DESIGN OF AN INTRAVENOUS DRUG DELIVERY DEVICE

By

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ABSTRACT

The use of intravenous implanted devices to deliver controlled drug dosage for the treatment of certain health problems is becoming more common as an alternative to regular injection procedures. This work proposes a conceptual design for a self-regulated device controlled by blood pressure and heart rate that can be implanted inside an artery and supply the controlled dosage of a specific drug in the event of a hypertension episode. The device is designed to discharge an established dosage of drug into the blood stream. The system of differential equations that describes the mathematical model of the selected device was simulated through the use of control block diagrams in a dynamic graphical interface software environment. The simulation of the device operation allowed for the graphical visualization of the drug delivery, aiding in the determination of device dimensions and parameters necessary to achieve a desired drug dosage for a given hypertension duration.

RESUMEN

El uso de dispositivos intravenosos implantados para entregar la dosificación controlada de droga para el tratamiento de ciertos problemas de salud se está tornando más común como una alternativa a los procedimientos regulares de inyección. Este trabajo propone un diseño conceptual para un dispositivo autorregulado controlado por la presión arterial y pulso cardiaco que pueden implantarse dentro de una arteria y pueden proporcionarse la dosificación controlada de una droga específica en caso de un episodio de hipertensión. El dispositivo se diseña para descargar una dosificación de droga establecida en el torrente sanguíneo. El sistema de ecuaciones diferenciales que describen el modelo matemático del dispositivo seleccionado fue simulado a través del uso de diagramas de bloques de control en un ambiente de software de interfaz gráfico dinámico. La simulación del funcionamiento del dispositivo permitió la visualización gráfica de la entrega de droga, ayudando en la determinación de dimensiones del dispositivo y parámetros necesario que ayudan a definir la dosificación de droga deseada para una duración de hipertensión dada.

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CHAPTER I: INTRODUCTION

Human health has been the center of attention of fields like Engineering, Biology, Medicine, etc., in issues related to the control of many complex physiopathological processes which have clinical manifestations. One example is, arterial hypertension, which is a serious risk factor when it comes to cardiovascular disease. Only about 50% of hypertensive people were identified as being affected during the 70's [13], but in recent years that amount has grown to be around 70%. That, in turn, means that the amount of treated patients has shown an increase from 31% to 55%, (about 29% of these being controlled), resulting in bringing their arterial indexes below the 140/90 levels. Many studies have shown that levels beyond 140/90 [11] have been related to more incidences in cardiovascular illness and even death, either by causes directly related to those levels or to other factors.

Advances in engineering and medicine have offered hope for those patients who have reduction or damage in some tract of their veins or arteries, with the so called *stents*. A stent is any material that is used to hold tissue in place. The problem with this is that there are few studies dedicated to the analysis of designs of intravenous devices that can be permanently implanted inside the organism to control different anomalies, and at the same time can secrete a substance to reestablish the systems. Hence the analysis and design of intravenous devices that can be permanently alert inside the system to detect hypertension anomalies are necessary. However such a device would present implant difficulties, like conditioning the drug, which would require clinical recommendations and an appropriate procedure based on the expertise of a cardiologist, even to appropriately administer the drug. This is important, since the physical characteristics of the device and dose should be adapted, to obtain the dimensions of the device, resulting in an effective treatment that would avoid too many consecutive implants. In other words, it should be a device that could deliver the drug during a period of several years.

The primary objective of this research is: to design an implantable intravenous drug delivery device (I_2D_3). Under this umbrella various secondary goals were set to achieve an appropriate design of the I_2D_3. The following are secondary objective:

1. To select and describe the suggested conceptual device
2. To create a mathematical model for the movement of the spool valve and to analyze the dynamic response of the mechanism.
3. To determine the dimensions of the device for specified dosage
4. To write the code for the model, simulate a perturbation and plot the corresponding response
5. Analyze results and recommend a detailed final design

CHAPTER II: LITERATURE REVIEW

Very little research has been carried out from the perspective of intravenous drug delivery implants. Literature mainly deals with Stents and related phenomena.

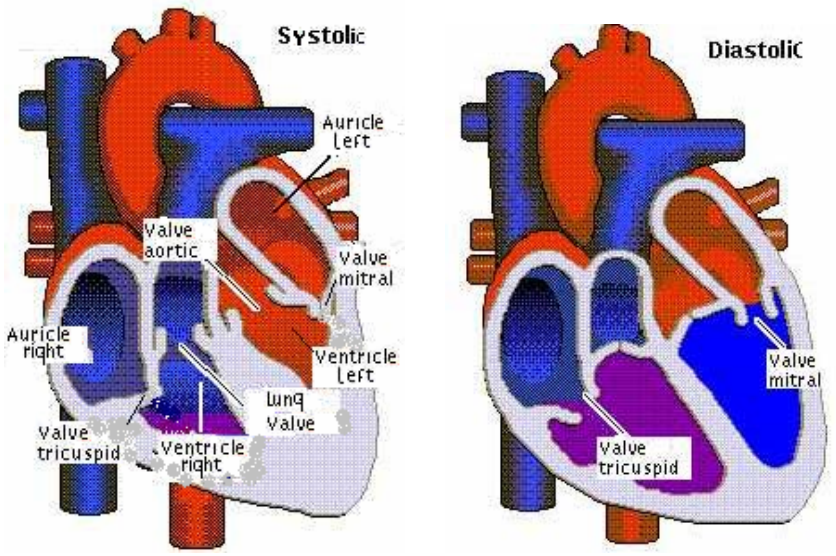
In this section, some proposed physiological-mechanical systems designed to address the drug deliverance problem will be analyzed and compared. Cardiovascular hemodynamic and blood flow characteristics will also be discussed from a general perspective.

II.1 Physical characteristics of blood

Blood has a behavior of Newtonian fluid, more viscous than water, with an average temperature of 38ºC (100.4ºF) and a range of pH between 7.35 and 7.45. Viscosity values for blood are μ= 100 dynes*(s/cm^2) y υ=3.3*10^{-2} cm^2/s, whole blood density is ρ=1.06 g/cm^3, Furthermore, it constitutes about 8% of total body weight [1]. Blood volume for an adult is 5 liters on the average, but depending of gender it can be 4 – 5 liters for women and 5 – 6 liters for men.

II.1.1 Blood pressure

The blood is pumped outside of the heart through hard elastic tubes called arteries. The aorta is the main artery of the heart. Blood pressure in an adult's aorta oscillates between 120 mmHg systolic (heart contraction, see Fig.1 (a)) to 80 mmHg diastolic (heart relaxation, see Fig.1 (b)). Work out, excitation, or aging can be factors that can drastically affect these pressure values. The vessels of the right side of the heart begin the lung circulatory system that takes the blood to the lungs to restock them with fresh oxygen. The left side of the heart receives the oxygenated blood from the lungs, impelling it through the arteries to all the tissues of the organism. Each heartbeat generates a pressure wave having about 75 to 80 pulses per minute.



(a) (b)

Fig. 1: Systole (a) and Diastole (b)

The blood coming back from the organism arrives to the right auricle through two main veins called the superior *vena cava* and the inferior *vena cava* [18]. When the right auricle contracts it impels the blood toward the right ventricle. The contraction of this ventricle drives the blood toward the lungs. The valve tricuspid avoids the reflux of blood toward the auricle, since it closes completely during the contraction of the right ventricle. In its journey through the lungs, the blood oxygenates itself. Then returns to the heart through four lung veins that end in the left auricle. When this auricle contracts, the blood passes to the left ventricle and ends in the aorta due to the ventricular contraction. The valve bicuspid or mitral avoids the reflux of blood toward the left auricle, and the sigmoid valves that are located in the root of the aorta avoid the reflux toward the left ventricle.

II.1.2 Hemodynamics

Circulatory physiology includes topics such as bloodstream flux velocity in veins and arteries, as also heart rate.

- *Blood Flow Velocity:* The cross-sectional area of the aorta is about 3 to 5 cm^2 and average speed of blood flow is more than 40 cm/s. In the *vena cava,* the

transversal section area is about 14 cm^2 with speeds from 5 to 20 cm/s. A high speed blood flow may lead to sight loss [2].

- *The Heart Rate (HR)* for adults is approximately 75 beats/min and the Stroke Volume ($sv.$) is 70 ml/beat. The maximum heart rate in humans is about 180 beats/min or an equivalent cardiac frequency of about 3 Hz [6].

- *Cardiac output (Co)* The blood flow volume is determined by $Co = sv * HR$, which is the amount of blood that flows out of the left (or right) ventricle to the aorta (or pulmonary trunk) every minute and it is given by.

$$Co = 70\frac{ml}{beat} * 75\frac{beat}{\min} = 5250\frac{ml}{\min} \quad or \quad 5.25\frac{Liters}{\min}$$

- *Timing of Systole and Diastole (T_{sd}):* Each cardiac cycle is determined by a diastole and a systole. The duration of this cycle is about 0.8 seconds. In the heart's atrium (heart's valve) the systole lasts 0.1 s and the diastole 0.7 s. In the ventricle these durations are 0.3 s and 0.5 s respectively.

II.1.3 The hypertension

The increase beyond normal limits of the blood pressure in the human body is termed hypertension. Hypertension boundaries are considered by many physicians to be 150 mmHg (systolic) and 90 mmHg (diastolic), which are equivalent to 20 kPa y 12 kPa respectively. Pulse is referred to as the difference between systolic and diastolic pressures.

The arterial tension is determined by several factors. For example, a high salt content in the body, retains more water in the circulation, and causes an increase in the arterial tension. Other factors that influence on the arterial tension are stimulation by the nervous system, the blood vessel thickening and a series of hormones.

The more common causes of hypertension are: endocrine illnesses (Cushing syndrome, tumors of the suprarenal glands), and illnesses of the kidney (narrowing of the renal artery and renal failure).

II.2 Previous Work

In 2002, Sanchez M. et al [7]. Made a study of non-Newtonian fluids applying techniques of finite volumes. In this work, a numerical study of 2D fluid mechanics in an abrupt contraction was made (see Figure2) for non-Newtonian flow with Ostwald-de Waele type power law. Two solution methods are used: finite volumes and finite elements.

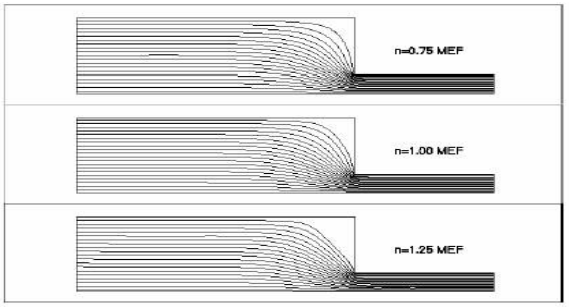


Fig. 2: Line of flow current in a contraction for different indexes of

In the finite volumes method, the SIMPLE algorithm was used to solve the linear momentum and continuity equations. In the finite element method, Fortran 90 language was used for writing our own program. In both methods the behavior of the fluid, for different indexes of power, was studied. The calculations made with rectangular variable mesh (method of finite volumes) and with mesh attached to the contour (method of finite elements). Power Model of Oswald of Waele [7], models dilatants and pseudo plastic fluids, given by the equation 1:

$$\tau=\eta\left(\frac{\partial v}{\partial y}\right) \Rightarrow \tau=\mu k^{n-1}\left(\frac{\partial v}{dy}\right) \qquad (1) \qquad\qquad \eta=\mu\left(\frac{\partial v}{\partial y}\right)^{n-1} \qquad (2)$$

The power law model defines the effective viscosity as:

For pseudo plastics (n>1), the power index *n* in equation (2) is grater than 1, the deformation strength reduces as τ increases. Examples: paints, rubber, blood, agitated mixtures, etc. For dilatants (n<1), the power index *n* in equation (2) is less than 1, the deformation strength increases as τ increases. Examples: Sugar, Boric solutions, wet soil, and others.

In 2000, Dumoulin C. et al [14], made a study of mechanical behavior modeling of balloon-expandable stents. The purpose of this work to provide models for evaluation and characterization of some mechanical properties of a balloon-expandable stent by using the finite element method. Several models constructed in order to determine the stent shape after dilation to assess the stress and strain field in its wall due to this transformation (see Figure3). This work offers an idea of the fixation mechanism in the artery for the device that we are designing here.

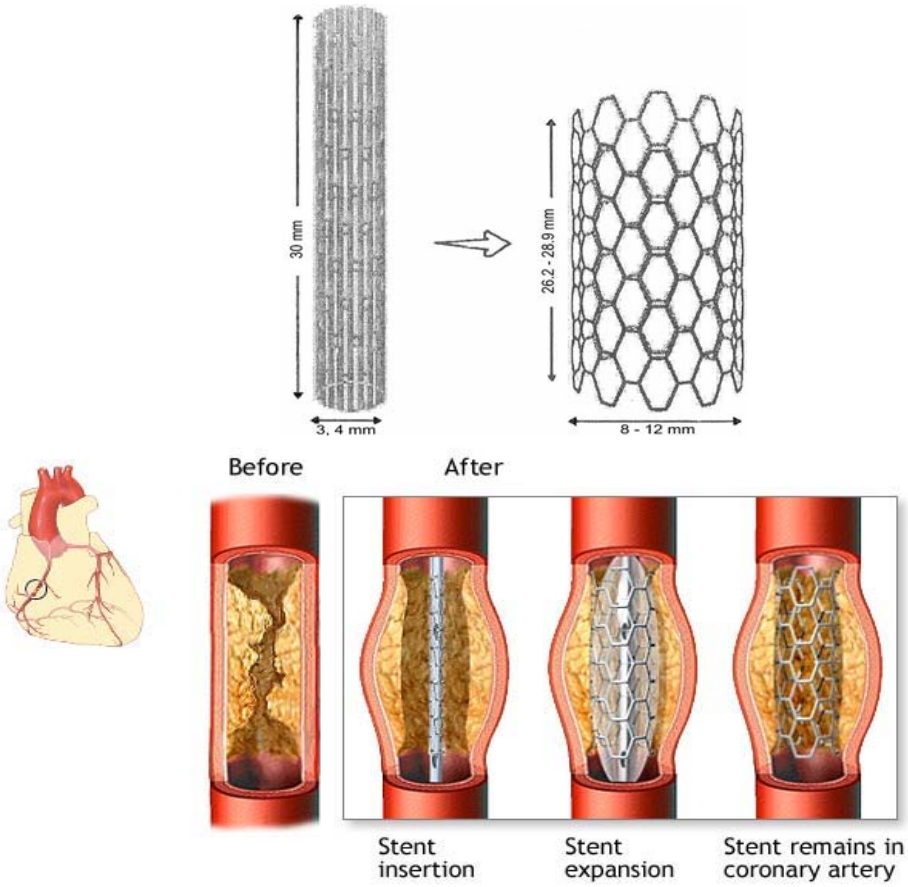


Fig. 3: Initial and expanded configuration of the stent with expanded range size

CHAPTER III: CONEPTUAL DESIGN OF THE INTRAVENOUS DEVICE

The suggested conceptual design was first based upon a device capable of delivering a drug under the action of pressure. Three conceptual designs were suggested and then one selected by the method of weight factor.

III.1 Device description

III.1.1 *Device 1*

This design involves implanting the device inside any Artery (A); where, the sanguine flow circulates from right to left passing through the point (1) region of higher pressure to the point (2) region of lower pressure. A change in pressure is achieved between points 1 and 2 due to the cone-shaped element located at the extreme (see Figure 4). The *moveable arc* acts as a piston, which is pressurized by the pressure P_1 into the device. The *dispenser* is the place where drug expulsion occurs, which can be achieved when blood pressure is high and overcomes the elastic resistance of the membrane surrounding the dispenser's outlet.

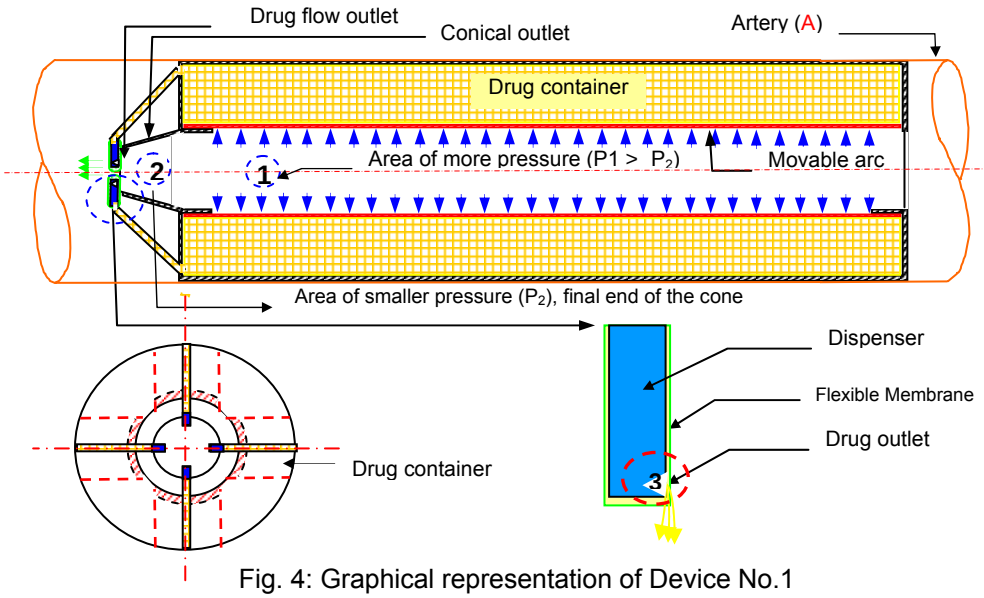


Fig. 4: Graphical representation of Device No.1

III.1.2 Device 2

The second design also involves implantation inside any Artery (A); where the sanguine flow circulates from right to left passing through point (1) region of higher pressure to the point (2) region of lower pressure (see Figure 5). A change in pressure is achieved between points 1 and 2 due to the cone-shaped element located at the extreme. The *moveable arc* acts as a piston, which is pressurized by the pressure P_1 into the device. The s*pool valve* is the place where the drug is dosed. When blood pressure is normal, the cylinder chamber is filled through inlet A. When hypertension occurs blood pressure overcomes the elastic resistance of the spring that is attached to the piston. It has a displacement that closes the drug admission path and leaves open the drug dispenser outlet B, which provides drug delivery to the bloodstream due to the change in pressure present at point 2.

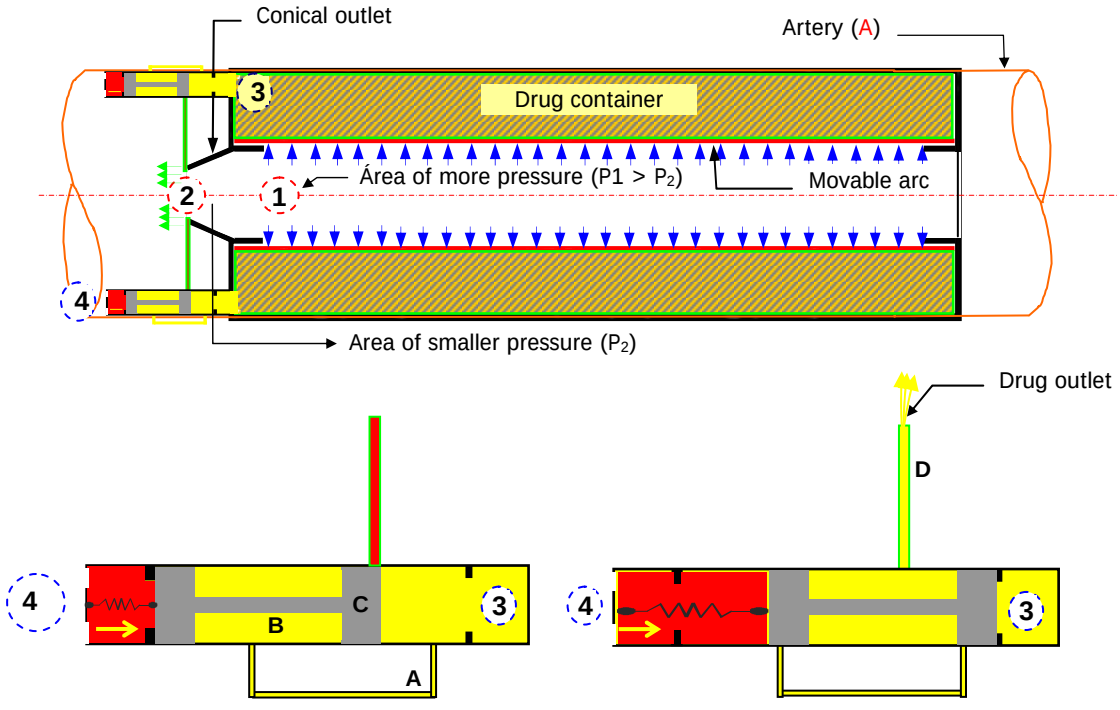


Fig. 5: Graphical representation of Device No.2

III.1.3 Device 3

Device 2 was further modified by shifting the location of the cone, to the edge of the device. This helped to avoid the obstruction problem in the artery. The resistance of the spring R_3 under normal conditions, that is to say, in the absence of an episode of hypertension, has to be enough to maintain the mobile cylinder of mass M_2 in the position closed to the exterior. Also, to counteract this the presence of an elastic spring R_1 that works to tension is introduced and adapted at point (4) which helps spring R_3 acting in (3) to maintain the valve closed. The chamber (B) it is filled by the drug that flows of the point (3) through the duct (A).

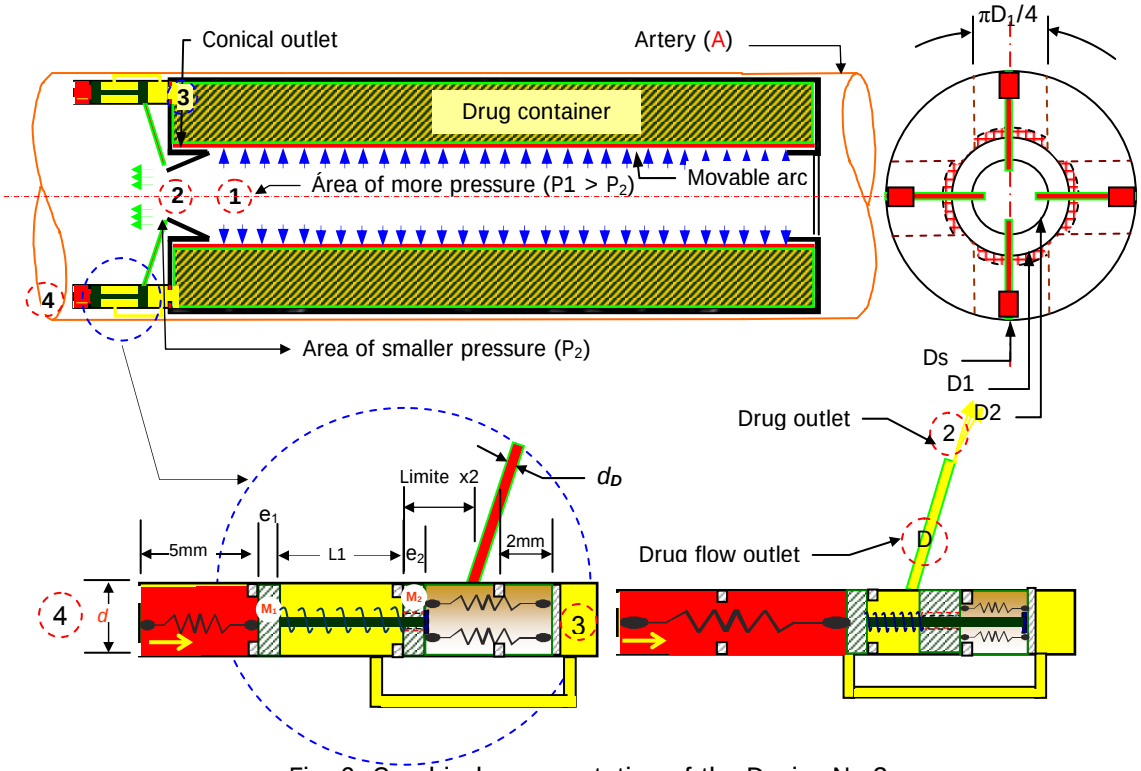


Fig. 6: Graphical representation of the Device No.3

When the episode of hypertension occurs, the pressure P_4 acquires high values which are able to surmount the elastic resistance of the spring located in (4). This allows the displacement of the mobile cylinder of mass M_1. Here the spring (2) that works in compression inside the chamber (B) helps to displace the cylinder of mass M_2 until

locating it in the open position (to the exterior) and to allow the drug contained in the chamber to come out (B) through the duct (D). The conical form at the edge of the device is exactly what would allow the existence of the area of low pressure, at point (2) that facilitates the drug delivery. This valve does not fill the chamber again (B), until concluding the duration of the Systole and the pressure P_4 will be present in the high level causing the liberation of the drug.

The forced movement that is generating the compression of the cylinder of mass M1 on the drug in the chamber (B), assures that the whole drug contained in (B) leaves for the duct (D) during the time that the systole lasts. When the diastole begins P_4 will be at a low level, and the valve closes, at that instant the drug stops to be liberated and will try to fill the damping (B) while the diastole lasts. The time that takes for the drug to react is what limits the time for which the valve will remain open during each systole. The exit of the complete dose is caused by the group of volumes that were able to leave in each systole while the valve remains open.

This device presents the advantage that assures the dose stored in (B) is completely delivered. The disadvantage that is has complex mobile elements.

One goal of this study is to identify the constants of the appropriate springs which will not deform for values of P_4 under normal conditions and to be allowed to deform in the presence of an episode of hypertension. Also, the dimensions for the diameter of the cylinder and diameter of the exit conduit, to supply the necessary dose, will be determined, it is important to identify the physical properties of the drug that completes these conditions of the model.

III.2 Selection Criteria

A Mode and Effect Analysis for the design of the implantable intravenous drug delivery device is performed for the selection criteria (*MEA-D-I_2D_3*). This is a tool designed to determine the important or critical characteristics for the design of an *I_2D_3*. It answers the following:

1. ¿What really needs to be controlled?
2. ¿Why is this necessary?

The *MEA-D-I_2D_3* consists in the assignment of a grade as an answer to a series of questions in order to obtain the degree of importance of a certain characteristic or effect for a design. The outcome is some knowledge about which effect is more relevant and its impact on the patient. The steps describing the method are:

a) Enumerate the dimensional, physical, esthetical, safety, and performance characteristics or relevant effects in the I_2D_3.

b) Assign a value ranging from 1 to 10 for each one of these characteristics according to the impact on the patient, presuming that those characteristics are not performing as expected.
For example, not delivering the necessary amount of drug is a safety characteristic. Determine if this variation is harmful to the patient and if its impact is a negative one and up to what extent.

c) A second value is assigned to each characteristic related with the impact on the device, presuming that they do not fulfill their function.

For example, determine if not fulfilling its function has a negative impact on the normal functioning of the device, either by being required for the control of the device or by being expensive for its design. If a characteristic is irrelevant or has a positive influence on the patient or the design, a grade of 1 is assigned to it, If the effect is totally opposite, then a grade of 10 is assigned.

d) A third value, from 1 to 10, will be assigned to the probability of the presence of a non-conformity.

e) The importance number (NI) will be the product of these three values and will represent the importance of each characteristic. The device with the lowest total NI will be selected.

To efficiently develop the *MEA-D-I_2D_3*, the critical characteristics about what purpose the drug will have and where the device will be located should be known in depth. In this case, the *MEA-D-I_2D_3* will be applied to deliver a drug to correct hypertension problems. The following results were obtained:

Table 1. *AME-D-I_2D_3* for device#1

Dosage System Needle-shaped dispenser with its outlet surrounded by a flexible membrane			**Mode and Effect Design Analysis for I_2D_3**				**Device #1** Date: March 20, 2004		
Effects or Characteristics			Impact on the Patient		Impact on the Design		Failure Probability		NI
Ítem	Aspects	Function	Description	Value #1	Description	Value #2	Variability	Value #3	Score
1	Drug container, dimension and application	Stores and pressurizes the drug, and supplies drug to the dispenser	Drug dosage is depleted before the proposed duration	9	Adequate dosage is not supplied to the dispenser	7	Traps air bubbles, has difficulty overcoming membrane resistance because of compressing air.	5	315
2	Dispenser	Produces the emission of the drug	Complications in stabilizing the blood pressure	9	Improper selection of membrane resistance impedes device operation	8	Supply of insufficient dosage	5	360
3	Conical outlet	Facilitates the emission of drug	Outlet is blocked due to stenosis	7	Cannot overcome membrane resistance, difficulty in supplying drug	7	The differential in pressure to facilitate drug supply does not occur	5	245
4	Dose control	Adequate Dose	Complications in stabilizing the blood pressure	8	Relevant	1	Drug supply depends on how membrane resistance is overcome and how long this status is maintained	8	64
5	Mathematical model	Design parameters and ease of programming	Relevant	1	Low element complexity	5	Difficulty in simulation	5	25
Total									*1009*

Table 2. *AME-D-I_2D_3* for device#2

Dosage System Spool valve			**Mode and Effect Design Analysis for I_2D_3**				**Device #2** Date: March 20, 2004		
Effects or Characteristics			Impact on the Patient		Impact on the Design		Failure Probability		NI
Ítem	Aspects	Function	Description	Value #1	Description	Value #2	Variability	Value #3	Score
1	Drug container, dimension and application	Stores and pressurizes the drug, and supplies drug to the dispenser	Drug dosage is depleted before the proposed duration	9	Adequate dosage is not supplied to the dispenser	7	Traps air bubbles, has difficulty overcoming membrane resistance because of compressing air.	5	315
2	Spool valve	Supplies dosage needed	Complications in stabilizing the blood pressure	8	Improper selection of spring constant impedes device operation	7	Inadequate drug supply results in incomplete drug emission	6	336
3	Conical outlet	Aids in obtaining an adequate pressure differential	Outlet is blocked due to stenosis	6	Inadequate pressure values resulting in difficulty in drug emission	7	The differential in pressure to facilitate drug supply does not occur	5	210
4	Dose control	Adequate Dose	Complications in stabilizing the blood pressure	7	Complete emission of drug from Chamber B is not assured	4	Drug emission depends on spring constants and duration of hypertension episode	8	224
5	Mathematical model	Design parameters and ease of programming	Relevant	1	Element complexity	5	Low level of difficulty in simulation	6	30
Total									*1115*

Table 3. *AME-D-I_2D_3* for device#3

Dosage System Spool valve			**Mode and Effect Design Analysis for I_2D_3**				**Device #3** Date: March 20, 2004		
Effects or Characteristics			Impact on the Patient		Impact on the design		Failure probability		NI
Ítem	Aspects	Function	Description	Value #1	Description	Value #2	Variability	Value #3	Score
1	Drug container, dimension and application	Stores and pressurizes the drug, and supplies drug to the dispenser	Drug dosage is depleted before the proposed duration	9	Adequate dosage is not supplied to the dispenser	7	Traps air bubbles, has difficulty overcoming membrane resistance because of compressing air.	5	315
2	Spool valve	Supplies dosage needed	Complications in stabilizing the blood pressure	8	Improper selection of spring constant impedes device operation	7	Insufficient drug supply	4	224
3	Conical outlet	Aids in obtaining an adequate pressure differential	Relevant	1	Inadequate pressure values resulting in difficulty in drug emission	7	The differential in pressure to facilitate drug supply does not occur	5	35
4	Dose control	Adequate Dosage	Complications in stabilizing the blood pressure	7	Relevant	1	Drug emission depends on spring constants and duration of hypertension episode	8	56
5	Mathematical model	Design parameters and ease of programming	Relevant	1	Element complexity	5	Difficulty in simulation	6	30
Total									*660*

Based on the high NI indexes, Devices #1 and #2 are not recommended. Device #3 was selected because of its lower NI index, which means that it is a feasible design.

The selection is supported assigning total percentages from 0 to 100 percent for each device that indicated the grade of viability and execution of the objectives of the investigation. Also, each aspect has a different valuation depending on the impact

and importance to help to complete the objectives, for example the aspect “dose control” is of much care and it largely solves the final objective of the investigation, for this reason we will assign 40 percent for its valuation, now, the results obtained in the previous charts, help to choose the percentage qualification assigned to each aspect appropriately. Of the three devices proposed, device No. 3 was selected on the basis of an approximately 15% advantage over the others as the following shows:

Table.4 Selection criteria

Devices	Aspect						Total
	Dose control (40%)	No Complexity of elements (20%)	No Arteries obstruction (10%)	Ease of Assembly (5%)	No Equations complexity (15%)	Few Component (10%)	
1	10	20	4	5	15	10	54%
2	20	10	5	3	12	5	55%
3	40	6	10	3	8	3	70%

In Table 5 we see that the “Dose Control” aspect is the most important due to the safety of the design. The “Equation Complexity” aspect will be limited by the “Few Component” aspect because an increase in elements will increase the model equation complexity.

III.3 Issue description of the systems

Blood movement through Device No. 3 will be studied due to its advantages. In general, it is a circular duct with a sudden change in transversal section.

The blood can be considered to be a Newtonian fluid, with characteristics of permanent, isothermal, and bidimensional flow. It can also be considered to have laminar flow because the Reynolds number for the blood can be found as:

$$\mathrm{Re} = \frac{vD_1\rho}{\mu} = \frac{(81cm/s)(1.4cm)(1.06g/cm^3)}{100dynes\cdot s/cm^2)} \approx 1.21 \;<<\; 2300$$

where ρ, μ, and v are the blood density, viscosity, and average blood flow speed within the device, respectively, and the magnitude of the number shows that the

Reynolds number for the blood flow, by being much less than 2300, is assured to be laminar flow. No turbulence will be present due to the device in the blood flow. It can be physically assumed that the sanguineous flow crosses the device, which is a circular duct with an abrupt change of transversal section in one of its ends. The device has valve that doses the drug, and that valve has a dosing mechanism in the form of pistons. The movement of these pistons is simulated by solving the equations that govern the dynamic response of the system, and thus characterize the output dose at point 2. The continuity and energy conservation equations are given next.

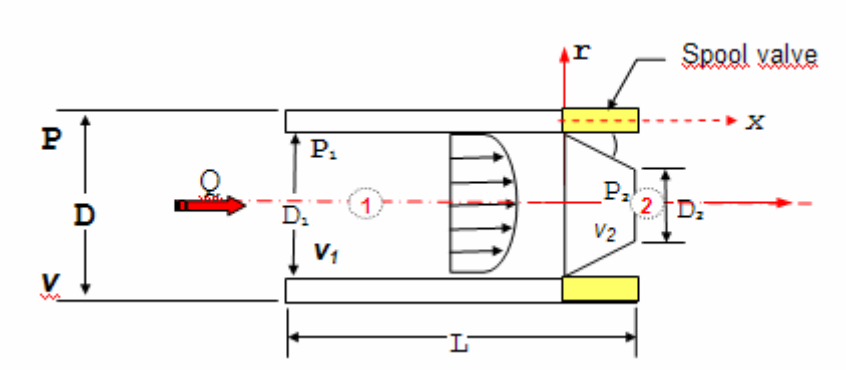


Fig.7 Physical representation of device

III.3.1 *Continuity Equation*

$$Q_1 = Q_2 \qquad V_1 A_1 = V_2 A_2$$
$$A_1 > A_2 \quad V_1 < V_2$$

$$Q_s = Q_1 \qquad v_s A_s = v_1 A_1 \qquad v_1 = v_s \left(\frac{D_s}{D_1} \right)^2 \Rightarrow (3)$$

$$Q_1 = Q_2 \qquad v_1 A_1 = v_2 A_2 \qquad v_2 = v_1 \left(\frac{D_1}{D_2} \right)^2 \Rightarrow (4)$$

III.3.2 *Energy Conservation*

$$Z_1 + \frac{P_1}{\gamma} + \frac{V_1^2}{2g} = Z_2 + \frac{P_2}{\gamma} + \frac{V_2^2}{2g} \qquad Z_1 = Z_2 \Rightarrow \qquad \frac{P_1}{\gamma} + \frac{V_1^2}{2g} = \frac{P_2}{\gamma} + \frac{V_2^2}{2g}$$

$$\frac{P_1 - P_2}{\gamma} = \frac{V_2^2 - V_1^2}{2g} > 0 \quad \rightarrow \quad \text{positive quantity, we have that: } V_2 > V_1 \quad \text{where} \quad \begin{matrix} P_1 - P_2 > 0 \\ P_1 > P_2 \end{matrix}$$

Where P_1 and P_2 are:

$$P_1 = P_s - \frac{1}{2}\rho . v_s^2 \left[\left(\frac{Ds}{D_1} \right)^4 - 1 \right] \quad (5) \qquad P_2 = P_1 - \frac{1}{2}\rho . v_1^2 \left[\left(\frac{D_1}{D_2} \right)^4 - 1 \right] \quad (6)$$

Here the parameters are:

D_s= Arterial diameter

D_1= Device diameter

D_2 =Diameter of device reduction

P_s= Blood pressure

P_2= Pressure in the device reduction

ρ = The blood density

v_s= Average Arterial velocity

v_1= Device velocity in the point 1

v_2= Velocity at the device reduction

P_1= Drug pressure

P_3= Drug pressure inside of elastic container.

III.4 Spool valve description

When blood pressure is normal, the cylindrical chamber (B) is filled through inlet A.

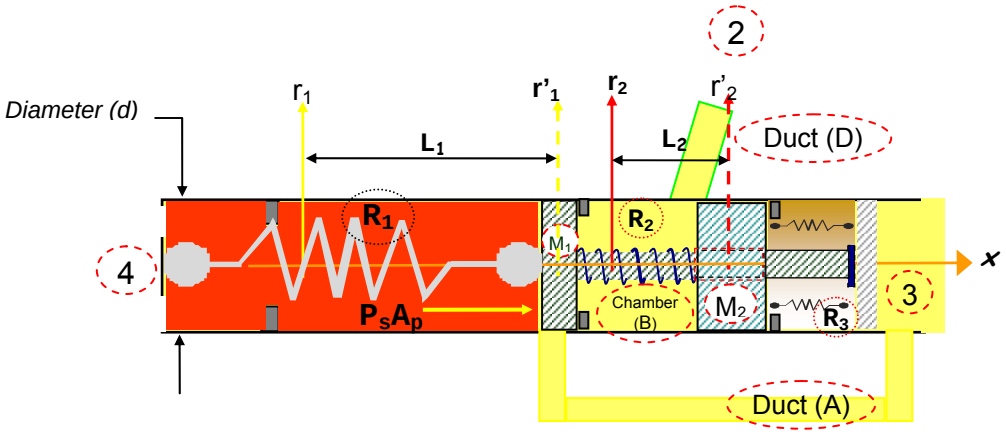


Fig.8 Spool valve description

During hypertension, the blood pressure overcomes the elastic resistance of the spring R_1 attached to the mass M_1 (see Figure 8). This mass displaces periodically as defined by the systole and diastole of the medium, and it induces the movement of mass M_2 at each systole as shown in Figure 7. Furthermore, it closes duct A, which allows for the drug admission in chamber B. Spring R_2 is working in compression inside of the chamber (B) and also helps to displace mass M_2 towards the outlet (D) where the bloodstream drug delivery is accomplished due to the pressure difference at point (2). The chosen material for the valve will be titanium, for its blood compatibility characteristics.

Where:

R_1 = Spring 1	L_1 = Cylinder Runway 1
R_2 = Spring 2	L_2 = Cylinder Runway 2
R_3 = Spring 3	A_p = Traversal area of the piston
D = Piston Diameter	M_2 = Piston Mass 2
M_1 = Piston Mass 1	B = Dose Chamber

CHAPTER IV: MATHEMATICAL MODELING OF SPOOL VALVE

In this chapter a mathematical model describing the function of the spool valve is presented. The used methodology for the development of mathematical model will require the following general stages:

1. Valve description: To define operation and dimensions
2. Representation of the loads on the valve: Free body diagram.
3. To analyze the dynamic response of the mass M_1 and M_2
4. To choose the material for the valve and of the spring
5. To estimate the volume of the drug.
6. Programming the equations and to analyze the results.

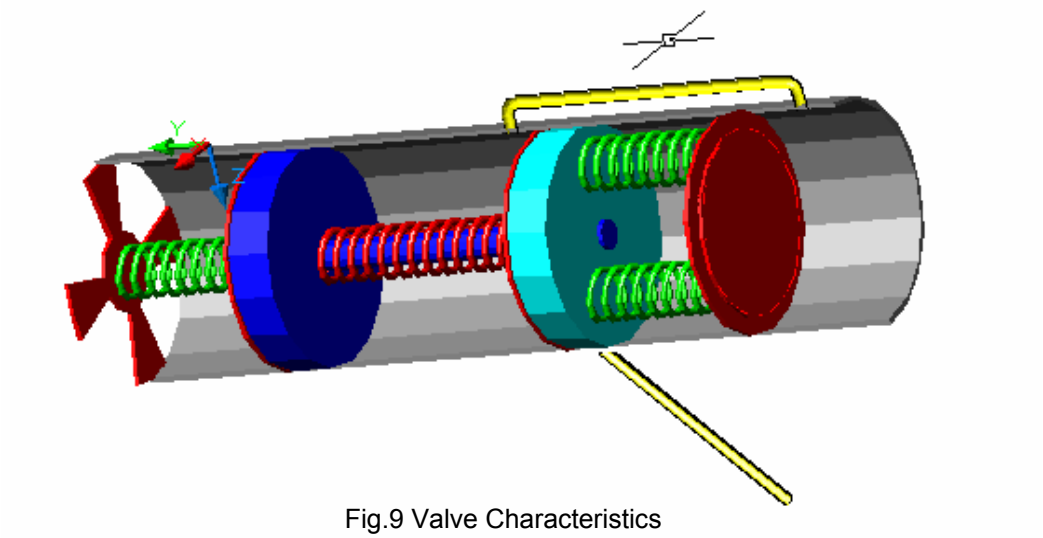


Fig.9 Valve Characteristics

The internal details and elements of the spool valve can be seen in Fig.9. Figure 10 shows an equivalent load diagram. Here M_1 is chosen for the mass from the near cylinder to the point (4), M_2 for the mass of the near cylinder to the point (3), Fs for the force that induces the wave of blood pressure on the cylinder on the face (4).

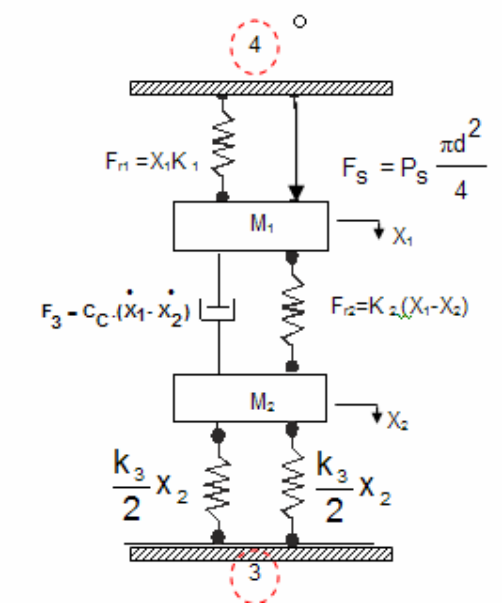


Fig.10 Schematic representation of the loads on the valve

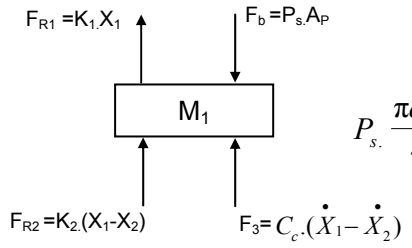
Furthermore $F_{r1} = K_1.X_1$ represents the force of elastic resistance that acts on the spring R_1 at point (4) to cause the displacement of the mass M_1. Where $F_{r2} = K_2(X_2-X_1)$, represents the force of elastic resistance that spring R_2 exerts to cause the displacement of the mass M_2, (d) is the diameter of the piston of the valve.

IV.1 Mathematical Formulation of the Spool Valve

The mathematical relationship that defines the two-degrees-of-freedom system was found analyzing its free body diagram, where the displacement orientations for the masses and the load interactions were identified for hypertension episode, remembering the details of the dynamic and static analysis, are explained bellow.

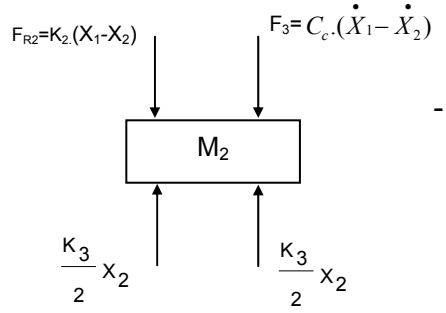
IV.1.1 *Dynamic Analysis of the Spool Valve*

For an hypertension episode we observed that the loads acting on mass M_1, the pressure force F_b, the spring forces F_{R1} and F_{R2}, and the friction F_3 which represents the damping of the system for the spool valve model, made the masses m1 and m2 acquire a displacement periodic with amplitude X_1 and X_2, being the force Fs the one who promote the disturbance. The forces F_{r1} and F_{r2} help the system to recover its original state. We can observe the loads on each piston during hypertension in the following figure..



$$P_{s.}\frac{\pi d^2}{4} - (K_2 + K_1)X_1 + K_2 X_2 + C_c \dot{X}_2 - C_c \dot{X}_1 = m_1 \ddot{X}_1 \quad (7)$$

The loads acting on mass M_2 are twice the spring force F_{R3}, force F_{R2}, and the friction.



$$-(K_2 + K_3)X_2 - K_2 X_1 + C_c \dot{X}_1 - C_c \dot{X}_2 = m_2 \ddot{X}_2 \quad (8)$$

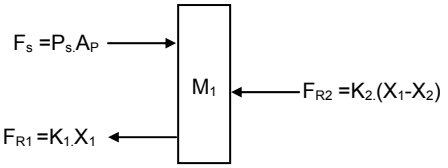
IV.1.2 Static Analysis of the Spool Valve

IV.1.2.1 Boundary conditions

Boundary conditions are determined by time t_1 (given for a diastole under normal conditions) before any initial movement from masses M_1 or M_2, and time t_2 (given for a systole under hypertension conditions) after masses movement during a hypertension episode.

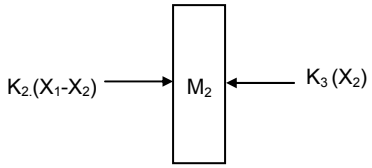
$$t_1 = 0 \quad \begin{cases} X_1(0) = 0 & \dot{X}_1(0) = 0 \\ X_2(0) = 0 & \dot{X}_2(0) = 0 \end{cases} \qquad t_2 = t \quad \begin{cases} X_1(_{L_1}) = L_1 & \dot{X}_1(L_1) = 0 \\ X_2(_{L_2}) = L_1 & \dot{X}_2(L_2) = 0 \end{cases}$$

IV.1.2.2 Free body diagram:



$$P_{s.}A_p - (X_1 - X_2)K_2 - K_1 X_1 = 0$$

$$K_1 = P_s \frac{A_p}{X_1} - \frac{(X_1 - X_2)}{X_1} K_2 \qquad (9)$$



$$K_2(X_1 - X_2) - K_3 X_2 = 0$$

$$K_2 = \frac{X_2 K_3}{(X_1 - X_2)} \qquad (10)$$

IV.2 Dynamics of the drug

IV.2.1 Volume of the drug:

The drug used the most in the treatment of high blood pressure is hydralazine [12]. Although it has many secondary effects, it is available in 20 mg/ml concentrations. During hypertensive emergencies, the administered intravenous dose is 10~20 mg. Another drug is the Propranolol hydrochloride [16]. It is a stable white crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.81. Propranolol HCl is available as concentration of 1 mg/ml sterile injectable solution for intravenous administration. The rate of administration should not exceed 1 mg (1 ml) per minute. The usual dose is from 1 mg to 3 mg, which should be carefully

administered. Intravenous Diazoxide ([12], [17], [19]) also acts directly and in few minutes. Its action begins between 1 and 5 minutes, whose dosage is 5 mg/kg of body weight (used dose is from 7,5 to 30 mg/min) with the effect lasting for 24 hours.

To estimate the quantity of drug mass that leaves during the time of systole ($t_{sistole}$), we find an expression for the drug volume that leaves (V_{df}), which will be different from the stored initial volume in the chamber (B).

$$V_d = \frac{m_d}{\rho_d} = \frac{\pi}{4}(d^2 - d_2^2).L_1 \qquad (11)$$

$$V_{df} = \frac{\pi}{4}(d^2 - d_2^2)(x_1 - x_2) \qquad (12)$$

Where:

V_d = Initial drug volume, in the camera (B)
V_{df} = Final drug volume, delivered
d_2 = Diameter of the cylinder bar
$K_{1\text{-}2}$ =Stiffness of the spring R_1 and R_2
K_3 =Stiffness of the spring R_3
Cc = Damping constant
ρ_d = Drug density
m_d =Drug mass
L_1 = Initial distance of drug volume

IV.2.2 Drug Flow:

As an example for the drug, Propranolol, flow of mass (Q_m), is from 1 to 3 mg/min. Since there are four valves in the device proposed, it is necessary to distribute the delivery.

Therefore: $$Q_m^{'} = \frac{Q_m}{4} = \frac{m_{drug}}{t_{sitole}} \qquad (13) \qquad Q_m^{'} = \dot{X}_1 . A_B . \rho_d \qquad (14)$$

IV.3 Parameters of the exit duct

To find the diameter (d_D) appropriate for the duct (D) that satisfies flow of the dose during the time for which the systole lasts, $t_{systole}$ = 0.3s, apply: $Q_D = v_s A_D$, where v_s,

is the speed that the drug acquires the points of exit of the chamber (*B*) to the duct (*D*) that is similar to the average speed of the blood flow.

IV.4 Mass of the pistons

To define the mass M1 and M2 of the cylinders, we find the value of density of the equation, the mass and using like simulation of density that of the material Platinum or Titanium since we have the respective volumes of each piston. ($\rho_P = 21.45\, mg/mm^3$ or $\rho_T = 4.51 mg/mm^3$).

IV.5 Damping constant:

It is the parameter to which all the reduction for the displacement of the mass is attributed. We can we find de value of (*Cc*) of the equation (5).

$$C_c = \frac{m_1.\ddot{X}_1 + (K_2 + K_1).X_1 + K_2.X_2 - P_s.A_p}{(\dot{X}_2 - \dot{X}_1)} \qquad (15)$$

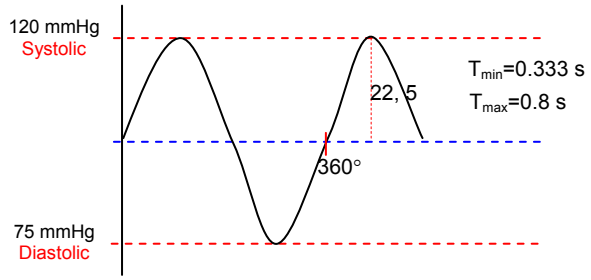
CHAPTER V: SIMULATION CODE

The commercial software was used to describe all the mathematical equation. The Matlab tool® (Simulink) was used successfully.

V.1 Blood pressure wave modeling

The blood pressure was modeled using several wave forms such as, sinusoidal, square or saw tooth, the frequency is $f = 3Hz$, which is obtained for the maximum heart rate (*180beats/min*) found in the human body. For normal conditions $T = 0.8s$ per cycle with a frequency of $f = 1.25Hz$.

- Sinusoidal: $P(\theta) = 75 + A\sin(\theta) \rightarrow P(\theta) = 75 + 22{,}5\sin(\theta)$



- Square: $P(\theta) = 75 + 45\,\delta(\theta) \rightarrow \delta(\theta) = \begin{cases} 1 & si \quad 0 \le \theta \le n\dfrac{T}{2} \\ 0 & si \quad n\dfrac{T}{2} < \theta \le nT \end{cases}$

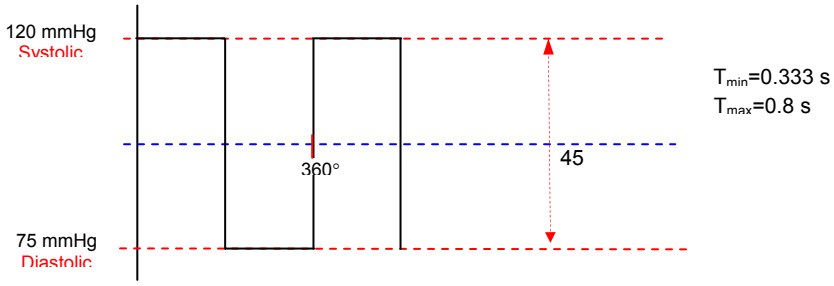


Fig.11 Some well-known functions used to simulate the pressure wave, sinusoidal and square

- Saw tooth: $P(\theta) = 75 + \frac{1}{8}\delta(\theta) \rightarrow \begin{cases} 1 & si \quad 0 < \theta < T \\ 0 & si \quad \theta = 0 \quad \theta = T \end{cases}$

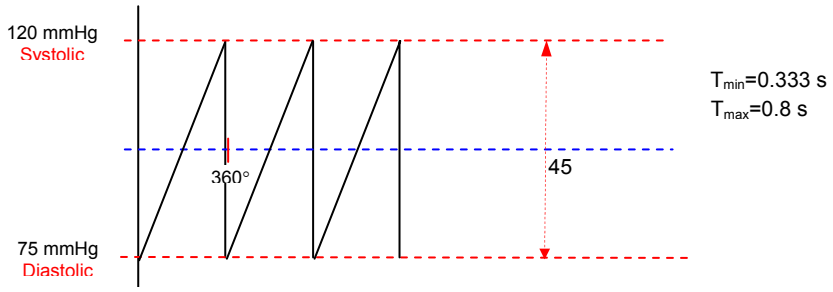


Fig.12 Known functions of Saw tooth

However, the actual pressure wave does not adjust very well to any of the above assumptions; consequently, a function that approaches the actual blood pressure quite well is adopted (see equation (16)).

$$Ps = [(slope + basic * swell) * pulse + constant] * factor \qquad (16)$$

Where:

$$basic = \sin(2\pi f) + \sin(4\pi f) * 0.54$$

$$slope = [\cos(-t2 * pulse + t) * \frac{\pi}{t1} + 1] * \frac{High\_offset}{2} + zero\_offset$$

$$swell = [\cos(-t2 * pulse + t) * \frac{\pi}{t1} + 1] * \frac{wide}{2} + w$$

$$constant = [(\sin(2\pi f) + \sin(4\pi f) * 0.54) * wide\_2 + offset2] * pulse$$

Furthermore

wide = 4	offset2 = 115
wide_2 = 18.5	zero_offset = 100
w = 14.7	High_offset = 14.85

The following is a description of the above equation using the Matlab tool Simulink.

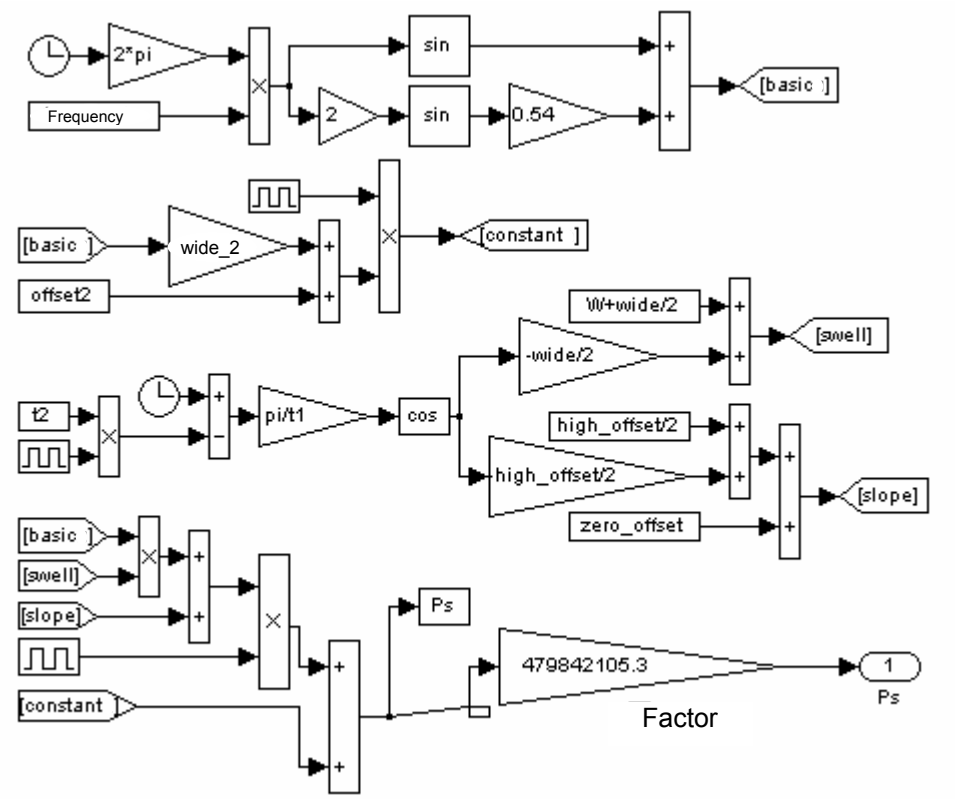


Fig.13 Assumed function for the simulation of the wave pressure.

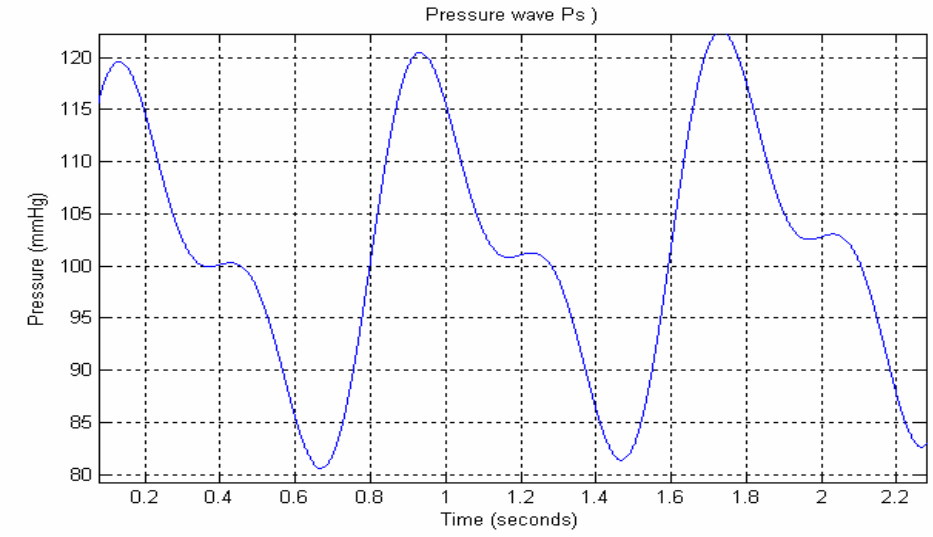


Fig.14 Graphical of pressure wave

V.2 Programming code to solve the system of equations

$$P_{s.}\frac{\pi d^2}{4} - (K_2 + K_1)X_1 + K_2 X_2 + C_c \dot{X}_2 - C_c \dot{X}_1 = m_1 \ddot{X}_1 \quad (7)$$

$$-(K_2 + K_3)X_2 - K_2 X_1 + C_c \dot{X}_1 - C_c \dot{X}_2 = m_2 \ddot{X}_2 \quad (8)$$

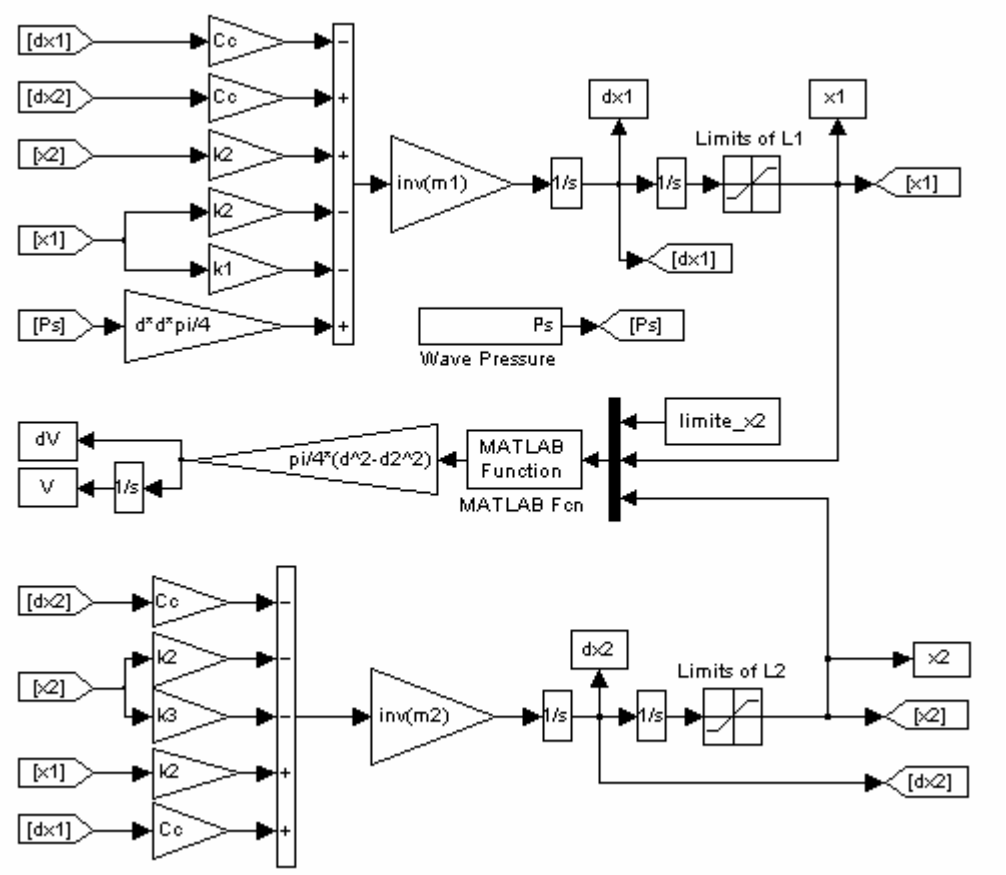


Fig.15 Simulation of the equation in Simulink.

CHAPTER VI: RESULTS AND DISCUSSION

VI.1 Sample data and units

Certain initial values were assumed to execute the code. For example, L_1 and L_2 which are the maximum runway of the pistons inside the spool valve in the presence of an hypertension episode, the internal diameter of the device D_1= *Ds-7,* the reduction diameter $D_2 = D_1$*-4,* the internal diameter of the spool valve (*d*), and the pistons thickness e_1 and e_2 for the masses m_1 and m_2 respectively. These assumptions were based mostly on the results of an iterative process of performing a series of simulations in order to select the values for the previously mentioned variables, verifying that the required dose was being delivered. The amount of delivered drug was being controlled constantly to verify that it was the expected for the drug under analysis, all of this by modifying the device dimensions.

The design of the pressure waveform function that simulates an episode of hypertension is fundamental for this work. The value of Ps (the waveform magnitude) were selected to simulate a hypertension episode with a steady maximum of 140/90 mmHg for a short time lapse (10 to 40 seconds). The design was adjusted so that the drug started to be delivered as soon as the hypertension value for Ps was about 135/88 mmHg. The parameters and initial values needed to perform the simulations are presented in Table 5.

Table. 5 Known values and parameters for the design

PARAMETERS	***VALUE AND UNITS IN THE CALCULATION***	***KNOWN VALUE AND UNITS***
Normal Blood Pressure (*Ps*)	$\frac{5.7581\text{E}10}{3.8387\text{E}10}\ \frac{mg}{mm.\min^2}$	120/80 mmHg
Cardiac Frequency (*f*)	1.25 Hz	1.25 Hz
Arterial Diameter (*Ds*)	20 mm -25 mm	20 mm – 25 mm
Arterial speed average(*vs*)	24000 mm/min	40 cm/s
Blood Density (ρ)	1.06 mg/mm^3	1.06 g/cm3
Timing of Systole and Diastole (T_{sd})	0.005 min and 0.0083 min	0.3 s and 0.5 s
Dose for Propranolol	1 mg/ml	1 – 3 mg/min
Dispenser longitude for a full year dose *(L)*	20-34 mm	20-34 mm
Density of Material Platinum (ρ_p) Titanium (ρ_T)	21.45 mg/mm^3 4.51 mg/mm^3	21.45 g/cm^3 4.51 g/cm^3

VI.2 Simulations under different parameters

The values t_1 and t_2 represent simulation periods of time used for the Ps (see Figure 13) waveform generation. The value t_2 indicates the lapse of time during which the maximum hypertension magnitude is held constant to simulate the hypertension episode. The value t_1 is the rising time needed for the waveform to go from the normal 120/80 mmHg to the 140/90 mmHg hypertension maximum, and is the same time needed to return these conditions back to normal. The time t that corresponds to the 135 mmHg value will indicate the starting point for the drug delivery, and the device will keep delivering the drug until t_2 has passed. That amount of time will be used to determine the time needed for the drug to react, which is computed as $t_{reaction} = 2(t_1 - t) + t_{systole}$.

The amount of drug being delivered depends also on the position of the duct used to discharge the drug into the bloodstream, identified in the code as *Limit_x_2*. This dimension depends on the displacement of mass m_2, because the displacement x_2 must overcome the necessary *Limit_x_2* limit in order to start delivering the drug.

VI.2.1 Iteration Parameters and Graphical Result

Some results obtained by varying these above mentioned parameters are presented in Figures 15 to 24.

The parameter units are given by:

L_2, L_1, Ds, d, Limit_x_2, e_1, e_2 = [mm]

ρ_p=mg/mm^3

m_1, m_2 = mg

Cc= mg/min

K=mg/min^2

t1, t2=seconds

- Simulation #1:

ITERATION PARAMETERS	RESULT
L2 = 4 mm	m1 = 328.8494 mg
L1 = 4.5 mm	m2 = 231.8118 mg
Ds = 20 mm	Cc = 5.9193e+005 mg/min
d = 4 mm	k1 = 1.8741e+011 mg/min^2
Limite_x2 = 3.8 mm	k2 = 1.6531e+009 mg/min^2
e1 =1mm	k3 = 2.0663e+008 mg/min^2
e2 =1mm	t1=10 seconds
Platinum (ρ_p) = 21.25 mg/mm^3	t2=10 seconds

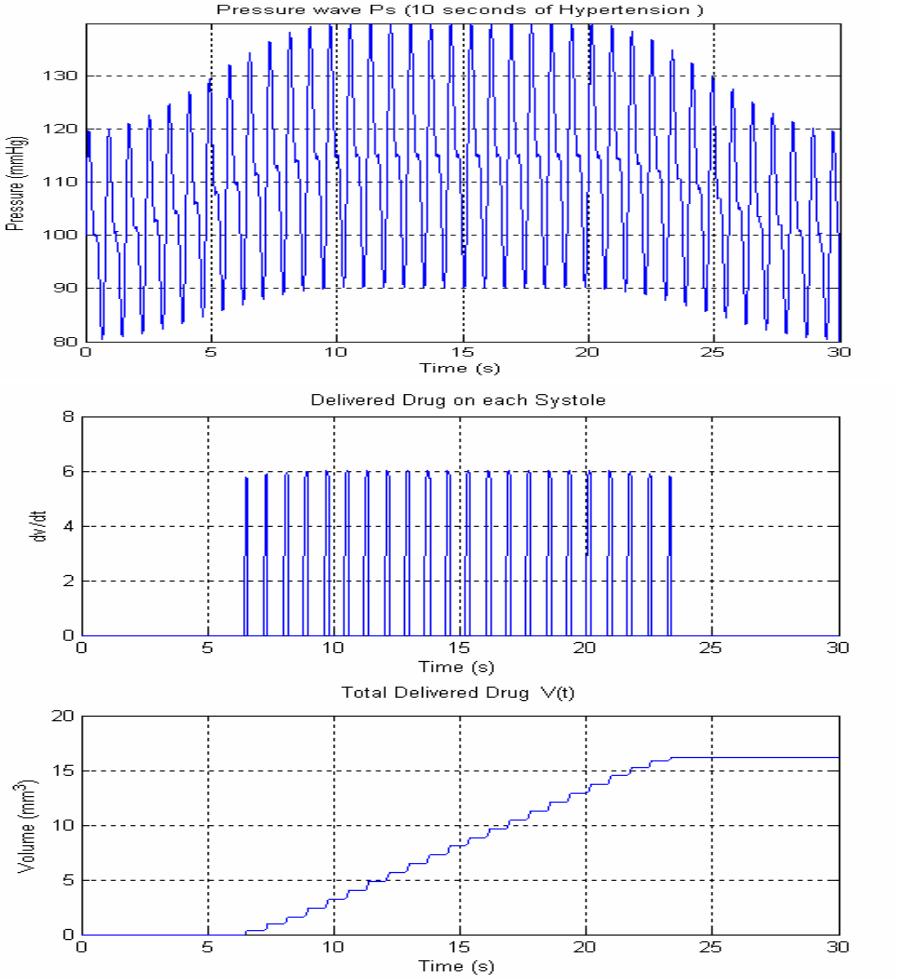


Fig.16 Pressure wave (top), Delivered drug per systole (center) , and total delivered drug (bottom) for Simulation #1.

- Simulation #2:

ITERATION PARAMETERS	RESULT
L2 = 4.5	m1 = 334.2403
L1 = 5	m2 = 231.8118
Ds = 25	Cc = 6.6848e+005
d = 4	k1 = 1.6867e+011
Limite_x2 = 4.3	k2 = 1.6675e+009
e1 =1	k3 = 1.8528e+008
e2 =1	t1=10
Platinum (ρ_p) = 21.25	t2=20

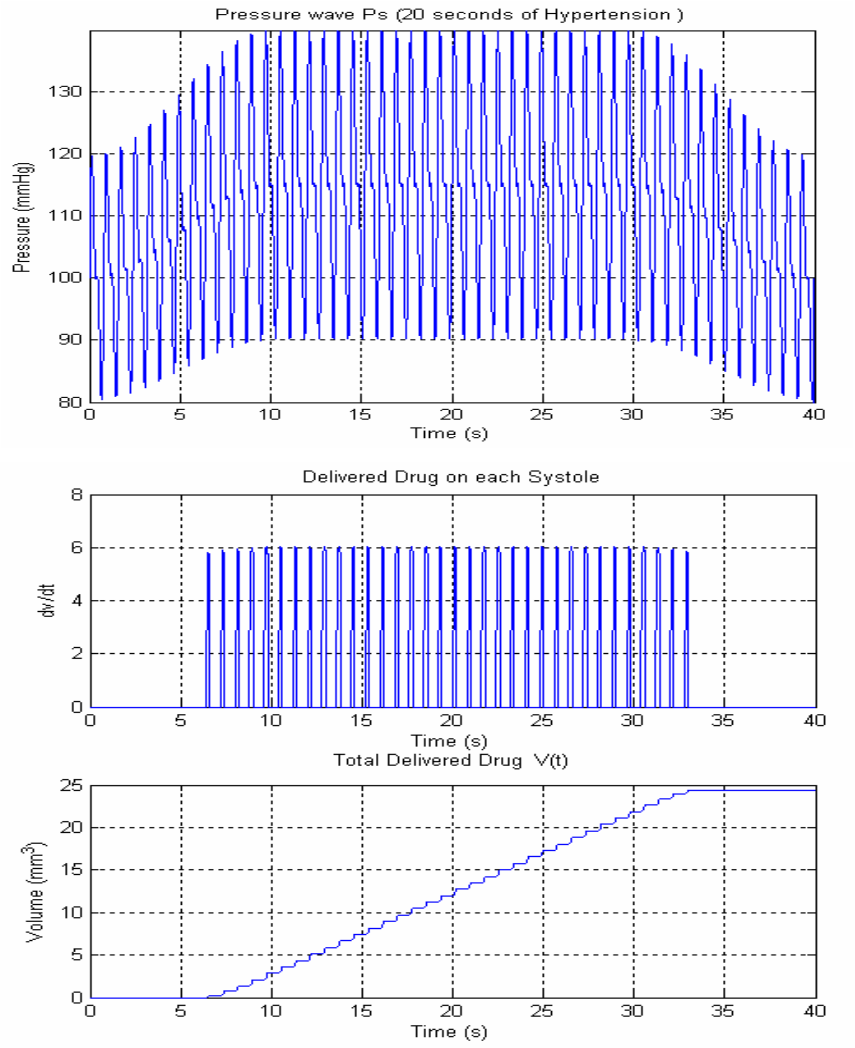


Fig.17 Pressure wave (top), Delivered drug per systole (center) , and total delivered drug (bottom) for Simulation #2.

- Simulation # 3:

ITERATION PARAMETERS	RESULT
L2 = 5	m1 = 71.1830
L1 = 5.4	m2 = 48.7399
Ds = 25	Cc = 1.9219e+005
d = 4	k1 = 1.5618e+011
Limite_x2 = 4.8	k2 = 2.0844e+009
e1 =1	k3 = 1.6675e+008
e2 =1	t1=10
Titanium (ρ_p) =4.51	t2=20

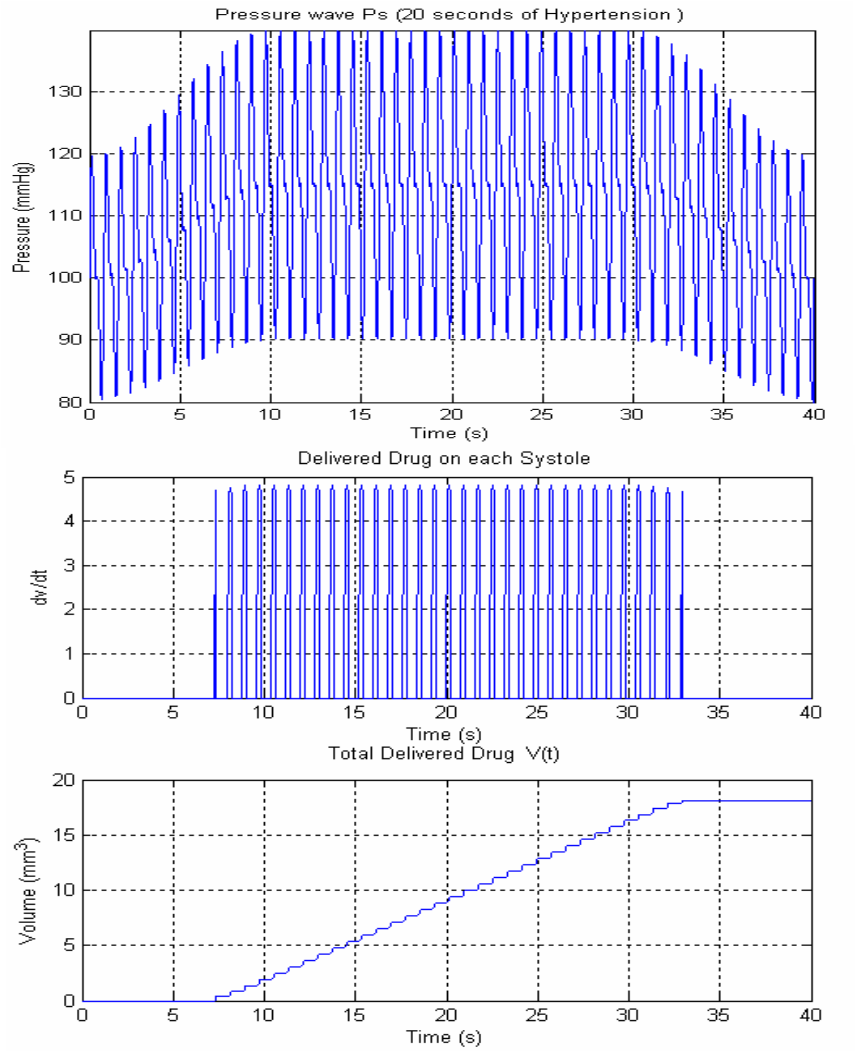


Fig.18 Pressure wave (top), Delivered drug per systole (center) , and total delivered drug (bottom) for Simulation #3.

Simulation #4:

ITERATION PARAMETERS	RESULT
L2 = 5.2	m1 = 71.4097
L1 = 5.5	m2 = 54.4074
Ds = 25	Cc = 2.6184e+005
d = 4	k1 = 1.5332e+011
Limite_x2 = 5	k2 = 3.0879e+009
e1 =1	k3 = 1.7815e+008
e2 =1	t1=10
Titanium (ρ_p) =4.51	t2=10

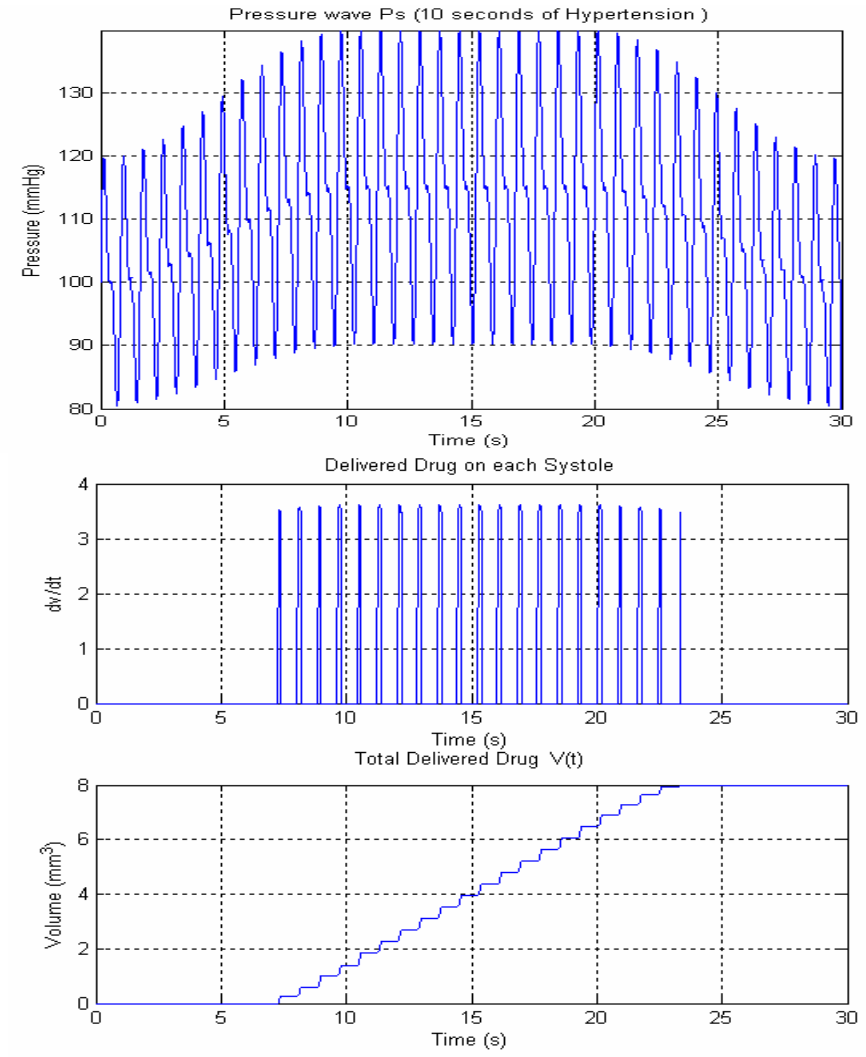


Fig.19 Pressure wave (top), Delivered drug per systole (center) , and total delivered drug (bottom) for Simulation #4.

- Simulation #5:

ITERATION PARAMETERS	RESULT
L2 = 5.7	m1 = 539.0973
L1 = 6	m2 = 404.3230
Ds = 25	Cc = 2.1564e+006
d = 5	k1 = 2.2855e+008
Limite_x2 = 5.5	k2 = 4.3424e+009
e1 =1	k3 = 2.2855e+008
e2 =1	t1=10
Platinum (ρ_p) = 21.25	t2=10

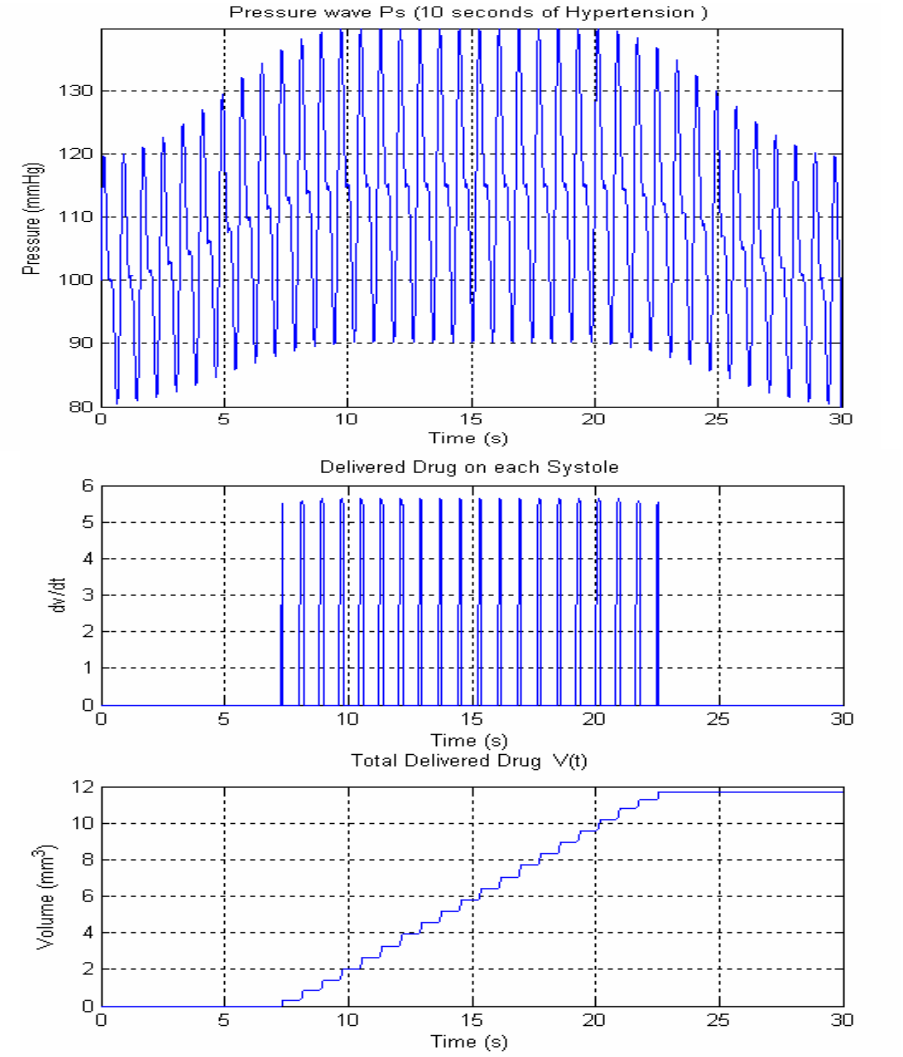


Fig. 20 Pressure wave (top), Delivered drug per systole (center) , and total delivered drug (bottom) for Simulation #5.

- Simulation #6:

ITERATION PARAMETERS	RESULT
L2 = 5.7	m1 = 345.0223
L1 = 6	m2 = 258.7667
Ds = 25	Cc = 1.3801e+006
d = 4	k1 = 1.4056e+011
Limite_x2 = 5.5	k2 = 2.7791e+009
e1 =1	k3 = 1.4627e+008
e2 =1	t1=10
Platinum (ρ_p) = 21.25	t2=10

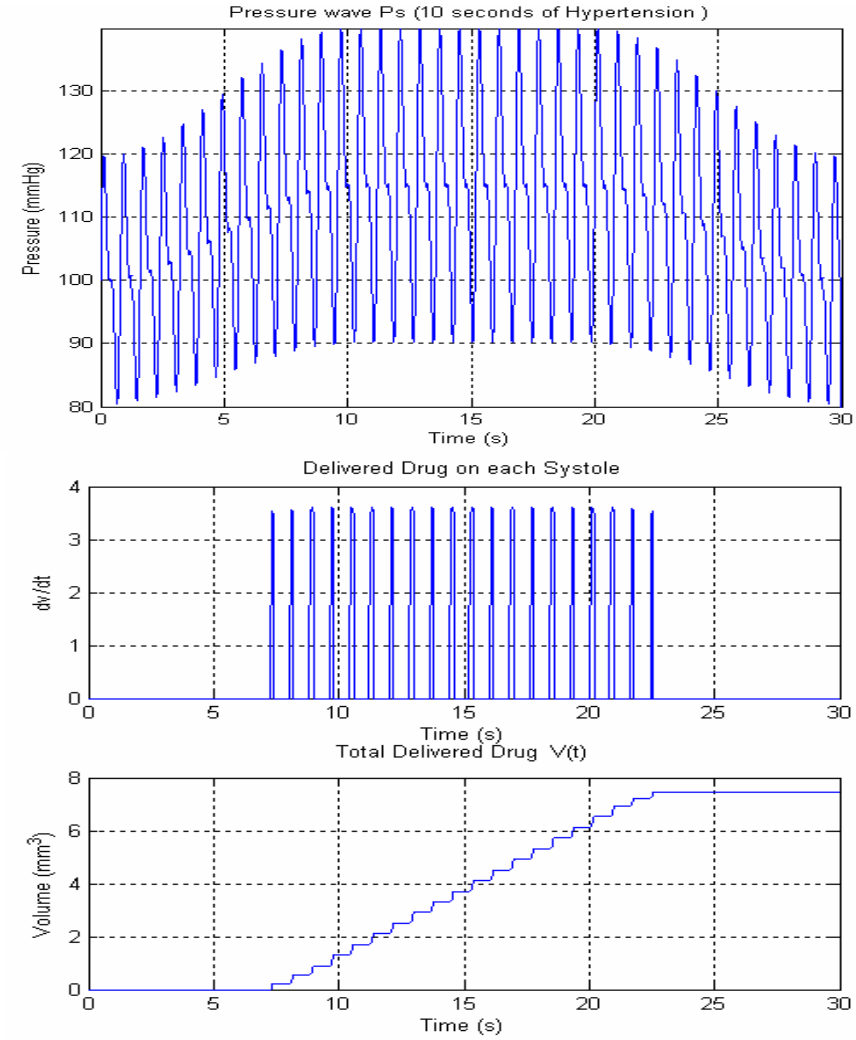


Fig. 21 Pressure wave (top), Delivered drug per systole (center) , and total delivered drug (bottom) for Simulation #6.

- Simulation #7:

ITERATION PARAMETERS	RESULT
L2 = 3.65	m1 = 67.5558
L1 = 3.80	m2 = 54.4074
Ds = 20	Cc = 3.4228e+005
d = 4	k1 = 2.2194e+011
Limite_x2 = 3.5	k2 = 5.5102e+009
e1 =1	k3 = 2.2645e+008
e2 =1	t1=10
Titanium (ρ_p) =4.51	t2=10

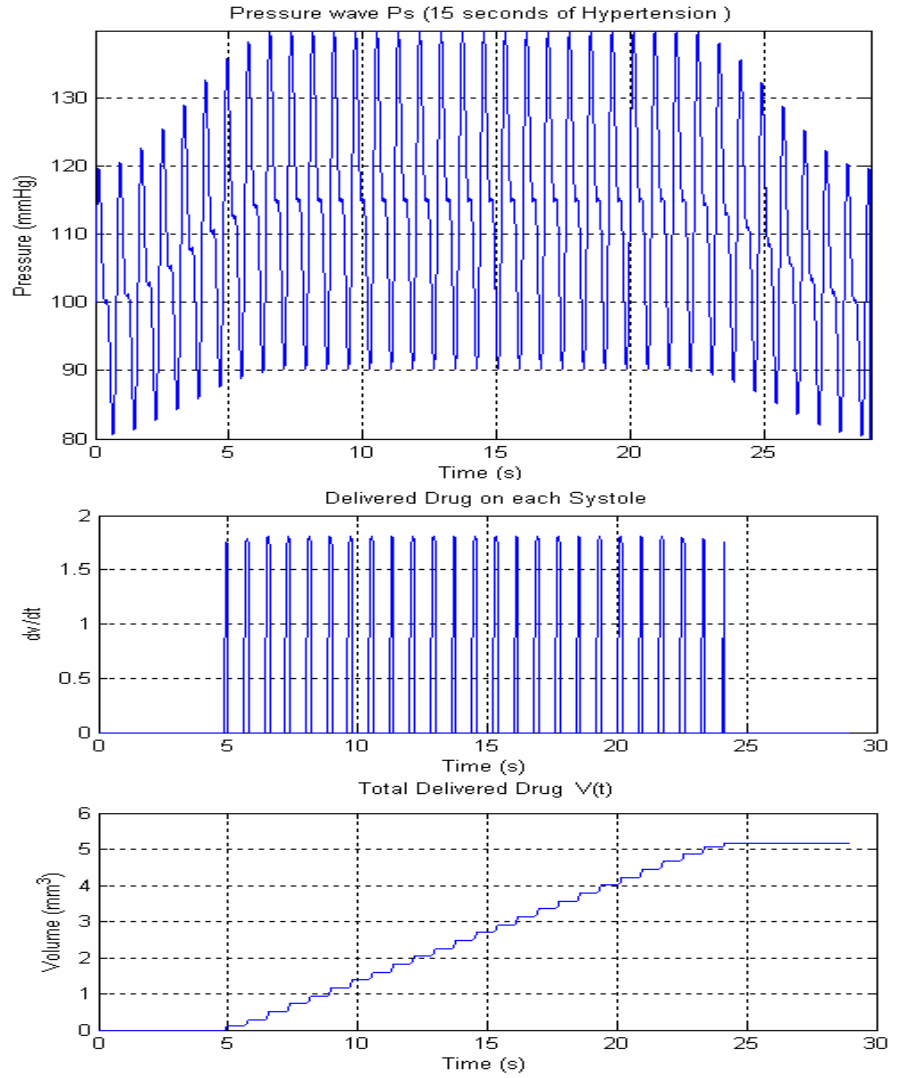


Fig. 22 Pressure wave (top), Delivered drug per systole (center) , and total delivered drug (bottom) for Simulation #7.

- Simulation #8:

ITERATION PARAMETERS	RESULT
L2 = 4	m1 = 603.7890
L1 = 5	m2 = 501.3605
Ds = 20	Cc = 6.0379e+005
d = 4	k1 = 1.6867e+011
Limite_x2 = 3.8	k2 = 8.3374e+008
e1 =1	k3 = 2.08435e+008
e2 =1	t_1=10
Platinum (ρ_p) = 21.25	t_2=20

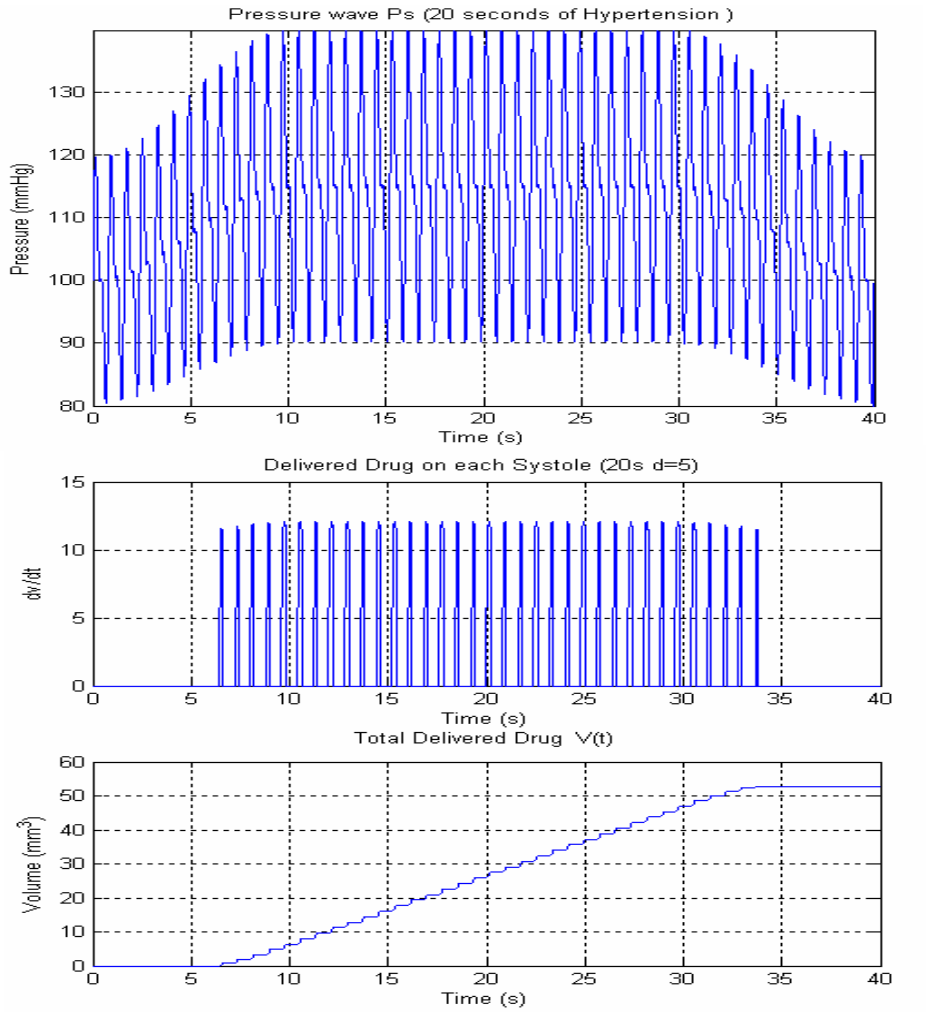


Fig. 23 Pressure wave (top), Delivered drug per systole (center) , and total delivered drug (bottom) for Simulation #8.

VI.2.2 Selection of the parameters and dimensions for the final design

The results from the series of simulations, trials 1, 4, 5 and 7 show a better conformity trend in terms of dimensions and the amount of volume being delivered. In order to reduce expenses in materials, titanium was chosen. Propranolol resulted to be convenient to comply with the volume amount needed according to the required dose and was selected by its density and dose concentration characteristic. The simulation trial 7 also offers a greater amount of time for the drug to react. The pistons movements within a selected range of displacement are shown in Figure 23.

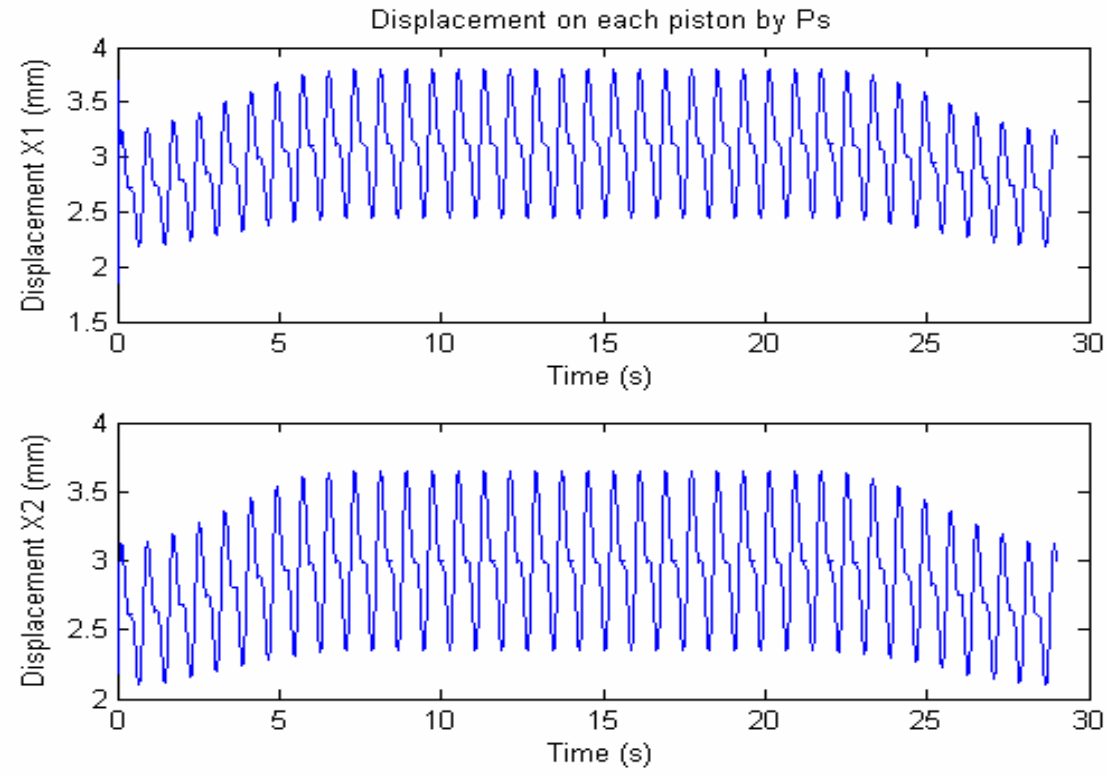


Fig.24 movement of piston masses M_1 and M_2 for simulation 7

The masses are always moving, even without a hypertension episode being present. As soon as an episode starts, there is an increase in displacement, and only when x_2 exceeds 3.5 mm limit of *Limit_*x_2 the drug starts to be discharge into the bloodstream, as Figure 24 shows. This 3.5 mm is the position of the output duct with respect to the mass m_2.

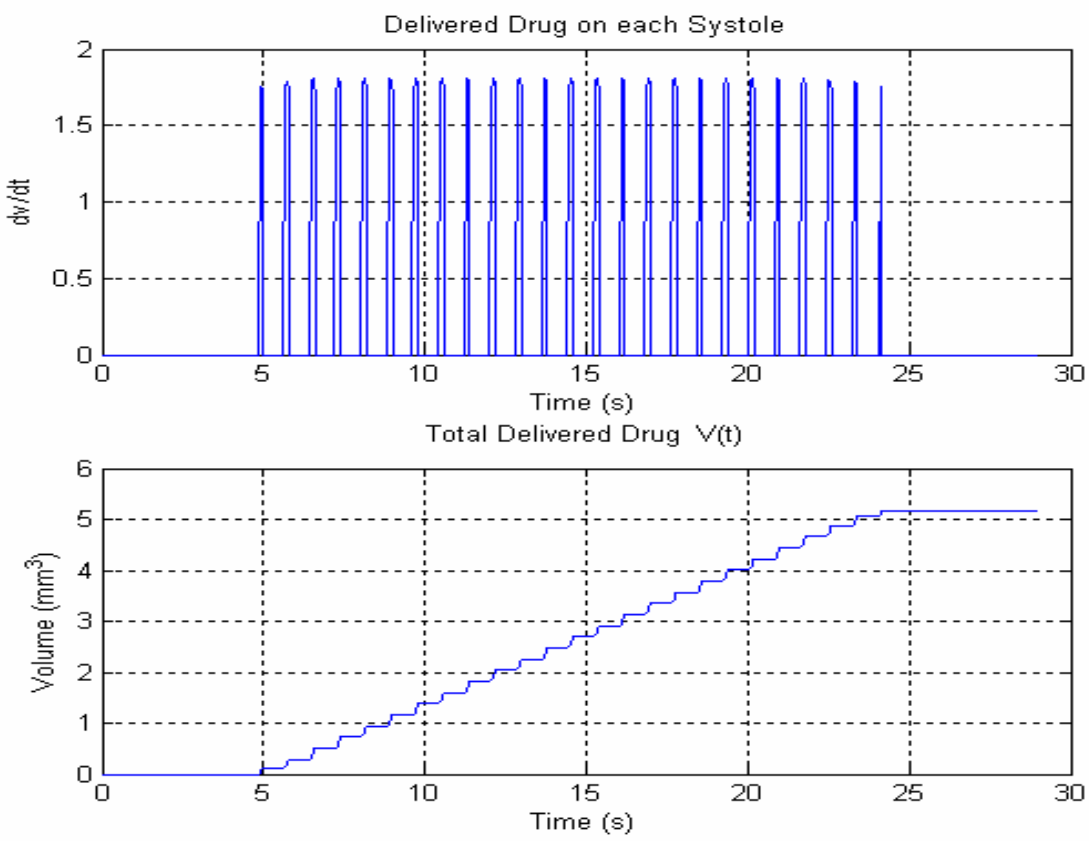


Fig. 25 Amount of drug delivered during simulation #7

After the first 5 seconds the drug starts to be delivered, and it remains being delivered for the next 19 seconds, which is assumed to be the drug reaction time. The 135 mmHg value appears at the 7 and at the 24 seconds marks confirming that it is the desired design point where the spring inertia is overcome and the valve starts to perform its drug deliverance task. The wave pressure is presented in Figure 25.

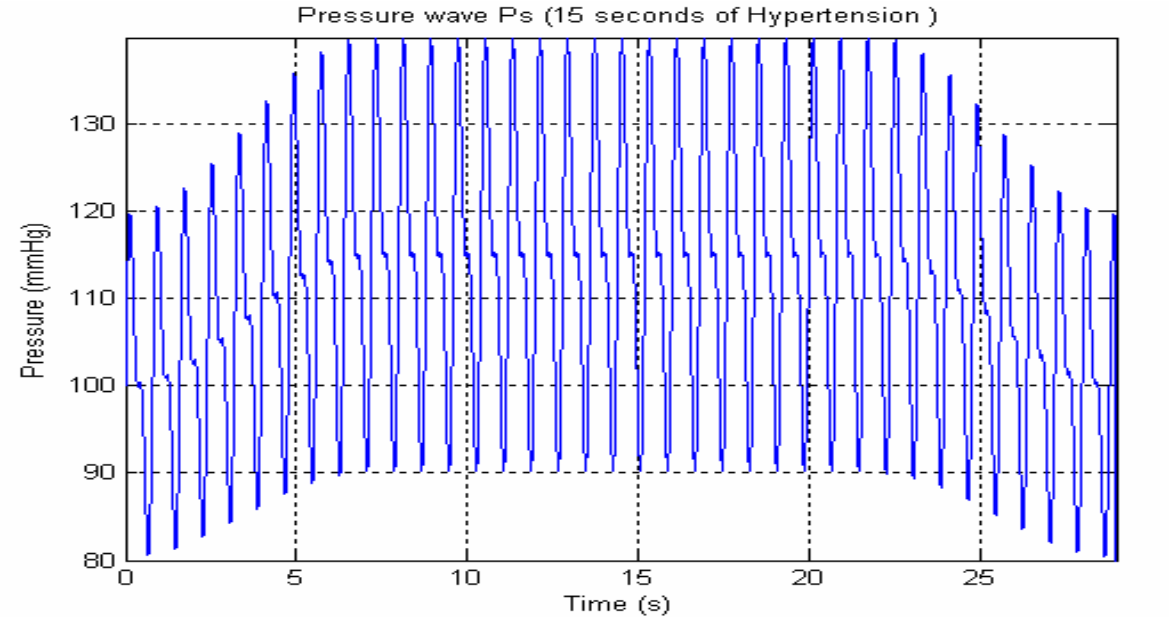


Fig. 26 Wave of blood pressure for simulation for simulation 3

The iteration parameter results are given by:

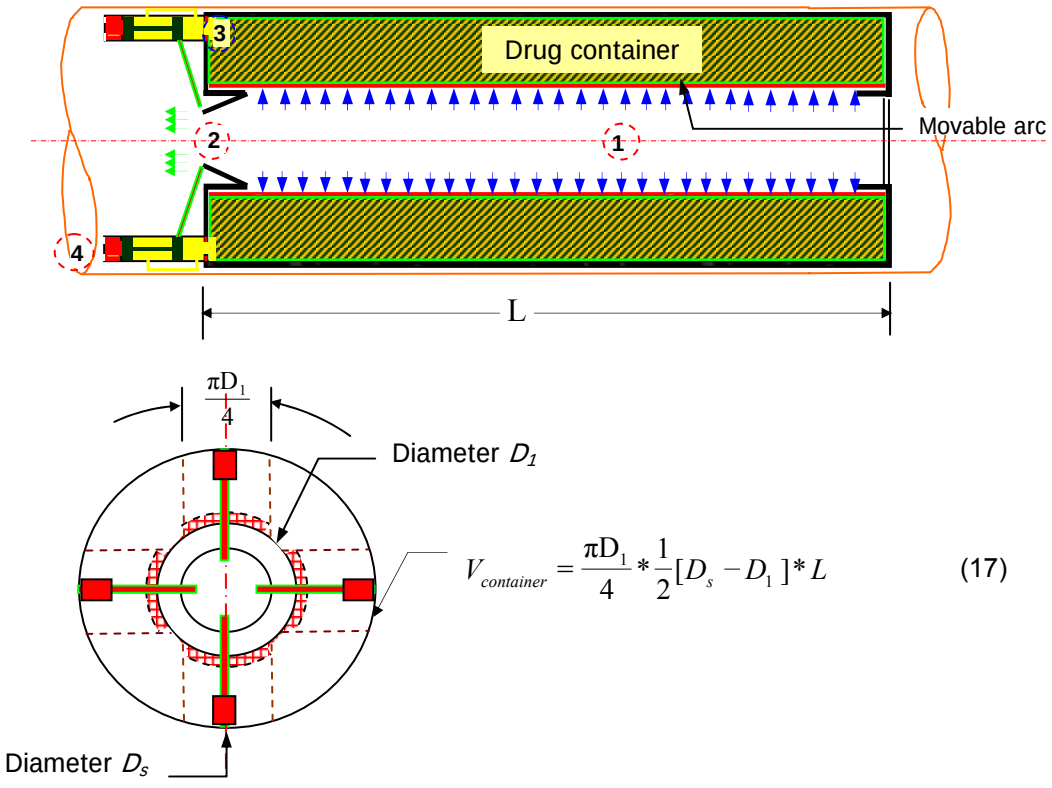
Table. 5 Final dimensions and parameters for the design

PARÁMETROS	**RESULTADOS**
L2 = 3.65 mm	m1 = 67.5558 mg
L1 = 3.80 mm	m2 = 54.4074 mg
Ds = 20 mm	Cc = 3.4228e+005 *mg/min*
d = 4 mm	k1 = 2.2194e+011 *mg/min*^{2}
Limite_x2 = 3.5 mm	k2 = 5.5102e+009 *mg/min*^{2}
e1 =1 mm	k3 = 2.2645e+008 *mg/min*^{2}
e2 =1 mm	t1=7 seconds
Titanium (ρ_p) =4.51 mg/mm^3	t2=15

VI.3 Final mechanical design

As part of the final design, the adjustable container needed to store the drug supply is chosen to be made of a polymer (polypropylene) whose dimensions will be adjusted to fit the necessary amount or drug volume needed to comply with the required release time, proposed originally to be a full year (to avoid frequent surgical procedures). It has an ultimate tensile strength of 51.7Mpa [20], more than enough to withstand the 20kPa of pressure from the blood flow. The rest of the device is constituted of an expandable stainless steel structure needed to facilitate and adjust the device implantation in the artery.

The equation that defines the volume for each container is given by:



$$V_{container} = \frac{\pi D_1}{4} * \frac{1}{2}[D_s - D_1] * L \qquad (17)$$

Fig. 27 Volume of the drug container

Equation (11) is an approximation of the volume of drug being contained. *L* can be determined since D_s and D_1 are known, and by knowing the amount of drug delivered daily from the analysis of the simulation results, the necessary year amount is be computed. We have:

$$\frac{5mm^3}{days} * 360 days = \frac{\pi * 20}{8}[20 \ -13 \ ] * L \longrightarrow \boxed{L = 32.7\ mm}$$

The design of the duct diameter that allows for the drug delivery is considered. That is done by applying the flux continuity equation $Q = v_s.A_D$ and taking the output speed as the speed necessary to avoid blood flow reflux. The diameter obtained is $d_D = 0.1mm$.

The device springs design method used for this work is presented in [15]. According to this, the design was developed to avoid fatigue failure, by using the Gerber and Zimmerli criterion. They suggest the following:

Material: Piano wire (ASTM A228-51 or UNS-G10850)

Variables: d_{r1}, d_{r2}, d_{r3} : wire diameter

D_{r1}, D_{r2}, D_{r3} : spring helix diameter =2, 0.85 and .0.85 mm.

L_{r1}, L_{r2}, L_{r3} : free length = 5, 3.8 and 6.65 mm

K_1, K_2, K_3 : Stiffness = 2.219E11, 5.5 E9, 2.2645 E8 mg/min^2

Active spirals : R_1=10, R_2= 8 y R_3= 12

Deformations: these are obtained from the displacement graphs for X_1 and X_2, noting that they present a minimum and a maximum, depending on the systole or diastole conditions, and are given by:

$\delta_{1\min} = 2.4\ mm$ $\quad$ $\delta_{1\max} = 3.8\,mm$

$\delta_{2\min} = 0.1\ mm$ $\quad$ $\delta_{2\max} = 0.15\,mm$

$\delta_{3\min} = 2.3\ mm$ $\quad$ $\delta_{3\max} = 3.65\,mm$

1. Calculating the preloads, for F_1:

$F_1 = \delta_1 K_1$:

$$F_{1\min} = 2.4.(2.2194E11) = 5.326E11 \frac{mg.mm}{\min^2}$$

$$F_{1\max} = 3.8.(2.2194E11) = 8.43E11 \frac{mg.mm}{\min^2}$$

2. The desired design security factor is chosen as $n=1.5$, now evaluating the criterion security factor for the fatigue $\eta_f = \frac{S_{sa}}{\tau_a} > 1.5$.

3. Calculating the alternating component of the shear stress τ_a:

$\tau_a = k_B \frac{8.F_a D_{r1}}{\pi.d_{r1}^3}$ where F_a and k_B are given by:

$$F_a = \left| \frac{F_{1\max} - F_{2\min}}{2} \right| = \frac{8.43E11 - 5.326E11}{2} = 1.552E11 \frac{mg.mm}{\min^2}$$

$$k_B = \frac{4c+2}{4c-3} = \frac{8+2d_{r1}}{8-3d_{r1}} \quad \text{where,} \quad c = \frac{D_{r1}}{d_{r1}} = \frac{2}{d_{r1}}$$

Substituting in the τ_a equation we get: $\tau_a = \frac{8+2d_{r1}}{8-3d_{r1}} . (\frac{7.9E11}{d_{r1}^3})$

4. Finding the load line slope: $r = \frac{\tau_a}{\tau_m}$:

First we calculate the average shear stress component τ_m as:

$$\tau_m = k_B \frac{8.F_m D_{r1}}{\pi.d_{r1}^3}$$

Where F_m is given by: $F_m = \frac{F_{1\max} + F_{2\min}}{2} = 6.878E11 \frac{mmg.mm}{\min^2}$, substituting in τ_m, we get: $\tau_m = \frac{8 + 2d_{r1}}{8 - 3d_{r1}} . (\frac{3.5E112}{d_{r1}^3})$

Finally, $r = 0.2257$

5. To determine S_{sa}, we evaluate the following components:

- Final tension resistance: $S_{ut} = \frac{A}{d^m}$

A and m, obtained from [15] as A=2211Mpa.mm^m and m=0.145, which offers some fabrication diameter standards for the piano wire spring minimum and maximum. Substituting S_{ut} we get:

$$S_{ut} = \frac{7.9596E15}{d^{0.145}} \quad (\frac{mg}{mm.\min^2})$$

- Final shear resistance: $S_{su} = 0.67.S_{ut} = \frac{5.333E15}{d^{0.145}} \quad (\frac{mg}{mm.\min^2})$

- The constructive intersection for the Gerber ordinate for Zimmerlie data is given by:

$$S_{se} = \frac{S_{sa}^*}{1 \quad (S_{sm} / S_{su})^2} = \frac{8.67.E14}{1 \quad 0.2559.d^{0.145}} \quad (\frac{mg}{mm.\min^2})$$

Where: S_{sa}^* and S_{sm} are the Zimmerlie fatigue strength components corresponding to without grain refinement piano wire data are given by:

$$S_{sa}^* = 8.67E14 \ (\frac{mg}{mm.\min^2}) \quad \text{y} \quad S_{sm} = 1.3644E15 \ (\frac{mg}{mm.\min^2})$$

S_{sa} comes out finally as:

$$S_{sa} = \frac{r^2 S_{su}^2}{2S_{se}}[1-+\sqrt{1+(\frac{2S_{se}}{rS_{su}})^2}\ ] = \frac{8.377_E 14.(1-0.256.d^{0.145})}{d^{0.145}}.[1-+\sqrt{1+\frac{(2.07d^{0.145})^2}{(1-0.26d^{0.145})^2}}\ ]$$

6. Evaluating safety factor $\eta_f = \frac{S_{sa}}{\tau_a} > 1.5$ for different values of d_{r1}, we find:

d_{r1} (mm)	η_f
0.1	0.7
0.15	2.4
0.2	5.6
0.25	10.9
0.3	18.58
0.4	42.4

So, we can finally chose a diameter of d_{r1} = 0.2 *mm*, which would correspond for a very reliable design security factor. The same steps from (1) to (6) are repeated for springs R_2 and R_3, from which we obtain wire diameters of: d_{r2} = 0.1 *mm* and d_{r3} = 0.1*mm*.

After evaluating the resonance conditions, it finds that, the system is not resonance undergo the work regimen, see Figures 27 and 28:

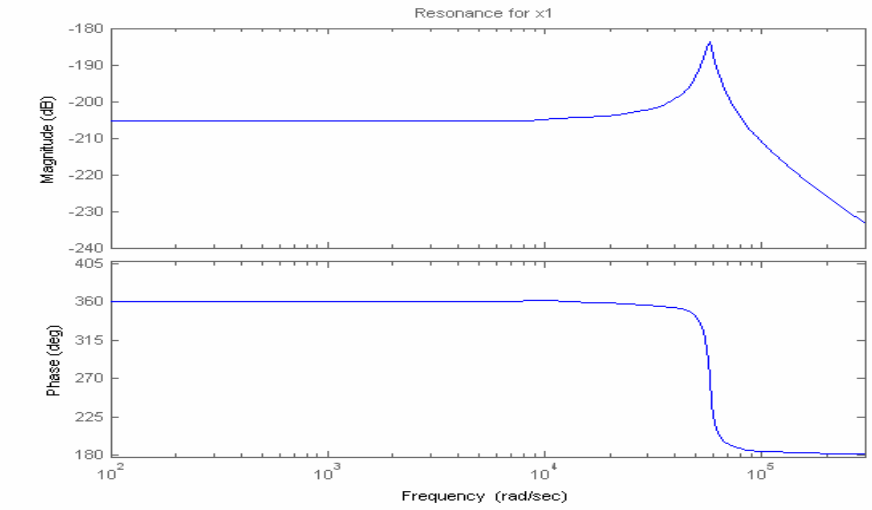


Figure 28 Resonance plot for x1

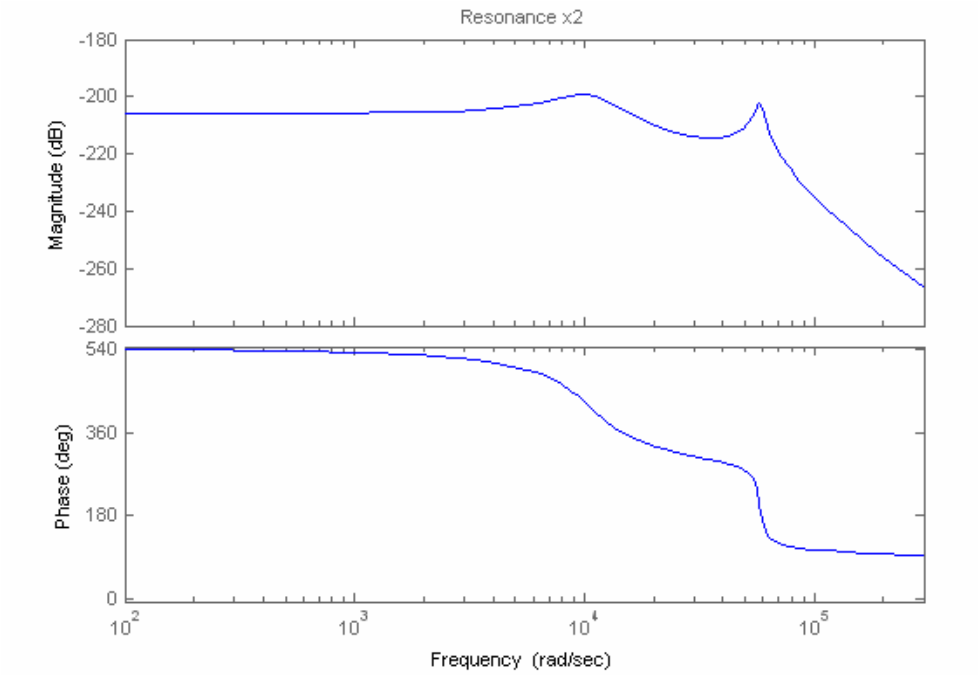


Figure 29 Resonance plot for x2

Where the system excitation frequency is:

$$w_{ex\_blood} = 9.4247 \frac{rad}{s}$$

Since the transfer function for both variable (x_1 and x_2) is equal:

Transfer function x_1:

$$\frac{\text{-9.095e-012 s^3 + 0.186 s^2 + 1170 s + 1.961e007}}{\text{s^4 + 1.136e004 s^3 + 3.472e009 s^2 + 2.172e013 s + 3.633e017}}$$

Transfer function x_2:

$$\frac{\text{-9.095e-012 s^3 – 4.768e-007 s^2 + 1170 s – 1.884e007}}{\text{s^4 + 1.136e004 s^3 + 3.472e009 s^2 + 2.172e013 s + 3.633e017}}$$

From these values it follows that resonance never occurs because the natural resonance of blood lies below the system values determined. Finally, a schematic showing all the necessary dimensions and determined simulation parameters will be presented in the figure 29.

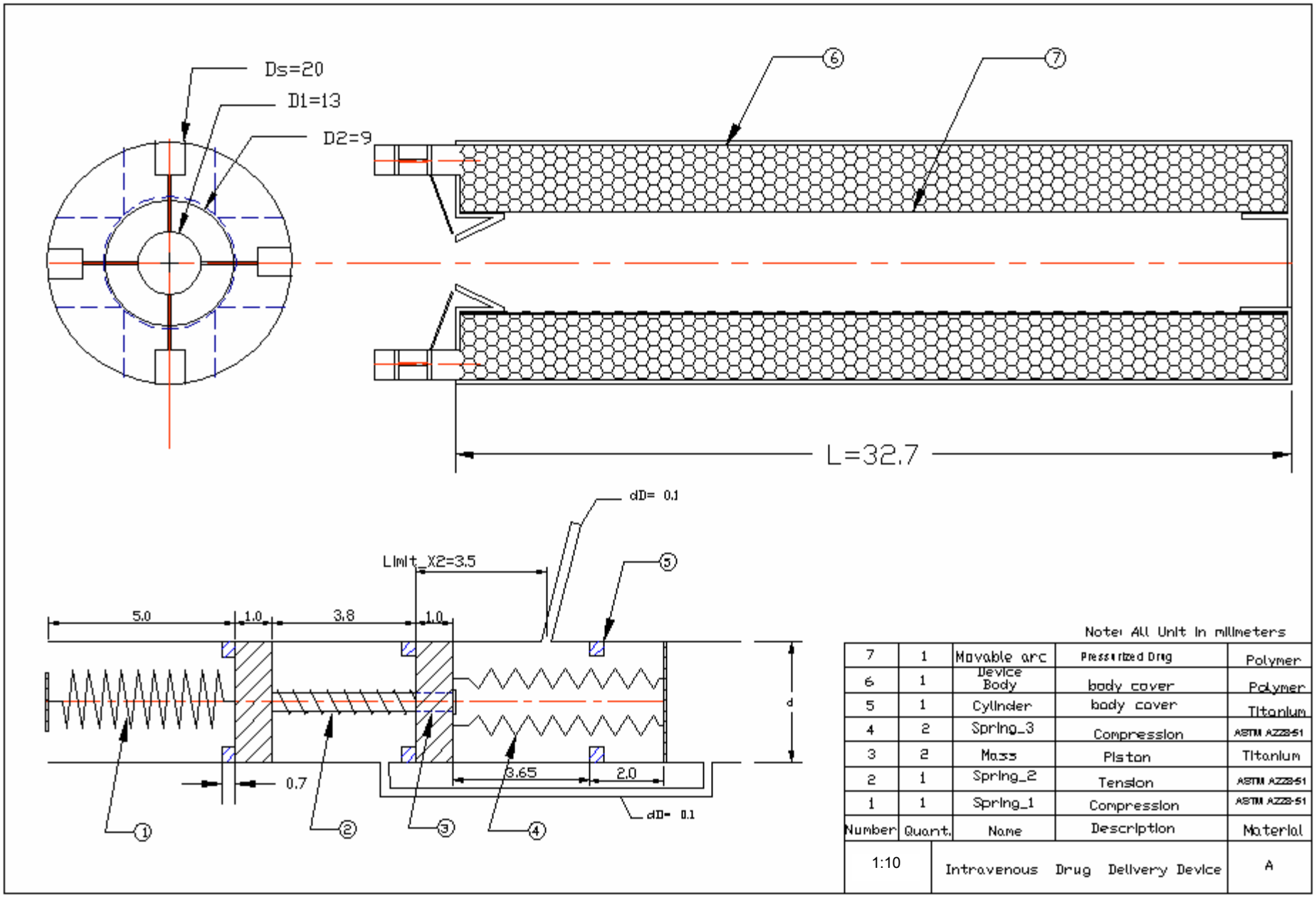


Fig.30 Final design

CHAPTER VII: CONCLUSIONS AND RECOMMENDATIONS

VII.1 CONCLUSIONS

- The proposed objectives were achieved due to the good results obtained from the titanium simulations, in which the proposed dose for the propranolol drug was adequately delivered.

- Being a fully mechanical system, the simulations 7, show a good drug delivery behavior, but these results must be validated in the presence of real blood flow conditions due to the many uncertainties derived from the drug physical properties of the drug.

- The design of this self-regulated device may help to aid in the control of high blood pressure.

- Although the arterial hypertension cannot be definitively cured, the design of an self-regulated device would offer an alternate control method for many patients.

VII.2 RECOMMENDATIONS

- Create a simulation based on the physical parameters of the system, using the power law of Ostwald of Waele. Blood flow circulation inside the device must be simulated to examine the pressure wave and the boundary layer profiles of the blood flow. During its way through points 1 and 2, the both

pressure and boundary layer profits a will be observed at different times, both during nominal conditions and when a hypertension period is present

- Implement a mechanism of chemical response for the dosage, based on principles of chemical reaction.

- Adapt a totally electronic dosage system to quantify and to optimize the quantity of necessary dose.

- Carry out a prototype from this device type to scale and to observe its functionality in laboratories with animals

- There are still some challenges regarding to the design of implantable device, like:

    - Blood/implant biocompatibility interaction problems
    - Drug stability in aqueous solution
    - Overdosing due to spool valve failure
    - Drug fouling and possible immune system attack

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