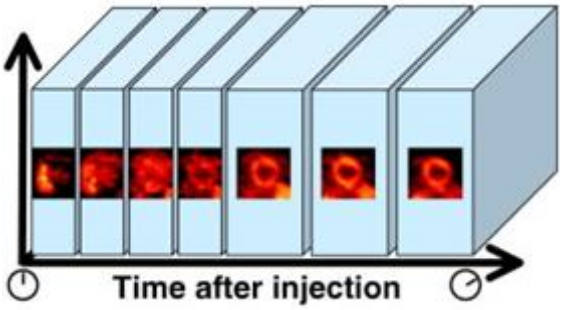

Figure 1 Dynamic imaging sequences of the tracer are recorded over time after the injection of the tracer [41]

In general, during the physical stress tests (e.g., exercise on treadmill or exercise bicycle) and while the rest tests, MPI test evaluates the flow of blood into the myocardial tissue. For patients who are unable to perform physical stress tests (For e.g., the elderly patients), the chemical stress is given to the patients to increase the blood flow of the myocardial tissue which resembles the physical stress test [15]. In some cases, if the patient has a perfusion defect and has undergone only a rest test, there are high chances that the patient's heart might look normal. This is because, for instance, while performing the physical stress test, the heart muscles require more oxygen than the normal rest state and there is a higher probability to diagnose CAD at the right time. Thus, it is highly significant that the physician should recommend both the tests and, in some cases, only stress tests.

A contrast-agent is used to assess the arterial and microcirculatory blood flow by visualizing contrast kinetics as it travels via intravascular capillary pathway. These contrast agents are small molecules (solutes) which are distributed to the interstitial space and each contrast agent has different diffusion constants. To acquire contrast in the myocardial perfusion scans, different types of contrast agents are used for different imaging modalities. Usually, Iodine contrast agents are used in CT or X-ray fluoroscopic based imaging modalities. These contrast agents are injected at the rate of 3-5 ml/sec with the volume of 60-70 mL [16]. The longer the contrast agent in the myocardial tissue, more clear interpretations can be made. However, providing a contrast agent for a longer period is not permitted and this will affect the efficiency of quantification [16].

Although several processes like visual assessment, semiquantitative approaches and absolute quantification acts as an investigation tool to evaluate myocardial perfusion images, they are not adopted into clinical routine [17]. This is because they lack standardization of analysis methods and somewhat due to the lack of gold standard for validation of the results [18]. Several varieties of software are available for analysing the cardiac functions for instance in SPECT. These softwares are essential for ensuring the reproducibility and accuracy in calculating parameters of volume, elimination rate etc., [19].

In general, validations of these softwares are performed using real physical phantoms [20]. Nowadays, Phantom studies are often used to evaluate the performances and properties of this software which are used in imaging modalities like SPECT [30]. Several perfusion phantoms were designed and developed in various imaging modalities like MRI, CT, PET, US etc., The general perfusion phantoms are available to validate quantitative perfusion imaging and there are few other flow phantoms which mimics the brain and myocardial tissue perfusions. Only one or two commercially available general perfusion phantoms exist. The existing perfusion phantoms are briefly described in the following sections.

Kamphuis et al. [22], have performed a systematic review on the perfusion phantoms and described different types of phantoms based on the phantom design features which includes, anatomical, physiological, and pathological simulations [22]. They also have distinguished flow-based phantoms namely, continuous, and pulsatile [22].

Anderson et al. [29], developed two semipermeable hollow fibre phantoms, which was made out of haemodialysis fibres (which was taken from hemodialyzer) that are commercially available to perform dialysis. These general phantoms (which was sensitive to perfusion rates) were developed to validate the

MR method. In this study, gadolinium-based CA were used to observe the process of diffusion of water and solute (which occur over the walls of the haemodialysis fibres) [29]. These study results showed that the developed semipermeable hollow fibre phantoms were reliable and resembled the tissue capillary functions [29].

Veltmann et al. [27], used ultrasound imaging techniques to perform the measurements. They developed a capillary perfusion phantom that mimicked the microcirculations of the contrast agent. These general phantoms were used to validate the ultrasound imaging techniques and followed the properties (physical) of microbubbles [27]. The design used in this study to make the capillary flow phantom was different from other phantom studies. They were designed such that, 25% of the capillaries were perfused and the remaining portion of the phantom were glued completely. The equal distribution of the CA was made possible with this type of designs [27]. Noguchi et al. [24], aimed to analytically validate the quantitative perfusion imaging by comparing the flow rates in real time cases and the theory-based flow rates and the results showed good linearity between them [24]. The cerebral blood flow phantoms were designed to study PASL (Pulsed Arterial Spin Labelling), which is the magnetic resonance method that is used for measuring cerebral blood flow [24].

Mathys et al. [23], created a perfusion phantom which was compatible with Computer tomography CT imaging modality software. This phantom was developed to identify the influence of several parameters like configuration of the contrast agent, scan parameters etc., and the results obtained from those phantoms showed good reproducibility [23]. Moreover, Suzuki et al. [25], also developed hollow-fibre phantom like [29], where this study aimed to determine the quantitative accuracy of perfusion phantoms on the effect of long scan interval with bolus length. In addition to the work performed by [25], Hashimoto et al. [26], used dry (neither dialysate space around the fibres or the hollow space was filled with liquid) type of hollow fibre hemodialyzer, similar to the phantom which was developed by [25]. In this study, 8000 hollow fibres were used with 200nm diameter to make the perfusion phantom. The contrast agents were injected at a rate of 1 ml/s with the programmable power-controlled injector [26].

Chiribiri et al. [18], successfully developed a novel hardware perfusion phantom which aimed to use myocardial MR perfusion tool to diagnose myocardial ischemia. The material used for making the myocardial segment was polypropylene (PP) tubes. The different types of parameters like flow rates, dosages of CA and cardiac output were varied. The results obtained from MR perfusion images showed that perfusion phantoms were reproducible, reliable and were able to produce efficient simulation [18]. However, Ziemer et al. [42], created cardiac flow phantom which uses pulsatile pumps to model the pulsatile mixing dynamics of the heart. The Polymethyl methacrylate (PMMA) tube was filled with plastic beats. In addition to that, one more PMMA was used at the myocardial compartment, where it was filled with contrast agent (Iodine based CA). This study aimed to evaluate the accuracy of a dynamic CT myocardial perfusion technique [42].

Few studies aimed on high resolution comparison studies between two different imaging techniques. To do this, Otton et al. [43], constructed a simple model of cardiovascular circulation of the human and visualized contrast dispersion within this model with the help MR and CT imaging techniques. This simple phantom model consists of tubing and mixing chambers which mimicked the human cardiovascular circulations and the myocardial compartments was made of polypropylene straws to perform the diffusion phenomenon without CA trapping [43]. In contrast, O'Doherty et al. [44], used PET-MRI techniques to examine the simultaneous perfusion calculations. PET used radiotracer and Magnetic Resonance (MR) used gadolinium-based contrast agent. This study used the hardware which was developed by [18], to perform feasibility study showing first pass dynamics of both the imaging modalities which was used. To our knowledge, there are no myocardial perfusion phantom which could validate the quantitative myocardial perfusion imaging techniques.

In addition to these physical perfusion phantoms, there are also digital phantoms which are available for visual based perfusion validation. For instance, the study by Pianykh et al. [30], developed a digital myocardial phantom named "Myo-Simu" which was designed to solve the problems of introducing the perfusion deficit and also the case where the most of the existing real physical phantoms could not mimic perfusion of the patient's heart [30]. The most common problem which was noticed in the existing studies

were to validate and standardize multimodal imaging techniques. Additionally, above-mentioned studies used perfusion phantoms in common to resolve the above-mentioned problem.

Our previous study worked on the validation and standardization of the multimodal quantitative myocardial perfusion imaging. They developed a myocardial perfusion phantom (prototype 1) to serve the above-mentioned purpose. The results of this study (TACs) was compared with the patient's TACs as shown in the figure. The analysis results of Arterial input function (AIF) by using prototype 1 was good yet, the main problem was that, the tracer enters the tube and gets flushed out at faster rate i.e. the residence time of the tracer was shorter in phantom (prototype 1) on comparison with the residence time of the tracer, which was injected into the myocardial tissue (in patient). Moreover, the measurement of tissue perfusion and the presence of tissue mimicking materials were lacking in our previous study. The schematic representation of the problem is shown in Figure 2. Basically, the longer the contrast agent stays in the myocardial tissue, more efficiently we could diagnose CAD. Thus, mimicking the tissue is essential in these types of phantom studies.

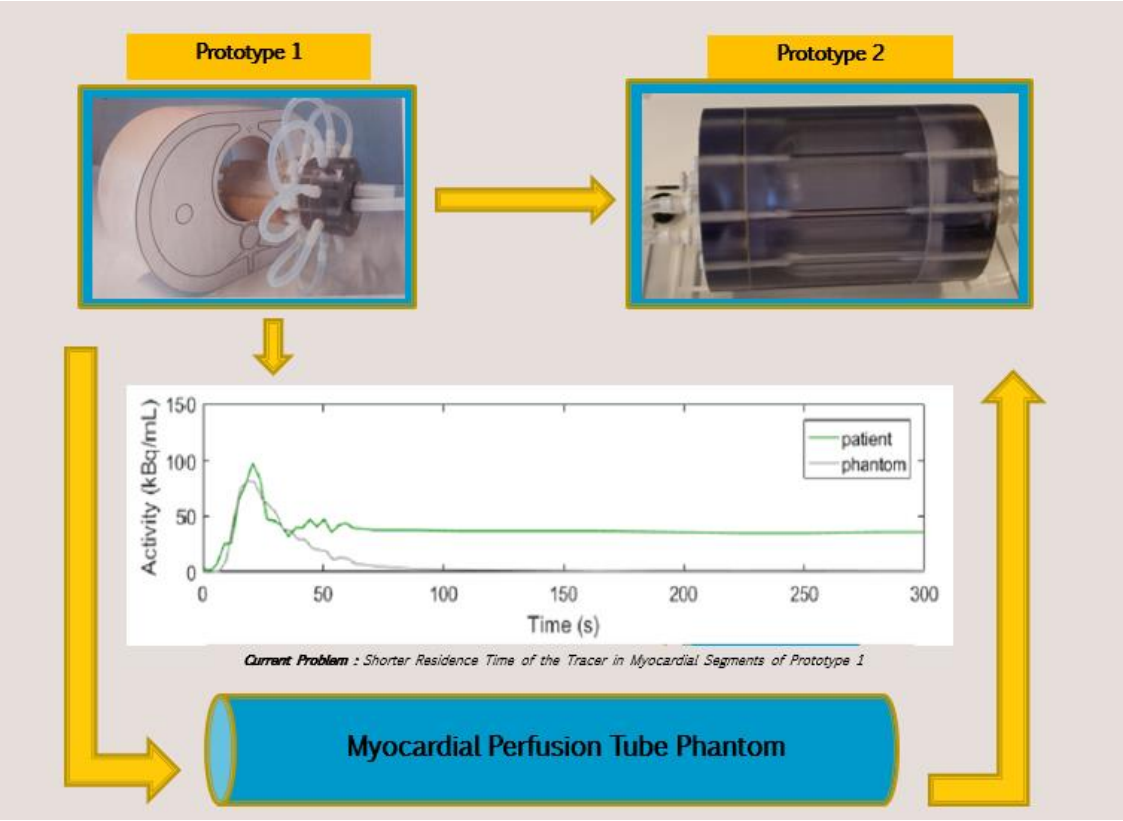

Figure 2 Schematic Representation of the current problem (i.e. the shorter residence time of the tracer in myocardial segments of prototype 1). In our study, we are developing a myocardial perfusion tube phantom (represented as blue colour cylindrical tube) which could resolve this problem. This myocardial perfusion tube phantom is later incorporated into the latest version of prototype 2. (Prototype 1 design is shown towards the left block and prototype 2 design is shown in the right block)

Figure shows the TACs of patient and the phantom. These results are obtained by simulating prototype 1 helps the researcher to improve the residence time of the contrast agent. In graph, we could observe that at t = appx. 70 s, the tracer was fully eliminated from the phantom, whereas, in patient the tracer was absorbed by the myocardial tissues the tracer stayed for longer time (t >300s). To resolve this problem (i.e. the shorter stay of the tracer/CA inside the phantom), second version (prototype 2) of the prototype 1 was designed and developed and named as "3D printed myocardial perfusion phantom". This prototype contained an empty volume / empty space left in the middle portion. yet the main purpose of developing this prototype 2 is to resemble the physiology of myocardial tissues. In prototype 1 and prototype 2, the tissue mimicking materials were not used. Thus, our project aims to contribute to prototype 2 by designing and developing different types of tube phantom. These tube phantoms could later be incorporated into the latest version of the prototype 2.

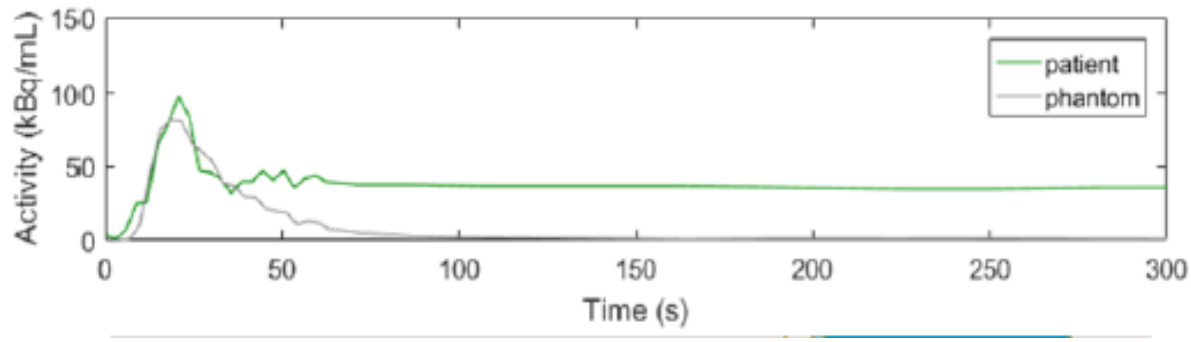

Figure 3 Time Activity curves (TACs) which was generated from the patient and the phantom (which was developed by our previous study (prototype 1)). The green colour curve represents the TACs of the patient and the grey colour curve illustrates the TACs of the phantom. The phantom TACs showed shorter retention time of the tracer compared to the patient's TACs and this is the current problem in prototype 1

Project Goal

The main purpose of this study is to resemble the physiological tissue perfusions by contrast kinetics. This can be done by finding the way to increase the residence time of the contrast agent in the systems (Myocardial Perfusion Tube Phantom and Pharmacokinetic (PK) Compartment models). The uptake of the Contrast agent could be improved by designing and developing a myocardial phantom named "Tube Phantom" which could resemble the contrast kinetics in myocardial tissues or in other terms, which could replicate the physiology of human myocardial tissue. These tube phantoms should be tested, evaluated before incorporating it directly into the prototype 2. It is highly essential to investigate the newly developed tube phantom in a controlled simplified environment.

Our project aims to develop the myocardial perfusion tube phantom. Figure 4 shows the project flow diagram, which includes the processes that are involved in the development of the tube phantom. To achieve the main goal of this current study, different types of tube phantoms were designed, optimized, developed, tested, and evaluated by comparing experimental study with the simulation study. Using Solid works (Dassault systems. Massachusetts, United States), the design proposals were made, followed by that, the simulations of the basic tube phantom were performed. These simulations helped us to optimize the different types of tube phantoms. Four types of tube phantoms were selected for further study and were developed.

These four developed types of tube phantoms were tested experimentally using simple flow setup (open model) and the modern Fluoroscopy (using X-ray) imaging technique, where the real-time kinetics of the contrast agent into the tube phantom can be visualized and these are stored in the form of a video file, and these image raw dataset could help us to obtain Time Intensity curves (TICs) using image processing techniques. Additionally, we also performed simulations using Simbiology tool, which is a part of MATLAB software (MathWorks, Massachusetts, United States), to obtain the Time concentration curves (TCCs) from the existing compartment based Pharmacokinetic (PK) models.

In this tool, the distribution of the drug that passes through the compartment can be analysed for different types of compartments. These simulations could help the researcher to validate the experimental study. The simulation results and the experimental results could further be used to compare our current study with the previous study. It is assumed that the tube phantom with tissue mimicking materials could prolong the residence time of the Contrast Agent (CA) compared to the tube without the tissue mimicking materials. It is also expected that the tube phantom with higher concentration dose of the CA and with lower flow rate conditions might produce longer residence time compared to the other parametric conditions.

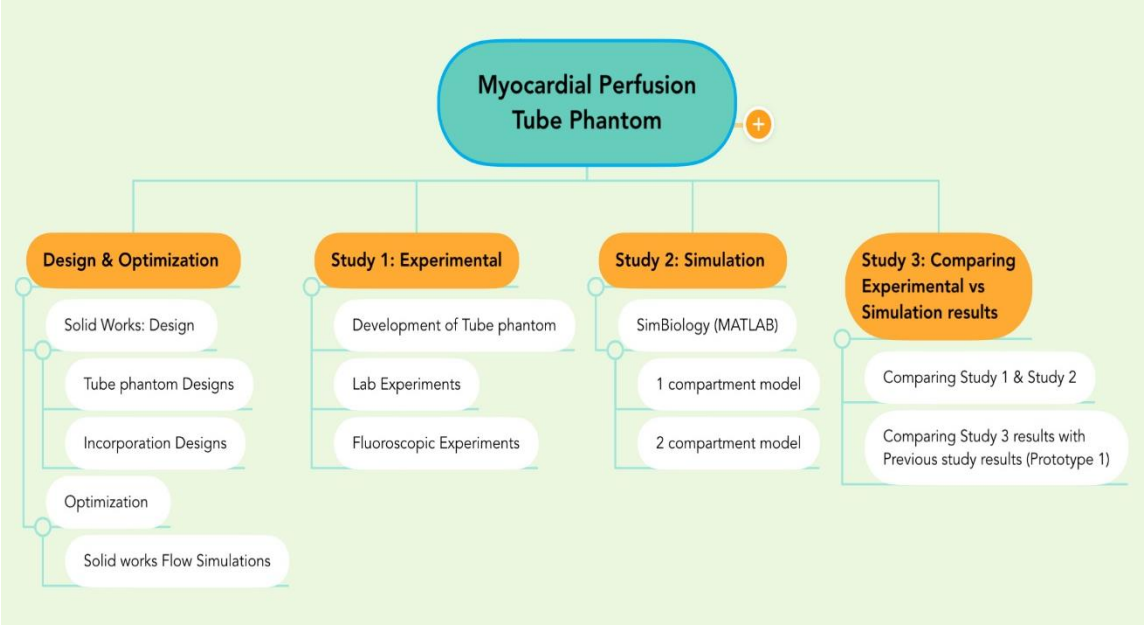

Figure 4 Project flow diagram. The development of the myocardial perfusion tube phantom is categorized into four types. Initial step which is involved in development of the tube phantom is the design and optimization of the tube phantoms. Followed by that three different types of studies are conducted. Further classification under each category is given in this diagram

The research questions and sub questions are given below:

To what extent do the systems (Myocardial Perfusion Tube Phantom and Pharmacokinetic compartment models) mimics the myocardial tissue perfusion of contrast kinetics in the human heart?

- How to design and optimize the myocardial perfusion tube phantom?
- How can the myocardial perfusion tube phantom be developed to resemble the microcirculatory kinetics of the contrast agent (Iodine) in the myocardium?
- Which pharmacokinetic compartment model is best suited for imitating the drug/contrast kinetics in the myocardial segments?

Project Requirements

The project requirements are that the Myocardial perfusion tube phantom should:

- Be able to display contrast behaviour that is comparable to that of the physiology of the Human myocardial segments
- Be compatible with clinical software
- Be portable and easy to handle
- Be leakage proof, flexible and unbreakable

Approach

This project is categorized into three main studies.

The Study 1 experiments are used to identify whether the tube phantom meet the project goals and to check whether these tube phantoms are capable to prolong the uptake of the contrast agent. The outcome of these experiments which is obtained by varying the dosages (3,5,7 ml) should be comparable to the simulation results and to the tissue perfusion of contrast kinetics in Human. Few other experiments were also performed by varying the flow rate (100-300 ml/min) and by varying the different types of tube phantoms. Reproducibility experiments will also be performed.

The Study 2 aims to determine which compartment model is best suitable to imitate the drug kinetics in myocardial segments. To do this, the sensitivity of the one compartment and two compartment models can be analysed by introducing the Intravenous (IV) bolus administration of the drug (CA) and by varying the dosages which is supplied to both the compartments.

Both studies aim to mimic the patient's myocardial tissue perfusion of Contrast Kinetics. Third Study includes the comparison of the Study 1 (TICs) & Study 2 (TCCs) results by varying the dosages and these curves could be compared with results obtained from previous study as shown in Figure 3.

General Concept

The schematic outline of the involved systems is given in the below figure 5,

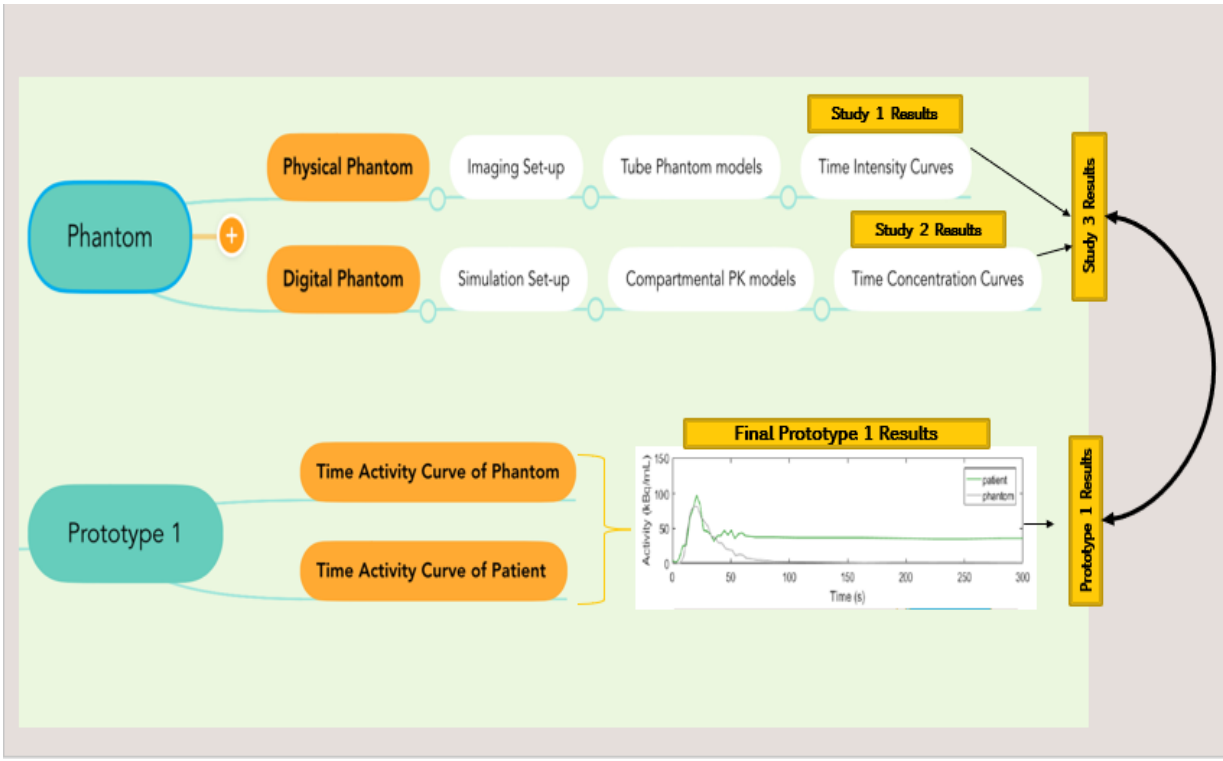

Figure 5 General Concept. The step by step process which is involved in attaining the Time Intensity Curves (TICs) and Time Concentration curves (TCCs) are explain in this figure. The phantom models which will be used in our studies are physical phantom (different types of tube phantoms) and the digital phantom (Pharmacokinetic compartmental models). Physical phantom (study 1) used imaging set-up to perform the experiments. Digital phantoms (study 2) used the simulation set-up to perform the simulations. The study 3 compared the results which was obtained from the study 1 and study 2. The Study 3 results are later compared with the results which was obtained by our previous study (figure 3). Our previous study obtained Time Activity Curves (TACs) from the phantom which they developed and from the patient by performing dynamic scans. Final prototype 1 results show this comparison in the form of a graph (Figure 3)

Structure of the Report

According to the research questions and the goals, this thesis is organized as follows: Chapter 2 discusses the theoretical topics which are relevant to this study. It includes a brief description of the different types of heart diseases and the physiology of coronary arteries. Additionally, the theory of the compartment models, and the software and the hardware which were used as a part of this project are described. Chapter 3 proposes the requirements of the tube phantom. In addition, the different types of designs, optimization of those designs are discussed. Chapter 4 introduces the process of making the physical tube phantoms. Followed by that, the brief explanation of the methodologies which were used in different studies of this project are described. Chapter 5 displays the results obtained from all the three studies. Chapter 6 evaluates the phantom designs and the results which were obtained through all the studies. Chapter 7 summarizes the whole work and gives the general remarks. Chapter 8 gives out the recommendations for the future works.

Chapter 2: Theory

This chapter gives a brief description about the anatomy and physiology of coronary arteries, followed by its relevant diseases. The basic introduction on the software and hardware which was used in this project is given in this chapter. Additionally, Pharmacokinetic modelling, compartment models and the fluoroscopic techniques are explained briefly.

Brief Description

The Human Heart is the organ which pumps the blood into the cardiovascular system for distribution to all the tissues in the body, including the heart itself. The myocardial tissue of the human heart receives blood through the coronary arteries. Coronary arteries are located at the outer region of the heart (See figure 6) and like other organs, heart also needs oxygen-rich blood to perform its work. Left main and right coronary arteries are the two largest coronary arteries. The Left ventricle and left atrium receive blood from the left main coronary artery. The left anterior descending artery branches and circumflex artery branch out from the left main coronary artery. The front portion of the left side of the heart receive blood from left anterior descending artery and outer side and the back portion of the heart receive blood from the circumflex artery.

The right coronary artery delivers blood to the right ventricular region, right atrium, and the sinoatrial and atrioventricular nodes. They further divide to the right posterior descending artery and acute marginal artery. The middle and septum of the heart receives blood from these arteries [31].

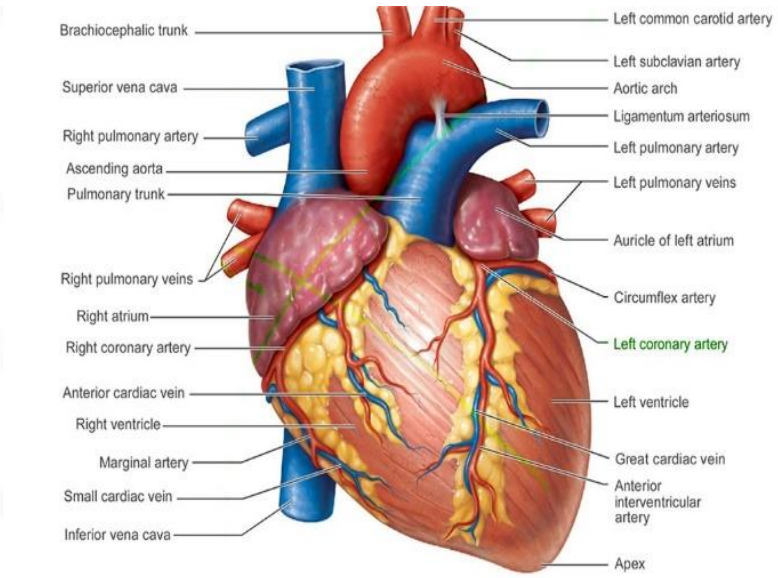

Figure 6 Anatomy of the human heart. The anatomical location of the coronary artery is highlighted with green colour (labelling) [45]

Types of Coronary artery Diseases

Coronary artery disease (CAD) is a condition in which the yellow coloured substance called plaque gets built up inside the inner layer of the coronary artery. The concurrent deposition of these substances will eventually narrow down the pathway of blood and as a result, the oxygen-rich blood supply gets restricted to the heart muscle. Any blockage which is caused inside the walls of coronary arteries might lead to serious health conditions like Myocardial Infarction and even lead to death.

The most prevalent source of heart disease is Atherosclerosis, the condition where the plaque build-up may partially or totally block (in later cases) the blood flow through the arteries. The comparison of the supply of blood through the normal artery and the artery which has this plaque build-up is clearly represented in the below figure 7. Ischemia is a condition which is caused due to the limited supply of

blood in the heart. The heart muscle does not receive adequate amount of oxygen rich blood. This condition reduces the heart muscle's ability to pump the blood.

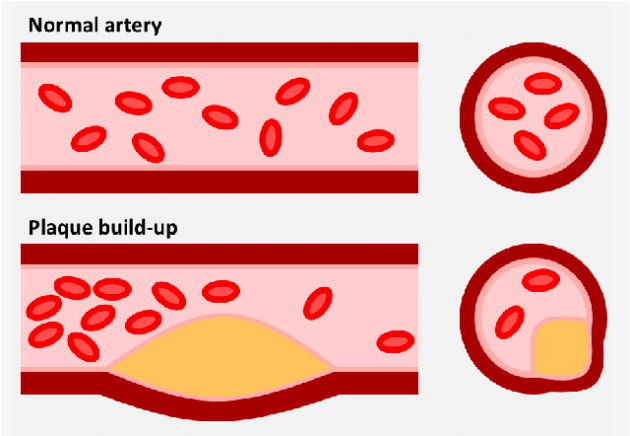

Figure 7 Comparison between the normal artery and the artery with plaque build-up. The yellow deposition in the below artery represents the plaque and the oval red colour particles represents the blood flow through the artery [46]

Examined Softwares

Solid Works

Solid Works software (2019 SP5.0) is a modelling tool which acts as a 2D, 3D solid modeller that helps engineers to create 2D, 3D solid models. This software was used for designing and executing flow simulations using Solid Works flow simulations. These flow simulations help the user to analyse the fluid flow within a solid geometry. These are intuitive computation fluid dynamics (CFD) solution embedded within Solid works 3D CAD. It generally helps the engineers to design and validate their designs and to use this software to calculate the product performances and capabilities [32].

Simbiology

Simbiology is a package, which is available within MATLAB (MathWorks, Massachusetts, United States). It provides apps and programmatic tools that automates and makes it easy to model the dynamics of biological systems. It provides a block diagram editor which helps the user to create the models where in normal cases, an engineer requires a prior expertise in differential equations. It includes library of the most used pharmacokinetic models which we can customize and integrate with any other biological models. It uses ordinary differential equations (ODEs) and stochastic solvers to simulate the time course profile of drug exposure [33]. In Simbiology, there are four types of expression, called reactions, rules, events, and observables. We can write the set of mathematical expressions (reactions, differential equations, discrete events) in the form of quantities (Compartments, species, parameters) [33]. A compartment is a physically bounded region which is characterized by capacity expressed in terms of volume, area, or length. Simbiology model analyser app helps us to analyse the models of dynamic systems.

Pharmacokinetic Modelling

Pharmacokinetic modelling is an integral component of the drug development process. It helps in predicting the effect and efficacy of the drug concentration over time. Pharmacokinetics is a branch of science which involves kinetics of drug absorption, distribution, and elimination [34]. It refers to the rate at which the drug gets distributed inside the tissues and the rate at which they are eliminated. They can be reduced to simple mathematical equations that describes the transit of the drug all over the body. Pharmacokinetic models help the researcher to understand the body reaction on a delivered drug. Pharmacokinetic models are categorized as compartment model, non-compartment model and physiological Model. Ordinary differential equations (ODEs) are used to describe the dynamic drug transport through the blood perfusion to the different tissue or organs [34].

Compartment Models

Compartment models are one category of pharmacokinetic models which can simulate the kinetic processes of drug absorption, distribution, and elimination process. Compartment are used to describe the distribution of the drug within a physically bounded region. For the movement of the drug, the different types of compartmental pharmacokinetic models are called as “open model” i.e. the drug can easily enter and leave the body. There are different types of compartmental models and here in this chapter, the one-compartment model and two compartment models are described.

One-Compartment open model

One-compartment open model (as shown in figure 8) is otherwise known as instantaneous distribution model, in which the body is considered as a single homogenous unit. This model is used only when there is a rapid distribution of the drug in body. It involves instantaneous absorption and elimination of the drug inside the body and the elimination occurs as first order process with first order rate constants. In this model the rate of input is greater than the rate of output. Based on the rate of inputs, these models are of different types namely, one compartment model with bolus administration, Continuous Intravenous (IV) infusion, Extravenous (EV) Administration, zero order absorption and first order absorption. In this project, our aim is to inject the Intravenous bolus administration into the myocardial segment. In IV bolus administration, the drug is injected into the body at a rapid rate and it takes about one to three minutes for completing the circulation and thus the rate of absorption is neglected [35].

Figure 8 One compartment open model. ka = absorption rate constant (h-1), k = elimination rate constant (h-1). The drug enters the compartment and then leaves the compartment [47]

Two-compartment open model

The plasma level time curve which is produced by injecting the drug with IV bolus administration declines biexponentially as the sum of two first order processes which includes distribution and elimination process. The distribution of the drug takes places in two compartments i.e., central compartment and tissue or peripheral compartment. Highly perfused tissue, blood or extracellular fluids represent central compartment and the distribution happens quickly and is distributed uniformly. However, in the tissue or peripheral compartment the drug takes longer time to attain equilibrium. The transfer of drug between these two compartments (as shown in figure 9) takes places by first order processes.

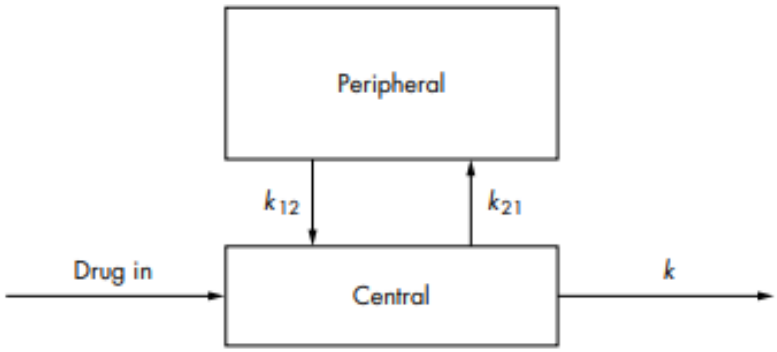

Figure 9 Two-compartment open model. The drug enters the central compartment, followed by that it enters the peripheral compartment. The reverse reaction takes place and eventually the drug enters back to the central compartment from the peripheral compartment. Finally, the drug gets eliminated. k12, k21 and k are first-order rate constants: k12 = rate of transfer from central to peripheral compartment; k21 = rate of transfer from peripheral to central compartment; k = rate of elimination from central compartment [47]

In the TCCs, the initial phase is the distribution phase and later phase is called elimination phase where the time after dose is set to x-axis and plasma level concentration of the drug is marked in y-axis. Based on the drug elimination process, they differ into three types where in first type they eliminate from central compartment. In second type, they eliminate from peripheral compartment and on third elimination takes place from both the compartments. Major elimination of drugs takes place in organs like kidney and liver [36].

Examined Hardware

Fluoroscopy

In this era, medical imaging is highly developed, and many types of advanced medical equipment are serving the physicians for diagnosing and prognosis. Many clinical applications which are available in the market that can anatomically or functionally gather information of the patient's body. Each imaging techniques has their pros and cons. There are various types of X-ray techniques in medical imaging, such as X-ray radiography, computer tomography (CT), mammography, angiography, and fluoroscopy. In our project, we have used fluoroscopy imaging technique as shown in the figure 10. The clinical images are obtained from the detectors or the films which captures the attenuated X-rays. Usually, the X-ray tube produces X-ray beams which travels through the body and little amount of energy of X-ray beam is absorbed by the body. This process is known as the attenuation of the X-rays. In general fluoroscopy is used when there is a requirement of visualizing the functions of the organs in real time. The most commonly used applications of fluoroscopy include performing surgeries to place the implants. Prior to diagnoses, before performing surgery, the contrast agents are used to visualize the organs or the structures of interest of the organs and view them. Contrast agents like Iodine, barium is given to the patients. To avoid risk, the administration of the drug is kept minimal for the patients [35].

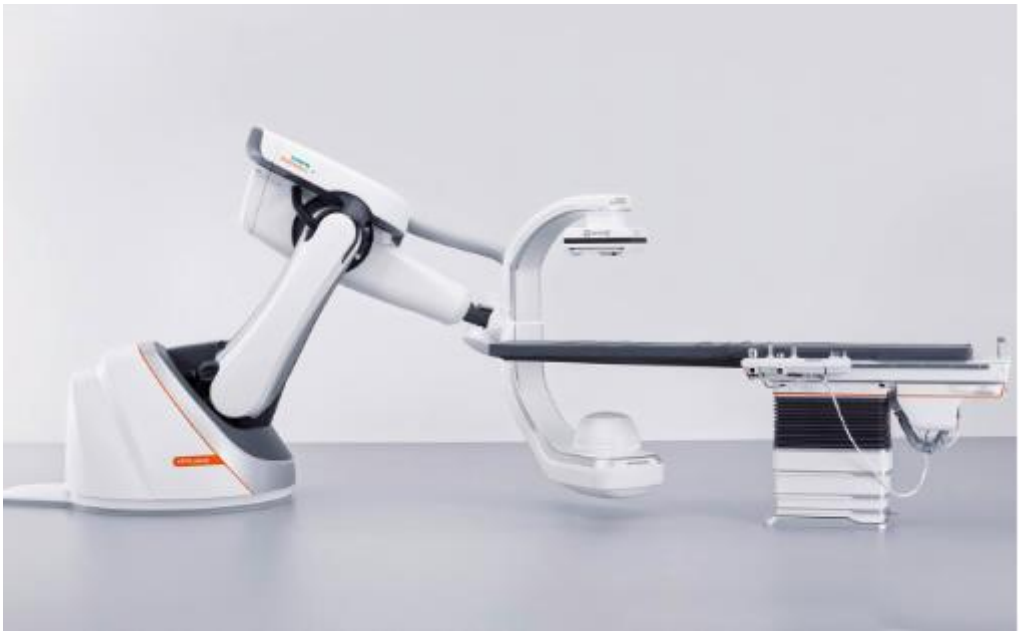

Figure 10 Artis Pheno-Siemens Healthineers. The patient bed is adjustable, and the detector's gantry can freely rotate to acquire and project the X-ray beams at several angles [36]

Chapter 3: Development of a Tube Phantom

Requirements

This chapter initially starts with the requirements section. Followed by this, several design ideas are generated. This chapter gives a brief description about the designs and optimization of the tube phantom. At last, the point goal analysis is discussed in detail to understand the Contrast kinetics into the tube phantom.

Prior to the design process of the tube phantom, it is important to set up the requirements which falls under our main project goals. The requirements are listed as follows:

1. Dimensionally fit into the empty volume of the myocardial segment of the prototype 2 design
2. The materials used for making different types of the tube phantoms should possess the following phenomena namely:
    a. Permeability
    b. Adsorption
    c. Diffusion process
3. The materials (semi-permeable membrane) which is used inside the tube phantom should allow the Contrast agent to pass through the pores.
4. The tube phantoms can be used independently without the main design (i.e., the prototype 2)
5. It should withstand at least the maximum pressure of 10 bar
6. It should comprise a simplified physiologic model of perfusion that can be translated into tissue compartment models
7. It should be leakage proof and should be unbreakable
8. It should be compatible to the computational software
9. It should be able to create a wide range of physiologically relevant Time Intensity curves (TICs) under various experimental conditions (like varying the flow rate, varying the dosages of contrast agent (CA) etc.,)
10. The size of the adsorption material should be larger than the pore size of the membrane module (>20 nm)
11. The simulation software which will be used during our study, should be able to obtain the Time Concentration Curves (TCCs)
12. The design models and the tube phantom should lie within the boundary conditions (For e.g., Inlet flow rate, the capacity or the volume of the compartment, the pressure conditions)

The tube phantom should be handy, unbreakable and leakage proof. It is important to design the tube phantom which are smaller in size so that the incorporation process (Implanting the tube phantom into the main design (prototype 2)) could be done with ease. It is very essential that the size of the tube phantom should not be greater than 10 cm for a reason that tube phantom design can fit in the newly developed, latest version of prototype 2. The tube phantom should be leak proof, just to avoid unnecessary leakages while carrying out the experiments. The higher concentration of Iodine-based contrast agent produces a higher peak enhancement, yet they are often viscous (which are sticky in nature) and thus, it is highly necessary to prevent leaks in the entire flow setup. The important aspects that should be considered include, the dimensions of the tube phantom, the different types of membrane module (fibres) patterns which will be harvested inside the tube phantom (whether it is twisted or normally glued or in the form of braided), the material used for making the tube phantom. The compatibility of the tube phantom to the computational softwares are crucial to perform the experiments.

The materials which will be used to build different types of tube phantoms should allow the contrast agent to pass through the pores. The adsorption, diffusion and permeability phenomenon should be performed by the materials which will be chosen for developing the tube phantom. The size of the adsorption material should be greater than the pore size (>20nm) of the fibre since, there might be high probability that the chosen adsorption material could get flushed out along with the water (if the size of the adsorption materials are smaller than the mentioned pore size). Using tube phantoms independently will helps the researcher to redesign and iterate the tube phantoms by performing lab experiments and also saves additional material and fabrication costs. Moreover, using the tube phantom along with the main prototype 2 design and redesigning them could be a tedious process. The design and development of the tube

phantom should follow step by step approach (i.e., the design process should start with a simple design for instance, the basic tube phantom followed by tube phantom with membrane module (fibres) and then the complex design which is the tube phantom with both membrane module and the adsorption material). Before designing or developing the different types of tube phantoms, the above-mentioned requirements should be considered.

Design generation phase

The tube phantom requirements play a major role for generating the design ideas and while making the important decision on designs. This section briefly discusses the pre-concept design ideas of tube phantom, incorporation designs and 3D printed scaffold designs. Following this, the concept design ideas which were proposed will be described.

Pre-Concept Design Phase

Tube Phantom Pre-concept design ideas

In this section, to obtain the pre-concept design ideas, initially hand sketches were made using online drawing tools (i.e. google doc drawings & draw.io) and followed by that few ideas were shortlisted, out of which, four designs were proposed during the initial phase of the project work. The four proposed pre-concept design ideas are briefly described below. Figure 11 shows the different types of proposed pre-concept designs.

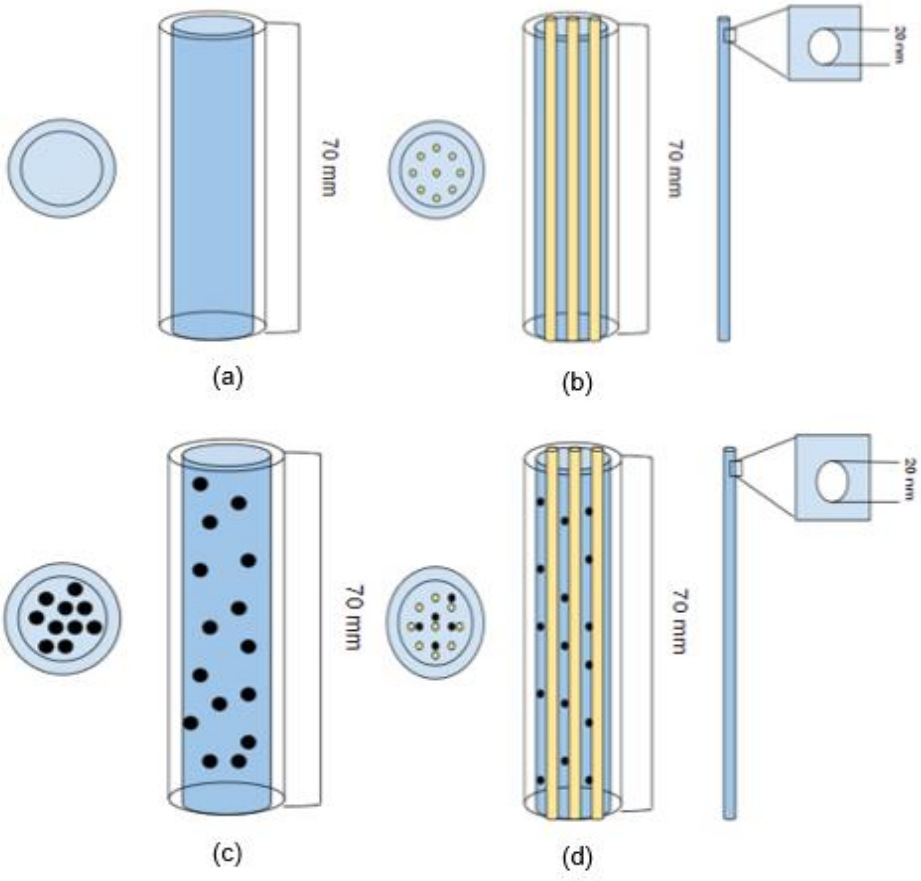

Figure 11 Tube Phantom Pre-concept designs with specifications (Length (L)= 70 mm; Inner diameter (I/D) = 6 mm; Outer diameter (O/D) = 8 mm); (a) Basic tube phantom (BTP) (without any membrane modules (Fibres) and adsorption materials); (b)Membrane Module filled tube phantom (MMTP) (with Normal type of fibres); (c)Adsorption tube phantom (ATP) (with only adsorption materials); (d)Mixed tube phantoms (with both normal type fibres and adsorption materials). Black circles represent the adsorption materials and the yellow cylindrical tubes inside the main tube phantom illustrates the fibres. These fibres have pores with pore size of 20nm

Basic Tube phantom

The basic tube phantom (BTP) is cylindrical in shape and is made out of plastic, which is flexible. These are simple hollow tubes (flexible, transparent) with an outer diameter (O/D=8 mm), inner diameter (I/D=6 mm) and with the overall length (L=70 mm). The fabrication of this type of tube phantom is without fibres and adsorption materials. This tube phantom looks similar to the one-compartment pharmacokinetic model. This tube phantom was initially proposed to understand the basic concepts of contrast kinetics inside the one compartment model.

Membrane Module filled Tube phantom

The membrane module filled tube phantom (MMTP) is cylindrical in shape, with large number of membrane modules (fibres) that are glued into the flexible plastic tubes. The fibre (Modified Polyethersulphone (PES)) which was used in this project have a pore size of S (size of the pore) =20 nm. These fibres (semi-permeable membranes) allows the solutes to pass through the pores and the process of diffusion takes place. Based on these properties, the MMTP is assumed to mimic the perfusion in microcirculatory networks. While designing this type of tube phantoms, few insights were proposed to alter the fibre designs (based on different types of patterns) (See Figure 1.2 in Appendix A). The different possible designs of the fibres were made, and they were categorized as follows: (1) Normal type; (2) Twisted Type; (3) Braided Types.

In Normal type, the membrane modules were harvested directly into the plastic tube in a straight manner. In Twisted type, the membrane modules were twisted (Turn one fibre over another fibre and repeat this pattern of design for the n number of fibres used) and then glued by inserting them into the plastic tube. Final type of patterns involves the making of the braided fashion followed by the insertion of those patterns into the plastic tube. The length of those membrane modules was 100 mm (this length was chosen based on the making process of tube phantom and this is discussed in detail under Methods section). The tube specifications were (O/D=8 mm; I/D=6 mm; L=70 mm). Though several ideas were proposed, only two types of membrane modules based on structures (fibre design) were chosen and they were normal and twisted type of membrane module filled tube phantom.

Additionally, the number of fibres which was used for making the tube phantoms varied from 1 to 20. Out of these, the MMTP which could withstand maximum pressure (which could fulfil the requirement 5) were chosen (For instance, the tube with 10 plus membrane modules). Braided type was discarded since they were blocking the flow of water while performing the experiments.

Adsorption filled Tube phantom

As the name describes, this type of tube phantom was filled with the adsorption materials. As a part of lab experiments, the plan was proposed to use sieves which have pore size that is less than the size of the adsorption material, so that these adsorption materials could get trapped by them. Activated charcoal in the form of tablets (125 mg per tablet) was used as the adsorption material. These tablets were crushed and powdered, and introduced into the plastic tube with L=70 mm; O/D = 8 mm; I/D=6 mm. This was chosen as a part of pre-concept design idea phase, but later discarded during the concept phase, since the next type of tube phantom itself fulfilled the goal to be achieved.

Mixed Tube Phantom

Tube phantom with both the membrane module and the adsorption materials were harvested inside the flexible plastic tube and it was glued on both sides. The membrane module specifications include (L=100; S=20 nm) and the adsorption material's specification include (125 mg per tablets of activated charcoal). Two tablets were used per tube phantom. Tube Phantom's specifications include Outer diameter of 8 mm, inner diameter of 6 mm and with the final length of the tube as 70 mm. This tube phantom is assumed to mimic the tissue perfusions in microcirculatory networks and also it is assumed that the activated charcoal can trap the solutes (contrast agent) and this is based on the type of the adsorption material used and their properties. The process of diffusion followed by adsorption of the solutes happens with the help of this tube phantom.

Incorporation pre-concept design ideas

Incorporation ideas were suggested as a part of this current study and they enabled the researcher to restrict the selection of choices by selecting the specifications for the tube phantom designs (i.e. the

length, diameter etc.,). Some types of pre-concept designs are shown in figure 12. Three incorporation pre-concept inlays were designed and out of which the third design i.e. (c) was selected to perform further simulations. Initially one fibre normal type MMTP was designed and then the same type of tube phantom with reversed fibres (i.e. where the fibres are placed horizontal) were proposed as second incorporation design. Followed by these two designs, the direct incorporation of fibres (without the hollow plastic tube) into the arc shaped myocardial segment designs (designed in form of a rectangular box with empty space in it) were initiated and at last these designs were used to perform the velocity based simulations. The velocity-based simulations (See Figure 1.13 in Appendix A) helped the researcher to design the final incorporation design. During the simulations, the velocity-based comparisons were made between the tube with pores and without pores. It was observed that the incorporation designs with pores (d) undergoes the process of diffusion and it prolongs the uptake of the dye comparatively to the tube design without pores.

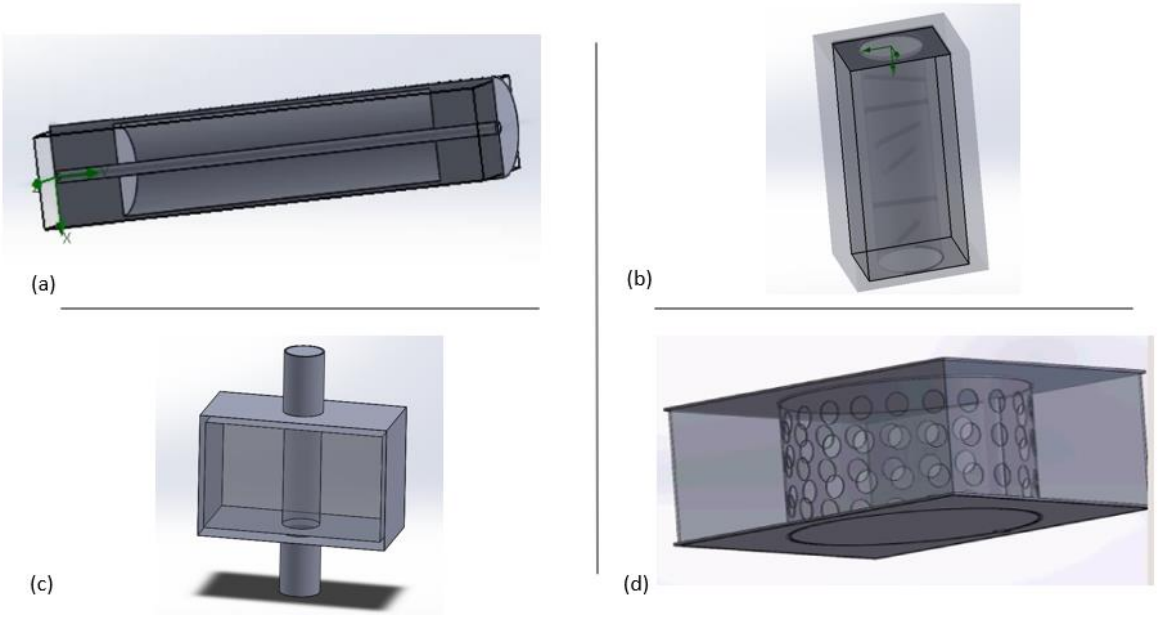

Figure 12 Incorporation Pre-concept designs. (a) The normal type membrane module filled tube phantom (MMTP) with one fibre inside the hollow cylinder (cross-sectional view); (b) The normal type MMTP with numerous fibres places in-between the cylindrical tube in horizontal manner; (c)The normal type MMTP with one 3D printed fibre which is inserted into the box hollow box with pores in it with pores size of 20nm; (d) The normal type MMTP with one fibre which is the zoomed view of (c) to display the pores

Scaffold incorporation design ideas

The most commonly used technology for the rapid prototyping is 3D printing. While designing prototype 2, 3D printers were used to fabricate the myocardial perfusion phantom. In our study, the tube phantom designs were fabricated using manual methods. As a part of an idea generating phase, the scaffold pre-concept design ideas were proposed. One of the applications of the tissue engineering is the 3D printed scaffolds, where it has both pros and cons. This 3D structure is highly porous in nature, where customizable pores with pore size (20 nm, that is similar to the fibres used in this study) can be made. This scaffold pre-concept design idea was generated to serve the main purpose of this project (i.e., to resemble the physiology of the myocardial tissue). Thus, two design ideas were proposed and are shown in the figure 13. The first design shows the incorporation of the developed tube phantoms directly into the 3D printed scaffolds structure (Geometry of this scaffold is arc shaped hollow segment and is based on the prototype 2 design). The second design depicts the 3D printed tube phantom which consists of cylindrical tubes or otherwise known as 3D printed fibres with numerous pores with pores size 20nm that is fabricated along with the 3D printed scaffold structure. Additionally, the adsorption materials (for instance, the activated charcoal) can be introduced into the arc shaped hollow scaffold in between the cylindrical tubes (i.e. in the empty air spaces). The size of the activated charcoal should be greater than

the pore size so to avoid the flush out of these materials along with the water. The whole setup with the fibres and the arc shaped hollow scaffold is collectively known as “3D printed tube phantom”.

In this design (b), the water enters through the cylindrical tubes (3D printed fibres), followed by this the diffusion process takes place and the exchange of CA/dye happens from the cylindrical tube to the empty air space and the dosages of CA/dye are assumed to get adsorbed by the activated charcoal (i.e., the adsorption material). The second design more resembles the mixed tube phantom and it is assumed that it will behave in similar way as that of mixed tube phantom. By removing the adsorption materials from the second design, then the design might resemble and perform the functions as that of the membrane module filled tube phantoms (Normal type). The main advantage of introducing these 3D printed scaffold design or 3D printed tube phantom is to facilitate the purpose of reusing the tube phantoms “n” number of times for performing the analysis, testing, and several experiments. Initial design idea was discarded since it would be hard to measure the flow rate separately for each type of tube phantom. Instead, only one type of tube phantom could be introduced into each myocardial segment of prototype 2. The second design was proposed as a part of future recommendation. These design ideas could be incorporated later into the design prototype 2.

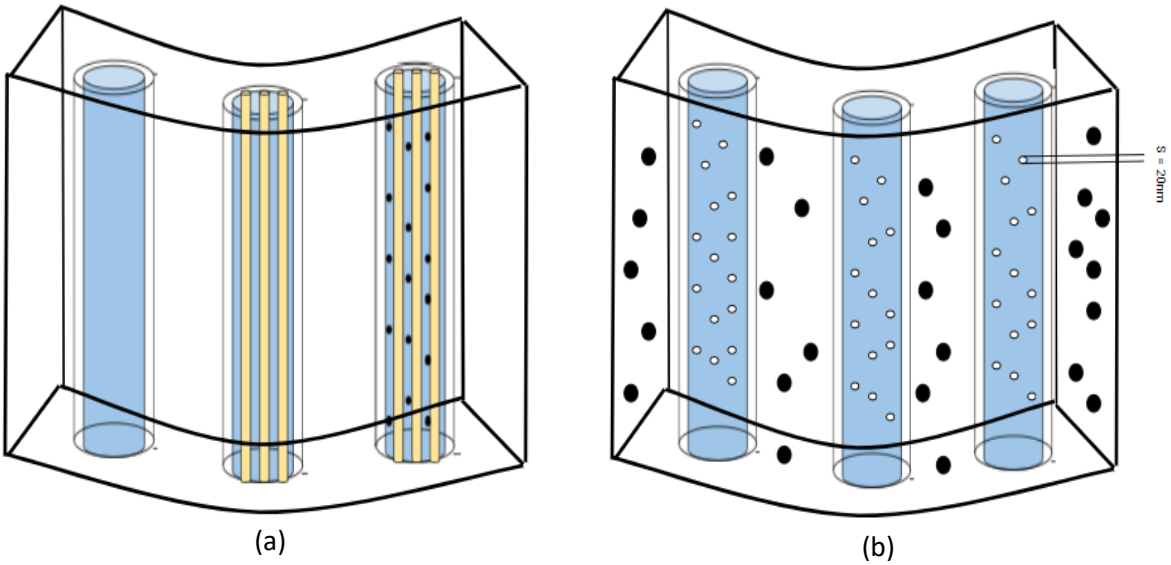

Figure 13 Scaffold Pre-concept designs. (a) Design 1 shows the direct insertion of the different types of tube phantom designs into the arc shaped hollow scaffold structure; (b) Design 2 illustrates the 3D printed tube phantom which consists of the cylindrical tubes which resembles the fibres which has pores in it with pore size 20 nm. These cylindrical tubes or otherwise known as 3D printed fibres which were fabricated along with the arc shaped hollow scaffold structure. The Black circles represent the adsorption materials (Activated charcoal) and the white circles shows the pores. The yellow cylindrical tubes in (a) is the fibres (Modified Polyether sulphone (PES))

Concept Design Phase

Pre-concept design ideas of the tube phantom designs were synthesized, and the tubes were tested in lab settings to decide the final pre-concept selections. For this selection, based on the requirements, different pre-concepts were analysed and checked for the practical feasibility and the availability of the resources.

Due to the fact that, the purpose of using adsorption filled tube phantom was already fulfilled by the fourth type of the design plan i.e. Mixed tube phantom, which had both adsorption material and semi-permeable

membrane module in it, the third pre-concept design idea (i.e. the adsorption filled tube phantom) was discarded.

Instead, another sub type of tube phantom which was proposed during the concept design phase under type 2 i.e., the twisted type membrane module filled tube phantom with 20 fibres (fully filled). The twisted style pattern of membrane module filled tube phantom with maximum number of fibres (membrane module) in it was used for further design and development. In addition to this type three other pre-concept design ideas where shortlisted. Thus the final four concept designs are classified as follows: (a) Basic tube phantom; (b) Normal type membrane module filled tube phantom (10 fibres (half filled)); (c) Twisted type membrane module filled tube phantom (20 fibres (fully filled)); (d) Mixed tube phantom (10 Fibres, Normal with adsorption material (2 quantity of 125 mg tablet of activated charcoal)). Figure 14 shows the newly proposed final concept designs. The specifications of the tube phantoms were same as presented during the pre-concept design phase.

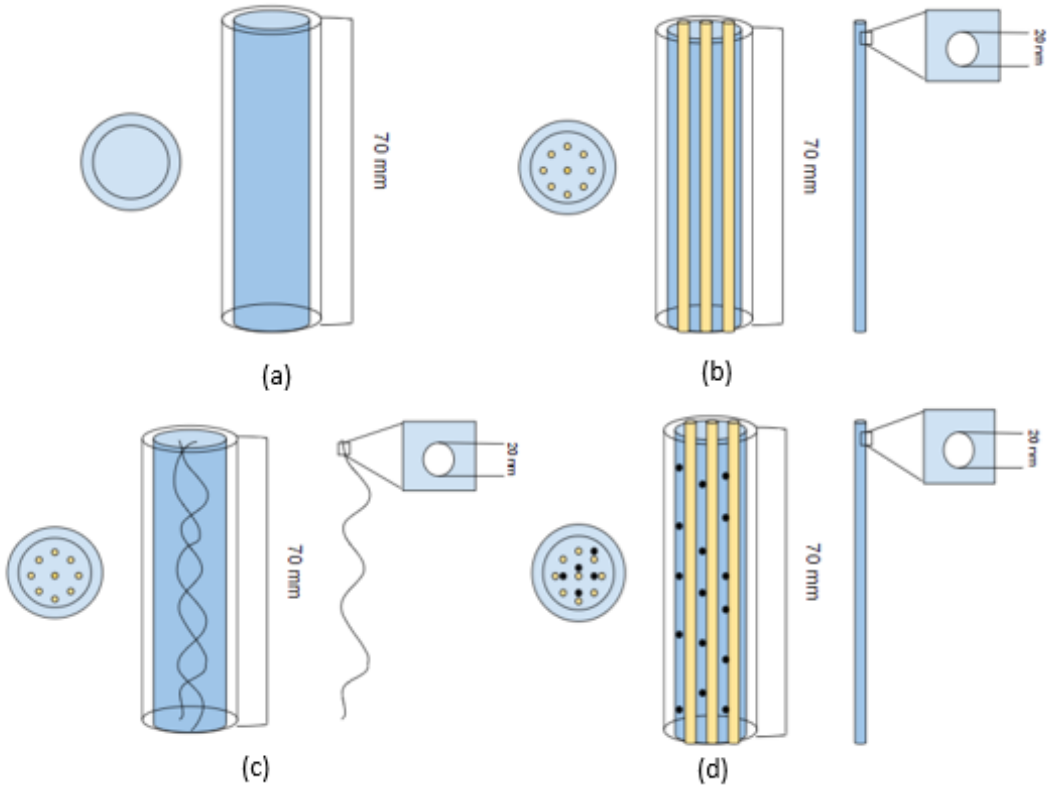

Figure 14 Tube Phantom concept designs with specifications (Length (L)= 70 mm; Inner diameter (I/D) = 6 mm; Outer diameter (O/D) = 8 mm); (a) Basic tube phantom (BTP) (without any membrane modules (Fibres) and adsorption materials); (b)Membrane Module filled tube phantom (MMTP) (with Normal type of fibres); (c) Membrane Module filled tube phantom (MMTP) (with Twisted type of fibres); (d)Mixed tube phantoms (with both normal type fibres and adsorption materials). Black circles represent the adsorption materials and the yellow cylindrical tubes inside the main tube phantom illustrates the fibres. These fibres have pores with pore size of 20nm.

Designs

Tube Phantom designs

Among the four types of final concept designs, first two types of tube phantom were designed using Solid Work 3D Software. The basic tube phantom which is the first type was designed by considering the tube phantom specifications (L=70 mm; I/D=6 mm; O/D=8mm). Using the sketch tabs with the different shapes, that is available in solid works (Dassault systems. Massachusetts, United States), the hollow cylindrical tube phantom was designed. The proposed concept sketches for the type two tube phantom (MMTP) was designed by introducing the membrane module cylindrical tubes (L=70 mm; Diameter (D) =0.7mm) inside the hollow tube design. The no of fibres (membrane modules) varied from 1 to 20 (n=1,2,3,5,10,15,20). Figure 15 (a) shows the basic tube phantom design; (b) pre-concept design ideas which was designed for normal type membrane module filled tube phantom (MMTP), (b) MMTP with one

fibre; (c) MMTP with two fibres; (d) MMTP with three fibres; (e) MMTP with four fibres; (f) MMTP with five fibres; (g) MMTP with 10 fibres; (h) MMTP with 20 fibres.

Figure 15 Tube phantom designs with specifications (Length (L)= 70 mm; Inner diameter (I/D) = 6 mm; Outer diameter (O/D) = 8 mm). (a) basic tube phantom (BTP); followed by that the pre-concept design ideas which was designed for normal type membrane module filled tube phantom (MMTP), (b) MMTP with one fibre; (c) MMTP with two fibres; (d) MMTP with three fibres; (e) MMTP with four fibres; (f) MMTP with five fibres; (g) MMTP with 10 fibres; (h) MMTP with 20 fibres.

Incorporation Designs

In this section, two design plans for incorporating the tube phantom into the final design of prototype 2 were made. The prototype 2 design (was taken from our previous study) has three arc shaped hollow

myocardial segments in total and they are located at the middle portion of the 3D printed heart (novel myocardial perfusion phantom).

Design Plan 1 Figure 16 shows the plan 1 of incorporation design, where the tube phantom itself is directly inserted into the prototype 2 design. The orange arrow shows the location of the tube phantom which was inserted into one of the arc-shaped hollow myocardial segments.

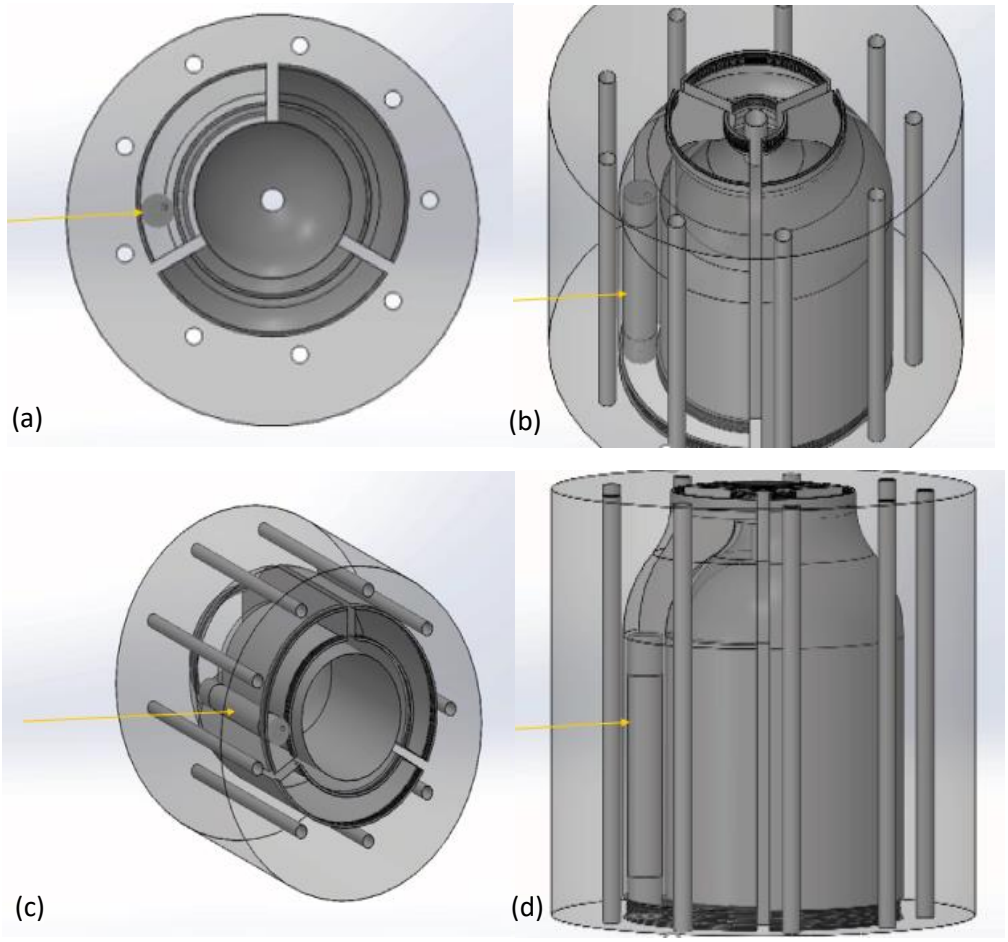

Figure 16 Incorporation designs 1 of membrane module filled tube phantom (MMTP) into the final prototype 2 design. (a) Top view of the MMTP; (b) Top side view of MMTP; (c) Right side view of MMTP; (d) Front view of MMTP. Orange arrow shows the position of the MMTP

Design Plan 2 Figure 17 shows the different views of the final designs which was made for the 3D printed tube phantom scaffold design (Design Plan 2), where the 3D printed fibres were inserted into the final prototype 2 design. This scaffold design idea could be implemented later once this project goals are met.

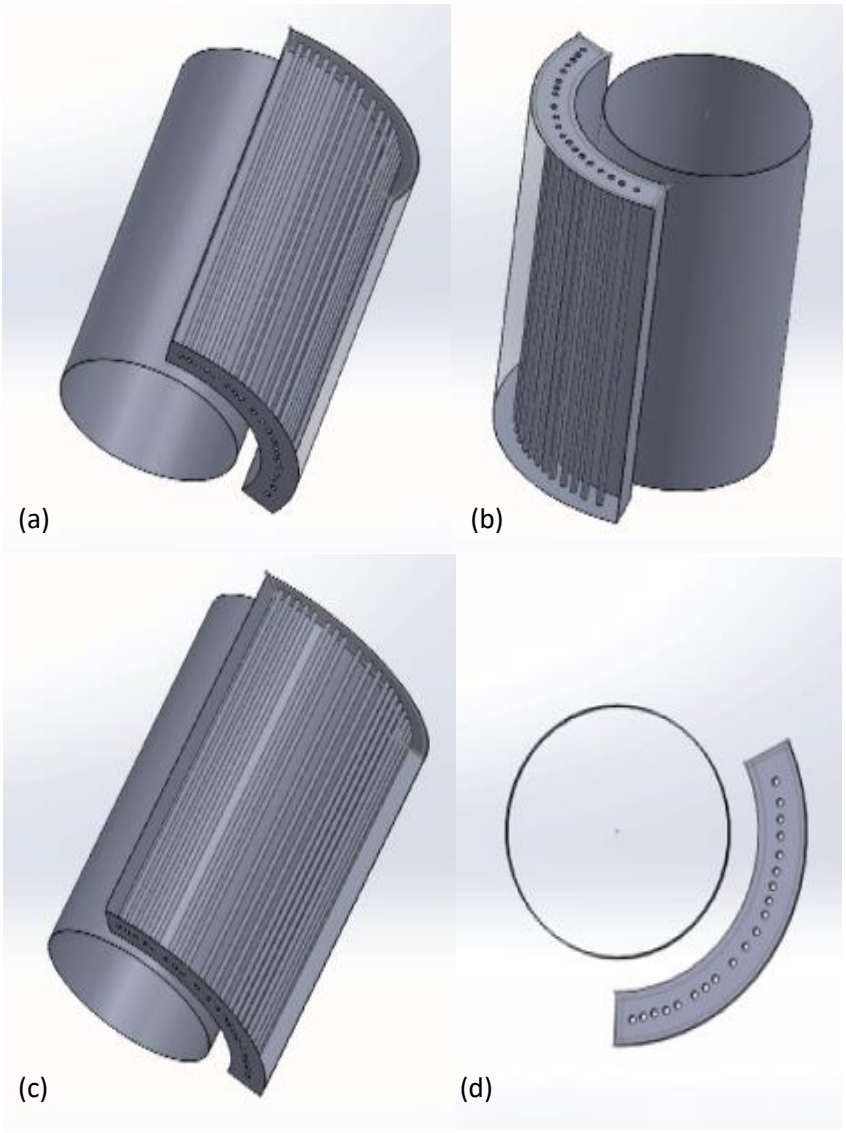

Figure 17 Incorporation designs 2 of 3D printed tube phantom scaffold (that resembles membrane module filled tube phantom (MMTP)) into the final prototype 2 design. (a) Design 2 idea with the right-side view; (b) Design 2 idea with the left side view; (c) Design 2 idea with the Front view; (d) Design 2 idea with the top view.

Optimization of the tube phantom

Simulation setup

To optimize the final designs, it is essential to perform simulations and to identify the design that best suits the purpose. For the sake of simplicity, the basic tube phantom design was chosen though several designs were proposed. The final simulation setup design resembles the simple flow setup with one extra inlet tube (where the dye and the water get mixed before entering the tube phantom, and it is shown in the figure 18. This simulation flow setup design was used to obtain the TICs, and to understand the basics of contrast or dye kinetics inside the tube phantom. To do that, the volume fraction of contrast or dye was injected into the simulation flow setup which includes the basic tube phantom. Two parts from the main flow setup (one connecting tube with the basic tube phantom) was considered. This simulation flow setup is divided into two parts: (1) initial tube with the diameter of 5 mm and with the length of 50 mm; (2) the basic tube phantom's specification includes (L=70 mm; I/D=6 mm; O/D=8 mm). The idea of using this extra tube was to visualize the initial progression of the dye even before it passes through the tube which is filled with water. Q_{in} represents the flow of the ethylene dye (contrast dye or contrast agent) which was

used for this study, that enters the inlet of the part 1 flow tube and the Q_{out} represents the flow of the dye which leaves the tube from the outlet of the part 2 tube.

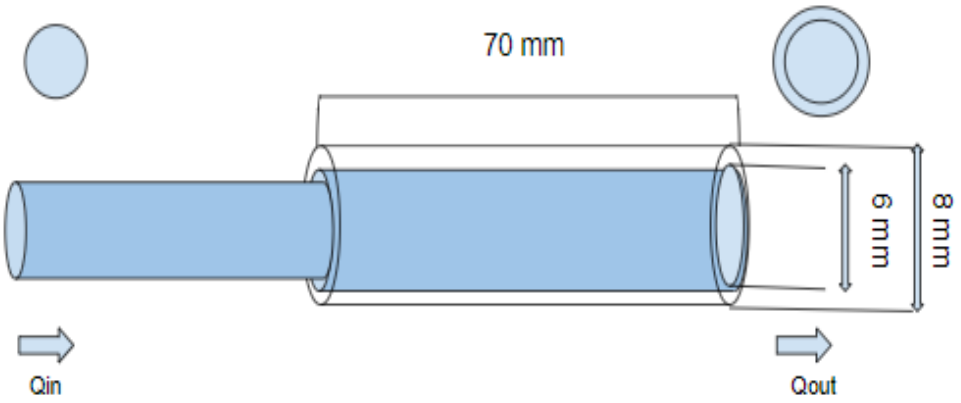

Figure 18 Simulation flow setup design of the basic tube phantom. Q_{in} represents the flow of the ethylene dye (contrast dye or contrast agent) which was used for this study, that enters the inlet of the part 1 (Extra tube) and the Q_{out} represents the flow of the dye which leaves the tube from the outlet of the part 2 (basic tube phantom) tube.

General procedure

There are several steps that are involved as a part of the process, where the dye is injected into the tube phantom to perform further simulation and analysis using solid works flow simulation. Initially the flow simulation new wizard setup is opened. Followed by that, pre-checks (like to check for the fluid flow in the geometry, and to check whether the lids are used to close the simulation flow setup) needs to be done. Before performing simulations, pre-set up steps involved in setting up the parameters (Like setting up the pressure to environmental pressure at the Outlet of the tube phantom, setting up the flow of water at the inlet of the tube with the flow rate (100 ml/min to 300 ml/min for different experiments)) have to be completed.

Next, we need to perform the simulation by clicking the run tab. It takes some time for the simulations to perform and once the simulation is finished, under output section, we can see different display settings that are available to visualize the results. Surface flow of the particles can be visualized using the feature “surface plots”. “Flow trajectories” are used to visualize the particles moving through the tube over time (by setting up the time-dependent analysis settings). Additionally, the particle study can be performed, where we could visualize the injected particles traveling through the solid geometry (Tube phantom) which was designed earlier, and various analysis can be done. The simulation raw data is exported in the form of excel-sheets and using these data TCCs can be plotted.

Simulations

Three types of simulations were performed, and these three simulations were carried out with basic simulation flow setup (As shown in the figure 18). Visual analysis method was used for all the three types of simulations to understand the basic concept of contrast dye kinetics inside the basic tube phantom. Initially we started with the visualization-based flow simulations experiments (See Figure 1.6-1.10 in Appendix A) and this type of simulation depicts the display of the water flow into the tube over a period of time for 20 seconds and they also helped the researcher to visualize the flow of water along with the injected dye particles (Ethylene dye; no of particles n =100 per injection; diameter d=0.03 mm). Ethylene dye was chosen because it has similar properties as that of the red dye which was used for lab experiments and the contrast dye which was used for the final experiments.

The second type of simulation (Particle analysis) was made to visualize the trajectory time of the injected particles and the velocity profile of those particles inside the tube. One large sized particle was injected with the diameter of 0.09 mm and was compared with the smaller sized particle (100 particles) with

diameter of 0.01 mm over a time of 20 seconds. These simulations were performed to identify the variations which occurs while using less particles and more particles inside the flow setup up.

The third type of simulation (Time-dependent transient analysis) visualizes the dye kinetics after ethylene dye was injected into the tube filled with water over a period of 30 seconds and the cut plot was made to represent the flow of the dye inside the tube over a period of time. Figure 19 shows the simulation of the final basic tube phantom with the cut plot representation. It is observed that, after the injection of the ethylene dye, the mass fraction of ethylene was initially set to one and thus the ethylene dye enters the tube with maximum value (100%). Then it gradually decreases as the ethylene dye gradually leaves the tube. After the ethylene dye is fully removed from the tube, the whole tube is filled with water.

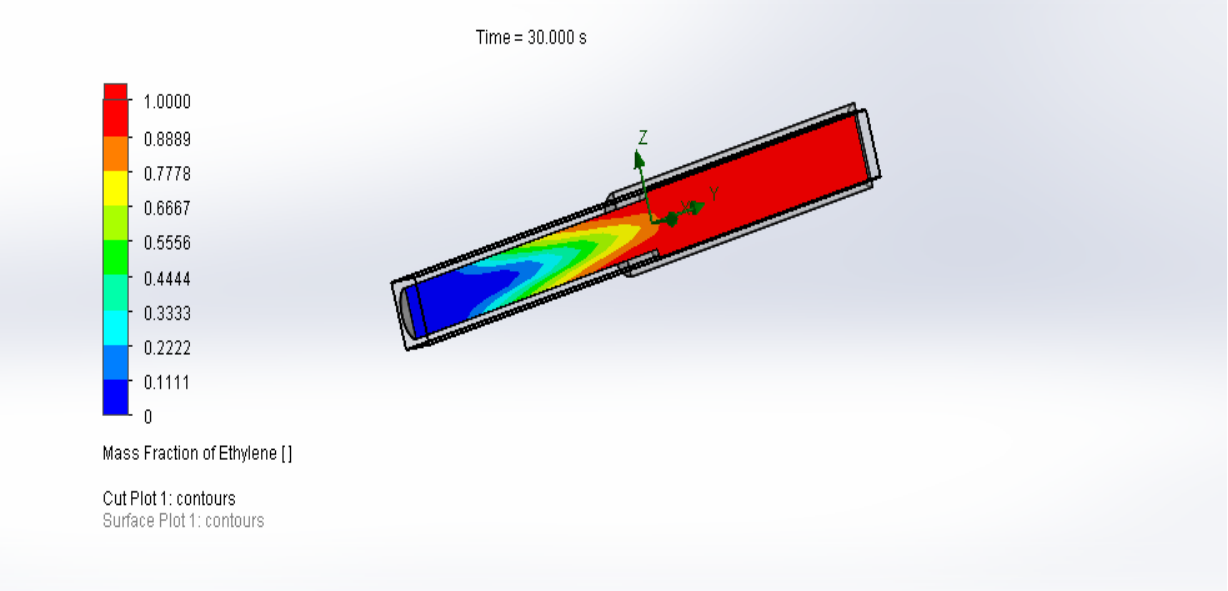

Figure 19 Simulation of the final basic tube flow setup with the cut plot representing the mass fraction of ethylene dye (Red colour represents the maximum concentration value of ethylene and the blue colour represents the minimum concentration value of ethylene or absence of ethylene). The simulation time is 30 seconds

Followed by this simulation, the point goal analysis was performed. The point goal analysis is essential to determine the concentration values at the selected points over time. After setting up the points of interest, it was assumed that the volume fraction of ethylene dye (concentration) in those points over time will be able to obtain the time concentration curve after the injection of the ethylene dye.

Point Goal Analysis

In Solid Works flow simulation, the point goal means setting up a set of goal at the point of interest (this could be either as a single point or as 3 coordinated points). In our project, The point goal analysis was performed by selecting the three points manually in the tube (point 1 = at the inlet of the tube phantom; point 2 = at the outlet of the tube phantom; point 3 = at the inlet of the whole simulation setup. Two experiments were performed over a period of 5 seconds with different parameter settings. These experiments were performed to analyse the progression of the ethylene dye as it travels through the tube at these three points.

Experiment 1

The simulation flow set up shows the three-point goals that are highlighted in light blue colour and those are shown in the figure 20.

Simulation specifications

Initial flow settings were made, and the mass fraction of the water was set to the value 0 and the mass fraction of the ethylene dye was set to the value of 1. Mass flow rate was set (Mass flow rate = 0.01 kg/s). Boundary conditions of the inlet mass flow were set, and the volume fraction of the water was set to the

value 1 and the volume fraction of ethylene was set to 0. Followed by these, the three points was assigned as mentioned before to perform this experiment 1. The analysis results are shown in figure 21.

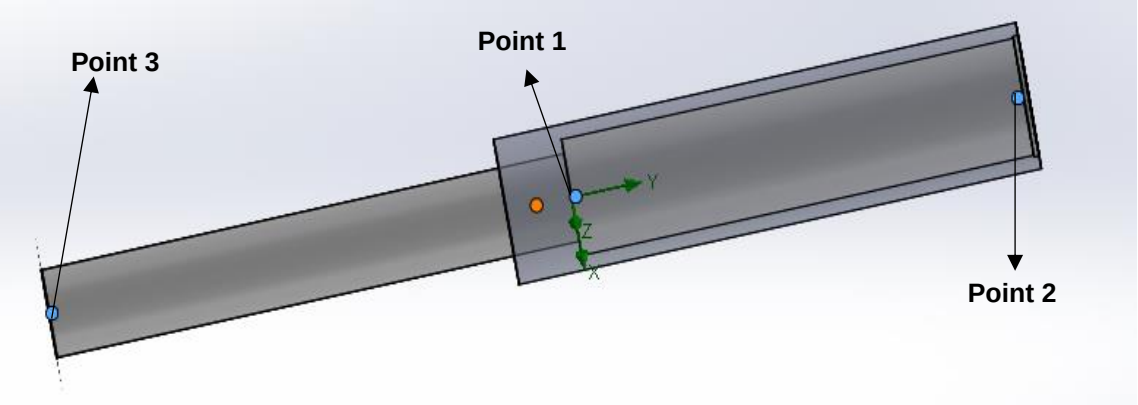

Figure 20 Schematic representation of the simple flow setup which was used for performing the point goal analysis. Three points were initially set, and the blue circle represents these points. Point 1 is located at the inlet region of the basic tube phantom (Part 2 of this setup); Point 2 is located at the outlet region of the basic tube phantom. Point 3 is positioned at the inlet of the part 1 tube. The orange circle represents the offset point which was set.

Experiment 2

The simulation flow set up shows the three-point goals that are highlighted in light blue colour and those are shown in the figure 20.

Simulation specifications

Initial flow settings were set up and the mass fraction of the water was set to the value 1 and the mass fraction of the ethylene dye was set to the value of 0. Mass flow rate was set (Mass flow rate = 0.01 kg/s). Boundary conditions of the inlet mass flow was set, and the volume fraction of the water was set to the value 0 and the volume fraction of ethylene was set to 1. Followed by this, these three points as mentioned before was assigned to perform this experiment 2. The analysis results are shown in the figure 22.

Analysis results

Experiment 1 results showed that since the mass fraction of ethylene was initially set to 1, At t=0s, the volume fraction of ethylene was 1 and the elimination of this dye can be explained with the help of the results which were obtained. Grey colour curve represents the volume of ethylene dye at that point 3 over time and it showed that the volume fraction of the ethylene value reaches 0 at t = approx. 0.5 s. This clearly shows the distribution of the dye which initially enters the tube with value 1 and gradually decreases as the time gets increased. At t= approx.0.5 s it reaches a steady state value where there is no flow of dye at this point 3. The same observations were made for the other points as well (for point 1 & point 2, the volume fraction of ethylene reaches 0 at time t = approx. 2.2 & 3.4 s, respectively.

Only difference is that at point 2, it took a little longer time (t = approx. 3.4 s) to flush off the dye from the tube compared to the other points. This was done to understand that the simulation of the dye kinetics throughout the simulated tube. The visualization results of these analysis are given in (See Figure 1.11 in Appendix A).

In experiment 2, the tube was filled with maximum amount of water initially followed by the injection of ethylene dye. The settings were reversed where the initial mass fraction of the ethylene dye was 0 and it gradually gets increased over time. At T=0 s, the volume fraction of ethylene was also 0 and at point 3, the volume fraction of ethylene reaches the maximum value of 1 at time t= approx. 0.2 s. At point 1, the maximum value is reached approximately at T= approx. 1.4 s and for point 2, the maximum value is reached approximately at T= approx. 2.4 seconds. The visualization results of this experiment are given in (See Figure 1.11 in Appendix A).

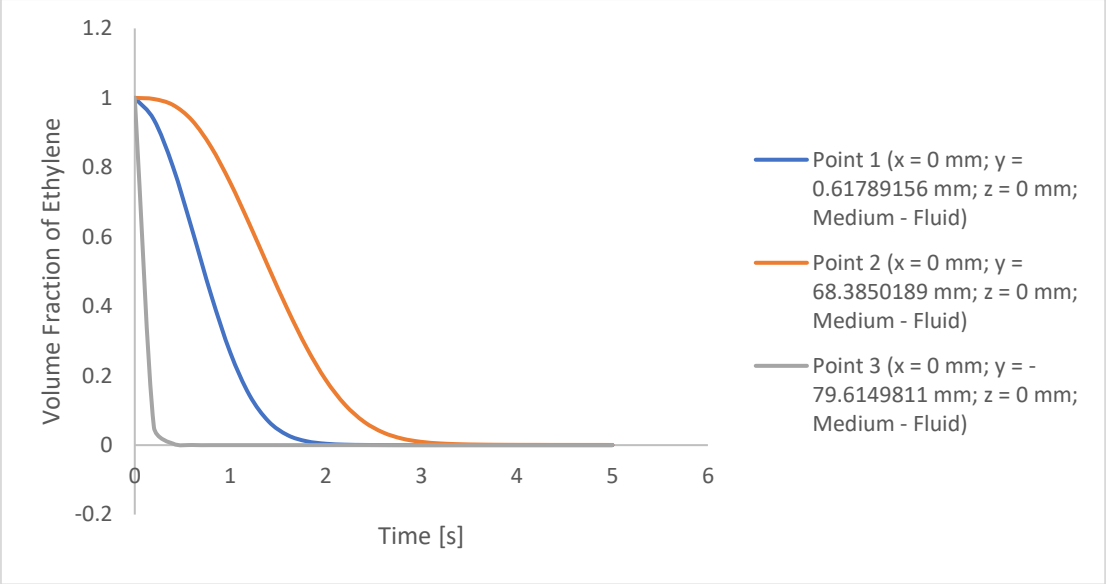

Figure 21 Point goal analysis results of experiment 1 (Point 1 : Blue colour and this shows the point at the inlet of the part 2 tube (tube phantom) and the Red colour represents the point 2 which was selected at the outlet of the part 2 tube and the grey colour represents the point 3 at the inlet of the part 1 tube

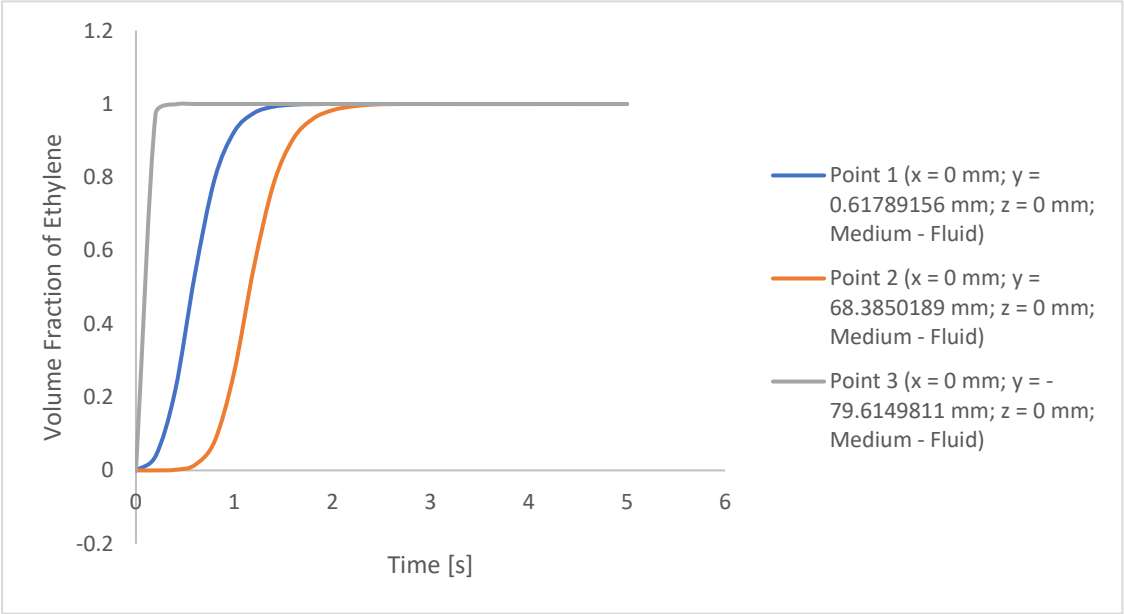

Figure 22 Point goal analysis results of experiment 2 (Point 1 : Blue colour and this shows the point at the inlet of the part 2 tube (tube phantom) and the red colour represents the point 2 which was selected at the outlet of the part 2 tube and the grey colour represents the point 3 at the inlet of the part 1 tube.

The main requirements for designing and developing the myocardial perfusion tube phantom was proposed in this chapter. Under tube phantom design generation phase, pre-concept design ideas, concept design ideas were also proposed. The final four types of tube phantoms which was proposed during the concept design idea phase were developed and the process which is involved in making the tube phantoms will be discussed in the next chapter. The methods involved in different studies which was performed as a part of this project is also discussed under the method section in the next chapter.

Chapter 4: Methods

Initially, this chapter describes the general process engaged in the fabrication of the tube phantom, called “Membrane Module gluing” or “Fibre Gluing”. The membrane modules are the hollow fibres with nanopores of pore size (S) 20nm. Following this section, the methodologies which were involved in performing several experiments (Physical and simulation) have been explained in two separate studies. Followed by that the study 3 explains the steps involved in comparing the study 1 and study 2. Overall, this chapter addresses the steps that are taken towards achieving the project goals.

Fabrication of tube phantom

Pre-setup steps

There are four steps which have been executed prior to the main fabrication process of the tube phantom. They are categorized as follows: (1) Glue Preparation; (2) Tube Preparation; (3) Membrane module preparation; (4) Syringe Preparation. The detailed explanations on these processes are given below.

Glue Preparation

The first step which must be taken, as a part of the fabrication process is glue preparation. To meet the most important requirement of the tube phantom (i.e., to avoid the water leakage while performing the measurements), it is highly essential to prepare the glue mixture properly so that they firmly fix the membrane modules to both the sides of the tube. It should also satisfy one another requirement, which is to allow the type 2,3 & 4 tube phantom ((Membrane module filled tube phantom (Normal and Twisted)); and (Mixed tube phantom respectively)) to perform the diffusion process. This glue mixture provides unbreakable and firm sealing on both the sides of the tube. The glue mixture should be well fitted between the membrane modules and the tube. It should be glued carefully that the membrane modules do not touch each other. To prepare this glue mixture (Polyurethane Lime (Bison-2k expert Colle Polyurethane)), 1:7 proportion of the hardener and glue were taken, respectively. The same protocol must be followed throughout the making process of any type of tube phantom. Thus, 4 grams of the hardener is initially poured into the disposable coffee cup (plastic) and should be weighed accurately. Then 28 grams of glue paste needs to be added and it should be mixed thoroughly using a small iron spatula. Once it attains the smooth state (See figure 1.2 a in Appendix A), this mixture is kept aside to perform the main membrane module gluing process.

Tube Preparation

The entire tube (I/D=6 mm; O/D=8 mm) is made from plastic, which is flexible and transparent. This tube is cut with a sharp blade during the tube cutting process. The measurements of the tube sizes must be taken before making the tube phantom and the four markings are made using blue whiteboard markers (See figure 1.1 a in Appendix A). These markings are essential to compare the different types of tube phantoms. It eventually should meet the requirement 1 (i.e., to dimensionally fit the main design (the latest version of the prototype 2)). Based on requirement 1 as stated in the chapter 3 of this study, the tube is cut with the length 80mm using a tube cutter. Two lines were marked with 15 mm each from the end of the tube and the same is followed on the other side of the tube. Thus, the visible region (glue-less region) should be 50 mm and with the overall size of the final tube phantom should be of 70 mm in length (which includes the glue part (10*2 mm) plus the visible region (50mm) (See figure 1.3 in Appendix A)).These measurements were made with the note that this tube phantom could later be incorporated into the final design of the 3D printed novel myocardial perfusion phantom (Prototype 2).

Membrane Module Preparation

Several membrane module types were designed (See figure 1.2 c in Appendix A) based on the described patterns (a) Normal; (b) Twisted; (c) Braided. The number of fibres which were used to make the tube phantoms varied from 1 to 20 with the range, n=1,2,3,4,5,10,15,20 (were designed and used during the lab measurements). Based on the requirement 8 (i.e., the tube phantom should be leak proof) , tube phantom was fabricated to produce low pressure by increasing the quantity of fibres (For e.g., n=10 (half filled tube), 20 (fully filled tube)), because at high pressure values, there are high chances of leakages while performing the experiments. The membrane module is cut with the size approximately 1 mm bigger to the size of the tube on both sides (Length of the fibre = 82 mm) (See

figure 1.3 in Appendix A). The different types of patterns like normal, twisted, and braided are made and are harvested into the plastic tube and these membrane modules along with the plastic tube are kept aside for performing the next steps.

Syringe Preparation

As a part of the tube phantom fabrication process, we need to inject the glue slowly inside the tube by dispersing the glue equally around the regions where the fibres are present and around the tube. Initially a 10 ml syringe is taken, and the piston is removed, and the syringe is fully filled with the prepared glue mixture using an iron spatula. Then the piston is inserted and pressed until the air bubbles escape from the syringe (See figure 1.2 b in Appendix A). Keep all these prepared items ready for next steps.

Membrane Module Gluing

To make the tube phantom, several steps need to be followed and they are as follows: (1) Place a piece of tissue on the flat table and wear gloves to avoid the glue getting stuck on the bare hands. (2) The materials which were prepared during the pre-step process should be kept ready on the table. (3) Now, take the syringe and fill the plastic tube with the glue completely to 15 mm until it reaches the second marked blue lines from both the sides of the tube. There should not be any air bubbles left in the glued surface. The membrane modules should be rotated slowly both anti-clockwise and clockwise, which helps in removing the air bubbles. Leave the tube phantom for drying overnight.

Drying and cutting process

The drying process of the tube phantom overnight is to bring the glue mixture to the state where it gets hardened and stiff to an extent that the glue portion of the tube phantom does not break while performing the flow measurements (See figure 1.4 in Appendix A). Once the tube phantom has dried completely, the cutting process is initiated. For this, initially a cutting board is placed on the flat surface and a sharp blade is taken to cut off the tube phantom 5mm from both the sides of the tube. After cutting, use the corner sharp end of the blade to clear off the unwanted dirt which lies at the edges of the membrane modules. The passage of the membrane should be made clear so that the water can flow freely through these fibres. If there are no air bubbles in the glued part and if the passage of the fibres is clear (See figure 1.5 in Appendix A), then the tube phantom is ready for testing and for performing experiments.

Study 1: Experimental study

In Artis Pheno, X-ray fluoroscopy imaging technique, several images were captured in the form of frames (with one image captured per frame) and these sequences of image frames are recorded as one video file and this video file is saved in the form of DICOM format. Since this imaging techniques involves exposure to X-rays (which are hazardous if they are given at higher dosages), the overall time duration to perform the experiments per session should not exceed 2 minutes. The Image dataset (in form of a video file) which is obtained using this X-ray fluoroscopy imaging techniques helps the researcher to obtain Time Intensity curves (TICs), by performing further image analysis using Image Processing Toolbox which is the package in MATLAB tool (MathWorks, Massachusetts, United States). The obtained TICs help us to visualize the distribution of the injected Iodine (Contrast Agent (CA)) inside different types of tube phantoms (One tube per measurement was used).

The aim of this study is to resemble the microcirculatory kinetics of contrast agent in the myocardial segments. To do this, we have developed different types of tube phantoms (As mentioned in chapter 3). It is hypothesized that tube phantoms (Mixed tube phantom (MTP), 10 Normal type membrane module filled tube phantom (10NMMTP), 20 twisted type membrane module filled tube phantom (20TMMTP)) except the basic tube phantom (BTP) should have longer residence time of CA by varying parameters like flow rates and dosages of contrast agent. Additionally, it is also assumed that the 20TMMTP should have longer residence time of CA compared to other tube phantoms (MTP,10NMMTP, BTP).

Flow setup

The developed tube phantoms have to be tested by performing several measurements. To do that, we need a basic open flow setup (with continuous flow) (as shown in figure 23) which contains a Gear pump, Pressure sensor, Flow sensor, 3D printed connectors (3), two reservoirs, Interlock Syringe (2), Intravenous line, Connecting tubes (6), Flow sensor measuring unit and a control unit. Other than the Tube phantom itself, remaining all other parts of the flow setup were placed away from the scanner gantry.

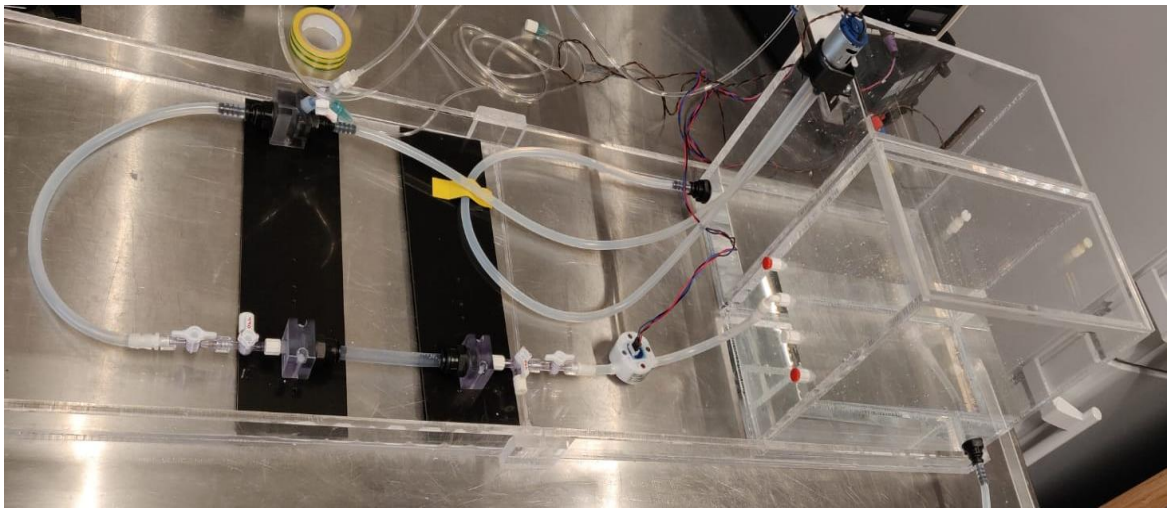

Figure 23 Basic open flow setup which was used to perform the final experiments. This setup consists of the gear pump (1), pressure sensor (1), connecting tubes (6), 3D printed connectors (3), Reservoirs (2), Intravenous line which is connected to the interlock syringes (2), Flow sensor (1) which is connected to both measuring and control unit, Three-way stopcocks (4), Two-way stopcocks (2), different types of tube phantom (4)

When the contrast bolus (Iodine-based contrast agent) is injected into this basic flow setup, the contrast agent travels through the connecting tubes and gets mixed well before it reaches the tube phantom. This mixed fluid passes through the tube phantom and gets dispersed inside the tube and is collected in a closed outlet reservoir. Additionally, one more container is used to collect these contrast agents, so we could constantly remove those contrast agents from the outlet reservoir. Figure 24 shows the

schematic representation of a basic open flow setup. Movement of the contrast bolus (Iodine-based contrast agent) is represented with the black circle in the tube phantom.

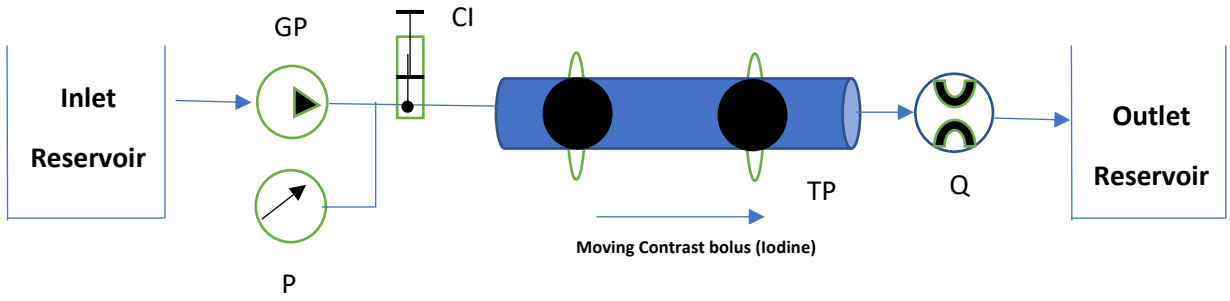

Figure 24 Schematic representation of a basic open flow setup. GP as Gear Pump; P as Pressure sensor; CI as contrast injection; TP as Tube Phantom; Q as flow sensor. The black circle with green ring surrounding it, inside the tube phantom illustrates the contrast bolus and two black circle contrast bolus are shown to represent the movement of the contrast agent inside the basic tube phantom (type 1) moving from left to right direction

General Procedure and flow setup specifications

The whole flow setup was placed on the patient bed in supine position. Scanner gantry was placed closer to the setup where the tube phantom is placed. The gear pump produced a continuous flow throughout the flow setup. Initially, the control unit which controls the gear pump is switched on and the gear pump starts pumping the collected tap water which is placed inside the inlet reservoir. For a few minutes, the gear pump is on to have a continuous flow throughout the flow setup and this also serves the purpose as to remove the air bubbles from the tube phantom. Before performing the measurements and in between the measurements, this step is followed to obtain accurate results.

We had to inject the contrast bolus (the Intravenous (IV) bolus administration of Iodine) manually. One syringe was used for injecting the Iodine Contrast agent and another syringe is filled with water to flush off the contrast agent. 10ml interlock syringes were used to perform these activities. Several lab testing and measurements were made using this setup. Same size of tubing (connecting tubes) which is flexible (Outer diameter (O/D) = 8 mm & Inner Diameter (I/D) = 6 mm) and which is made of plastic was used throughout the setup.

The flow sensors (FCH-m-POM-Art.Nr.150392, low flow turbine flow meter, B.I.O-TECH, Germany) were used to measure the flow inside the tube phantom. To easily change the tube phantom between every set of measurements, two adjustable three-way stopcocks (HT Geertsema, Netherlands) were used. These three-way stopcocks can control the flow of water, based on the experimental requirements (Flow on or off), and these were used to avoid leakages while replacing the tube phantoms. Additionally, two more three-way stopcocks were used in the flow setup to control the flow of the contrast agent. One was attached to the 3D printed connector and another one was placed where the syringes are fixed. Interlocked syringes were used to avoid the backflow of the Contrast agent.

Flow sensors helped us to control the flow which was created by the gear pump. The flow rate inside the flow setup was varied with the help of the gear pump and they varied between 50 to 500 ml/min. A pressure sensor (Bourdon with 10 bar pressure as maximum) helped us to prevent the leakages, which might be caused when there is a pressure drop to zero or when there is a high pressure. Based on the lab test measurements, it is found that all the tube phantoms are below 7 bar pressure, where 9 bar pressure was the maximum with the maximum flow rate of 400 to 500 ml/min. The geometry of this tube phantom was selected to match the prototype 2 (based on the requirement 1 as stated in chapter 3).

Artis Pheno Method

All the acquired image datasets in a single video file from Artis Pheno, siemens Healthineers, Netherlands was gathered. In general, the acquisition frame rates vary from 0.5 fps to 7.5 fps up to 30 f/s (optional). The pre-image processing was performed using this system (Artis Pheno) where the regions of interests were initially selected and this helped the us to visualize the contrast kinetics inside the tube phantom in the same image (in one frame) and these sequence of frames were recorded and saved in a DICOM video format (2f/s as default setting). Approximate time taken for every measurement was 2 minutes and the number of frames varied based on the visualization of the contrast agent distribution in tube phantom (these two parameters varied for each experiment). During the experiment, different dosages of contrast agent (Ultravist, Iodine based contrast agent) (3,5,7 ml Iodine of 300 mg/ml solution was injected at a faster pace (5 ml/sec). After the injection, water flush out is done (1-2 ml/sec).

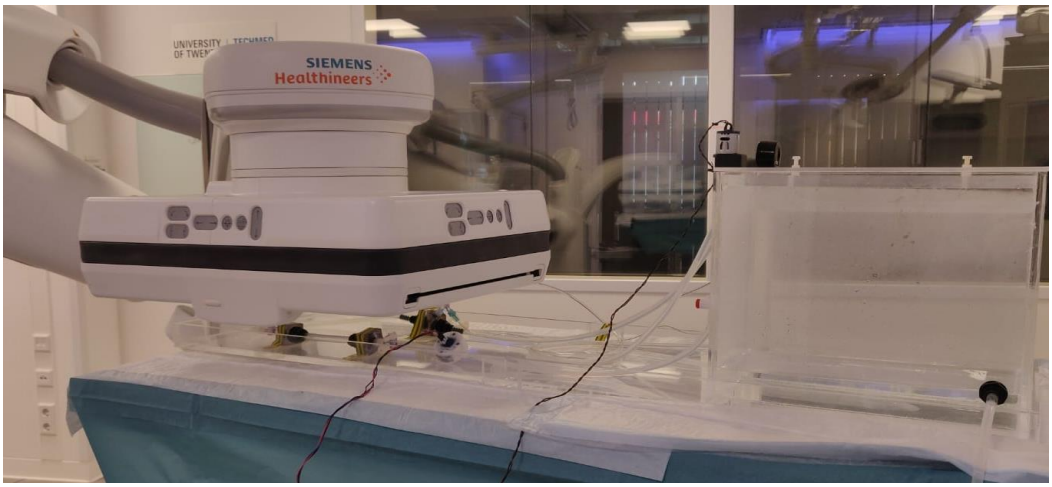

Figure 25 Artis Pheno Siemens Healthineers, Netherlands. Scan room where the experiments were performed with Scanner gantry along with the whole experimental setup

Testing the contrast agent protocol

Before performing the main measurements, it is essential to know the contrast protocol. To identify the suitable contrast protocol, several ranges (3,5,7 ml) of dosages of the CA were selected. Iodine (300 mg/ml) based contrast agent was used to perform our experiments. A 10 ml syringe was used to inject the contrast agent. Test one result showed the progression of contrast agent with 3 ml of Iodine. The image obtained while using 3ml of Iodine was good (the progression of the contrast agent was visible) with less contrast visualization. Thus, the dose was increased to 5ml of Iodine and this was set as reference for most of the measurements. As a maximum dose, 7ml of Iodine was used. The contrast agent was injected at faster rate (5 ml/s) and this was maintained throughout the measurements (might vary between 3 ml/sec to 5 ml/sec for each measurement and this variation is due to manual injection method). From these tests, the dosages of the contrast agent which needs to be administered for each experiment was finalized as 3,5,7 ml of 300mg/ml of Iodine.

Image visualization and Image analysis

The resulting DICOM format (video file) was visualized using Radiant (Medixant, Poznan, Poland) and the frames were selected from each measurement (The number of frames varied per measurement) and the visual assessment were made. Image processing was done using MATLAB (MathWorks, Massachusetts, United States). The steps followed to obtain the TICs were performed by initially reading the DICOM file in MATLAB (MathWorks, Massachusetts, United States) with the help of an image processing toolbox. After displaying the image in the first frame, region of interest (ROI) was selected manually. The area under the tube phantom was selected as ROI (ROI was maintained same for all the measurements). Followed by this, average of the pixels was identified and plotted as intensity values in y-axis and the respective frames were converted to time (2 f/s) and the time is plotted along x-axis. The obtained fluoroscopic image (fluoroscopic images are digitally manipulated to produce

inverse of X-ray) is an inverted image and thus the derived TICs are reversed. Thus, the obtained TICs are inverted by exactly reversing the intensity values. The selection of the frames varied for each measurement and for each tube since the frame rates varied for each measurement. Additionally, the horizontal and vertical shifts are done in the obtained result plots (for few plots which required time or intensity shift) for better comparison (between different types of tube phantoms).

Tube Phantom Measurements

From the development phase till testing phase, several types of tube phantoms were made of which 8 tubes were chosen and optimized (i.e. This optimized tube phantom should have same measurements as of the myocardial segment and should fit inside the arc shaped hollow myocardial segment of prototype 2, and those tubes are shown in the figure 26. Out of which, only four types of tube phantoms which met the requirement 1 (See Chapter 3 under the concept design section for detailed explanation), were used to perform the measurements. The tube phantom was made of plastic cylindrical hollow tube and its specifications are mentioned in Table 5.

The measurement protocol is included in the tables (1.1-1.8) under Appendix B. Those four types of tube phantoms are as follows,

(1) Basic Tube phantom (BTP)

(2) 10 Normal type Membrane module filled Tube phantom (10NMMTP)

(3) 20 Twisted type Membrane module filled tube phantom (20TMMTP)

(4) 10 Normal Mixed tube phantoms (With adsorption material (Activated charcoal (Norit-125gms per tablet)) and membrane module / fibres) (MTP)

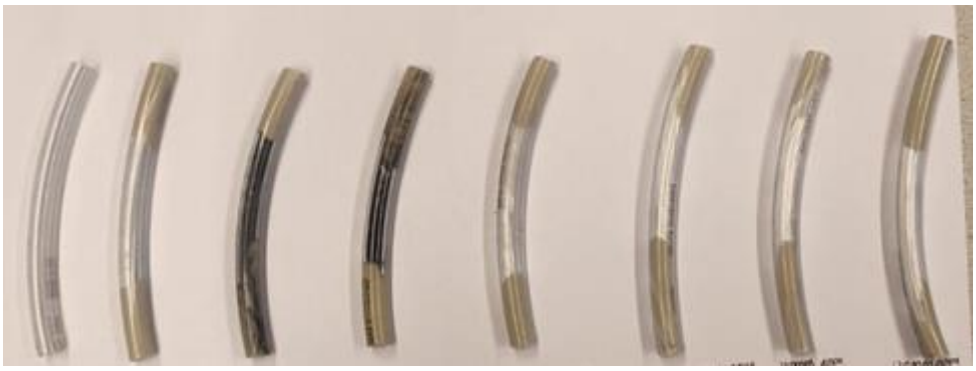

Figure 26 Different types of Tube phantoms. Basic tube phantom (1st); 10 Normal Membrane module filled tube phantom (2nd); 10 Normal Mixed tube phantom (3rd and 4th); 10 Twisted Membrane module filled tube phantom (5th); 15 Normal Membrane module filled tube phantom (6th); 15 Twisted Membrane module filled tube phantom (7th); 20 Twisted Membrane module filled tube phantom (8th) (from left to right)

In general, the time taken to make the tube phantoms would be approx. 24 hours for 10NMMTP and 20TMMTP tube phantoms and for the MTP, it takes around approx. 48 hours, since it involves the additional steps of adding the adsorption material into the plastic tube. Thus, the gluing procedure is done at one side of the tube first and it is dried overnight. Once the tube phantom is dried (on one side), the plastic tube is filled with powdered adsorption material. Then the other side of the tube is also glued after the filling process and this additional process takes 24 hours. All tubes were fabricated with the same measurements for comparability. Since the tubes are flexible, two markings were made, and these tubes were taped (using coloured cellophane tapes) to the flat glass surface of the flow setup as shown in figure 25. These markings facilitate the identification of the correct geometry during the scanning process and also while performing the post image processing steps with ease.

Table 1 Specifications of tube phantom and Membrane Module or Fibres

Tube Phantom Measurement	**Specifications**
Tube Phantom Outer Diameter O/D	8 mm
Tube Phantom Inner diameter I/D	6 mm
Tube Phantom Length	70 mm
Membrane Module measurements	**Specifications**
Membrane material	Modified PES (Polyethersulphone) (MexFil-WMC200-Dnf40-tds-1908)
Pore size	20 nm
Membrane inner diameter I/D	0.7 mm
Membrane surface area	43 m^2

For all the tube phantoms, the flow rate varied from 100-300 ml/min and the contrast agent dose administration varied from 3-7 ml of Iodine. Three flow measurements, three contrast agent dose variation measurements and three repetitions of the reproducibility measurements were performed for both the BTP and MTP (Flow rate = 150 ml/min with 5ml of Iodine based contrast agent for reproducibility measurements). On the other hand, three flow measurements, three contrast agent dose variation measurements were done for the other two types of tube phantoms (10NMMTP and 20TMMTP). Additionally, three contrast agent dose variation measurements and three flow measurements were performed for BTP with higher dose values. For most of the measurements the flow rate of 150 ml/min & 250 ml/min was followed and with the 5ml of Iodine was used. Overall, the experiments were performed by varying the type of tube phantoms, type of flow rates and by varying the dosages of the contrast agent. For all the experiments, Visual analysis method was used to analyse the obtained data. Time intensity curves (TICs) and Pressure were noted as the output variables (See Table 6). In total, three test measurements (to identify the contrast protocol), fifteen flow measurements, fifteen contrast dose variation measurements and six repeatability experiments were performed, with the total count of thirty-nine measurements (for all the four tube phantoms).

Table 2 Parameter setup for the experimental measurements

Input Variables	**Symbol**	**Unit**	**Range**
Type of Tube Phantom	TP	mm	70
GP Flow rate	Q	$mlmin^{-1}$	[100 150 200 250 300]
Contrast Bolus Injection	CI	ml	3-7
Output Variables	**Symbol**	**Unit**	**Range**
Time Intensity curve	TIC	a.u.	0-2080
Pressure	P	bar	0-10

However, the data (video file in DICOM format) from only 31 measurements were used to perform analysis and the detailed explanation of those experiments and their corresponding measurement protocols are explained in the next sections. The Tmax (The time point at which the intensity reaches its peak or maximum value) and Cmax (Maximum concentration = Intensity reaches the Peak or maximum value) values are observed. To characterize the passage of contrast agent through the tissues, several qualitative parameters were used. They are Time to Peak (TTP), Bolus arrival time (BAT) and Mean residence time (MRT). TTP & BAT were noted from the TICs, which was obtained. The overall stay of the contrast agent in the tube phantom is measured in terms of residence time.

Comparison of the different types of tube phantoms

Comparison: BTP vs MTP vs 10NMMTP vs 20TMMTP

Several measurements were performed, out of which four measurements (with all the four types of tube phantoms) were chosen to evaluate and to compare the sensitivity of the different types of tube phantoms by keeping the flow rate and the dose of the contrast agent as constant (i.e., 200 ml/min with 5ml of Iodine). The time taken for performing these experiments was around 1 to 2 minutes. TICs which will be obtained for all the four types of tube phantoms are compared and the visual analysis is carried out. For comparison, 51 frames from all the four tubes were chosen which produces TICs. It is assumed that 20TMMTP will have longer residence time of CA compared to other tube phantoms. Additionally, it was expected that MTP should have longer residence time of CA than 10NMMTP though they had same number of fibres.

Comparison: MTP vs 10NMMTP vs 20TMMTP

The measurement plan was made to assess and compare the sensitivity of the MTP, 10NMMTP and 20TMMTP by keeping the flow rate and the contrast agent dose value as constant (200 ml/min with 5 ml of Iodine). The residence time of the contrast agent will be noted, and this can be analysed from the obtained TICs. Three measurements (one from MTP, second one from 10NMMTP and from 20TMMTP) were taken to perform these analyses. 93 frames were chosen to compare the tube phantoms. These three tubes had closer intensity range compared to the BTP. Thus, additionally this comparison is made to closely compare and to determine the characteristics of the tube phantoms. It is expected that 20 Twisted tube phantoms should have longer residence time of CA compared to the other two tube phantoms (MTP and 10NMMTP).

Comparison: BTP vs 10NMMTP vs 20TMMTP

The measurement plan was made to assess and compare the sensitivity of the BTP, 10NMMTP and 20TMMTP by keeping the flow rate (at high flow conditions) and the contrast agent dose value as constant (250 ml/min with 5 ml of Iodine). The same procedure will be followed to do the analysis. Three measurements (one from BTP and one from 10NMMTP and one from 20MMTP) was used to perform these analyses. Overall, 96 frames were used, and it was assumed that BTP should have shorter residence time compared to the other tubes (10NMMTP and 20TMMTP). This comparison was made to understand the behaviour of the tube phantoms at high flow conditions.

Variation of flow rates

To evaluate the sensitivity of the tube phantoms to different flow rates, three measurements which was performed with basic tube phantoms were taken by varying the flow rate from 100 to 200 ml/min (100 ml/min,150ml/min, 200ml/min) with the constant dose of contrast agent (5 ml of Iodine). On an average, 1 to 2 minutes was taken to perform each measurement. 51 were chosen to perform analysis and the TICs which will be obtained for the different flow rates are analysed. Additionally, the MTP was analysed by varying the same parameters that was followed for the BTP. 105 frames from MTP raw data was selected and the response of MTP is observed. It is assumed that the tube phantom with lower flow rates should have longer residence time of CA compared to the tube phantom with higher flow rates.

Variation of Contrast agent dose

To evaluate the sensitivity of the tube phantom by the variation of the dosages of the contrast agent, nine measurements were chosen (three measurements from basic tube phantom and three measurements from the 20 Twisted tube phantoms and three measurement from Mixed tube phantom). The three TICs will be obtained by varying the dosages of the contrast agent i.e., 3 ml, 5ml and 7ml of Iodine (for each tube phantom) and at constant flow rate (150 ml/min for BTP and MTP and 250 ml/min for 20TMMTP). For simplicity, the behaviour of the BTP (63 frames) is analysed first and followed by that the sensitivity of the MTP is analysed. The sensitivity of the 20TMMTP on contrast dosages variations is analysed and compared in Study 3 as a part of the comparison study. It is assumed that the tube phantom with higher concentration have longer residence time of CA compared to the tube phantom with lower concentration.

Reproducibility experiments

In total, six measurements were performed, out of which three measurements were repeated for BTP (76 frames) and three measurements were repeated for MTP (116 frames). For simplicity, the BTP measurements were first used to assess the reproducibility by repeating these measurements thrice under same experimental conditions (150 ml/min with 5 ml of Iodine). Same was done for MTP and the reproducibility check is done. Visual analysis is performed. The measurement protocol for all the above-mentioned experiments are given in table 1.1 – 1.8 in Appendix B.

Study 2: Simulation Study

Compartmental modelling is the most appealing model to perform simulations and analyses. The distribution of the Contrast Agent (CA) in myocardial compartment can be analysed using this type of modelling. In two-compartment model, the initial one is the blood plasma compartment and second one is the tissue compartment. The exchange of the drug (drug refers to CA since it has the similar properties of Contrast agent) between the capillary and the adjacent spaces can be investigated with the help of this model. The Concentration of the CA in the tissues are recorded over time and as a result, the time concentration curves (TCCs) are obtained. Different types of tasks like performing simulation, scanning different parameters, curve fitting etc., can be assigned to the selected model, and the assigned tasks (In this study it is simulation task) are simulated to understand the behaviour of the curves. The theoretical description for both the compartmental models are given in Chapter 2.

The aim of this study is to analyse the distribution of the drug/CA through different types of compartmental (PK) models using Simbiology app. This can be achieved by finding the sensitivity of the compartment on varying the parameters like the dose of the drug and by varying the volume or the capacity of the compartment. These parameters are analysed and the procedure to obtain TCCs are discussed in this section.

Pharmacokinetic (PK) Model Design

After the IV (Intravenous) bolus administration of the drug/CA, it travels through the compartments and then gets eliminated from the systems itself. The time taken for the elimination of the drug varies from one compartment to the other. Several hypotheses were made, out of which one of them were in alignment with the project goal. It is assumed that “the two compartment PK model could mimic the microcirculatory contrast kinetics in the myocardial tissue”. To confirm our hypothesis, we need to initially design and simulate one compartment and two compartment model separately and later compare their results and conclude which compartment is more suitable for our project goal.

The simulations and the model analysis were performed using Simbiology app which is a package available in MATLAB (MathWorks, Massachusetts, United States). The Kinetics of the CA can be described using a Simbiology model, which consists of set of expressions like reactions, differential equations, discrete events. The one compartment PK model consists of single compartment and it is named as central. The two compartment PK model consists of Two compartments and they are central and peripheral.

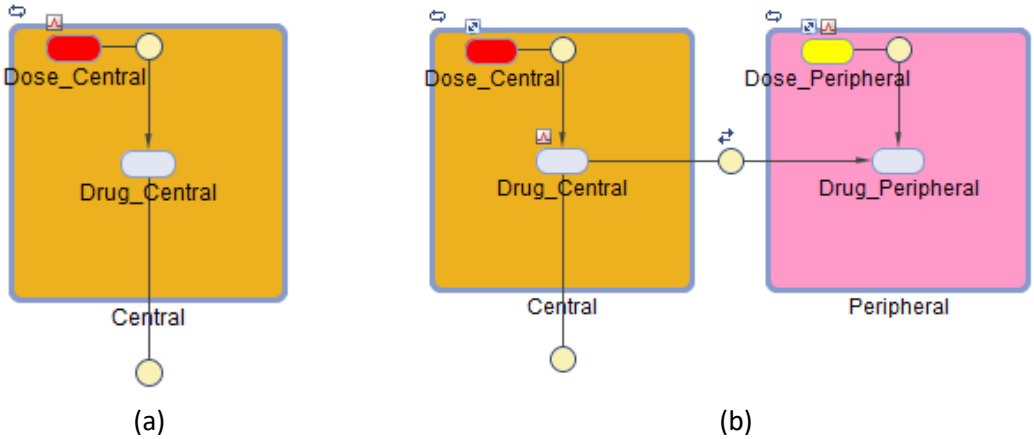

Figure 27 Simulation model designs in the form of block diagrams. (a) One compartment Pharmacokinetic (PK) model which contains the central compartment that is represented in yellow colour; (b) Two-compartment PK model which contains two compartments (central (represented in yellow colour) and peripheral (represented in pink colour)) (from left to right). Red colour is the dose which will be supplied to the compartments and the White colour represents the Drug at central compartment. Dose_Central: Dose at central compartment; Drug_Central: Drug at central compartment; Dose_Peripheral and Drug_Peripheral represents the dose and drug at peripheral compartment

General study parameters and specifications

To perform the simulation experiments, model a PK compartment design or use the pre-defined models which are available in the libraries. After the model gets loaded into the main screen, the required parameter settings need to be done. The table 3 shows the summary of the pre general settings which needs to be done.

Table 3 General parameter settings

Settings	**Description**
Project	This is the Simbiology project file that is open
Model	Different types of models which were used as a part of Simbiology tool
Dosing	Dosing information like the start time, the dose, and the number of times to repeat the session and the repeat interval
Functionality	For selection process, the radio button is used
Menus	**Description**
File Menu	This includes opening the file, save, import and export to obtain the output of each functionality
Edit Menu	It has property inspector which helps in modifying the obtained plots
Functionality menu	Several functionalities can be performed by the user like simulation, fitting, or population simulation studies

During the simulations, the concentration of the drug/CA gets absorbed and gets distributed inside the compartment models. Followed by these processes, elimination occurs (usually from central compartment). The type of elimination used in this study is linear {Clearance, Time}. With regards to dosing regime, we can use two types of dose objects using Simbiology tool. Those objects are (a) Schedule dose (this type is used in this study) and (b) Repeat dose. There are several dosing types such as, bolus, infusion, zero-order and first order dose types.

Simulations

In our simulation study, we have used bolus as a dose type and a schedule dose as the dose object. The dose objects can be selected in two ways, either using programming tools in MATLAB (MathWorks, Massachusetts, United States) or by just drag-drop method into the field of interest. The dosing information can be altered by the user as per their requirements. To perform simulations, we need use solvers and, in this tool, ODE or SUNDIALS solvers are used. In our study, ODEs i.e., the ordinary differential equations are used. Next steps would be to set up the parameters followed by initiating the simulation tasks. In the simulation task window, the duration of the simulation, the required type of plot needs to be set up before performing the simulations. Additionally, the live plots can be visualized by varying the quantities (the amount of dosages, the rate of those dosages and time at which the dose is given). The same steps need to be taken for different types of compartments. Once the simulation is finished, different plots are visible, and these results can be exported in the form of excel sheets.

One-compartment model

This PK model has a single compartment with a constant capacity of 150 ml with two species (which is the amount of a chemical that participates in the reactions during the simulation, for instance ($Dose_{Central}$ and $Drug_{Central}$ are species), two reactions and two parameters with no rule. The initial condition values were set to zero. The parameter values are shown in the table 4. For this simulation experiment, ode15s solver (stiff/NDF) is used and their respective equations are given below:

$$\frac{d(Dose_{Central})}{dt} = -[Central\ Absorption] \quad (4.2.1)$$

$$\frac{d(Drug_{Central})}{dt} = \frac{1}{Central} * ([Central\ Absorption] - [Central\ Elimination]) \quad (4.2.2)$$

$$[Central\ Absorption] = ka_{Central} * Dose_{Central} \quad (4.2.3)$$

$$[Central\ Elimination] = (ke_{Central} * Drug_{Central}) * Central \quad (4.2.4)$$

$ke_{central}$ = Elimination rate at central compartment

$ka_{Central}$ = Absorption rate at central compartment

After the administration of the drug, the reaction 1 occurs where the drug gets distributed from the $Dose_{Central}$ to $Drug_{Central}$ ($Dose_{Central} \rightarrow Drug_{Central}$) with the reaction rate as follows:

$$ka_{Central} * Dose_{Central} \quad (4.2.5)$$

And this, reaction 2 occurs ($Drug_{Central} \rightarrow null$) where the drug gets eliminated from the $Drug_{Central}$ with the reaction rate as follows,

$$ke_{Central} * Drug_{Central} \quad (4.2.6)$$

Parameter Setup and Simulation

The simulation is performed by varying the dosages of the drug (CA) with the ranges from 0 to 3 by increasing over a range of 0.5 (i.e., 0,0.5,1,1.5,2,2.5,3 mole) for the duration of 10 s. The drug (CA) enters the central compartment and it gets instantaneously distributed within the compartment. The drug (CA) reaches the peak (Cmax) and then the drug (CA) gets eliminated via the central compartment. It is assumed that the one-compartment model resembles the mechanisms which was performed in basic tube phantom with an exception of the geometrical variations (i.e., the size and volume of the compartment).The Time Concentration Curves (TCCs) which are obtained during this simulation is compared with TCCs which will obtained during the two-compartment model-simulations.

Table 4 Parameter values used in one-compartment model (ka=absorption rate; ke=Elimination rate)

S.no	Name	Value	Value Units
1	$ka_{Central}$	1.0	s^{-1}
2	$ke_{Central}$	1.0	s^{-1}

Table 5 shows the dose regimen which was followed for this simulation experiment for both one compartment and two-compartment model. The same dose regimen is followed for both the compartments so that it is comparable.

Table 5 Dose regimen used for both one and two-compartment model

S.NO	Dose (mole)	Simulation Time (s)
1	0	10
2	0.5	10
3	1	10
4	1.5	10
5	2	10
6	2.5	10
7	3	10

Two compartment model

This Pharmacokinetic (PK) model has two compartments (central and peripheral) with a constant capacity of 150 ml along with four species ($Dose_{Central}, Drug_{Central}, Dose_{Peripheral}, Drug_{Peripheral}$), four reactions and seven parameters with three rules. The initial conditions were set to zero. The parameter values are shown in the below table 6. The absorption rate is set to 1 for both Central and peripheral compartment since it involves both the blood or plasma flow through the central compartment and the tissue representing the peripheral compartment. For this simulation experiment, the ode15s solver (stiff/NDF) is used and those equations are given below:

$$\frac{d(Dose_{Central})}{dt} = -[Central\ Absorption] \tag{4.2.7}$$

$$\frac{d(Drug_{Central})}{dt} = \frac{1}{Central} * ([Central\ Absorption] - [Central\ Elimination] - [Central \leftrightarrow Peripheral\ Transport]) \tag{4.2.8}$$

$$\frac{d(Dose_{Peripheral})}{dt} = -[Peripheral\ Absorption] \tag{4.2.9}$$

$$\frac{d(Drug_{Peripheral})}{dt} = \frac{1}{Peripheral} * ([Peripheral\ Absorption] + [Central \leftrightarrow Peripheral\ Transport]) \tag{4.2.10}$$

$$[Central\ Absorption] = ka_{Central} * Dose_{Central} \quad (4.2.11)$$

$$[Central\ Elimination] = (Ke_{Central} * Drug_{Central}) * Central \quad (4.2.12)$$

$$[Peripheral\ Absorption] = ka_{Peripheral} * Dose\_Peripheral \quad (4.2.13)$$

$$[Central \leftrightarrow Peripheral\ Transport] = ([(k_{12} * Drug_{Central}) * Central] - [(k_{21} * Drug_{Peripheral}) * Peripheral)] \quad (4.2.14)$$

Three rules were set up for this experiment and it is as follows:

$$ke_{central} = \frac{Cl_{central}}{Central} \quad (4.2.15)$$

Where,

$ke_{Central}$ = Elimination rate at central compartment

$Cl_{Central}$ = Clearance at central compartment

$$k_{12} = \frac{q_{12}}{Central} \quad (4.2.16)$$

Where,

k_{12}, q_{12} = Rate constants from central to peripheral compartment

$$k_{21} = \frac{q_{12}}{Peripheral} \quad (4.2.17)$$

Where,

k_{21}, q_{12} = Rate constants from peripheral to central compartment

After the administration of the drug, four reactions occur and reaction 1 occurs where the drug gets distributed from the $Dose_{Central}$ to $Drug_{Central}$ ($Central.Dose_{Central} \rightarrow Central.Drug_{Central}$) with the reaction rate as follows:

$$ka_{Central} * Central.Dose_{Central} \quad (4.2.18)$$

And the reaction 2 occurs ($Central.Drug_{Central} \leftrightarrow Peripheral.Drug_{Peripheral}$) where the drug gets transported from central compartment to the peripheral compartment and vice versa with the reaction rate as follows,

$$([k_{12} * Central.Drug_{Central}] - [k_{21} * Peripheral.Drug_{Peripheral}] \quad (4.2.19)$$

And the reaction 3 occurs ($Peripheral.Dose_{Peripheral} \rightarrow Peripheral.Drug_{Peripheral}$) where the drug gets absorbed in the peripheral compartment with the rection rate as follows,

$$ka_{Peripheral} * Peripheral.Dose_{Peripheral} \quad (4.2.20)$$

And the reaction 4 occurs ($Central.Drug_{Central} \rightarrow null$) where the drug gets eliminated from the $Drug_{Central}$ with the rection rate as follows,

$$ke_{Central} * Central.Drug_{Central} \quad (4.2.21)$$

Parameter Setup and Simulation

The simulation is performed by varying the dosages with the ranges from 0 to 3 by increasing over a range of 0.5 (i.e., 0,0.5,1,1.5,2,2.5,3 mole) for the duration of 10 s. The drug enters and fills the central compartment. Then the drug gets transported from central to peripheral. The drug is absorbed in the peripheral compartment and few portions are left in peripheral compartment for a while and then the drug gets back to central compartment and gets eliminated from the central compartment.

Table 6 Parameter values used in two-compartment model (Ka=absorption rate; Cl=clearance; Ke=Elimination rate)

S.no	Name	Value	Value Units
1	$ka_{Central}$	1.0	s^{-1}
2	$Cl_{Central}$	1.0	ml s^{-1}
3	$ke_{Central}$	1.0	s^{-1}
4	$ka_{Peripheral}$	1.0	s^{-1}
5	q_{12}	1.0	ml s^{-1}
6	k_{12}	1.0	s^{-1}
7	k_{21}	1.0	s^{-1}

The remaining dosages of drugs will slowly get eliminated from peripheral compartment. The drug travels through the two compartments and reaches the peak (Cmax value) and the respective time is noted as Tmax. The TCCs which are obtained during this simulation is compared with the TCCs which is obtained during the 1-compartment model-simulations. Table 6 shows the parameter values which are used in two-compartment model.

Study 3: Comparison study: Simulation vs Experimental

The simulation results which was obtained using the compartmental Pharmacokinetic (PK) models by varying the dosages of the drug (contrast agent) are compared with the experimental results which was attained by performing similar measurements (i.e., by varying the dosages of the CA). Initially the several experiments were performed to find out the suitable contrast agent protocol. Using the dose regimen (3,5,7 ml of Iodine (300 mg/ml) (drug)) with constant flow rate of 250 ml/min, experiments results were expected to be similar to the simulation results (Capacity of Compartment were set to 250ml/min and calculated dose regimen is followed).

The aim was to compare these results (Study 1 & Study 2 results) and to evaluate them qualitatively by performing visual assessments. Additionally, the experiments results could be validated by comparing them with the simulation results. For the sake of simplicity, we initially used one compartment model comparison and followed by that, two-compartment model comparisons were made in Study 2. Two-compartment model from simulation study and 20 Twisted type membrane module filled tube phantom (20TMMTP) from experimental study were chosen to perform this comparison study. To compare these results, we need to either convert concentration to intensity values or vice versa. To do that, we obtain a graph with linear fit between the intensity and the iodine concentration. We used contrast calibration factor to obtain the linear fit. The graph which is obtained using these two results should fall closer to the linear straight line (See figure 1.23 in Appendix A)

It is hypothesized that the two-compartment model simulation results and the experimental results (20 twisted membrane module tube phantom) shows longer residence time of CA. It is also essential to determine to what extent these results could mimic the patients TACs. To do this, the final obtained results from this study (study 3) is compared with the previous study results (Which includes the patient's TACs which was compared with the phantom's TACs) (See figure 3). We assume that these two comparisons (experimental vs simulation results) will show longer residence time of CA than the residence time of the phantom (i.e. this study should have residence time greater than the previous study (figure 3).

From experimental measurements, we can use the results obtained by varying the dosages of contrast agent (3,5,7 ml of Iodine) in 20 twisted membrane module filled tube phantom. We can perform simulation experiments by creating three different dosages and perform the task simulation and obtain the results for each dose. Table 1.9 in Appendix B shows the dosing regimen used for performing the experiments in study 1 and study 2. The mole values corresponding to the concentration values of dosages were obtained. Same procedures were followed throughout the Study 3. Overall time taken for performing this simulation was setup to 50 s so we could compare both the results. To compare the study 3 with the previous study, we had additionally performed few experiments with 20TMMTP (high flow rate with high concentration) and with MTP (low flow rate with high concentration) to support the study 3 results.

Chapter 5: Results

Study 1: Experiment Results

Different types of comparison results between the proposed four tube phantoms are discussed in this chapter. Followed by that the results obtained from the experiments which were performed on BTP and MTP by varying the flow rates and by varying the dosages of the contrast agents are briefly described. At last the reproducibility experiment results for both BTP and MTP are outlined.

Comparison of the different types of tube phantoms

Comparison: BTP vs MTP vs 10NMMTP vs 20TMMTP

Figure 28 shows the comparison of the different types of tube phantoms by setting up the flow rate to 200ml/min and with the dose of Iodine 5ml (300 mg/ml). Time intensity curves (TICs) which were obtained using fluoroscopic imaging techniques are inversed graphs (since the fluoroscopic image obtained is an inverted image) and thus we have reversed it. The lower the intensity value in the graph implies the higher intensity value in the actual case. For instance, in figure 28, TICs shows the highest peak values 1725 au. Though the obtained values look like it has less intensity value, the actual peak value should have more concentration which means those are higher intensity value in actual case (since we inverted the graph).

For 20TMMTP, the measured TICs showed a peak intensity value of 1985 au at t = 13.5s (TTP). This curve started at t = 9s with the intensity value of 2064 au and it reaches the maximum intensity value. The intensity value slowly decreases and reaches a point where these curves starts to recover or reach zero value of concentration with increase of time. At t = 25.5s, the intensity value is 2047.5 au. MTP has a peak intensity value of 2028 au at t = 17s. The distribution of the contrast agent starts at t = 10s and with the intensity value of 2062 au. The intensity value of 2057 au is noted at t = 25.5s. For 10NMMTP, the contrast agent distribution starts at t = 9s with the intensity value of 2063 au. The peak intensity value of 2036 au is achieved at t = 14s. At t = 25.5s, the intensity value is 2060.9 au. For BTP, the peak intensity value was 1699 au at t = 15.5s and the distribution in this tube starts at t = 10s with the intensity value of 2062 au. The intensity value was 2006 au at t = 21.5s.

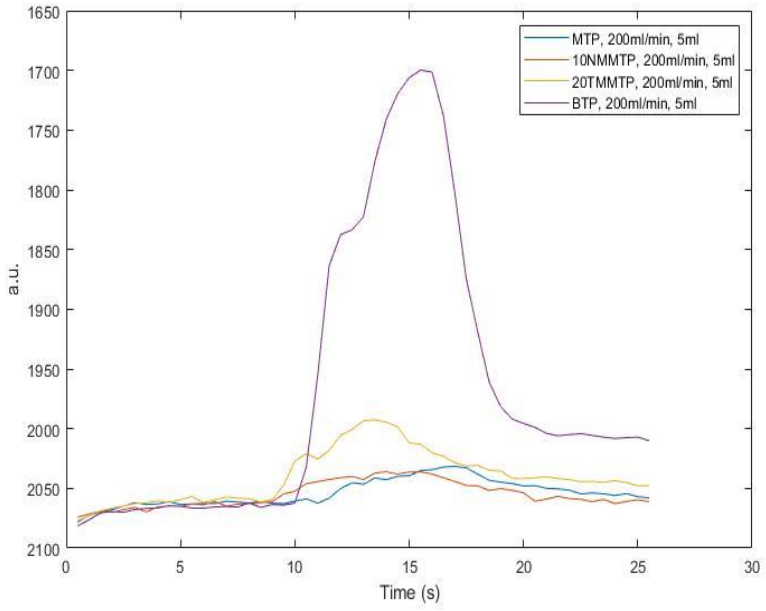

Figure 28 Comparing the results of different types of tube phantom with constant flow rate as 200ml/min and 5 ml of Iodine. The purple, orange, blue and red colour represents the TICs for BTP, 20TMMTP, MTP and 10NMMTP. TIC = Time Intensity Curve; BTP = Basic tube phantom; 20TMMTP = 20 twisted type membrane module filled tube phantom; 10NMMTP = 10 normal type membrane module filled tube phantom; MTP = Mixed tube phantom

The Membrane module filled tube phantom (20 twisted type) showed longer residence time of CA of the contrast agent with the overall time of contrast stay of 50 seconds on comparison with the other types of tube except BTP. On the contrary, the BTP had longer residence compared to the other tubes, which is against our expectation. Thus, additional comparisons were made by performing different measurements (BTP vs 10NMMTP vs 20TMMTP). While plotting all the graphs in a single plot the intensities except the BTP was not clearly visible to perform analysis. Thus, comparison between the MTP vs 10MMTP vs 20TMMTP measurements were compared separately with the same experimental parametric conditions.

Comparison: MTP vs 10NMMTP vs 20TMMTP

The comparison between the MTP, 10NMMTP and 20TMMTP were again compared to determine the behaviour of the different types of tube phantoms. Figure 29 shows that, this comparison of the TICs of all the three tube phantoms in one plot. It is observed that the peak intensity value (1985 au at t=13.5s) for 20TMMTP was higher compared to the other two phantoms. All the tubes started the distribution of the contrast agent at t = approx. 8s, with the intensity values (MTP = 2058 au, 10NMMTP = 2056 au, and 20TMMTP = 2059 au). At t = 46.5 the intensity values of all the tubes were between approx. 2049 au. to 2053 au. (MTP = 2053 au, 10NMMTP = 2053.4 au, and 20TMMTP = 2049 au). Time taken for the prolongation of the contrast agent in the all these three tube phantoms were noted to be approx. around 35 to 38s. Though the area under curve showed that 20TMMTP has greater area compared to other tubes (as shown in figure 1.17 in Appendix A).

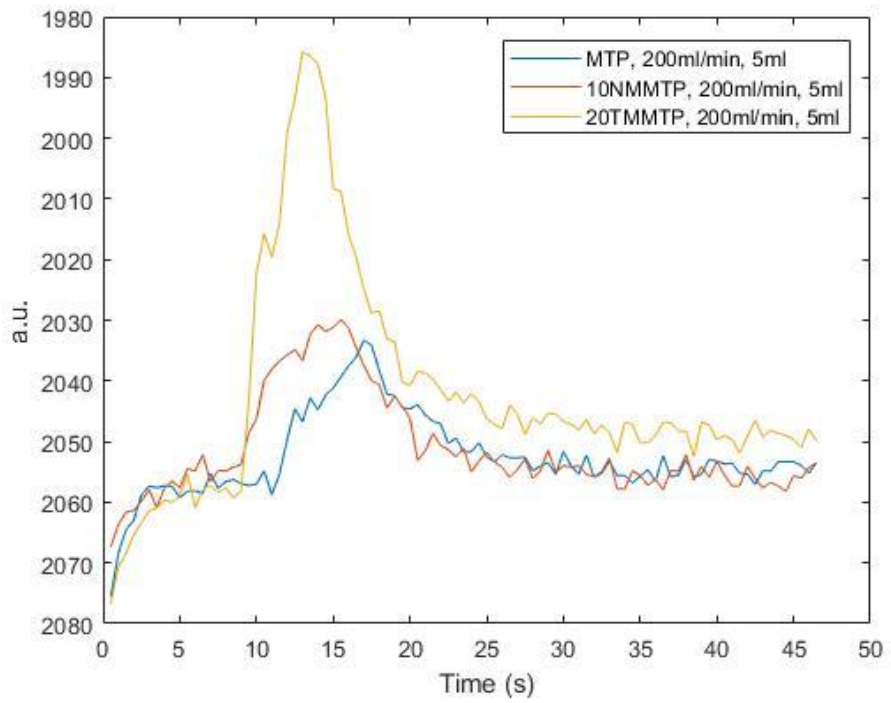

Figure 29 Comparing the results of three types of tube phantoms (MTP, 10NMMTP, 20TMMTP) with constant flow rate as 200ml/min and 5 ml of Iodine. These three tube phantoms had fibres in it. Orange, red, and blue colour represents the TICs for 20TMMTP, 10NMMTP and MTP, respectively. 20TMMTP = 20 twisted type membrane module filled tube phantom; 10NMMTP = 10 normal type membrane module filled tube phantom; MTP = Mixed tube phantom

Comparison: BTP vs 10NMMTP vs 20TMMTP

The figure 30 shows the comparison between the BTP, 10NMMTP and 20TMMTP. This was done to support the previous analysis while comparing the four different types of tube phantoms. In addition to that, it was aimed to determine the behaviour of the BTP with the constant parameters like the flow rate of 250ml/min and with 5ml of Contrast agent which was injected. The obtained TICs from all the three tube phantoms were plotted in one graph. In BTP, it is observed that the peak intensity value (1750 au. at t=21s) was higher compared to the other two phantoms. All the tubes started the distribution of the

contrast agent at t = approx. 13s with the intensity values (BTP = 2064 au, 10NMMTP = 2062 au. and 20TMMTP = 2052 au). At t = 48s the intensity values of all the tubes were between approx. 2044 au. to 2064 au. (BTP = 2064.5 au, 10NMMTP = 2061 au. and 20TMMTP = 2044 au. Time taken for the prolongation of the contrast agent in the all these three tube phantoms were noted to be approx. around 34 to 36s. The BTP had shorter residence time compared to the other tube phantoms with the intensity value of 2064.5 at t = 48s.

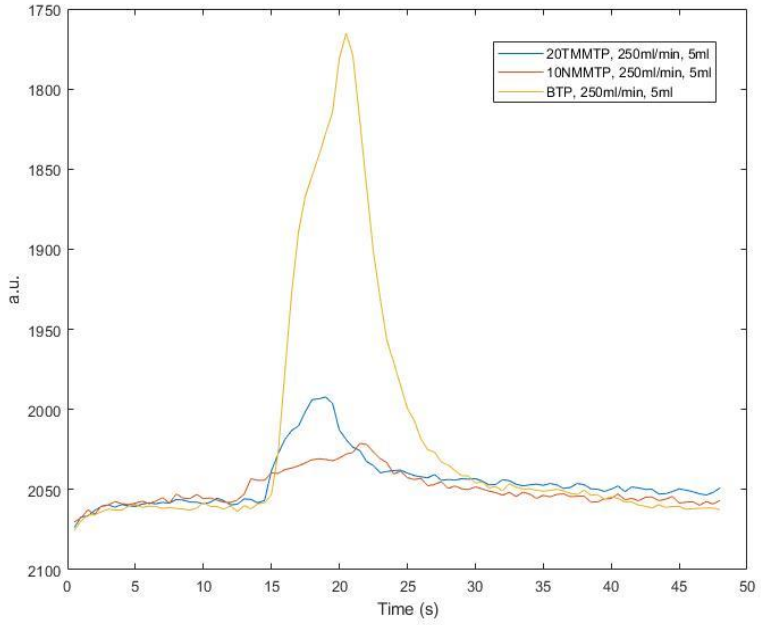

Figure 30 Comparing the results of three types of tube phantoms (BTP, 10NMMTP, 20TMMTP) with constant flow rate as 250ml/min and 5 ml of Iodine. Other than BTP, the other two tube phantoms had fibres in it. Orange, red, and blue colour represents the TICs for BTP, 10NMMTP and 20TMMTP, respectively. BTP = Basic tube phantom; 20TMMTP = 20 twisted type membrane module filled tube phantom; 10NMMTP = 10 normal type membrane module filled tube phantom

Variation of flow rates

The tube phantoms (BTP and MTP) with variations of different flow rates (100ml/min to 200 ml/min) and with the constant contrast dose of 5ml, were tested and analysed. Figure 31 shows the time intensity curves recorded for basic tube phantom for different flow rates (100,150,200 ml/min) with the constant dose of the CA (5 ml). At increased flow rate (200 ml/min) the results showed the highest peak intensity of 1680 au. at t = 17.5 with shorter residence time (t=15 seconds). At t = 25.5 the intensity value was 2090 au. At a lower flow rate values (100ml/min) in basic tube phantom, the TICs showed the peak intensity value of 1750 au. at t = 13s. The distribution of the contrast agent in the BTP starts at t = 10 s and the intensity value was found to be 2105 au. The BTP with flow rate of 150 ml/min showed longer stay of contrast with the intensity values of 2080 au. compared to the flow rate condition of 200 ml/min.

Figure 32 shows the time intensity curves obtained for mixed tube phantom for different flow rates (100,150,200 ml/min) with the constant dose of the CA (5 ml). At increased flow rate (200 ml/min) the results showed the highest peak intensity of 2033 au. at t = 18 with shorter residence time of CA (t=41.5 seconds). At t = 52.5s the intensity value was 2057 au. At a lower flow rate values (100ml/min) in MTP, the TICs showed the peak intensity value of 2040 au. at t = 15s. The distribution of the contrast agent in the MTP starts at t = 13 and the intensity value was found to be 2067 au. The MTP with flow rate of 100 ml/min showed longer stay of contrast with the intensity values of 2054 au.

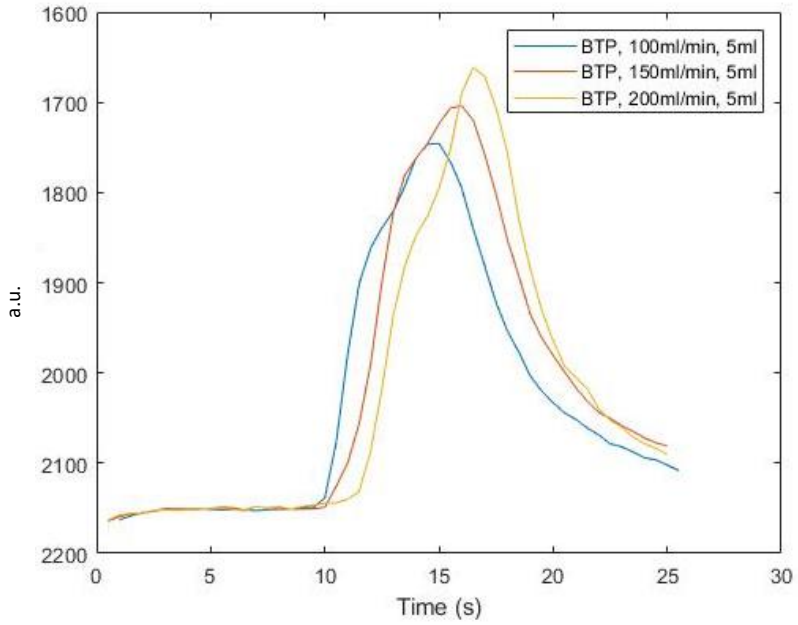

Figure 31 Sensitivity of the basic tube phantom by varying the flow rates (100,150,200 ml/min with dose of contrast agent as 5 ml). (Inverted graph). Orange, red, and blue colour represents the TICs for BTP with varying flow rates of 200,150 and 100ml/min, respectively. TICs = Time intensity curves; BTP = Basic tube phantom

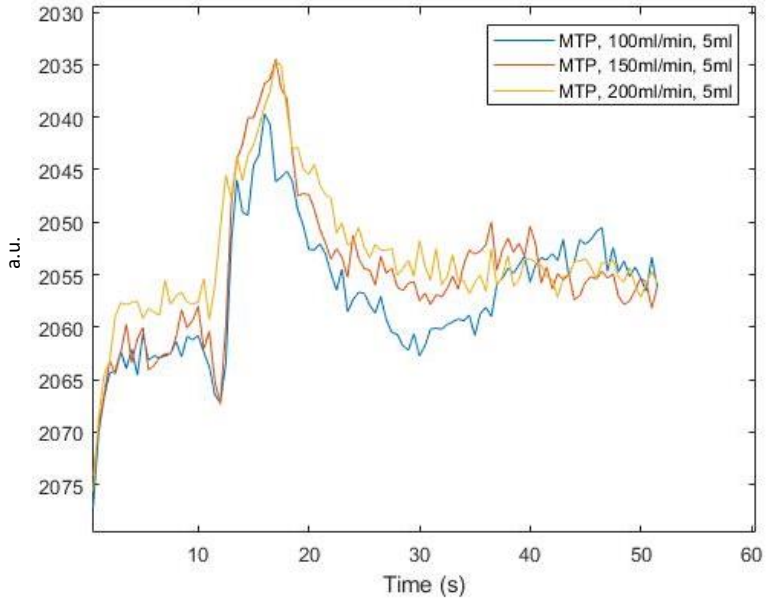

Figure 32 Sensitivity of the mixed tube phantom by varying the flow rates (100,150,200 ml/min with dose of contrast agent as 5 ml). (Inverted graph). Orange, red, and blue colour represents the TICs for MTP with varying flow rates of 200,150 and 100ml/min, respectively. TICs = Time intensity curve; MTP = Mixed tube phantom

Variation of Contrast agent dose

To understand the basic concepts, the basic tube phantom was chosen to investigate the behaviour of this tube when different dosages of contrast agent Iodine were injected into the flow setup. A progressive increase in the peak intensity was noted with an increasing dose of Iodine. A very low dose of 3ml of 300mg/ml of Iodine gave a peak intensity of 1780 au. at t = 12s. An injection of 5ml of 300mg/ml of Iodine gave a peak intensity of 1689 au. at t = 14s. An injection of 7ml of 300mg/ml of Iodine showed a peak intensity of 1650 au. at t = 15s. These findings showed a good agreement with the simulation data. At the higher contrast agent value (7ml), it showed longer stay compared to the other cases.

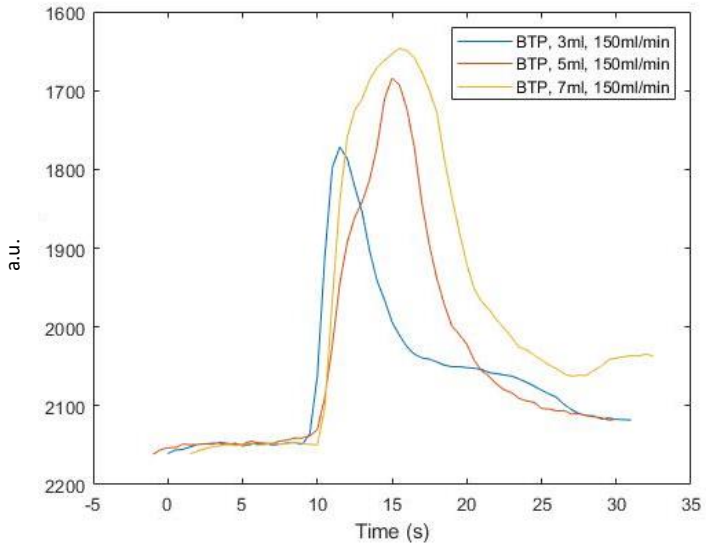

Figure 33 Sensitivity of the basic tube phantom by varying the contrast agent dosages (3,5,7 ml with dose of contrast agent as 150 ml/min). (Inverted graph). Orange, red, and blue colour represents the TICs for BTP with varying contrast agent dosages of 7,5,3 ml, respectively. TICs = Time intensity curves; BTP = Basic tube phantom

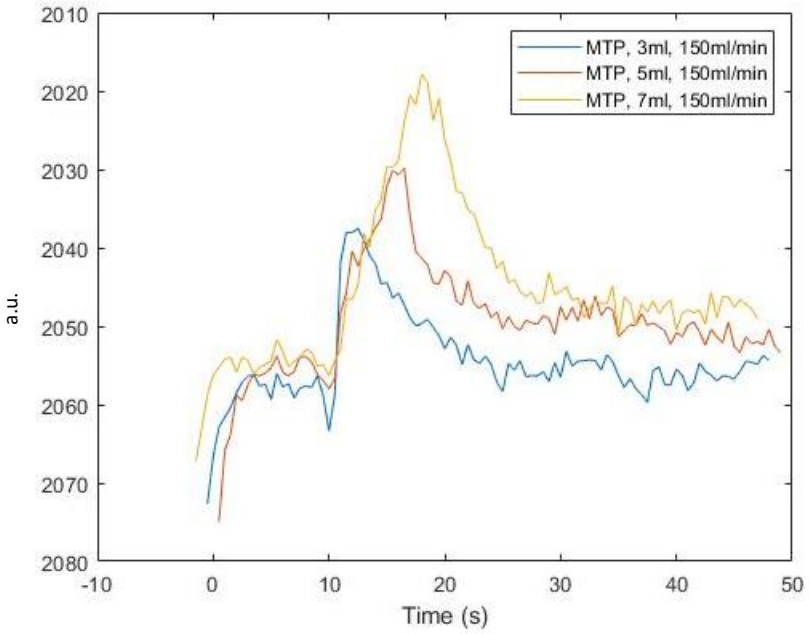

Figure 34 Sensitivity of the mixed tube phantom by varying the contrast agent dosages (3,5,7 ml with dose of contrast agent as 150 ml/min). (Inverted graph). Orange, red, and blue colour represents the TICs for MTP with varying contrast agent dosages of 7,5,3 ml, respectively. TICs = Time intensity curve; MTP = Mixed tube phantom

The mixed tube phantom was chosen to investigate the behaviour of this tube when different dosages of contrast agent Iodine were injected into the flow setup over a longer duration of time (i.e. greater than the time duration of the BTP). A progressive increase in the peak intensity was noted with an increasing dose of Iodine. A very low dose of 3ml of 300mg/ml of Iodine gave a peak intensity of 2038 au. at t = 13s. An injection of 5ml of 300mg/ml of Iodine gave a peak intensity of 2030 au. at t = 16s. An injection of 7ml of 300mg/ml of Iodine showed a peak intensity of 2018 au. at t = 18.5s. These findings showed a good agreement with the simulation data. At the higher contrast agent value (7ml), it showed longer stay compared to the other cases. In both the tube phantoms, the same observation was noted.

Reproducibility experiments

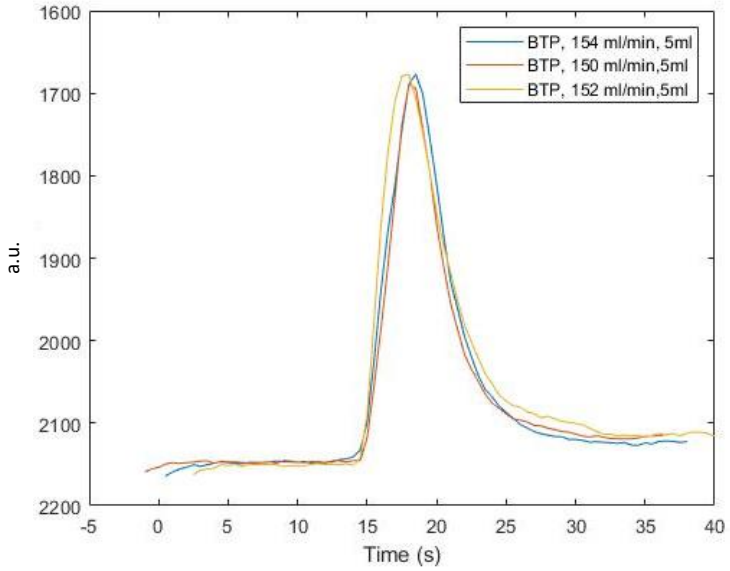

Figure 35 Reproducibility experiments that was performed for Basic tube phantom with same flow rate as approx. 150 ml/min with the contrast agent dose value as 5 ml (n=3). (Inverted graph). Orange, red, and blue colour represents the TICs for BTP with same approximated flow rates of 150 ml/min. TICs = Time intensity curves; BTP = Basic tube phantom

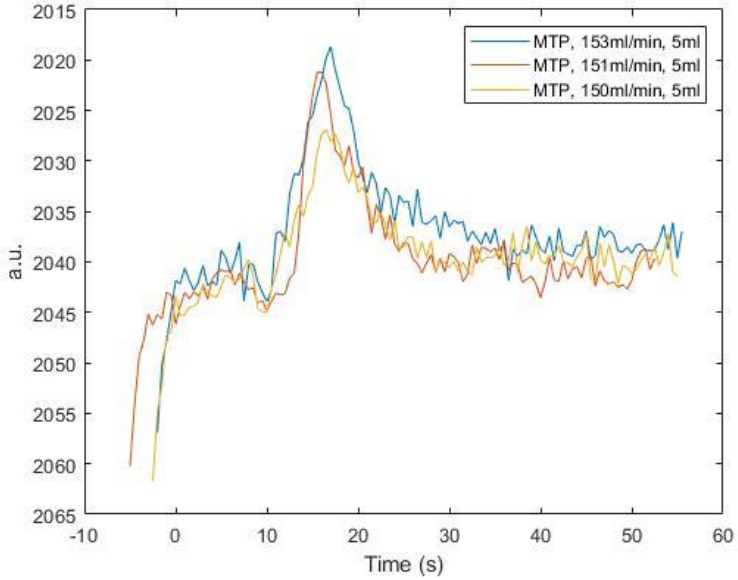

Figure 36 Reproducibility experiments that was performed for Mixed tube phantom with same flow rate as approx. 150 ml/min with the contrast agent dose value as 5 ml (n=3). (Inverted graph). Orange, red, and blue colour represents the TICs for MTP with same flow rates. TICs = Time intensity curve; MTP = Mixed tube phantom

The Final experiments on basic tube phantom measurements were repeated several times (n=3), showing good reproducibility on the same day for the flow rate value approximately 150ml/min with 5 ml of 300mg/ml as shown in the figure 35. In addition to the BTP reproducibility measurement, the MTP reproducibility experiments that was repeated for three times also showed good reproducibility as shown in the figure 36.

Study 2: Simulation Results

One-Compartment model analysis results

The Time concentration curves (TCCs) which were obtained by simulating the one-compartment model by varying the parameter (the dosages of contrast agent) are shown in the figure 37. In one-compartment model experiment, the variations in the distribution of the drug over time was performed within a single compartment. The drug entered instantaneously and got eliminated from the compartment at a faster rate. Each curve obtained for different dosages has a peak value and this is called Cmax (the point where it reaches the maximum concentration). Its corresponding time is noted down as Tmax (the time at which the concentration is maximum). After this peak, the drug gets eliminated gradually from the central compartment and after a while, it reaches Zero. This residence time is dependent on the dose that is used. With dose = 0 mole, there is no supply of drug to the system (compartment). It is noticed that there is a straight line with the concentration value 0 mg/ml for 10 seconds. With dose = 0.5 mole, there is an instantaneous increase of the drug into the compartment and the Cmax value for this dose is 0.3 mg/ml at Tmax = 0.88 s. Followed by this, the drug gets eliminated gradually and reaches zero as the time increases and when the concentration value reaches zero then it means that the drug is fully eliminated. The same observation is noted for all the other dosages. The Cmax values and Tmax values for the dosages of the drug (d=1,1.5,2,2.5,3 mole) are 0.72,1.09, 1.47,1.83,2.19 mg/ml (Cmax) and 1.03,0.884,1.03,1.03,0.88 seconds (Tmax) respectively. The time taken for the drug to get fully eliminated varied based on the amount of concentration. The dose with 3 mole has the highest peaks (Cmax) values with longer residence time of CA (at t = 10s, the concentration value was 0.0027 mg/ml i.e. approximately 0mg/ml) comparatively to all other lower dose values of the drug. Thus, it depicted that, higher the concentration of the drug dose, higher the residence time of the CA (drug). The analysis which was performed for these simulation experiments were based on visual inspection. The two-compartment analysis results will be discussed in the upcoming section.

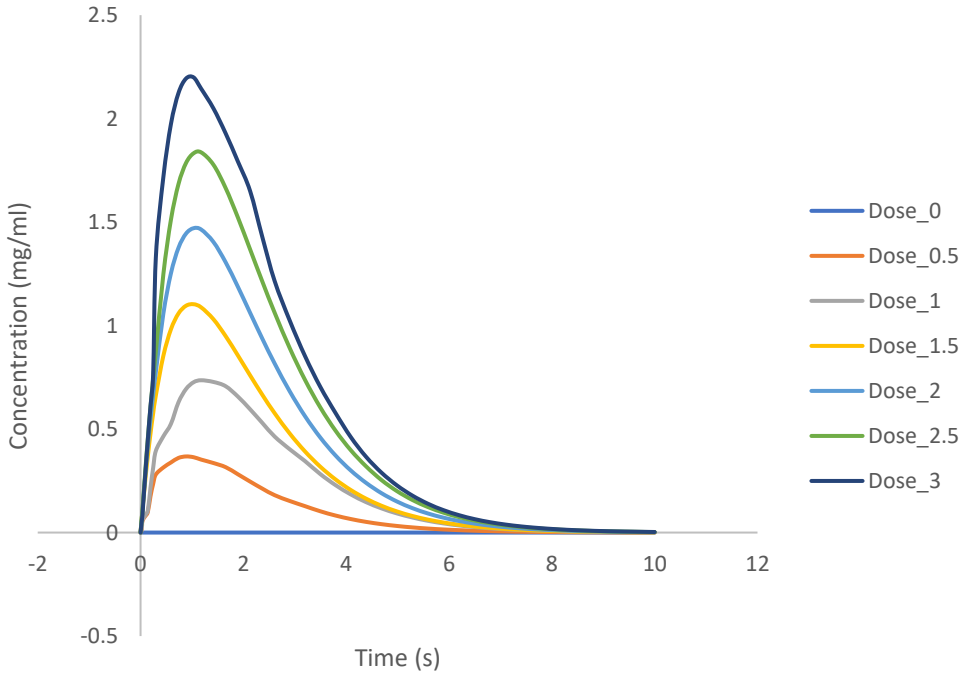

Figure 37 Time Concentration Curve (TCCs) - One compartmental analysis results with the elimination type – Linear {Clearance, Time}.

Two-Compartment model analysis results

Simulations generated by the two-compartment model, compared by varying the dosages are shown in the below figure 38. The simulation results which were obtained showed variations in the distribution of the drug/CA between the central and peripheral compartments. Initially the drug enters the central compartment, following this the peripheral compartment, where the drug gets absorbed. The distribution occurs until the equilibrium between the two compartments is reached. The point where the drug is filled to maximum is represented in the graph as the peak of the curve or Cmax (the point where it reaches maximum concentration). The corresponding time is noted as Tmax (Time at which the Cmax is achieved). After the maximum point is reached, the drug gets eliminated gradually from the central compartment but not fully and it reaches zero as the time increases. This is because there are some amount of drug/CA which is absorbed in the peripheral compartment. The drug with dose = 0 mole had no distribution, absorption, and elimination, since there is no dose set in the compartments. The drug with dose =0.5 mole had an increase of the drug and the Cmax or the peak value 0.27 mg/ml at Tmax = 0.75s. Then the drug is eliminated slowly and reaches zero after a longer duration of time. The Cmax values for the dose amount (d=1,1.5,2,2.5,3 mole) are 0.54,0.81,1.07,1.37,1.63 mg/ml. The corresponding Tmax values were noted to be 0.701 s for the Cmax values 0.54, 0.81, 1.37, 1.63 mg/ml and 1.07 s for the Cmax value 1.07 mg/ml. The time taken for the drug to fully eliminate, varied based on the amount of concentration. The dose amount with 3 mole has the highest peaks (Cmax) values with longer residence time of CA (>10 seconds since the curve did not reach zero at 10th second and at t = 10 s the concentration value was 0.05 mg/ml) comparatively to all other lower dose values of the drug. Thus, it depicted that, higher the concentration of the drug dose, higher the residence time of the CA (drug).

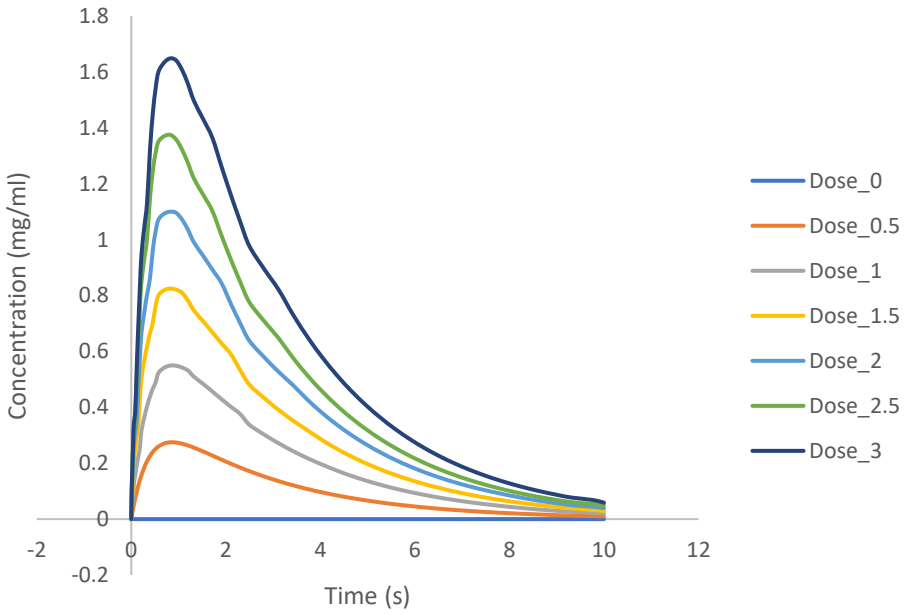

Figure 38 Time Concentration curve (TCCs) - Two compartmental analysis results with the elimination type – Linear {Clearance, Time}

The analysis which was performed for these simulation experiments were based on visual inspection. In one compartment model, at t=10s, the concentration (central compartment) of the drug was 0.0027 mg/ml with the dose value of 3 mole. Yet, the two-compartment model shows that the concentration value which was left in the central compartment for the dose value 3 mole was 0.05 mg/ml. The concentration at the central compartment was compared and thus, the concentration value at peripheral compartment were also noted and the value is 0.094 mg/ml at t= 10s. Thus, it clearly shows that the two-compartment model have longer residence time of CA than the one-compartment model.

Study 3: Comparison Study Results

This Study aimed to compare the results, between the experimental and simulation study. In study 1, the 20 twisted tube phantoms showed longer residence time of CA compared to the other tubes. In addition to that, the two-compartment model showed longer residence time of the drug compared to the one-compartment model. Thus, in study 3, Two-compartment model were designed and simulated to produce TCCs as shown in figure 40 and 20 twisted type membrane module tube phantoms (20TMMTP) was used to produce TICs as shown in the figure 41.

All the three TCCs started at t = 10s with the concentration value as 0 mg/ml. Cmax values for the dosages of the drugs (d= 2.5, 4.2, 5.8 moles) are 1.18,1.97,2.79 mg/ml at time Tmax = 11.95,12.58,12.37s respectively. Shown TCCs are for peripheral compartment and the TCCs with the combination of central and peripheral plots are shown in figure 1.22 in Appendix A. Since the 20TMMTP resembles the tissue compartment, they were compared with the peripheral compartment of 2-compartment model. It is observed that at t = 30s, the concentration values for the dosages of (d= 2.5, 4.2, 5.8 moles) were 0.002,0.0035,0.004 mg/ml and after t = 30s a steady curve is observed till t = 50s. The drug stayed in the compartment for longer when the dose values were high. The higher the concentration of the drug, the greater the residence time of the drug in two compartment model compared to the lower dose values. Thus, it clearly shows that the two-compartment model with higher dosages will produce longer residence time of CA.

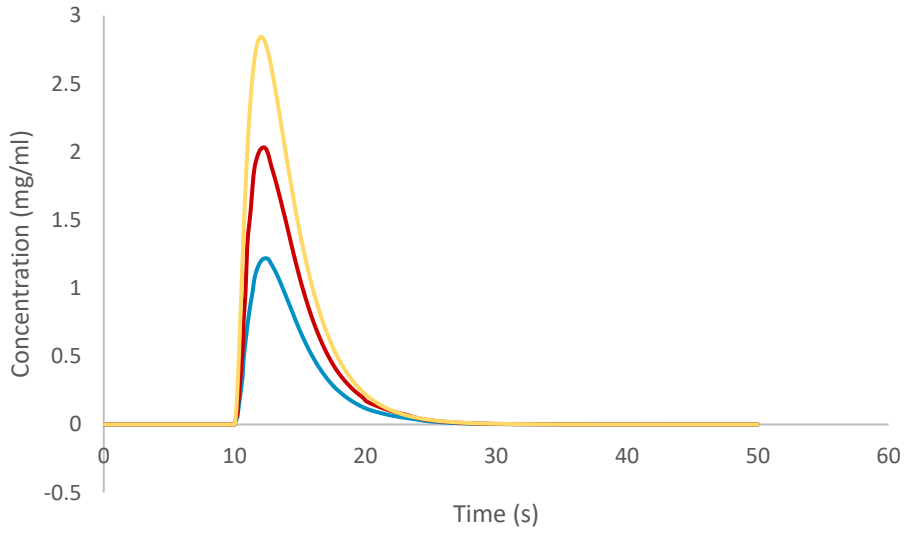

Figure 39 Time concentration curves (TCCs) which is obtained by performing simulations with the two-compartment pharmacokinetic modelling. The Blue, red and orange colour represents the TCCs which was obtained by varying the dosages of the drugs (d = 2.5, 4.2, 5.8 mole) respectively

These simulation results help the researcher to validate the experimental study. To compare the simulation results with the experiment, time taken for the contrast agent to stay in the 20TMMTP should be measured and analysed. Thus, three TICs were obtained by performing measurements with the 20TMMTP with same conditions which was used during the simulation study. All the curves start at t = 10s. Thus, the bolus arrival time (BAT) for all the curves were noted to be 10s. The peak intensity values were recorded, and their respective time was observed. At t = 13s the peak intensity value was 2038 au. (for dose = 3ml), at t =16s, the peak intensity value was 2030 au. (for dose = 5ml) and at t = 18.5s the peak intensity value was 2018 au. (for dose = 7ml). Lower the value of the intensity higher the value of concentration in real cases (since it is an inverted image). At t = approx. 30s, the intensity values for these dosages (3,5,7 ml) were 2058 au,2050 au,2046 au. Thus, in our case, it is evident that the little amount of contrast agent still stays in the tube at least till t = 50s as shown in the figure 41.

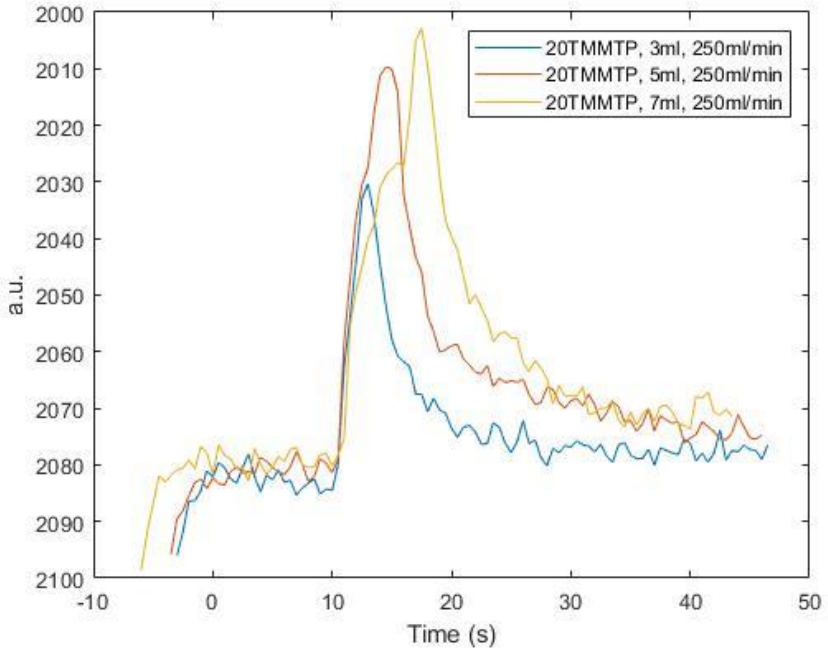

Figure 40 Time Intensity curve obtained on varying the dose for basic tube phantom. Blue, red and orange colour represents the TICs for the dosages (3,5,7 ml) respectively

On comparing the results of the simulation with the experiment, overall time taken for the CA or the drug to stay in the two compartment model and the 20 twisted type membrane module tube phantom showed almost same time duration of approx. t = 30 to 35 s. Further comparison of the study 3 results with the previous study is described briefly in discussion section.

Chapter 6: Discussion

This chapter aimed to evaluate this study by answering the research questions. The rationale for choosing the final four designs of tube phantoms and for conducting several studies are briefly described in this chapter. The effects of the main findings and suggestions for improvements are also discussed in this chapter.

Evaluation

One main research question with three sub questions were proposed and this section answers those research questions. The most important findings were also interpreted in this section. Initially, the main research questions are answered and followed by that the sub-questions were answered.

To what extent the systems (myocardial perfusion tube phantom and pharmacokinetic compartment models) mimic the myocardial tissue perfusion of contrast kinetics in the human heart?

The aim of this project was to resemble the physiological tissue perfusion by contrast kinetics. To do this, several studies were conducted. To evaluate these studies, the main research question is answered by combining the goals and results which was produced from study 1 and study 2 and comparing them with the previous study. Initially the study 1 was conducted to achieve the goal of developing the different types of tube phantoms and to identify which type of tube phantom could mimic the microcirculatory kinetics of CA in myocardial tissues in an efficient and reproducible way. Followed by that, the main findings of study 2 were analysed to determine the suitable model which could mimic the drug kinetics in myocardial segments. The findings from the simulation results helped the researcher to validate the experiment results by comparing both the studies (study 1 and study 2). In study 3, the experimental results which was obtained from 20TMMTP by varying the dose of the CA was initially compared with the two compartment results from study 2 by varying the same parameter (varying the dose of the drug). Additionally, few results from different types of tube phantoms were taken from study 1 and found that they also possessed longer residence time of CA (t = approx. 75 s) compared to the previous study (t = approx. 70 s). This measurement, which was taken from study 1 by using MTP, which had higher number of frames. Our previous study had developed a myocardial perfusion phantom (prototype 1) to validate and standardize the multimodal quantitative myocardial perfusion imaging (MPI). The obtained TACs from both phantom study (prototype 1) and from the patient data were compared, and the previous studies final result is shown in figure 3. Though our previous study was able to produce good results of Arterial input function by using their prototype 1, the main problem which still existed was that there was shorter residence time comparable to the residence time of the tracer in patient's myocardial tissue. This was because, the tissue mimicking materials were lacking in our previous study. Our current study had successfully resolved this problem. our study 3 results and few additional results from study 1 which was compared to the previous study results showed that myocardial perfusion tube phantom (20TMMTP & MTP) which was developed in our study was able to show good residence time of the contrast agent compared to the previous study phantom results. It was observed that our study could produce longer residence time of CA compared to our previous study and also mimics the myocardial tissue perfusion of the contrast kinetics in human heart to a greater extent.

How to design and optimize the myocardial perfusion tube phantom model designs?

In chapter 3, the various requirements were briefly explained. Out of 12 requirements, 8 requirements were fully met, and four other requirements were partly met. During the initial phase of the project these four requirements were not met. Later, these requirements were reconsidered, and the problems related to these requirements were resolved. The most important requirements were to design the tube phantom that could fit into the prototype 2. After several iterations of designs, the requirement 1 was fulfilled. The requirement 1 is essential because, this helped the researcher to configure and finalize the specifications of the tube phantom. The materials were chosen based on the requirement 2. The mixed tube phantom which contains the adsorption material (activated charcoal) showed good reproducibility, yet they could not trap the contrast agent fully. It would be interesting if we could develop tube phantom with only adsorption material by choosing different adsorption material. This could be helpful to know to what extent the newly proposed adsorption material could trap the CA. The tube phantom which contains more fibres (20TNMMTP) showed good and expected results based on

assumptions made. Hashimoto et al. [26], showed similar design where they used 8000 hollow fibres (greater number of fibres) with the diameter of 200nm to make perfusion phantom and they produced efficient results [26].Thus, we could conclude that the tube phantom with a greater number of fibres produces more efficient results. In addition, the reproducibility tests which was performed using MTP (which also contained the fibres) showed good reproducibility. Overall, the fibres which was used in our project was reliable and reproducible. The BTP, 10NMMTP and 20NMMTP and few other pre-concept designs were made using solid works software (Dassault systems. Massachusetts, United States). All the four types of tube phantom's hand sketches were made using online drawing tools. During the process of making the tube phantom, several insights were noted. Based on these insights, the incorporation designs were proposed. Out of which, the scaffold design could be used during the process of incorporation. Several types of simulations were performed using solid works flow simulations. For the sake of simplicity, BTP design was used to perform these simulations. the basic tube phantom simulation design was made with an extra tube to understand the basics of fluid mixing and fluid flows throughout the tube and to perform the optimizations. The visualizing results showed the injection of ethylene dye and the progression of this dye into the BTP that resembled the behaviour of BTP while injecting the CA. Visual based simulations, Time dependent analysis and Point goal analysis were performed using BTP design and these designs were optimized.

How can the myocardial perfusion tube phantom be developed to resemble the microcirculatory kinetics of the contrast agent (Iodine) in the myocardium?

The final four tube phantoms which was proposed in concept section was developed in this study and the whole process which was involved in the development phase of the different types of tube phantoms are discussed in Chapter 4. The testing and experimental measurements which were performed using these tube phantoms are explained in detail under Study 1 of Chapters 4 & 5. Initially, the comparison experiments were performed between different types of tube phantoms and the obtained results were analysed. Followed by that, the sensitivity of the tube phantoms on varying the parameters like flow rate and dosages of contrast agents were observed. During the initial phase of the project, few assumptions were made. The main hypothesis which was made was that all the three tube phantoms except the BTP might have longer residence time of CA of CA. Few other assumptions were made to support the main hypothesis. Using Study 1 results, we initially concluded that 20TMMTP had longer residence time of CA compared to the other tubes. It is also noticed that MTP showed good residence time of CA compared to the 10NMMTP and BTP. It was depicted that the tube phantom with greater number of fibres had longer residence time of CA compared to the tube phantom with less or without fibres. These conclusions were made from the comparison study which was performed under study 1. Few experimental parameters were varied, and it was assumed that the tube phantom with lower flow rate and with higher concentration should have longer residence time of CA compared to the other parameter variation. Even this was fulfilled by conducting the experiments by varying the different flow rates and also the different dosages of the CA. These results showed that the tube phantom with lower flow rate and higher dose of CA showed longer residence time of CA. Chiribiri et al. [18], performed similar analysis by developing a hardware perfusion phantom by varying different parameters like flow rates, dosages of the CA and cardiac outputs were varied. The results of this study showed good sensitivity of the different perfusion rates [18]. Our results showed good agreement with this study [18]. To support the main study 3, additional experiments were performed which is discussed under this section in study 1. These results showed that 20TMMTP had a longer residence time of CA of approx. 50 s with higher flow rate and higher concentration dosages and the MTP showed longer residence time of CA of approx. 75 s with lower flow rate and higher dosages of CA and eventually could mimic the microcirculatory kinetics of CA in myocardium.

Which pharmacokinetic compartment model is best suited for imitating the drug/contrast kinetics in the myocardial segments?

In study 2, the simulations were performed for one and two compartment PK models to obtain TCCs. These simulations results showed that two-compartment model could be a possible fit that could mimic the microcirculatory contrast kinetics. The simulations were performed by varying the contrast dosages of the drug (CA) from 0 to 3 moles. The volume of the compartments was set to 150 ml. The same dose regimen was followed for both. In one compartment, for the dose value of 3 mole, it was observed that the peak value of one compartment model was greater than the two-compartment model. The same

observation was noted from experimental results. This is because the drug is equally distributed between the two compartments where this does not happen in one compartment. On the other hand, the drug stayed longer in two compartment model than in the one compartment model. The time taken for the drug to fully eliminate, varied based on the amount of concentration. The dose amount with 3 mole has the highest peaks (Cmax) values with longer residence time of CA (>10 seconds since the curve did not reach zero at 10^{th} second and at t = 10 s the concentration value was 0.05 mg/ml) comparatively to all other lower dose values of the drug. Thus, it depicted that, higher the concentration of the drug dose, higher the residence time of the CA (drug). On comparing the higher concentration values of the one and two compartment model it was concluded that two compartment model showed longer stay compared to the one compartment model. The similar observation was made in the study conducted by xinghe et al [48].

Design and Development of the tube phantom

In Chapter 3, various requirements were suggested. Based on these requirements, several inlays were designed through step by step approach i.e. Initially ideas were generated to design the different types of tube phantom using online drawing tools, followed by that the selection of these design ideas were made in pre-concept phase and was finalized in concept phase. The final four shortlisted designs are illustrated in chapter 3 under concept design section. The final designs which were made using solid works software (Dassault systems. Massachusetts, United States), are displayed in chapter 3 under tube phantom design section. Additionally, tube phantom incorporation designs were proposed which could be useful while incorporating these tube phantoms into the prototype 2. The final incorporation designs can be found in chapter 3 under Incorporation design section.

The most important requirement is that the tube phantom should be designed in a way that it fits into the arc shaped hollow myocardial segment of the prototype 2. Though, we have designed and fulfilled this requirement (requirement 1), yet we need to consider that these designs need to be tested before incorporating them into prototype 2. Nevertheless, our aim in this project was to design, develop and test the tube phantom designs. These incorporation designs were considered as additional suggestions which could be used during the incorporation phase (as a part of future recommendations). To optimize the incorporation designs especially the scaffold designs, velocity-based simulations were performed as shown in figure 1.13 in Appendix. These designs were made to understand the flow rate when the contrast agent (dye) was injected. Design 1 of the incorporation designs were discarded since each arc shaped hollow scaffold had all the types of tube phantoms. In this case, the flow rates will be difficult to monitor for all these tube phantoms. Instead, harvesting one type of tube phantom in one segment could be introduced. Scaffold incorporation designs (design 2) could be fabricated and tested along with the final prototype 2 to avoid additional material costs.

The materials which were chosen for the fabrication of the tube phantom were based on requirement 2. The semipermeable fibres which was used, served the purpose by performing the phenomenon of the process of diffusion. These fibres also possessed the phenomenon of permeability. Anderson et al. [29], observed the process of diffusion of water and solute using gadolinium-based contrast agent. They used semipermeable hollow fibre phantoms (Length: ~ 15 cm with 1mm diameter holes) which was made out of haemodialysis fibres (which was commercially available) to perform this diffusion process. This study results showed that the developed semipermeable hollow fibre phantoms were reliable and resembled the tissue capillary functions [29]. Thus, it is evident that tube phantom with fibres will produce reliable and resemble the tissue capillary functions.

The adsorption materials were chosen that could trap the contrast agent to some extent. In our study we used activated charcoal (otherwise known as active charcoal) as the adsorption material to perform the adsorption phenomenon. Elizalde et al [49]., tested the three different carbon samples and showed that these adsorption materials could adsorb 70-90% of the contrast agent (Gadolinium based contrast agent). Thus, requirement 2 was satisfied. The size of the adsorption material was chosen in a way that the pore size of the powdered adsorption material was greater than the pore size (20nm). Because during diffusion process, there are high chances that these adsorption materials pass through the pores.

In this project, since we are aiming to increase the uptake of the contrast agent, it is crucial that the dye or contrast agent should pass through the pores of the fibres. The TICs results which were obtained

from different types of tube phantoms by varying several experimental conditions (flow rate of 200 ml/min, dose of gadolinium based CA = 5ml)) had shown that the tube phantom with fibres showed longer residence time of CA compared to the tube phantom without fibres.

Among twelve requirements, eight requirements were fully satisfied. Whereas the requirement 5,7,10,11 was partly fulfilled. The requirement 5 & 7 was aimed to produce the tube phantom with pressure value lesser than 10 bars and to avoid leakages. Though these requirement was met, while performing measurements with tube phantoms (MTP with 10 fibres and 10NMMTP), for one or two measurements, it was noticed that there was a backflow of contrast agent at the beginning of the tube and then the gear pump stopped running. This was because, high pressure was created while using low fibres (n<10). For low flow rates (100ml/min, 150ml/min), these tubes showed higher pressure whereas this problem was resolved by increasing the flow rates (>200 ml/min) and the measurements were repeated again. Nevertheless, this issue was not observed for tube phantom with 20 fibres in twisted fashion. While developing the tube phantom, membrane module gluing process is highly important. Gluing the fibres and sealing the tube should be done properly to avoid leakages.

3D (Computer aided designs) along with flow simulations like particle simulation, time-dependent analysis, point goal analysis etc., were made for the basic tube phantom and the membrane module filled tube phantoms. To simulate the designed models (BTP) and to obtain TICs, potential softwares were identified like COMSOL Multiphysics 5.0 (COMSOL Inc, Stockholm, Sweden), Solid works flow simulation in solid works software (Dassault systems. Massachusetts, United States), Simbiology app in MATLAB (MathWorks, Massachusetts, United States), PMOD (PMOD Technologies LLC, Zurich, Switzerland) etc., Out of which solid works were chosen to obtain TICs. Yet, after performing time-dependent analysis and point goal analysis, we concluded that, obtaining TICs by injecting a bolus was not achievable. Thus, we decided to choose the software which could fulfil our needs. Finally, the project goals were met by using symbiology app in MATLAB (MathWorks, Massachusetts, United States). Yet, the results obtained from point goal analysis showed the progression of the dye after getting mixed with water and helped us to understand the concepts of CA kinetics inside basic tube phantom. Overall, final four designs were selected and was used to perform the final experiments (Study 1).

Study 1: Experimental Study

In this study, several experiments were performed to obtain TICs. These TICs helped the researcher to understand the behaviour of the different types of tube phantoms at different experimental conditions like by varying the flow rates and by varying the contrast agent dosages. Initially, the comparison experiments were performed between different types of tube phantoms and the obtained results were analysed. Followed by that, the sensitivity of the tube phantoms on varying the parameters like flow rate and dosages of contrast agents were observed.

Manual injection method was used for the administration of contrast bolus injection. The starting time of the bolus could vary from one measurement to other. Moreover, accurately determining the rate at which the Contrast bolus is injected is hard to determine using manual method. Manual method could be replaced by using programmable power-controlled injector. Though we did not find any air bubble inside the tube phantom while performing the measurement, yet it is good to consider this while incorporating the tube phantoms. While performing incorporation experiments, mixed tube phantom will be hard to implement since we need to add the adsorption materials in-between the 3D printing fabrication process.

During the starting phase of the project, few assumptions were made. In general, it was hypothesized that all the three tube phantoms except the BTP might have longer residence time of CA of CA. Followed by that, it was expected that the tube phantom with low flow rates and with higher concentration of CA might increase the prolongation of the uptake of CA. The 20TMMTP was expected to produce longer residence time of CA of CA compared to all the other tubes. Additionally, it was also assumed that using large number of fibres in the tube phantom (20TMMTP) might increase the residence time of the CA compared to using a smaller number of fibres in tube phantoms (10NMMTP & MTP with 10 fibres). The MTP was expected to have greater prolongation of the uptake of the CA than 10NMMTP.

We conducted visual assessment to evaluate the conducted experiments. On comparing the different types of tube phantoms (flow rate = 200 ml/min, 5ml), it was noted that TICs obtained from BTP had longer residence time of CA compared to the other tubes, but the results were contradictory. The reason for this contradiction is that the overall comparison was made for 25 seconds which is only 50 frames were compared. On increasing the number of frames, we could have observed the expected results. Thus, to get better understanding, we excluded BTP initially and compared the other tubes since the intensity levels for these tubes were slightly closer to each other. Moreover, the comparison results between TICs obtained from MTP, 20TMMTP, 10NMMTP for flow rate 200 ml/min and with dose of the contrast agent as 5 ml, proved that 20TMMTP had longer residence time of CA compared to the other tubes. Though we ignored BTP, we performed additional comparison experiments which was conducted between BTP, 10NMMTP, 20TMMTP (flow rate = 250 ml/min, 5 ml). From these results, it clearly shows that 20TMMTP had longer residence time of CA compared to BTP and 10NMMTP. Thus, from comparison studies we could conclude that 20TMMTP is the best suitable tube phantom which could mimic the tissue perfusion by contrast kinetics. Interestingly, we could see a small line where the leftover of contrast agent in the 20 Twisted membrane module filled tube phantom even after the maximum frames was reached.

The sensitivity of the tube phantoms (BTP, MTP) on varying the flow rate were analysed by varying the range of flow rates from 100 to 200 ml/min (100,150,200 ml/min) by keeping the dose of the CA as constant (5ml). The results obtained from BTP showed longer residence time of CA with flow rate (150ml/min) compared to the higher flow rates (200 ml/min). Though it was to our expectation, the TICs produced for the flow rate 100 ml/min showed shorter residence time which was contradicting our assumptions. Additionally, MTP was used by varying the flow rates from 100 ml/min to 200 ml/min. Figure 32 illustrates that, MTP with lower flow rates (100ml/min) had longer residence time of CA compared to the tube with higher flow rates (200 ml/min).

The sensitivity of the tube phantoms (BTP, MTP) on varying the dosages of the CA (3,5,7 ml) were investigated by keeping the flow rate as constant (150 ml/min). Both the results from BTP and MTP showed that higher the concentration (7ml), prolonged the stay of CA in these tubes. These results were in good agreement with chiribiri et al. [18].

Reproducibility measurements were performed only for basic tube phantom and the mixed tube phantom. The reproducibility results which was obtained by repeating the same parameter (Flow rate = 150ml/min, dose of CA = 5 ml) thrice (n=3) for both the tube phantoms (BTP, MTP) showed good reproducibility. Chiribiri et al., conducted reproducibility test and repeated the measurements for 6 times and the results showed excellent reproducibility between different days and varying the different operators [18].

For future experiments, it would be interesting to find differences between the 20 Normal tube phantoms with 20 Twisted tube phantoms with low flow rate values and with higher concentration.

Study 2: Simulation Study

The simulation experiment results clearly showed that two-compartment model had longer residence time of CA in comparison with the one-compartment model. This is because the one compartment model involves only the flow of the drug in blood or plasma. In the two compartmental model, the peripheral compartment resembles the tissue and in central compartment only the flow of drug in blood or plasma happens. The process of absorption takes place in the peripheral compartment which resembles the mechanisms of the human tissue. Same dose regimen was followed for both the compartment models, yet the two-compartment model showed low peak (Cmax values) on comparison with the one-compartment models though the Tmax remained between approx. 0 to 2 seconds. For instance, with the dose value of 3 mole, the peak value of two compartment model was 1.63mg/ml, whereas the peak value for one compartment model was 2.19 mg/ml. The same observation was noted from the experimental results.

On the other hand, the drug stayed longer in two compartment model than in the one compartment model. The time taken for the drug to fully eliminate, varied based on the amount of concentration. The

dose amount with 3 mole has the highest peaks (Cmax) values with longer residence time of CA (>10 seconds since the curve did not reach zero at 10^{th} second and at t = 10 s the concentration value was 0.05 mg/ml) comparatively to all other lower dose values of the drug. Thus, it depicted that, higher the concentration of the drug dose, higher the residence time of the CA (drug).

This simulation study helped us to validate the experimental results. The model design which is used during the simulations is just a physical volume filled compartment, it cannot be compared physiologically like we perform the experiments with phantoms in real time scenarios. Simulation results produces smooth curves because they do not have any experimental complications like air bubbles, back pressures, leakages etc., as encountered while performing the physical experiments. Thus, before concluding the results right away from the simulation results, it is always sensible to consider the options like comparing the simulation results with the experimental results. These comparison results could then be compared to the previous study.

Study 3: Comparison study: Simulation vs Experimental

The combination of 20TMMTP measurements and the simulation results of the two-compartment PK model were found to be extremely robust. These simulated results (TCCs) and experimental (TICs) were compared in this study. To do the comparison, linear fit between concentration and the intensity values were made using contrast calibration factor as shown in the figure 5.10. These results showed that they are linear (As shown in figure 1.23 in Appendix A). Additionally, these results from study 3 is compared with the previous study and it is evaluated.

Comparison with the previous study

In addition to the experimental results, few additional measurements were taken to compare the current study with the previous study. For the BTP measurements (with higher flow rate and with higher concentration) were performed separately with experimental variations like flow rate (250ml/min) and the dose of CA as 7ml with 120 frames. In this BTP measurement it is observed that at t = 60 s, the intensity values were 2063 au. At t = 10.5 s, that is at the start of the curve, the intensity values were found to be 2060 au. From these results, it is noted that at t = 60 s, the intensity value was lower than the starting point of the curve. It means that the CA is fully eliminated from the tube phantom.

For 20TMMTP (high flow rate with higher concentration), the flow rate was set as 250ml/min and with the dose of the CA as 7ml. These measurements were recorded for 127 frames with overall duration of 63.5 s in total. It is observed that at t = 63.5 s, the intensity value was 2066 au and at t = 16.5s the intensity value was 2079 au. From this we could infer that intensity value at t = 63.5 s was higher compared to the starting point of the curve where the CA starts to distribute inside the tube phantom.

For MTP (with lower flow rate with higher concentration), the flow rate was set as 100ml/min and with the dose of the CA as 7ml. These measurements were recorded for 168 frames with overall duration of 84 s in total. It is observed that at t = 84, the intensity value was 2058 au. and at t = 12s the intensity value was 2064 au. From this we could infer that intensity value at t = 84s was higher compared to the starting point of the curve where the CA starts to distribute inside the tube phantom. This measurement was used to compare these results with the previous study.

The results from BTP shows that the CA was fully flushed from the tube phantom with higher flow rate with the higher concentration. Whereas the results which were obtained from MTP and 20MMTP shows that there is some amount of concentration left in the tube phantom.

The previous study had compared the residence time of the tracer between the phantom and the patient. Though the imaging modalities were different, we observed that TICs which was obtained from 20TMMTP and the simulation results (TCCs) which was obtained from Two-compartment model showed longer residence time of CA compared to the previous study and also showed good agreement with the patient's TACs.

Chapter 7: Conclusion

The main purpose of this study was to resemble the physiological tissue perfusions by contrast kinetics. The uptake of the Contrast agent was improved by designing and developing different types of myocardial perfusion tube Phantoms. The final four types of tube phantoms were tested, and it was found that 20TMMTP showed longer residence time of CA compared to all the other tubes. Additional experiments were performed on 20TMMTP and MTP and it was noticed that both prolonged the tissue residence time of the CA which was injected. One of the experimental (study 1) results showed that MTP tube had longer residence time of CA of t = 75 seconds with lower flow rates and with higher concentration. Both the BTP and MTP should good reproducibility and were reliable. From the study 1 results it is concluded that 20TMMTP had longer residence time of CA compared to other tubes and MTP also showed good residence time of CA compared to BTP and 10NMMTP with higher dose of CA and with lower flow rate. These results eventually mimicked the microcirculation of the contrast kinetics in myocardium.

On the other hand, the study 2 simulation results showed that two-compartment model had longer residence time of CA compared to the one-compartment model. From this study 2 it was concluded that 2-compartment model was best suitable to mimic the tissue perfusion in myocardial segments. Since the simulation results showed that the delay of the drug in the peripheral/ tissue compartment, where the actual absorption process takes place that mimicked the mechanism which happens in myocardial tissue.

The basic tube phantom and mixed tube phantom shows good reproducible results. The Tube phantom with fully filled fibres (20TMMTP) and two-compartment models have depicted the contrast kinetics and resembled the microcirculation in the myocardial segment tissues.

The results which was obtained from the simulation study produced smooth TCCs because in general they did not include additional complications that could be faced while performing experiments with phantom studies, animal studies and even human studies. Thus, the results from study 3 (which compared study 1 and study 2 results) was compared with the previous study (TACs of phantom study were compared with the TACs of patient). These results showed that 20TMMTP and MTP produced good residence time of CA than the previous study results which eventually mimicked the myocardial tissue perfusion of the contrast kinetics in human heart to a greater extent.

Chapter 8: Future Recommendations

The Tube phantom, which was developed in this project showed expected results. Yet, they require further improvement while incorporating them into the currently developed prototype 2. The scaffold incorporation designs which were discussed under pre-concept design idea section could be considered as additional suggestion which could be used while performing incorporations of the tube phantoms into the myocardial segment regions in Prototype 2.

The 3D printed tube phantom could also be designed in future to avoid extra material usages and to avoid the extra costs. While performing incorporation experiments, mixed tube phantom will be hard to implement since we need to add the adsorption materials in-between the 3D printing fabrication process. Though the adsorption materials which were used in this project showed expected results, the tube phantom with only adsorption material which was discarded could be reconsidered with different adsorption material or different lab settings so we could fully trap the CA. Thus, alternative adsorption biomaterials like polyvinylchloride (PVC), polypropylene, Hydrogels, Polymethyl methacrylate(PMMA), Silica gels could be tested [42].Since we used X-ray fluoroscopic technique to visualize the contrast agent kinetics, the region where the adsorption materials were present were not easily recognizable yet the time intensity curve which was obtained could help us understand that, the tube with both activated charcoal and the membrane module showed good uptake of CA.

Thus, we may consider varying the adsorption material for better visualization or try out different imaging modalities for performing the measurements. Additionally, the mixed tube phantom simulations and the adsorption tube phantom simulations could be performed using COMSOL Multiphysics software. These simulations could help us to predict the values of contrast kinetics which supports our experimental results and will also help in choosing the suitable fabrication materials.

While performing measurements, though there were not many issues with air bubbles detected during the measurements, while designing the final prototype 2, its always wise idea to find ways to avoid air bubbles which might later act as an hinderance for the final expected experimental outcome for prototype 2. For future experiments, it would be interesting to find differences between the 20 Normal tube phantoms with 20 Twisted tube phantoms with low flow rate values and with higher concentration.

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Appendix

A. Figures

Fabrication of the Tube phantom

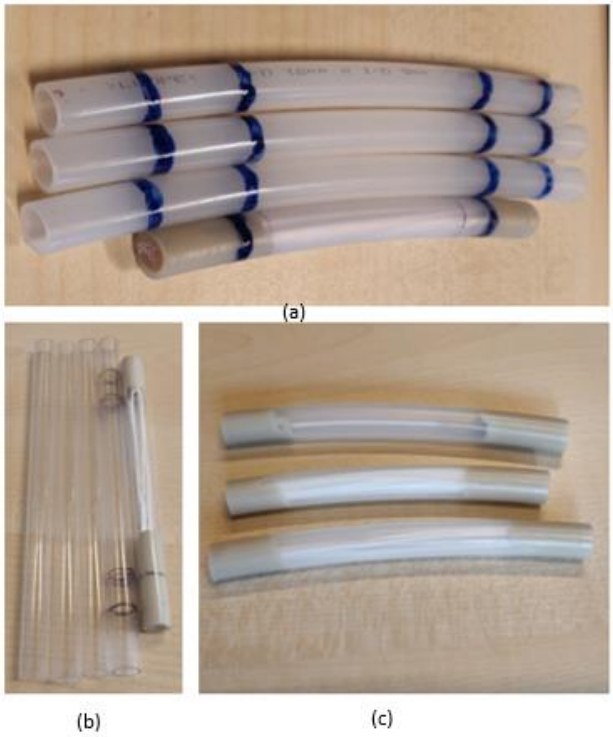

Figure 1. 1 Different types of tubes (based on the different types of tube properties) which were made during the development Study. (a) Shows the markings made on the tubes to optimize the tube phantoms; (b) Plastic Perplex transparent tube (c) Normal plastic non-transparent tubes

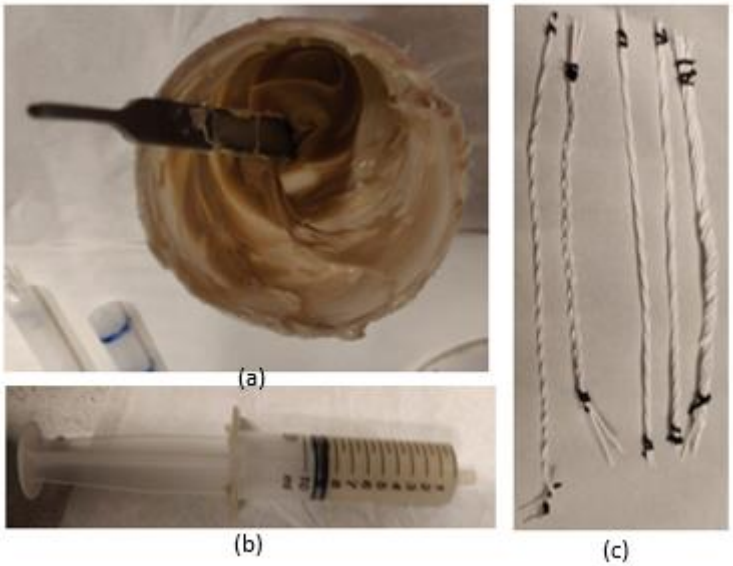

Figure 1. 2 First three steps involved in the making process of the tube phantom. (a) Glue mixture preparation; (b) Syringe preparation; (c) Membrane module preparation

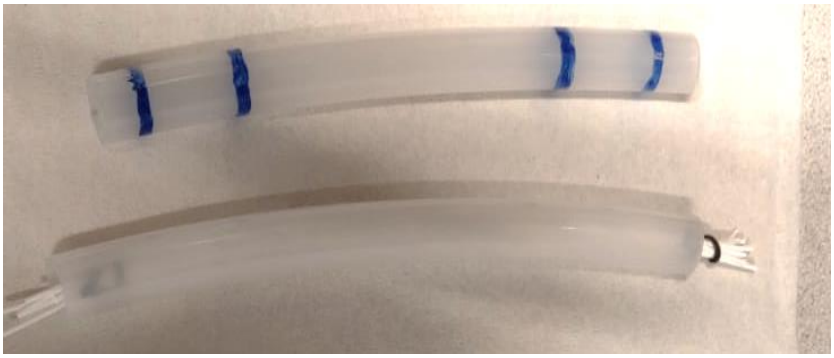

Figure 1. 3 Tube preparation step involved in the making process of the tube phantom

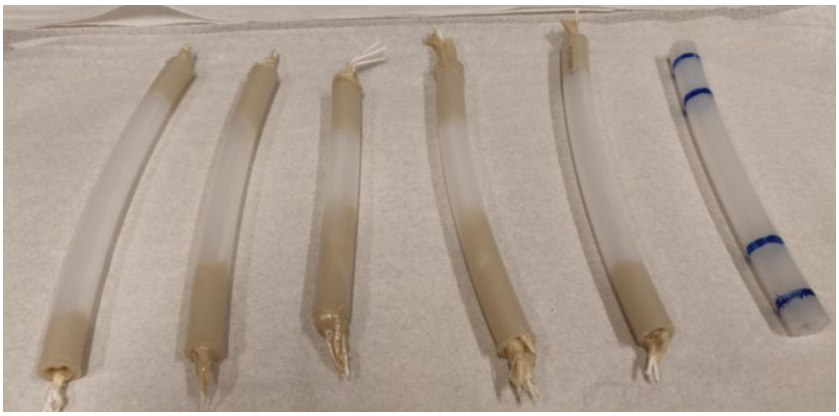

Figure 1. 4 Drying process involved in the making process of the tube phantom

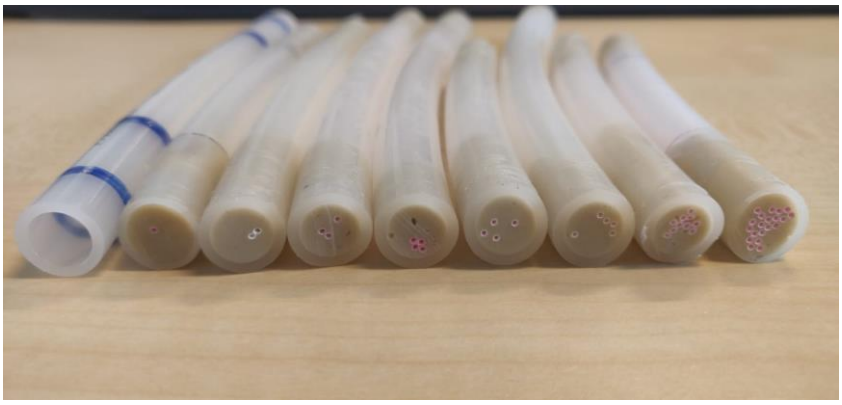

Figure 1. 5 Different types of membrane module filled tube phantom (n=0,1,2,3,4,5,10,20) (from left to right)

SolidWorks: Designs and simulations

Basic Tube optimization designs and simulations

Visualization of the basic tube phantom

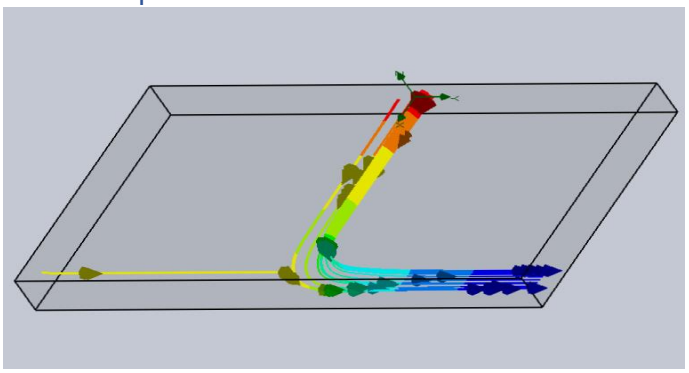

Figure 1. 6 Pre-concept design of the basic tube setup. The water enters from the top of the tube and the ethylene dye enters from left side of the tube. The yellow line represents the flow of ethylene dye.

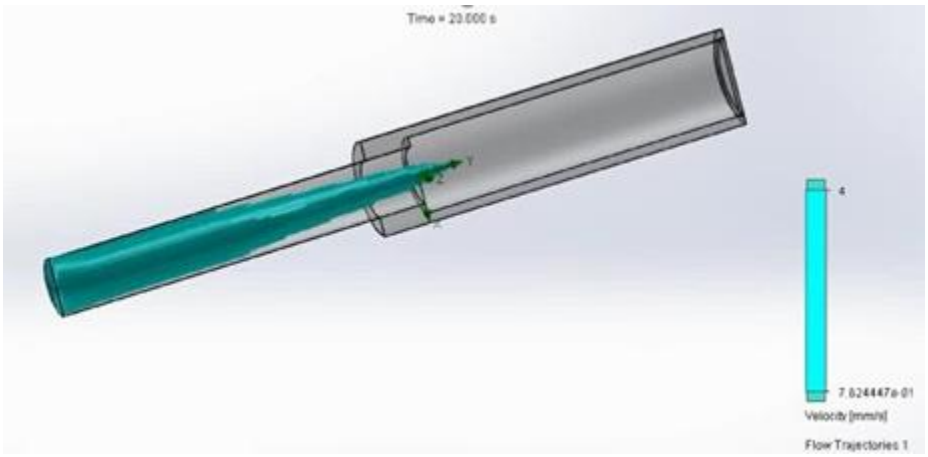

Figure 1. 7 Flow simulation of water inside the tube phantom (Time – 20 seconds)

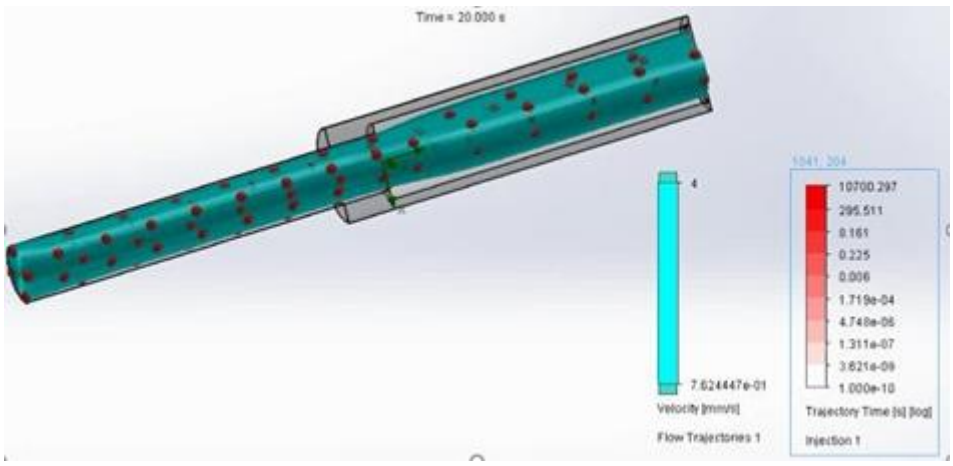

Figure 1. 8 Visualization of the Ethylene dye flowing along with the water inside the tube phantom (Simulation Time – 20 seconds)

Simulation of the basic tube phantom

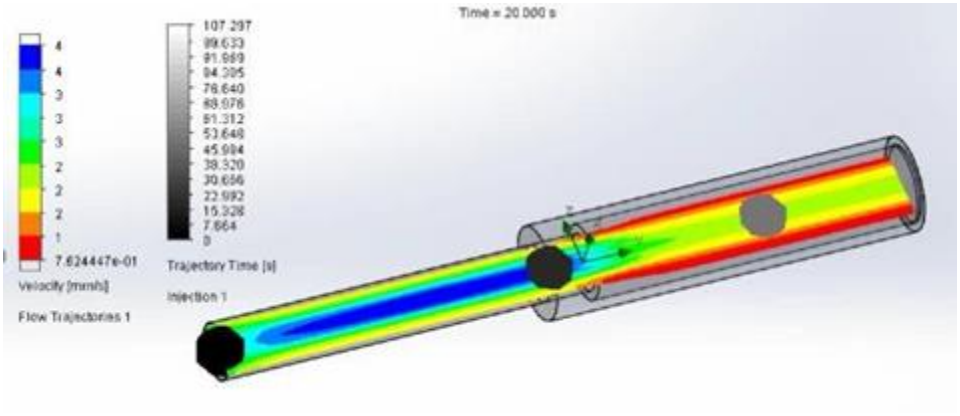

Figure 1. 9 Injection 1: Flow trajectories of the Ethylene dye (Larger sized particles) with the Velocity profile (Simulation Time – 20 seconds)

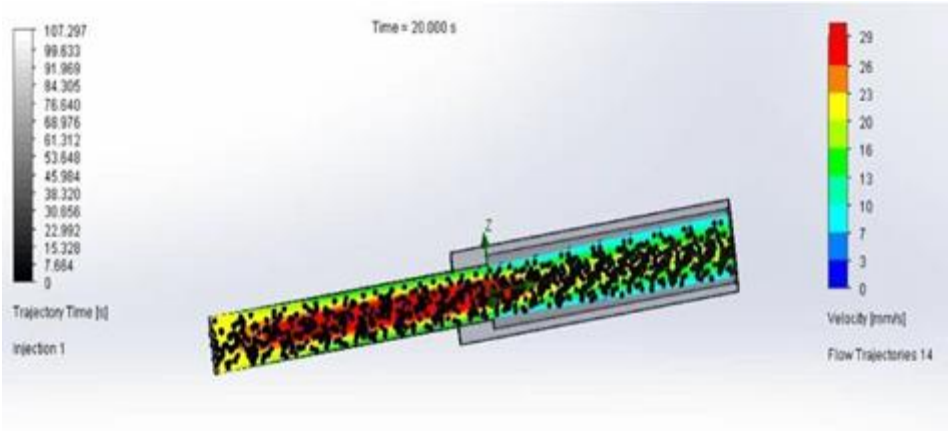

Figure 1. 10 Injection 1: Trajectory time taken by the Ethylene dye with 100 smaller sized particles (Simulation Time – 20 seconds)

Point Goal Analysis

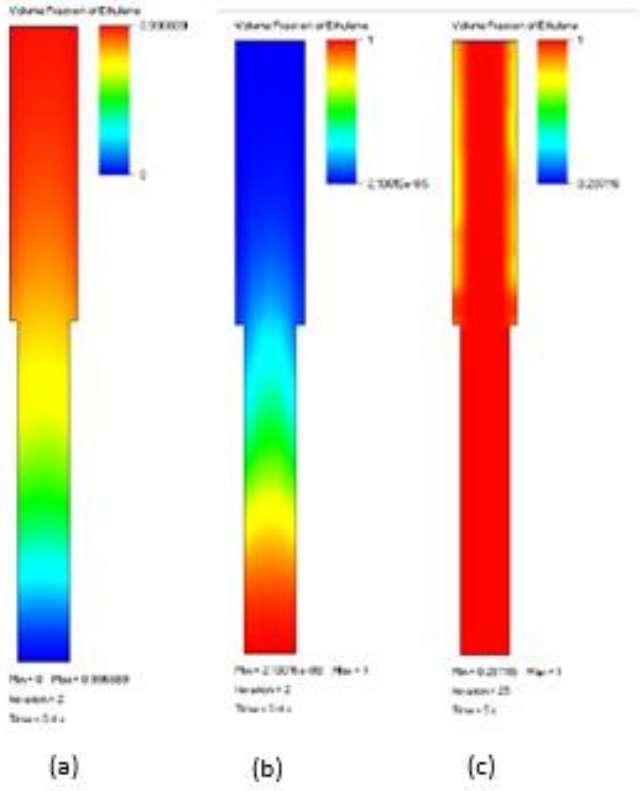

Figure 1. 11 The visualization of the flow of ethylene dye inside the tube phantom while performing the point goal analysis

Basic incorporation simulation

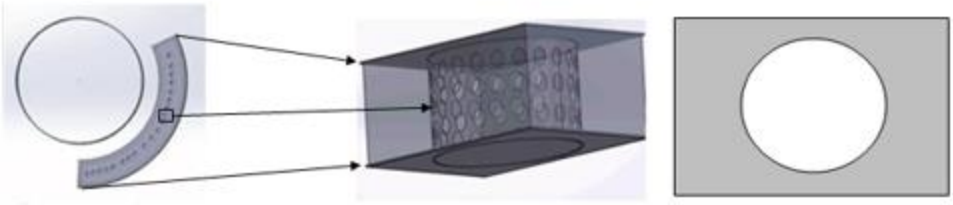

Figure 1. 12 Simple incorporation-based simulation flow setup originated from the scaffold design. This shows the side view and top view (from left to right)

Basic incorporation simulation

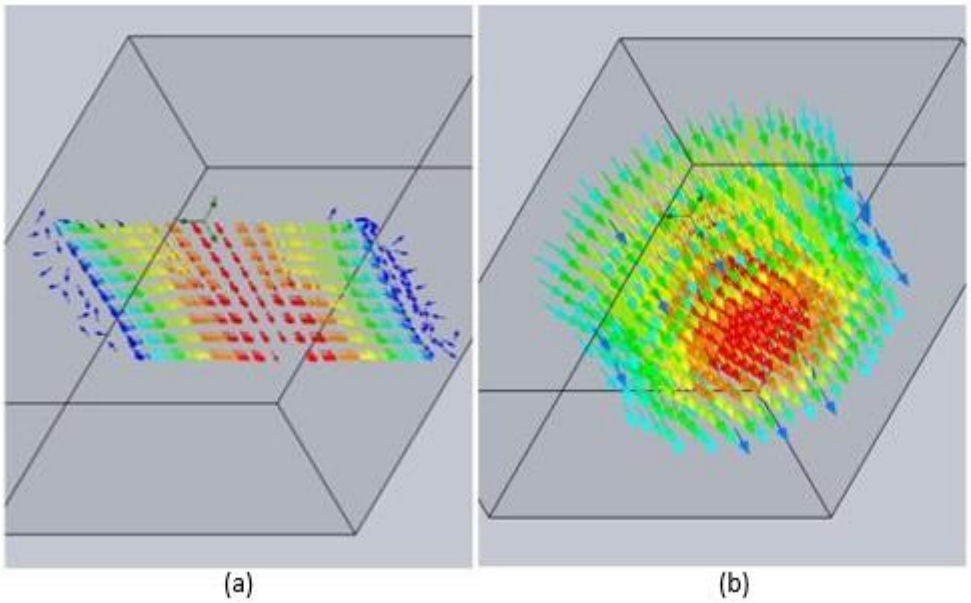

Figure 1. 13 Comparison of the velocity profile of the ethylene dye in basic tube phantom and membrane module filled tube phantom (maximum velocity = 0.01292705 mm/s and minimum velocity = 1.99725E-06 mm/s)

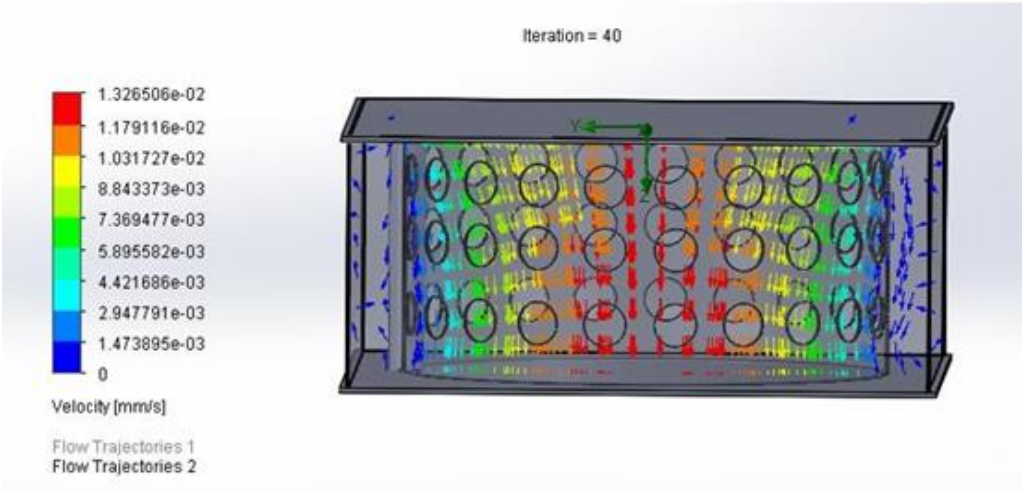

Figure 1. 14 Flow trajectory: The velocity profile of the concentration of the ethylene dye using the membrane module filled tube phantom (maximum velocity = 1.326506E-02 mm/s and minimum velocity = 0 mm/s)

Study 1: Experimental study

Figure 1. 15 Parallel flow setup with four types of tube phantom (lab settings)

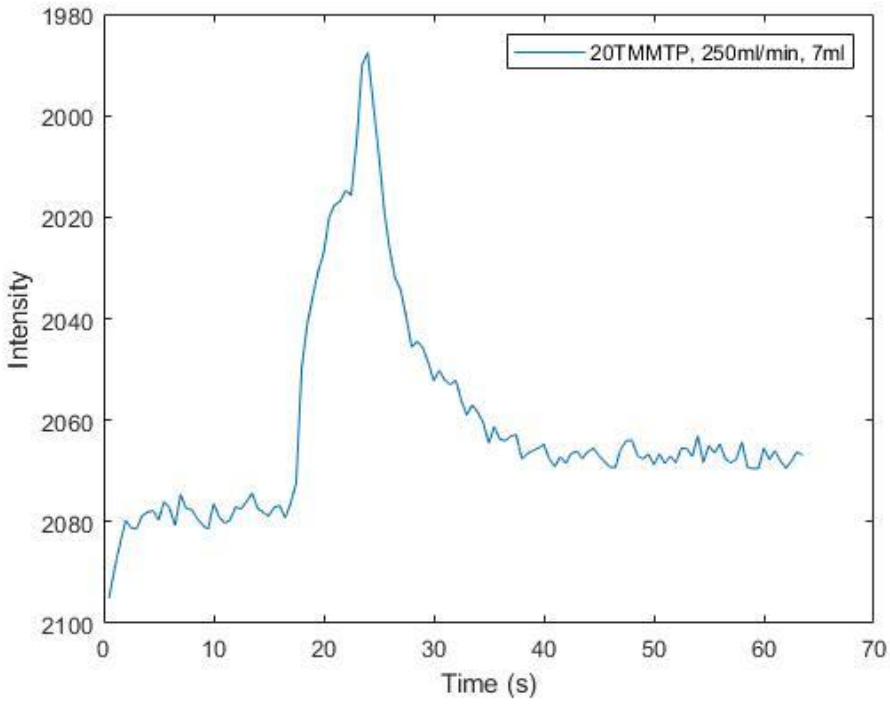

Figure 1. 16 Time Intensity curve obtained from 20TMMTP by keeping the flow rate at 250 ml/min and the dose of Contrast agent as 7 ml. Blue colour represents the Time intensity curve which was obtained from 20 twisted type tube phantom

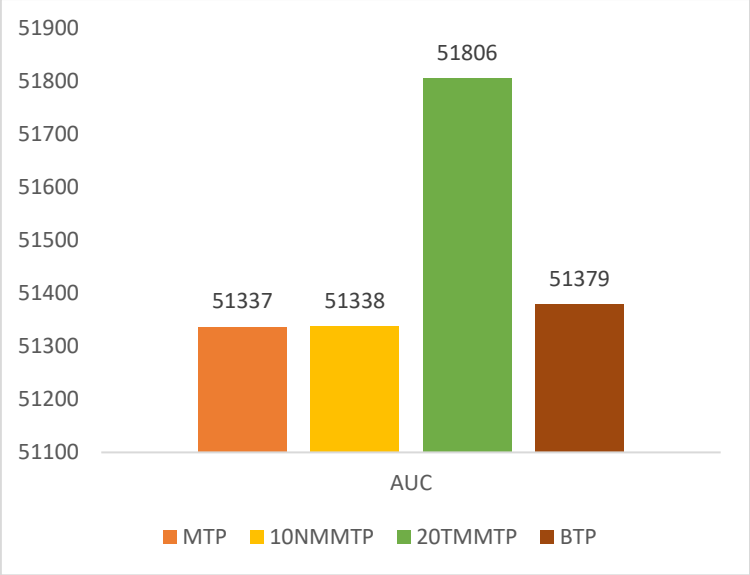

Figure 1. 17 The AUC which was calculated for different types of tube. The orange colour shows the AUC for MTP; Yellow colour represents the AUC for 10NMMTP; Green colour depicts the AUC for 20TMMTP, and brown colour shows the AUC for BTP. AUC = Area under curve; BTP = basic tube phantom; 20TMMTP = 20 twisted type membrane module filled tube phantom; 10NMMTP = 10 Normal type membrane module filled tube phantom; MTP = Mixed type tube phantom

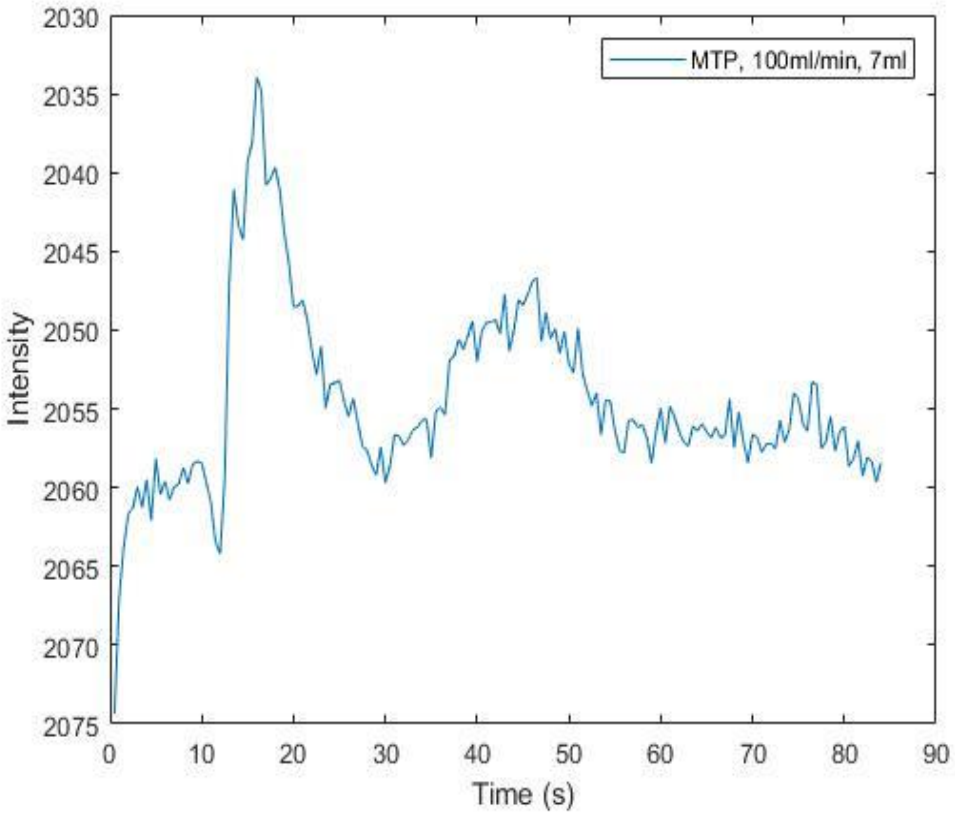

Figure 1. 18 Time Intensity curve obtained from MTP by keeping the flow rate at 100 ml/min and the dose of Contrast agent as 7 ml. Blue colour represents the Time intensity curve which was obtained from Mixed tube phantom

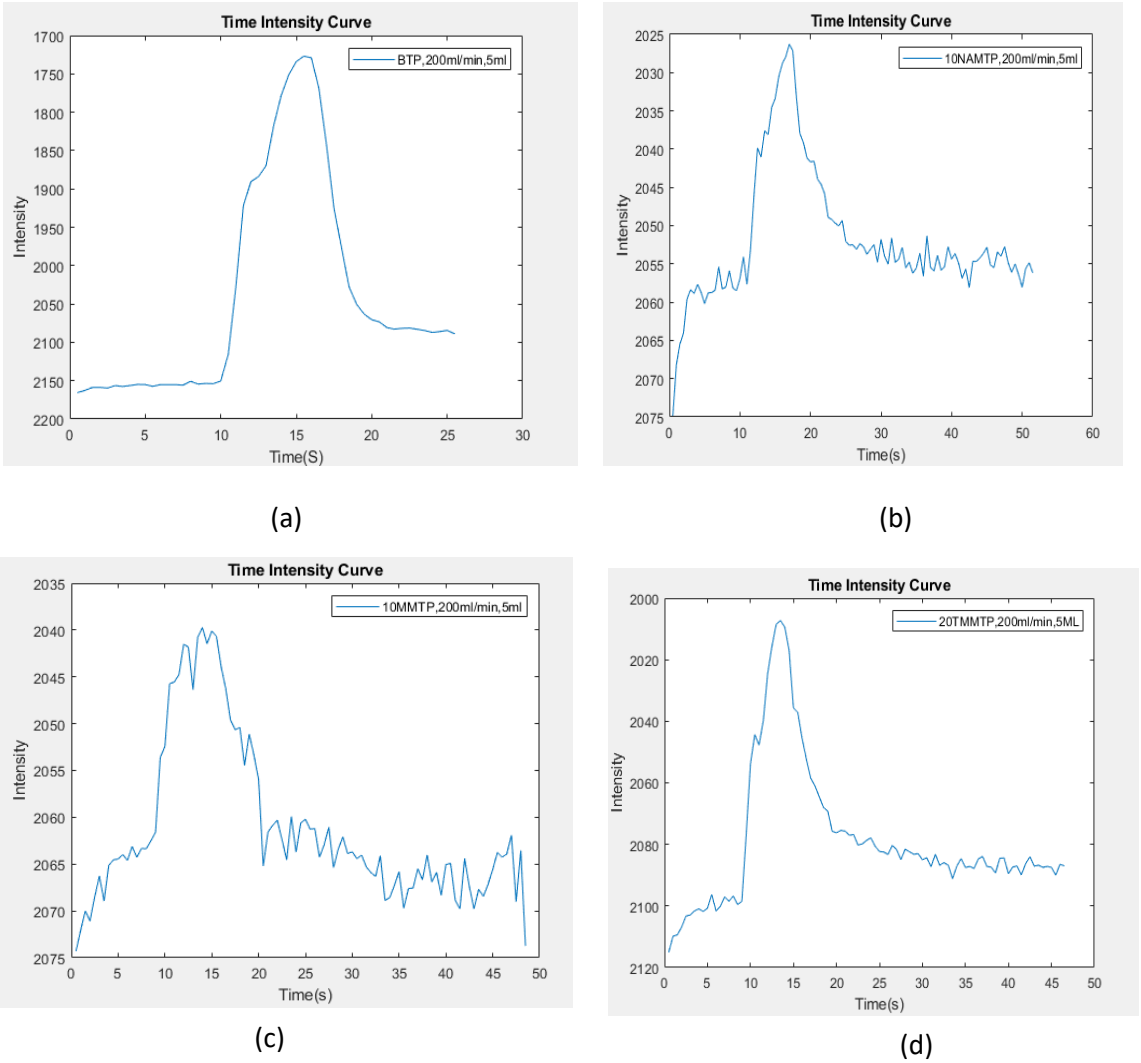

Figure 1. 19 Comparing the results of different types of tube phantom with constant flow rate as 200ml/min and 5 ml of Iodine. (a) Basic tube phantom (BTP); (b) Mixed Tube phantom (10Normal+Adsorption material) (10NAMTP); (c)Membrane module filled tube phantom (10normal) (10NMMTP); (d) Membrane module filled tube phantom (20 twisted) (20TMMTP)

Study 2: Simulation study

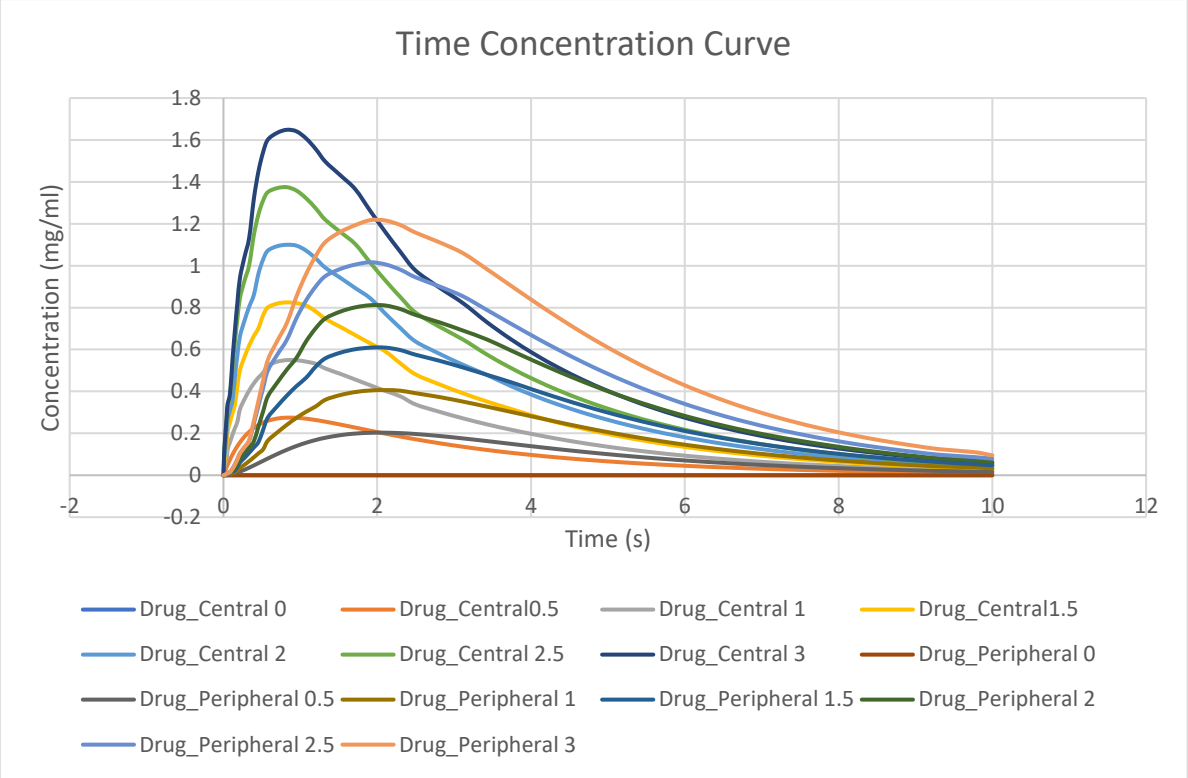

Figure 1. 20 Time Concentration curve – Two-compartmental analysis results with the elimination type – Linear {Clearance, Time}. This plot shows Time concentration curves which was obtained in both central and peripheral. The simulation time was run for 10 seconds. The curves are obtained by varying the dose values from 0 to 3 moles

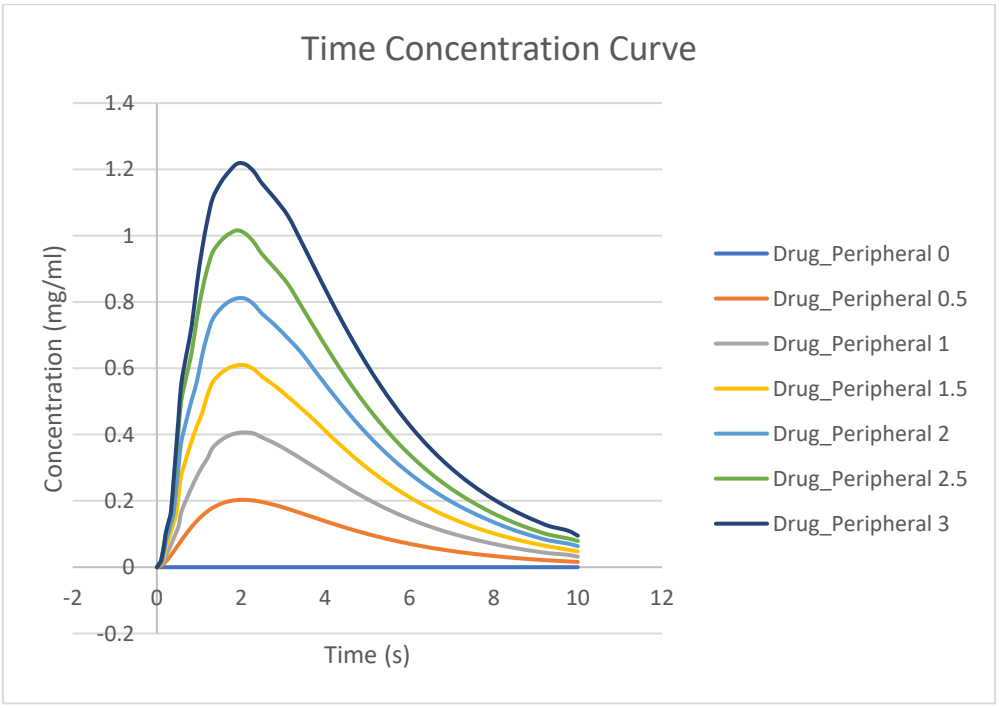

Figure 1. 21 Time Concentration curve – Two-compartmental analysis results with the elimination type – Linear {Clearance, Time}. This plot shows Time concentration curves which was obtained in peripheral compartment. The simulation time was run for 10 seconds

Study 3: Comparison study

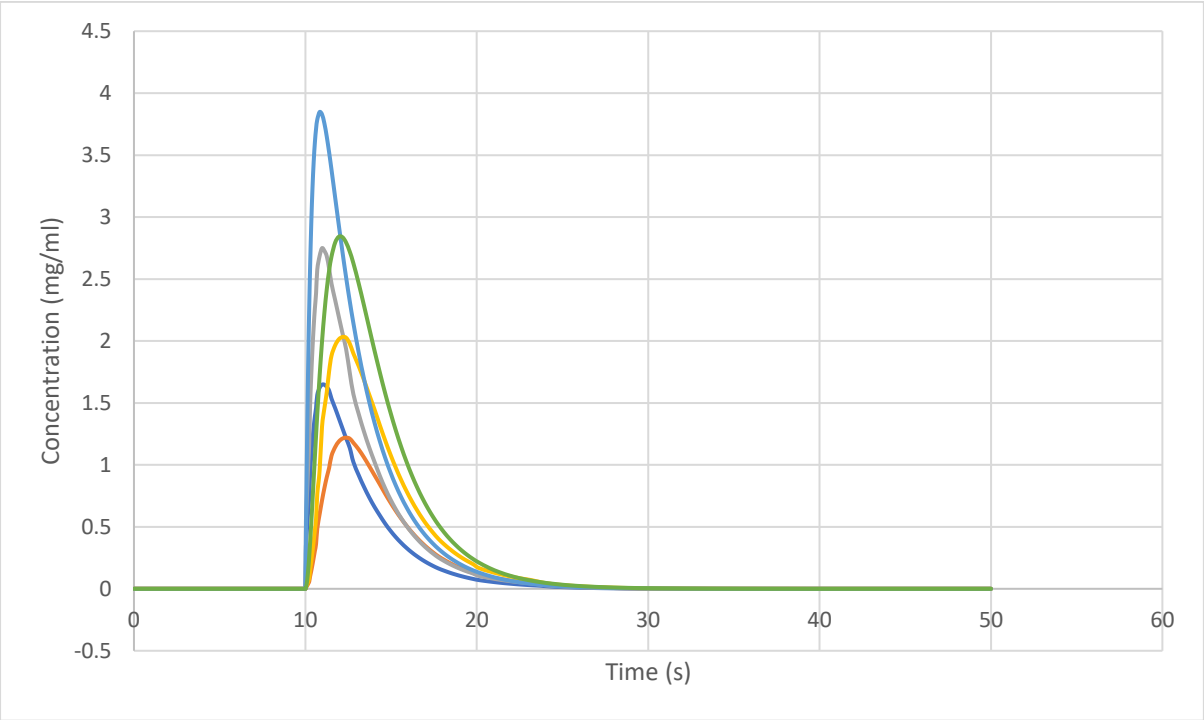

Figure 1. 22 Time Concentration curve – Two-compartmental analysis results with the elimination type – Linear {Clearance, Time}. This plot shows Time concentration curves which was obtained in central compartment and peripheral compartment by varying the dose (2.5,4.2,5.8 ml). The simulation time was run for 10 seconds

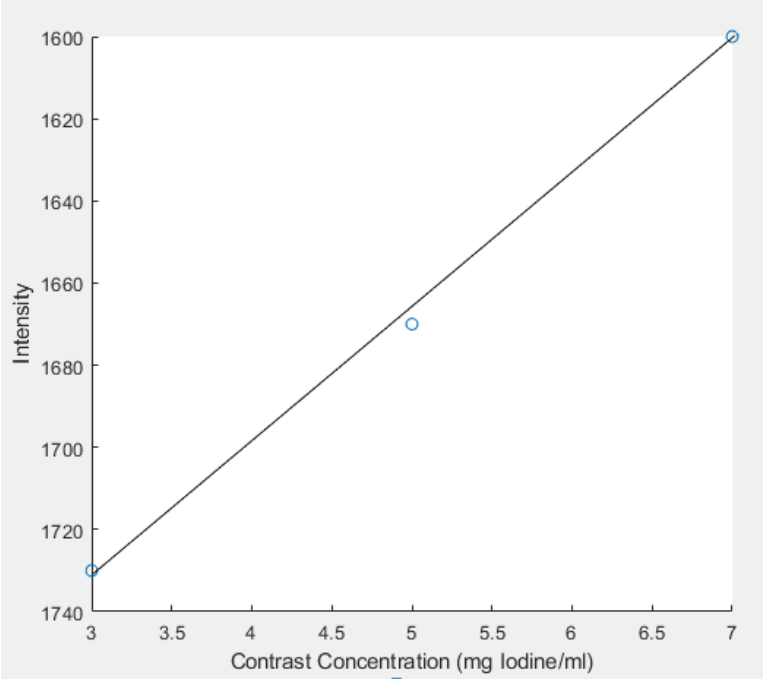

Figure 1. 23 Linear fit between intensity and iodine concentration (mg Iodine/ml)

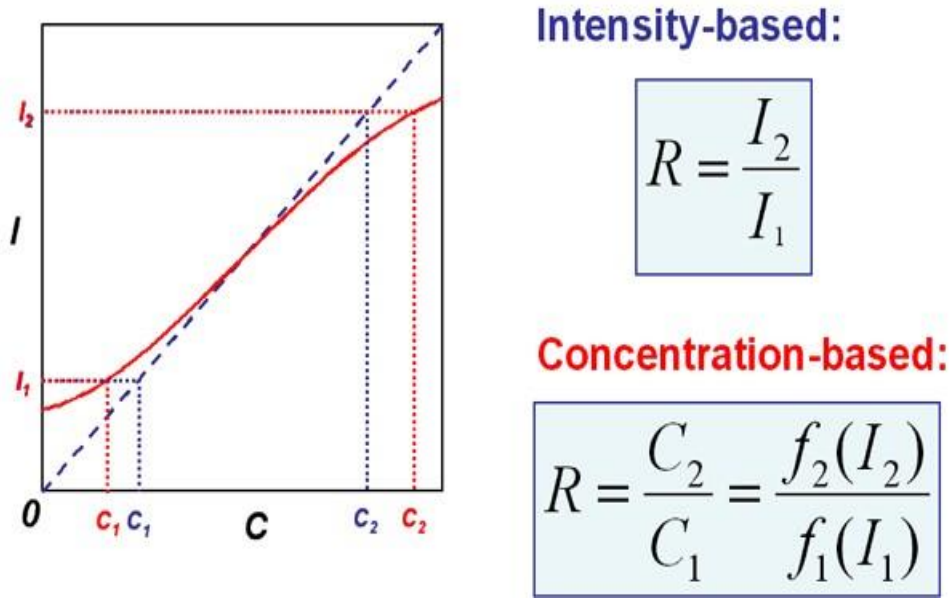

Figure 1. 24 Linear fit between intensity and iodine concentration (mg Iodine/ml) [39]

B Tables

Measurement Protocol

Table 1. 1 Contrast Agent Calibration protocol test

Contrast Agent Calibration Protocol test					
S. No	**Vary Parameter**	**Contrast Injection (ml)**	**Flow rate (ml/min)**	**Total No of Frames**	**Measurement No**
1	*Vary dose of the Contrast Agent*	*3*	*150*	*37*	*3*
		5	*150*	*84*	*4*
		7	*150*	*61*	*5*

Table 1. 2 Measurement protocol used for performing the final experiments for Basic Tube Phantom (scan1)

Basic Tube phantom (Scan 1) - Patient 1						
S. No	**Vary Parameter**	**Contrast Injection (ml)**	**Flow rate (ml/min)**	**Total No of Frames**	**Measurement Time**	**Measurement No**
1	*Vary flow rate*	*5*	*100*	*141*	*11:30*	*6*
		5	*150*	*84*	*11:37*	*8*
		5	*200*	*51*	*11:47*	*9*
2	*Vary dose of the Contrast Agent*	*3*	*150*	*63*	*11:49*	*10*
		5	*150*	*78*	*11:50*	*11*
		7	*150*	*94*	*11:54*	*12*

Table 1. 3 Measurement protocol used for performing the final experiments for Mixed Tube Phantoms (10 Normal type Fibres with Adsorption materials)

Mixed Tube phantom (10 normal type fibres with Adsorption materials) – Patient 2						
S. No	**Vary Parameter**	**Contrast Injection (ml)**	**Flow rate (ml/min)**	**Total No of Frames**	**Measurement Time**	**Measurement No**
1	*Vary flow rate*	*5*	*100*	*168*	*12:30*	*1*
		5	*150*	*138*	*12:36*	*2*
		5	*200*	*103*	*12:38*	*3*
2	*Vary dose of the Contrast Agent*	*3*	*150*	*108*	*12:40*	*4*
		5	*150*	*98*	*12:43*	*5*
		7	*150*	*100*	*12:50*	*6*

Table 1. 4 Measurement protocol used for performing the final experiments for Membrane Module filled Tube Phantom (20 Twisted Type fibres)

Membrane module filled Tube phantom (20 Twisted Type fibres) – Patient 3						
S. No	**Vary Parameter**	**Contrast Injection (ml)**	**Flow rate (ml/min)**	**Total No of Frames**	**Measurement Time**	**Measurement No**
1	*Vary flow rate*	*5*	*200*	*93*	*2:52*	*1*
		5	*250*	*107*	*2:54*	*2*
		5	*300*	*90*	*2:56*	*3*
2	*Vary dose of the Contrast Agent*	*3*	*250*	*100*	*2:57*	*4*
		5	*250*	*110*	*2:58*	*5*
		7	*250*	*127*	*2:59*	*6*

Table 1. 5 Measurement protocol used for performing the final experiments for Membrane Module Tube Phantom (10 Normal type fibres)

Membrane module filled Tube phantom (10 normal type fibres) – Patient 4						
S. No	**Vary Parameter**	**Contrast Injection (ml)**	**Flow rate (ml/min)**	**Total No of Frames**	**Measurement Time**	**Measurement No**
1	*Vary flow rate*	*5*	*200*	*97*	*3:25*	*1*
		5	*250*	*84*	*3:27*	*2*
		5	*300*	*93*	*3:32*	*3*
2	*Vary dose of the Contrast Agent*	*3*	*250*	*94*	*3:34*	*4*
		5	*250*	*108*	*3:36*	*5*
		7	*250*	*118*	*3:37*	*6*

Table 1. 6 Reproducibility measurement protocol for Basic Tube Phantom

Basic Tube Phantom Reproducibility Test (Patient 1)						
S. No	**Vary Parameter**	**Contrast Injection (ml)**	**Flow rate (ml/min)**	**Total No of Frames**	**Measurement Time**	**Measurement No**
1	*Vary dose of the Contrast Agent*	*5*	*150*	*76*	*11:54*	*13*
		5	*150*	*77*	*11:55*	*14*
		5	*150*	*86*	*11:57*	*15*

Table 1. 7 Measurement protocol used for performing the final experiments for Basic Tube Phantom (scan 2)

Basic Tube phantom (Scan 2) Patient 5						
S. No	**Vary Parameter**	**Contrast Injection (ml)**	**Flow rate (ml/min)**	**Total No of Frames**	**Measurement Time**	**Measurement No**
1	*Vary flow rate*	*5*	*200*	*141*	*11:30*	*6*
		5	*250*	*84*	*11:37*	*8*
		5	*300*	*51*	*11:47*	*9*
2	*Vary dose of the Contrast Agent*	*3*	*250*	*63*	*11:49*	*10*
		5	*250*	*78*	*11:50*	*11*
		7	*250*	*94*	*11:54*	*12*

Table 1. 6 Reproducibility measurement protocol for Mixed Tube Phantom

Mixed Tube phantom Reproducibility Test (Patient 2)						
S. No	**Vary Parameter**	**Contrast Injection (ml)**	**Flow rate (ml/min)**	**Total No of Frames**	**Measurement Time**	**Measurement No**
1	*Vary dose of the Contrast Agent*	*5*	*150*	*125*	*12:56*	*7*
		5	*150*	*133*	*13:24*	*8*
		5	*150*	*116*	*13:27*	*9*

Table 1.9 The dose regimen which was followed for performing Study 3 simulation experiments

S.no	Concentration (study 1) (ml)	Dose (study 2) (mole)	Time when the dose is injected (s)	Simulation Time (s)
1	3	2.5	10	50
2	5	4.2	10	50
3	7	5.8	10	50

C Scripts

MATLAB code

```
clc; %clear the command window
close all; %close all figures except those of imtool
imtool close all; %close all imtool figures
clear;%erase all existing variables
workspace;%make sure the workspace panel is showing
addpath(genpath('N:\FILES TO WORK FOR RESULT SECTION'));
info = dicominfo('N:\FILES TO WORK FOR RESULT SECTION\EXP_ABSORPTIONTUBEPHANTOM108XA4.IMA'); %To read metadata from dicom information
image = dicomread('EXP_ABSORPTIONTUBEPHANTOM108XA4.IMA','frames',1); %To read the Dicom image for the 1st frame
imagesc(image);%To display image with scaled colors
colorbar %To show color scale
e=drawrectangle; %To set up the region of interest by drawing the rectangle with shape or curved corners
a=zeros(1,98);%To create arrays of all zeros
for i = 1:98
   image = dicomread('EXP_ABSORPTIONTUBEPHANTOM108XA4.IMA','frames',i); %To read the dicom image for the frame range
   %%h = drawrectangle('Position',e.Position,'StripeColor','r');
   croppedImage = imcrop(image, e.Position); %To crop the image based on the position of the ROI
   a(1,i)=mean2(croppedImage);%Finding mean for the croppedImage
end

figure;
t = [0.5:0.5:49]; %Setting time for the frames
plot(t,a);%Plot the graph
set(gca, 'YDir','reverse')%To invert the graph obtained
```