Mathematical Modelling of Enterohepatic Circulation With Saturation Kinetics of Bile Delay Effect

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January, 2026

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A THESIS WRITTEN IN THE DEPARTMENT OF MATHEMATICS AND SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.) IN MATHEMATICS FROM THE DEPARTMENT OF MATHEMATICS, FACULTY OF PHYSICAL SCIENCES, UNIVERSITY OF BENIN, BENIN CITY, NIGERIA.

JANUARY, 2026

CERTIFICATION

This is to certify that this Doctorate degree (Ph.D.) thesis was done by **Stephen Onome Oyovwevotu** in the Department of Mathematics, Faculty of Physical Sciences, University of Benin, Benin City, Nigeria under the supervision of DR. Owin.O. Olowu and Dr. I. I. Ako.

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DECLARATION

UNIVERSITY OF BENIN

COLLEGE OF POSTGRADUATE STUDIES

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DEDICATION

This thesis is dedicated to God almighty the author and finisher of my faith. The memory of my late Father, Late Mr. David Atete and my mother, Mrs Patience Oyovwevotu for her ceaseless prayers

ACKNOWLEDGEMENTS

My sincere appreciation goes to the Almighty God; the fountain of my inspiration, my provider, sustainer and protector, in whom I have the strength to undertake and complete this journey to acquiring a PhD.

From the bottom of my heart, I sincerely thank the Head of Department, Department of Mathematics, Faculty of Physical Sciences, University of Benin, Benin City, Nigeria, **Professor Daniel Uhunoma Okuonghae, FNYA**, whose mentorship began during my Masters programme and has continued to inspire and guide my academic journey. His support, encouragement, and leadership have played a significant role in my academic and professional development.

Also, I express my sincere and unreserved gratitude to my Supervisor, Dr. Owin O. Olowu, for his invaluable guidance, support throughout my research work. I appreciate also, my Co-Supervisor, Dr. Ignatius I. Ako, for his professional assistance as regards the structure of my research.

I also extend my hearrfelt appreciation to the academic and non-academic staff of the Department of Mathematics, Faculty of Physical Sciences, University of Benin, Benin City, Nigeria for their assistance and for providing the academic environment and resources for the successful completion of this research.

I also appreciate the contributions of my colleagues and friends: Dr. Austin Obayuwana, and Dr. Otamere Blessing and Mr. John Ushie who provided helpful discussions, technical support and encouragement.

To everyone in my spiritual family that supported with their prayers and otherwise, I am most grateful for your immense benevolence and unbridled generosity.

Special thanks to my Mum, Mrs. Patience for her motherly counsel , and my Late

Father, Mr. David Atete, who created the path but left me to journey therein. I pray the Lord continue to grant my dad eternal rest. To my siblings and family members, thank you all.

ABSTRACT

Enterohepatic Circulation (EHC) is the process by which bile acid are secreted from the liver into the bile, excreted into the small intestine and then reabsorbed back into the liver. This efflux process is spurred by drug saturation, which is a condition in which the rate of absorption of the drug is limited by the rate of transport to the liver or the rate of secretion into the bile. EHC plays a crucial role for several liver and gastrointestinal functions such as bile flow, solubilization and excretion of cholesterol, clearance of toxic molecules, intestinal absorption of lipophilic nutrients, as well as metabolic and antimicrobial effects. Despite its positive impact in human homeostasis, it is known that EHC can increase toxicity of drugs(due to incomplete elimination during recycling), increased risk of gallstones which result to systemic diseases such as cholelithiasis, bile duct cancer, pancreatic cancer and hepatotoxicity(drug liver injury). In the formulation of a Physiologically Based Pharmacokinetic Model of EHC Drugs with Saturation Kinetics is formulated. The model is affected by secreted drug in the hepatocyte and gastrointestinal compartment with delay effect on metabolites. The drug toxicity threshold parameter and delay effect accounting for gallbladder and intestine disorder(alter the rate of bile circulation) will be discussed. The model is rigorously analyzed on Drug Free Equilibria, Drug Saturation Equilibria, Toxicity Equilibria and Drug Reabsorption Equilibria. Threshold value for Pathological parameter for which there exist a trans from Hoph bifurcation to periodic system was established. The direction of Stability (super critical and subcritical) was also established. Global and Local stabilities were also investigated.

The results from the analysis showed that drug saturation induces toxicity in the absence of pathological defect parameters when Drug Toxicity Number (DTN) is

greater than one .Whereas in the presence of pathological parameters (Mild Case), Drug Toxicity does not annul the physiological state of the compartments hence cannot effect drug reabsorption. There exist a threshold for pathological parameters for which drug reabsorption occurs, and defect in physiological compartment progresses from mild to acute case when pathological parameters exceed this threshold i.e $\tau_1 + \tau_2 > \frac{v_2+2m_2}{\eta_2}$. Hoph bifurcation analysis on the Drug Free and Drug Saturation Equilibria showed that there exist an upper bound for which the system remains asymptotically stable. Numerical results obtained from this work will provide a framework for Pharmaceutical Policies and decisions on EHC.

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Chapter 1

Introduction

Enterohepatic circulation (EHC) also known as Enterohepatic recycling, refers to the influx process of synthesize drug (metabolites) from the liver to the gallbladder, excreted through Bile into the Gastrointestinal tract and subsequently reabsorbed into the liver. This efflux process is spurred by drug saturation, which is a condition in which the rate of absorption of the drug is limited by the rate of transport to the liver or the rate of secretion into the bile. Enterohepatic circulaton is an indispensable concept in toxicology as many Lipophilic xenobiotics such as Phenytoin, Propranolol, Digoxin, Lidocaine etc causes repeated liver damage. EHC can increase toxicity of drugs (due to incomplete elimination during recycling), increased risk of gallstones which result to systemic diseases such as Cholelithiasis, bile duct cancer, pancreatic cancer and hepatotoxicity (drug liver injury).

1.1 ANATOMY OF EHC

In other to ascertain the influx and efflux processes of EHC process, a good understanding of anatomical features involved in EHC process is required . This establishes a foundation for the dynamics of EHC drugs as it relates to each compartment in the body. The organs involved in EHC processes includes the following organs:

- **LIVER**: Some of the physiological functions of the human liver are metabolism, detoxification, blood filtration, bile Production. It is major site for drug metabolism. Hepatocyte and cholangiocyte are the two cells found in the liver. Hepatocyte absorb substrate from the blood and secrete metabolite in the bile.They are the only cells in the body responsible for conversion of cholesterol to bile acids (Mehendale, 1987).

The human liver is segmented in lobes, the left and the right lobes (Plaa,

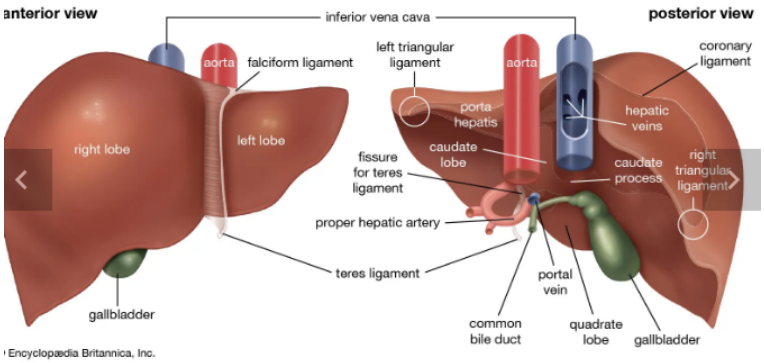


Figure 1.1: Anatomy of Liver

1991). The right lobes is section into posterior and anterior, while the left liver is section into medial and lateral sections.

- **PORTAL VEIN**

Portal vein is a connective tissue that transport blood from the gastrointestinal tract, gallbladder, pancrease and spleen to the liver (figure1 of portal vein). An estimate of 75% of liver blood is influx through the portal vein. The hepatic vein transport blood from the liver to the heart. It is formed by circuit of the superior mesenteric and splenic veins (Klaassen, 1984). Portal vein is divided into the left and right portal Veins at the helium (Hofmann, 1976).

The blood transported by these veins is rich in nutrients and metabolite that have been absorbed from the GIT . These nutrients and compounds are synthesize in the liver (bile secretion) or sustained in the central compartment. Despite the minimum oxygen influx by portal vein, it still accommodate 50-70% of its required oxygen for the liver. This is due to high influx rate of the portal vein where 75% of the blood provided to the liver comes through the portal vein. The hepatic artery provides the leftover 25% of liver blood supply(Plaa, 1991).

- **GALLBLADDER**

Gallbladder is a pear shaped sac attached to the posterior surface of the liver connected to the tissue. The average length and volume of the gallbladder are eight to ten centimeters and thirty to fifty Litres respectively. The gallbladder is anatomically divided into three parts;

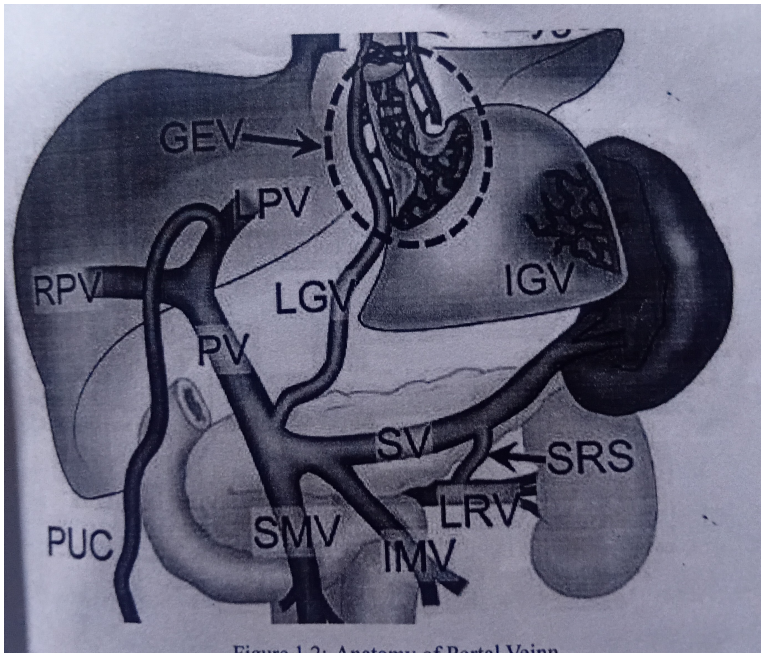


Figure 1.2: Anatomy of Portal Vein

the fundus, the body, and the neck (Richard, 2005). The neck of the gallbladder is attached to the hepatic duct via the cystic duct, which is around three to four centimeters long. The proximal part of the cystic duct contains the valves of Heister which is believed to aid in regulating gallbladder emptying and filling (Melnik, 1998). The gallbladder receives its blood supply via the cystic artery. The venous drainage of the gallbladder is carried out via the cystic vein draining to the portal vein.

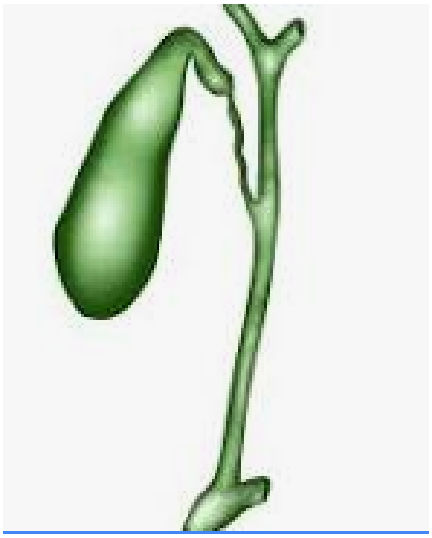


Figure 1.3: Anatomy Gallbladder

- **GUT ABSORPTION**

Orally administered drugs goes through an absorption process from the gut to the systemic circulation. Factors that determines the magnitude of absorption are classified into: physiological such as gastric emptying and lumen PH; physiochemical like pKa and drug solubility; and environmental including the presence of food and the gut composition of microflora (Plaa, 1991). Absorption begins with the drug crossing the gut wall, at where the drug may undergo metabolism and transport by the present enzymes and transporters, respectively (Jonsson, 1998). EHC process can be influence by metabolizing enzymes in the gut wall due to metabolite formation. Gut wall transporters like Pglycoprotein, present on the apical surface of the intestinal epithelium, may expel the drug back to the gut lumen and therefore reduce the drug absorption (Hellstern, 1990).

1.2 PHARMACOKINETICS OF EHC

The liver produces bile, which is stored in the gallbladder. When food is eaten, the gallbladder releases bile into the small intestine. Bile helps to digest fats and absorb nutrients. Some of the bile acids are not absorbed by the intestine and are excreted in the feces. The remaining bile acids are reabsorbed by the small intestine and transported back to the liver. The bile acids are then recycled and released back into the small intestine.

Enterohepatic circulation influences the dynamics of pharmacokinetic parameters. It is known that EHC increases drug bioavailability and changes plasma concentration curves of the drug (Phillips, 1986). Its also spurs multiple peaks in concentration time profile (Lenzen, 1999)

1.2.1 MODE OF DRUG ADMINISTRATION

Mode of drug administration also known as drug delivery is a method by which Xenobiotics get to the internal environment of the body to achieve a therapeutic effect. Drugs get to the body through different route. The choice of administration depends on Pharmacokinetics of the drug, drug formulation, therapeutic window, health status of patient, age and developmental stage, etc.

The main method of drug administration are:

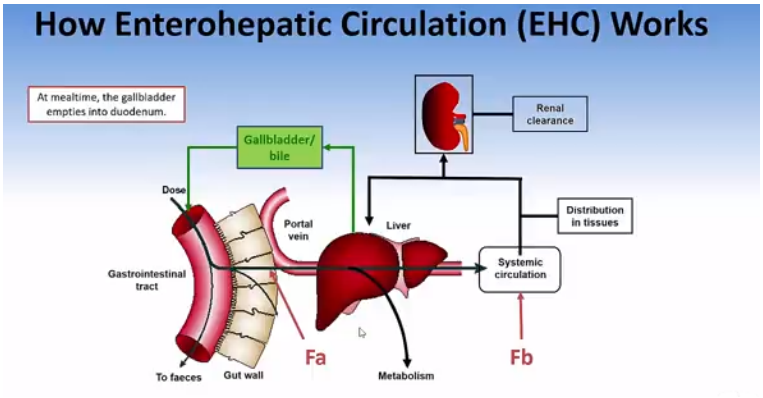


Figure 1.4: Flow diagram of EHC process (Influx Process)

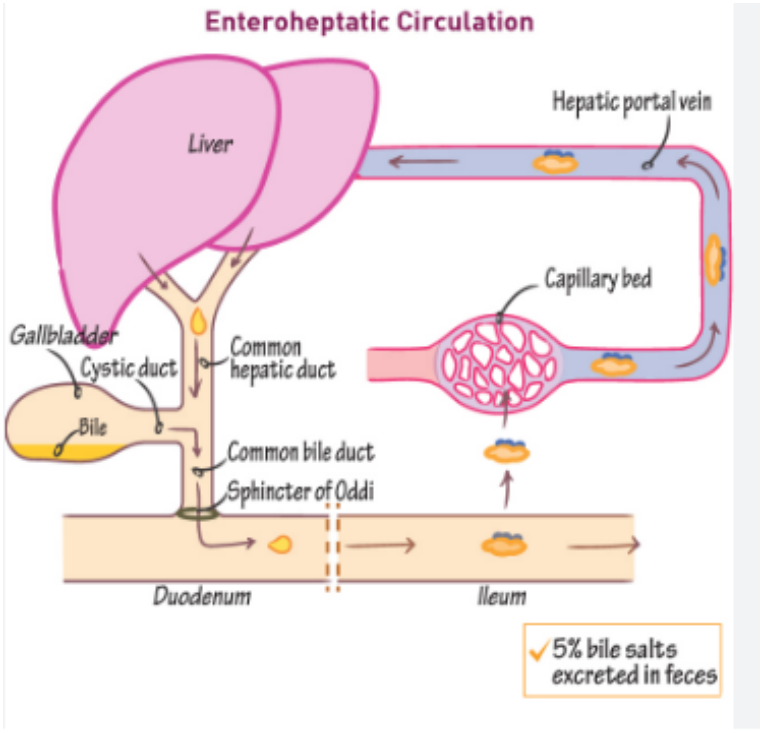


Figure 1.5: Flow diagram of EHC process (Influx Process 2)

- **Enteral Route**: This involved drug been administered orally through the mouth or nasogastric tube. The enteral route of can be Sublingual and buccal route. This means the drug is not swallowed but kept under the tongue or in the oral cavity between the gum and cheek. The mucosa of the oral cavity is highly absorptive, hence blood can enter the systemic circulation , avoiding the acid condition of the stomach.
- **Topical Route**: This involved application of drugs to the skin

or an orifice. The topical route of administration have numerous advantages, such as slow absorption and small amount of drug get to the area of the body other than where the drug was applied, which allows circulation through the blood stream once absorbed .

- **Parental Route**: Parental route involves injection of drugs with needle,which makes it a more invasive method of drug administration.There are different ways to make the injection. Which are: intradermal subcutaneous,intraveneous,intramuscular.

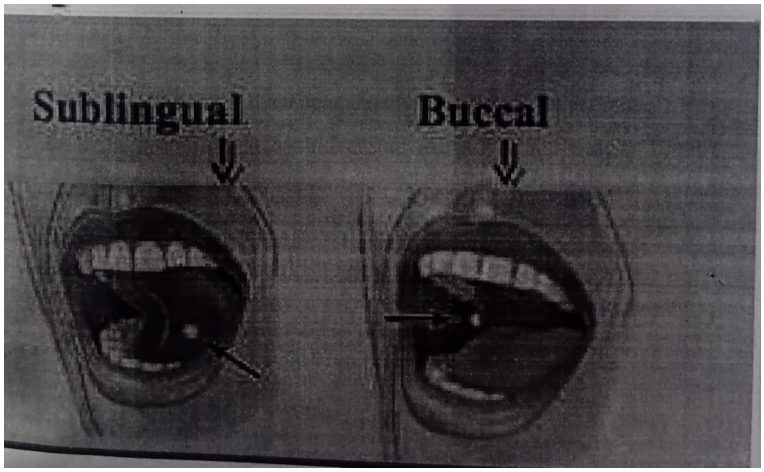


Figure 1.6: Sublingual and Buccal

1.3 NONLINEAR KINETICS OF DRUGS

The circular influx and efflux of enterohepatic drug spurred by drug saturation in the liver and intestine is best captured by nonlinear kinetics which involves the use of nonlinear function called Michealis Menten to relate drug saturable transport and metabolism (Michealis & Menten, 1913). The Michealis Menten equation is define as follows:

$$v = \frac{v_{max} \times s}{k_m + s}$$

where
v_{max} = the rate of reaction (transport or metabolism)
s = the drug concentration
k_m = Michealis Menten constant (half of the reaction rate).

There are various order of kinetics in Michealis Menten equation. These orders are :

- **Zero Order Kinetics**: The substrate concentration is by far higher than Michealis Menten constant(s$\gg k_m$).
- **First Order Kinetics**: The substrate concentration is by far lesser than Michealis Menten constant ($s \ll k_m$). Hence, the reaction rate becomes directly proportional to drug concentration.

1.4 PHARMACOKINETICS PROCESSES

Pharmacokinetics(PK) studies the dynamics of drug in relation to human homeostatis. Basically the study of the distribution, absorption, metabolism, excretion and the metabolism (ADME) of xenobiotics. Pharmacokinetics does not limit its scope to healthy or normal subjects but rather it includes variations in bioavailability, physiological or pathological conditions, disease related dose adjustment, and drug interactions. Combined, these aspects of PK allow customisation of drug dosage regimes to enhance outcomes.

- Absorption is an irreversible process that involves movement of drugs from the site of administration to the central compartment. Drug absorption rate is usually captured by gastrointestinal tract in PK models. The rate of absorption can be represented as either constant (zero order) or first order (amount of drug is proportional to eliminated drug) in the absorption compartment.
- Distribution is the influx and efflux of drug from systemic compartment to tissues compartments. Drug distribution rates in PK model are often represented by diffussion or linear rate constants between different compartment.
- Elimination is the irreversible process by which the body get rid of drug by excretion or by metabolism. Drug Elimination can be linear or nonlinear, The Elimination processes is said to be nonlinear if it is saturable i.e enzymes in metabolic compartment (Liver) are saturated by drug captured by Michealis Menten function. For

linear case enzymes are unbounded by drug, hence the rate of drug absorption is less or equal to the rate of elimination.

- Metabolism entails the synthesis of drug by enzymes.Enzymes are active by their cells,without which they cannot perform optimally. Hepatocytes and Enterocyte are the cells for liver and gastrointestinal tract compartment. Drug metabolism largely occurs in the liver but can also occur in the kidneys, lungs, skin (Golan, 2012).

1.5 SIGNIFICANCE OF THE STUDY

The EHC plays a key role in drug metabolism by continuously recycling bile acids and some drugs between the liver and the intestine. When this circulation is delayed or disrupted, it can cause changes in drug concentration and may lead to increased toxicity. Many existing pharmacokinetic models do not fully account for these nonlinear effects, which limits their ability to accurately predict such outcomes.
This study helps fill that gap by developing a mathematical model that includes both saturation kinetics and the bile delay effect to better understand how drugs behave in the body. By considering these physiological processes, the model provides a more realistic view of how bile flow and delay influence drug levels and toxicity.
The stability and Hopf bifurcation analyses identify the conditions under which drug levels remain steady or begin to fluctuate, revealing how changes in bile circulation can affect the overall system. The sensitivity analysis also shows that increasing bile delay leads to a higher drug toxicity number, meaning that drugs stay longer in the body and can reach harmful levels. Based on this finding, patients with bile excretion problems or delayed enterohepatic circulation should avoid drugs that rely heavily on this recycling process.
Overall, this research is significant because it improves understanding of how bile circulation affects drug safety. It provides a theoretical foundation for designing safer medications, optimizing dosage, and supporting better clinical decisions for patients with liver or bile-related disorders. It also opens new opportunities for future research in pharmacology, toxicology, and mathematical modeling.

1.6 STATEMENT OF THE PROBLEM

The enterohepatic circulation (EHC) is an important process that helps recycle bile acids and certain drugs between the liver and the intestine. This circulation affects how long a drug stays in the body and how it is metabolized. However, when there is a delay in bile flow or when bile excretion is impaired, drugs can accumulate in the system, increasing the risk of toxicity. Most existing pharmacokinetic models do not fully capture these complexities. They often assume that bile circulation happens instantly and overlook the effects of bile delay and saturation kinetics. As a result, such models may fail to predict changes in drug concentration accurately, especially in patients with liver or bile-related disorders. There is also limited knowledge about how different pharmacokinetic parameters affect the stability of the system, the possibility of oscillations in drug concentration, and the overall risk of toxicity. Without this understanding, it becomes difficult to design safe and effective dosing regimens for drugs that undergo enterohepatic recycling. For this reason, it is important to develop a mathematical model that realistically represents the enterohepatic circulation, including the effects of bile delay and saturation kinetics. Such a model can help explain how these factors influence drug levels, system stability, and toxicity, ultimately supporting safer drug development and better clinical decision-making.

1.7 AIM AND OBJECTIVES OF THE STUDY

The aim of the study was to develop a delay nonlinear differential models incorporated with saturation kinetics for enterohepatic circulation with drug reabsorption. The objectives of the study are to:

1. formulate nonlinear delay differential equation models for the study of EHC with drug saturation kinetics and bile delay effect; Two physiological model was established to capture with and without Pathological defect

2. apply mathematical techniques and tools from nonlinear dynamical systems to analyze the formulated model; Hoph bifurcation analysis,

global stability, direction of Hopf Bifurcation,backward bifurcation, local stability and sensitivity analysis.

3. study the delay effect of metabolite on EHC (with and without drug saturation) and investigate EHC efficiency with drug reabsorption number; generate the drug reabsorption number using the Next Generation Matrix

4. carry out sensitivity analysis so as to identify key factors affecting reabsorption of drug and pharmacokinetic parameters such as drug clearance, volume of distribution, half life and plasma concentration profile.

1.8 SCOPE OF STUDY

This study focuses on developing a mathematical model to better understand how enterohepatic circulation, saturation kinetics, and bile delay affect drug behavior in the body. The goal is to explore how changes in bile flow and delayed recycling can influence drug concentration, stability, and toxicity.
The research is mainly theoretical and computational. A system of differential equations is developed to represent how drugs move between the liver, bile, and intestine. The model includes factors such as bile secretion, reabsorption, and saturation effects, as well as a time-delay term to account for the delayed return of bile components to the liver. Several analytical methods are used to study how the system behaves under different conditions. These include local and global stability analysis, Hopf bifurcation analysis, backward bifurcation analysis, and sensitivity analysis. The sensitivity analysis focuses on how pharmacokinetic parameters affect the drug toxicity number, helping to identify which parameters have the strongest influence on toxic effects.
All pharmacokinetic and parameter data used in this study are sourced from DrugBank, a reliable and publicly available drug information database. No experimental or clinical data were collected. Instead, the study relies on mathematical modeling and computer simulations to analyze the system's dynamics.

Overall, the study provides theoretical insights into how bile circulation and delay influence drug toxicity. The findings can help improve drug formulation, guide dosage decisions, and support safer use of drugs—especially for patients with liver problems or bile flow disorders.

1.9 DEFINITION OF ENTEROHEPATIC TERMINOLOGIES

Enterohepatic terminologies encompass pharmacokinetic and physiological parameters that describe drug absorption, distribution, metabolism, elimination, and recycling between the liver, bile, intestine, and systemic circulation. These parameters are essential for understanding drug disposition and for developing pharmacokinetic models involving enterohepatic circulation.

- **Absorption:** The process by which a drug moves from the site of administration into the systemic circulation.
- **Bioavailability (F):** The fraction of an administered dose that reaches the systemic circulation in an unchanged form.
- **Distribution:** The reversible transfer of a drug between the systemic circulation and body tissues.
- **Volume of distribution (Vd):** A theoretical volume that relates the total amount of drug in the body to the plasma drug concentration.
- **Plasma drug concentration (Cp):** The amount of drug present in plasma at a given time.
- **Maximum plasma concentration (Cmax):** The highest plasma concentration attained after drug administration.
- **Time to maximum concentration (Tmax):** The time required to reach Cmax following drug administration.
- **Elimination:** The irreversible removal of a drug from the body through metabolism and excretion.

- **Clearance (CL):** The volume of plasma from which the drug is completely removed per unit time.
- **Half-life ($\mathbf{t_{1/2}}$):** The time required for the plasma concentration of a drug to decrease by 50%.
- **Area under the curve (AUC):** The area under the plasma concentration–time curve, representing total systemic drug exposure.
- **Metabolism (biotransformation):** The enzymatic conversion of a drug into metabolites, primarily occurring in the liver.
- **Excretion:** The removal of a drug or its metabolites from the body, mainly via renal or biliary routes.
- **Steady-state concentration ($\mathbf{C}_{ss}$):** The condition in which the rate of drug administration equals the rate of drug elimination.
- **First-pass metabolism:** The presystemic metabolism of a drug in the liver and intestinal wall following oral administration.
- **Hepatic blood flow ($\mathbf{Q}_h$):** The volume of blood delivered to the liver per unit time, influencing hepatic drug uptake and clearance.
- **Hepatic clearance ($\mathbf{CL}_h$):** The ability of the liver to eliminate drug from the systemic circulation via metabolism and biliary excretion.
- **Biliary excretion rate constant ($\mathbf{k}_{bile}$):** The rate at which drug or drug conjugates are transported from hepatocytes into bile.
- **Bile flow rate ($\mathbf{Q}_{bile}$):** The volume of bile secreted by the liver per unit time, determining drug delivery to the intestine.
- **Gallbladder emptying rate ($\mathbf{k}_{gb}$):** The rate at which bile containing drug is released into the small intestine.
- **Intestinal drug amount ($\mathbf{A}_{int}$):** The quantity of drug present in the intestinal lumen available for reabsorption.

- **Intestinal reabsorption rate constant ($\mathbf{k}_{reabs}$):** The rate at which drug is reabsorbed from the intestine into systemic circulation.
- **Fraction reabsorbed ($\mathbf{f}_{reabs}$):** The proportion of biliary-excreted drug that is reabsorbed from the gastrointestinal tract.
- **Intestinal transit time ($\mathbf{T}_{transit}$):** The time taken for drug to pass through the gastrointestinal tract, influencing the extent of reabsorption.
- **Gut wall metabolism ($\mathbf{CL}_{gut}$):** The metabolic clearance of drug by intestinal enzymes prior to systemic re-entry.
- **Enterohepatic recycling fraction (FER):** The fraction of the administered dose that undergoes enterohepatic circulation.
- **Bacterial hydrolysis rate constant ($\mathbf{k}_{bact}$):** The rate at which intestinal microflora deconjugate drug metabolites back to the parent drug.
- **Fecal excretion rate constant ($\mathbf{k}_{f}$):** The rate at which drug is eliminated via feces without reabsorption.

Chapter 2

LITERATURE REVIEW

Enterohepatic circulation (EHC) plays a vital role in EHC drugs, as it influences drug pharmacokinetics by decreasing drug clearance and influence plasma concentration of drugs, necessitating specialized models for accurate analysis. Several models have been formulated to investigate the dynamics of EHC process for drugs like Phenytoin. In this section,we shall consider some of the resent articles on the subject.

Hassan (2021) Formulated a three-compartment model incorporated with drug re-absorption parameter. His work demonstrating local asymptotic stability under certain conditions. His model is given as :

$$\frac{dX_1(t)}{dt} = D_1 - (k_{10} + k_{12} + k_{13})X_1(t) + k_{21}X_2(t-\tau_1) + k_{31}X_3(t-\tau_2) \tag{2.1}$$

$$\frac{dX_2(t)}{dt} = D_2 - k_{21}X_2(t-\tau_1) + k_{20}X_2(t) + k_{12}X_1(t) \tag{2.2}$$

$$\frac{dX_3(t)}{dt} = D_3 - k_{31}X_3(t-\tau_2) - k_{30}X_3(t) + k_{13}X_1(t) \tag{2.3}$$

His findings showed that time delays used as lags in re-absorption of drugs by central compartment from other two compartment causes rebounds or peaks and fluctuations in the time profiles for amounts of drug in all compartments.

Ibarra (2021) proposed deterministic pharmacokinetic model that captures enterohepatic and enterogastric circulation and compare their respective impact on primary pharmacokinetic parameters, with enterohep-

atic reabsorption (EHR) and enterogastric reabsorption(EGR) models.

$$\frac{dA_c}{dt} = k_a A_G + k_{hc} A_H - (k_{ch} + k_{cg} + k_r) A_C \tag{2.4}$$

$$\frac{dA_H}{dt} = k_{ch} A_C + k_{gh} A_G - (k_{hc} + k_{hb} + k_h) A_H \tag{2.5}$$

$$\frac{dA_G}{dt} = k_{cg} A_C + b(t) - (k_a + k_{gh} + k_g) A_G \tag{2.6}$$

$$\frac{dA_c}{dt} = k_{hb} A_H - b(t) \tag{2.7}$$

$$\frac{dA_c}{dt} = k_a A_G + k_{hc} A_H - (k_{ch} + k_{cg} + k_r) A_C \tag{2.8}$$

$$\frac{dA_H}{dt} = k_{ch} A_C + k_{gh} A_G + k_{sh} A_S - (k_{hc} + k_h) A_H \tag{2.9}$$

$$\frac{dA_S}{dt} = k_{cs} A_C - (k_{sc} + k_{sh} + k_s) A_S \tag{2.10}$$

$$\frac{dA_G}{dt} = k_{cg} A_C + s(t) - (k_a + k_{gh} + k_g) A_G \tag{2.11}$$

$$\frac{dA_{sl}}{dt} = k_s A_S - s(t). \tag{2.12}$$

His findings indicated that the magnitude of drug enterohepatic reabsorption is positively correlated with the volume of distribution, regardless of drug characteristics. Further, drug enterohepatic reabsorption can decrease the systemic clearance of drugs eliminated mainly through hepatic metabolism. In these cases, a greater impact is expected for drugs showing low hepatic extraction. For renally cleared drugs, no significant impact is expected. Finally, the oral bioavailability of drugs with high liver extraction could result increased following an increase in the extent of reabsorbed drug.

Ramanmoorthy (2021) designed a bio-compartmental model of enterohepatic circulation,which estimated the concentration of bile acid in different compartment.The model estimates various clinical manifestations of gallbladder and intestine describing the variable concentration of the bile acid.

$$\frac{dx_3}{dt} = k_g x_2 - (k_b + k_{e3}) x_3$$

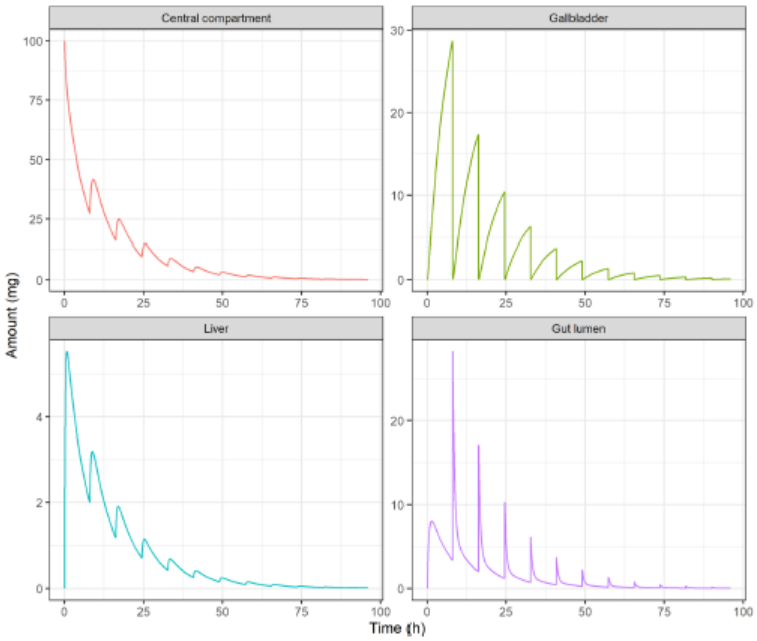


Table 2.1: Simulation of EHC Compartment

$$\frac{dx_1}{dt} = -(k_i + k_{ie})x_1 + k_b x_3 + k_l A_C$$

It was established that bile acid concentration in different pathological conditions alters the physiology of enterohepatic circulation.
Dengra et al., 2021 formulated a new physiological mathematical model, which includes the three most important factors in brain delivery (barrier transport, the disposition within the brain and drug–brain binding) and is able to predict brain concentration levels in rats for different drugs, has been developed.

$$V_d\frac{dC_p}{dt} = K_a A - PS_{BBBin}.C_{u,p} + PS_{BBBout}C_{u,p} - PS_{BCSFBin}C_{u,p} + PS_{BCSFout}C_{CSF} + Q_{sink}C_{CFS} - k_{el}C_p V_d$$

$$V_b\frac{dC_b}{dt} = PS_{BBBin}.C_{u,p} - PS_{BBBout}C_{u,p} - Q_{bulk}C_{u,b}$$

$$V_{CSF}\frac{dC_{CSF}}{dt} = PS_{BCSFBin}C_{u,p} - PS_{BCSFBout}C_{CSF} - Q_{sink}C_{CFS} + Q_{bulk}C_{u,b}$$

$$\frac{dA}{dt} = -K_a A.$$

They established that the physiologically based pharmacokinetic model (PBPK), incorporating the barrier resistance to transport, the disposition within the brain and the drug-brain binding combined with MDCK data, provided the best predictions for passive diffusion and carrier mediated transported drugs, while in the other cell lines, active transport influence can bias prediction.

Franchetti (2019) developed a physiologically based pharmacokinetic (PBPK) model consisting of seven compartment for intravenously administered erythromycin, incorporating transporter and cytochrome P450(CYP3A4) clearance in hepatic compartments . The model leverages on 14CO2 production rates from the erythromycin breath test to assess different nonrenal elimination route. The formulated model is given by:

$$\frac{dC_{LG}}{dt} = \frac{1}{V_{LG}}[Q_{Total}(C_{vein} - \frac{C_{LG}}{P_{LGP}/P_{BLP}}) - Q_{Total}(\frac{C_{LG}}{P_{LGP}/P_{BLP}} - C_{Art})]$$

$$\frac{dC_{vein}}{dt} = \frac{1}{V_{vein}}[Q_{kd}(\frac{C_{KD}}{P_{KDP}/P_{BLP}} - C_{vein}) + Q_{LV}C_{LV} +$$

$$Q_{OT}(\frac{C_{OT}}{P_{OTP}/P_{BLP}} - C_{vein}) - Q_{Total}(C_{vein} - \frac{C_{LG}}{P_{LGP}/P_{BLP}})]$$

$$\frac{dC_{OT}}{dt} = \frac{1}{V_{OT}}[Q_{OT}(C_{Art} - \frac{C_{OT}}{P_{OTP}/P_{BLP}}) + Q_{OT}(a\frac{C_{OT}}{P_{OTP}/P_{BLP}} - C_{vein})$$

$$-\mu C_{OT}]$$

$$\frac{dC_{KD}}{dt} = \frac{1}{V_{KD}}[Q_{KD}(C_{Art} - \frac{C_{KD}}{P_{KDP}/P_{BLP}}) - Q_{KD}(\frac{C_{KD}}{P_{KDP}/P_{BLP}} - C_{vein}) -$$

$$\delta_e GFR\frac{f_{uBL}C_{KD}}{P_{KDP}/P_{BLP}} - \frac{V_{Max,OUT1,KD}(\frac{f_{uBL}C_{KD}}{P_{KDP}/P_{BLP}})}{K_{m,OUT1,KD}+(\frac{f_{uBL}C_{KD}}{P_{KDP}/P_{BLP}})}]$$

$$\frac{dC_{ES}}{dt} = \frac{1}{V_{ES,eff}}[Q_{LV,Art}C_{Art} - Q_{LV,Vein}\frac{C_{ES}}{P_{ESP}/P_{BLP}} -$$

$$Q_{ES-LC,LV}(\frac{f_{u,ES}C_{ES}}{P_{ESP}} - \frac{f_{u,LC}C_{LC}}{P_{LCP}}) - \frac{V_{Max,UP1,ES}(\frac{f_{uBL}C_{ES}}{P_{ESP}})}{K_{m,UP1,ES}+(\frac{f_{uBL}C_{ES}}{P_{ESP}})}]$$

$$\frac{dC_{LC}}{dt} = \frac{1}{V_{LC}}[\frac{V_{Max,UP1,ES}(\frac{f_{uBL}C_{ES}}{P_{ESP}})}{K_{m,UP1,ES}+(\frac{f_{uBL}C_{ES}}{P_{ESP}})} + Q_{ES-LC,LV}(\frac{f_{u,ES}C_{ES}}{P_{ESP}} - \frac{f_{u,LC}C_{LC}}{P_{LCP}}) -$$

$$\frac{V_{Max,OUT11,LC}(\frac{f_{u,}C_{LC}}{P_{LCP}})}{K_{m,UP1,LC}+(\frac{f_{u,}C_{LC}}{P_{LCP}})} - \frac{V_{Max,OUT21,LC}(\frac{f_{u,}C_{LC}}{P_{LCP}})}{K_{m,UP1,LC}+(\frac{f_{u,}C_{LC}}{P_{LCP}})} - CL_{CYP}f_{uLC,}\frac{C_{LC}}{P_{LCP}}$$

$$\frac{dC^{**}_{LC}}{dt} = \frac{1}{V_{LC}}[CL_{CYP}f_{uLC}\frac{C_{LC}}{P_{LCP}}] - (k_{pool1} + k_{resp})C^{**}_{LC} + k_{pool2}C^{*}_{poolBL}$$

His findings showed that activity of non renal elimination pathway can be estimated within individual study subjects with a single probe drug.

Model reveal reasonable accord with observed epithelial lining fluid to plasma concentration ratios for erythromycin.

Guzev (2021), proposed a mathematical model to describe drug cytotoxicity of leukemic cells with melphalan, chloraambucil and cytarabine. Their model consist of three compartment; amount of living cell A , amount of dead cells A_d and concentration of cytotoxic adminstered drug (C) .

$$\frac{dA}{dt} = rA(1 - \frac{A}{K}) - \mu_A AA_d - \frac{\mu_{AC} AC}{a + C} \tag{2.13}$$

$$\frac{dA_d}{dt} = \mu_A AA_d - dA_d + \frac{\mu_{AC} AC}{a + C} \tag{2.14}$$

$$\frac{dC}{dt} = -\mu_C C - \frac{\mu_{CA} AC}{a + C} \tag{2.15}$$

Their findings indicated that Cytarabine is the most effective drug amongst those tested in killing A20 leukemic cells.

Fischer (2022), formulated a two compartment mathematical model of intestinal epithelium population dynamics that incorporates a known feedback inhibition of stem cells differentiation by differentiated cells. Their model consists of two cell compartments $S(t)$ and $D(t)$, denoting stem cells, and differentiated cells,respectively.

$$\frac{dS(t)}{dt} = \beta S(t) - \delta(D)S(t)$$

$$\frac{dD(t)}{dt} = \delta(D)S(t) - \varpi D(t)$$

His findings indicated that feedback regulation stabilizes the number of differentiated cells as these becomes invariant to changes in their apoptosis rate.

Peletier (2017) explore the impact of saturable distribution over the central and the peripheral compartment in pharmacokinetic models, whilst assuming that back flow into the central compartiment is linear.

$$\frac{dA_1}{dt} = q - k_a A_1 \tag{2.16}$$
$$V_2 \frac{dC_2}{dt} = k_a A_1 - k_{20} A_2 - H k_p A_2 + k_P A_3 \tag{2.17}$$
$$V_3 \frac{dC_3}{dt} = H k_p A_2 - k_P A_3 \tag{2.18}$$
$$\frac{dA_1}{dt} = q - k_a A_1 \tag{2.19}$$
$$\frac{dA_2}{dt} = k_a A_1 - k_{20} A_2 - B_{max} k_p \frac{A_2}{K_M + A_2} + k_p A_3 \tag{2.20}$$
$$\frac{dA_3}{dt} = B_{max} k_p \frac{A_2}{K_M + A_2} - k_p A_3 \tag{2.21}$$
$$\tag{2.22}$$

His findings pinpointed the relevance of considering saturable processes and membrane transport in pharmacokinetic modeling to precisely predict drug efficacy, toxicity, and optimal dosing strategies, particularly in complex clinical situations.

Stein et al (2018), derived a simple expression for C_{crit} for models involving linear and nonlinear (saturable) clearance,such as michealis Menten and target-mediated drug disposition (TMDD) models.

$$\frac{dC}{dt} = -k_{on} C.R + k_{off} CR - k_{e(C)} C \tag{2.23}$$
$$\frac{dR}{dt} = k_{syn} - k_{on} C.R + k_{off} CR - k_{e(R)} R \tag{2.24}$$
$$\frac{dR}{dt} = k_{on} C.R - k_{off} CR - k_{e(CR)} CR \tag{2.25}$$

Their findings indicated that when developing antagonists, it is often the goal to pick a dosing regimen where the drug concentration stays above C_{crit}.

Wagner et al. (1985) build a deterministic model consisting of four peripheral compartment, gallbladder compartment, intestinal compartment and liver compartment.Their aim was to investigate bile

acid recycling. The formulated model is shown below:

$$\frac{dAp}{dt} = -k_e A_p - k_b A_p + k_r A_g \tag{2.26}$$

$$\frac{dA_g}{dt} = k_b A_p - k_r A_g - k_f A_g \tag{2.27}$$

$$\frac{dA_i}{dt} = k_f A_g - k_a A_i \tag{2.28}$$

$$\frac{dA_l}{dt} = k_a A_i - k_b A_l \tag{2.29}$$

Their findings indicated that enterohepatic circulation prolongs drug half-life and increases bioavailability.

Yang et al. (2013), proposed a physiological base pharmacokinetic model with enterobacteria. Their model consist of two compartment: conjugate drug amount and unconjugated drug amount. Their model is as follows

$$\frac{dA_c}{dt} = k_c A_i i - (k_d + k_{abs}) A_{cd} \tag{2.30}$$

$$\frac{dA_u}{dt} = k_d A_c \tag{2.31}$$

Their findings showed that antibiotics reduce enterohepatic circulation and lower plasma drug levels.

Müller et al.(2021), derived a deterministic model to study the dynamics of nanoparticle-mediated enterohepatic circulation. Their model is given below

$$\frac{dA_t}{dt} = k_{rel} A_n - k_{clear} A_n \tag{2.32}$$

$$k_{clear} = k_{per} e^{-\lambda t} \tag{2.33}$$

Their findings indicated that mucoadhesive nanoparticles delay gastrointestinal residence, enhancing reabsorption.

Mudra et al., (2011), formulated a non compartmental disease state enterohepatic circulation model.The formulated model consist of serum bile acid concentration (SRM) and Cholestasis sensitivity parameter

(Υ). The model is as follows

$$k_b = k_{b,normal} e^{-\Upsilon} BSA \tag{2.34}$$

Their findings showed that cholestasis reduces biliary secretion by seventy to ninety percent.

Charman et al. (1996), formulated a deterministic model to investigate the role of lymphatic absorption in EHC.

$$\frac{dA_{lymph}}{dt} ce = k_{lymph} SAC_{lumen} \tag{2.35}$$

Their findings showed that lymphatic kinetics bypasses first-pass metabolism, enhancing bioavailability.
Li et al., 2016 build a deterministic model linking cellular transporter dynamics to whole-body pharmacokinetic. Their model comprises of one compartment. Below is their model:

$$MRPS2(t) = MRP2_0 + A.cos(\frac{2\pi}{24}(t - \phi) \tag{2.36}$$

$$\frac{dA_b}{dt} = k_{sec}.MRPS2(t).A_l \tag{2.37}$$

Their findings indicated that MRP2 peak expression at night spurs biliary excretion by thirty percent.

2.1 CORE INTEREST OF OUR STUDY

After critical review of relevant literature, it was observed that first order kinetics (linear), though realistic for non enterohepatic drug lacks the physiological merit as in the case of drug saturation and metabolism. Also, the case of physiological factor (ageing, pathological defect) as it relate to enterohepatic process is silent among pharmacokinetic researcher. Hence, the core objective of this research is to formulate a delay non linear differential equation that captures drug saturation and bile delay effect. We employ relevant mathematical tools and methods to analyze the models with the sole aim of understanding the dynamics of EHC processes in the presence and absence of pathological defect.

Chapter 3

FORMULATION OF EHC MODEL WITH PATHOLOGICAL DEFECT AND NON -LINEAR KINETICS

The proposed model consists of five physiological: Amount of drug in central compartment (A_c), Amount of drug in hepatocyte compartment (A_h), Amount of drug in kidney compartment (A_k), Amount of drug in gastrointestinal compartment (A_g) , Amount of drug in gall bladder compartment (A_g). And six non physiological compartment: Amount of drug in fluid compartment of the brain (A_{t1}), Amount of drug in tissue compartment of the brain (A_{t1}), Amount of drug in portal vein (A_{pv}), amount of drug in urine (A_u), amount of drug saturated by enzymes in the liver (E_h), amount of drug saturated by enzymes in gastrointesinal tract (E_g).The drug ingested at rate D is absorbed into the gastrointestinal mucosa at a rate $F_a D_i k_a e^{-k_a \theta_1}$, which is sustained by drug in the gallbladder and central compartment with drug transference rate $f(\theta)\lambda_{hb}$ and λ_{cg} respectively. Drug is eliminated from the blood stream at an hepatic uptake rate λ_{gh}. Further elimination occur at a rate k_g. The drug eliminated from the GI tract enters the central compartment at rate k_a. The metabolite formed as result of drug saturated enzyme are transported by P-glycoprotein at a nonlinear rate $\lambda_{hc}, \lambda_{hb}$ to the central compartment and gallbladder respectively. Bile salt, bilirubin, Cholesterol, metabolite are stored at rate ϕ in the gallbladder. Drug is eliminated to the kidney(renal) and portal vein from the central compartment at rate k_r and k_{pv}. respectively. The enterocyte and hepatocye enzymes are saturated with drug at rate k_{cath} and k_{catg} respectively. The delay parameters τ_1 *and* τ_2 accounts for prolong therapeutic effect and exposure of metabolite respectively.

$$\begin{aligned}\frac{dA_c}{dt} =& k_a A_g\left(t-\tau_1\right)+\lambda_m^{hc} A_h-\lambda_m^{ch} A_c-\lambda_m^{cg} A_c. \\ & -\left(k_r+k_{pv}\right) A_c-k_t A_c.\end{aligned}$$

$$
\begin{aligned}
\frac{dA_h}{dt} &= \lambda_m^{ch} A_c + \lambda_m^{gh} A_g - \lambda_m^{hb} A_h\left(t-\tau_2\right) - \lambda_m^{hc} A_h \\
&\quad - k_h A_h - \frac{k_{cath} f_u^h A_h}{k_{m1}} \\
\frac{dA_b}{dt} &= \lambda_m^{hb} A_h\left(t-\tau_2\right) - (\lambda_m^{bg} - \phi) A_b \\
\frac{dA_g}{dt} &= \lambda_m^{cg} A_c - \lambda_m^{gh} A_g - \tilde{Q} f_u A_g - k_a A_g\left(t-\tau_1\right) - k_g A_g - \\
&\quad - \frac{k_{catg} f_u^g A_g}{k_{m2}} + G(\theta_1) + \lambda_m^{bg} A_b \\
\frac{dA_{t1}}{dt} &= k_t A_c - k_{t1} A_{t1} + k_{t2} A_{t2}
\end{aligned}
$$

$$
\frac{dA_{t2}}{dt} = k_{t1} A_{t1} - k_{t2} A_{t2} \tag{3.1}
$$

$$
\begin{aligned}
\frac{dA_{pv}}{dt} &= k_{pv}(A_c - A_{pv}) + \tilde{Q} f_u A_g \\
\frac{dA_k}{dt} &= k_r A_c - \sigma_2 A_k \\
\frac{dA_u}{dt} &= \sigma_2 A_k - \varepsilon A_u \\
\frac{dE_h}{dt} &= \frac{k_{cath} f_u^h A_h}{k_{m1}} - k_{degh} E_h \\
\frac{dE_g}{dt} &= \frac{k_{catg} f_u^g A_g}{k_{m2}} - k_{degg} E_g.
\end{aligned}
$$

$$
\lambda_m^{ch} = \frac{V_m^{ch} f_u^{ch}}{k_m^{ch} + A_c},\ \lambda_m^{bg} = \frac{V_m^{bg} f_u^{bg}}{k_m^{bg} + A_b} f(\theta),\ \lambda_m^{hb} = \frac{V_m^{hb} f_u^{hb}}{k_m^{hb} + A_h}
$$

$$
\lambda_m^{hc} = \frac{V_m^{hc} f_u^{hc}}{k_m^{hc} + A_{hc}},\ \lambda_m^{gh} = \frac{V_m^{gh} f_u^{gh}}{k_m^{gh} + A_g},\ \lambda_m^{cg} = \frac{V_m^{cg} f_u^{cg}}{k_m^{cg} + A_c}
$$

flow of metabolite from liver to gallbladder (λ_m^{hb}),drug transference from gallbladder to gut (λ_m^{bg}),drug transference from central compartment to gut and liver λ_m^{cg} and λ_m^{ch} respectively,
flow of metabolite from liver to central compartment(λ_m^{hc}),flow of metabolite from gut to liver (λ_m^{gh}).

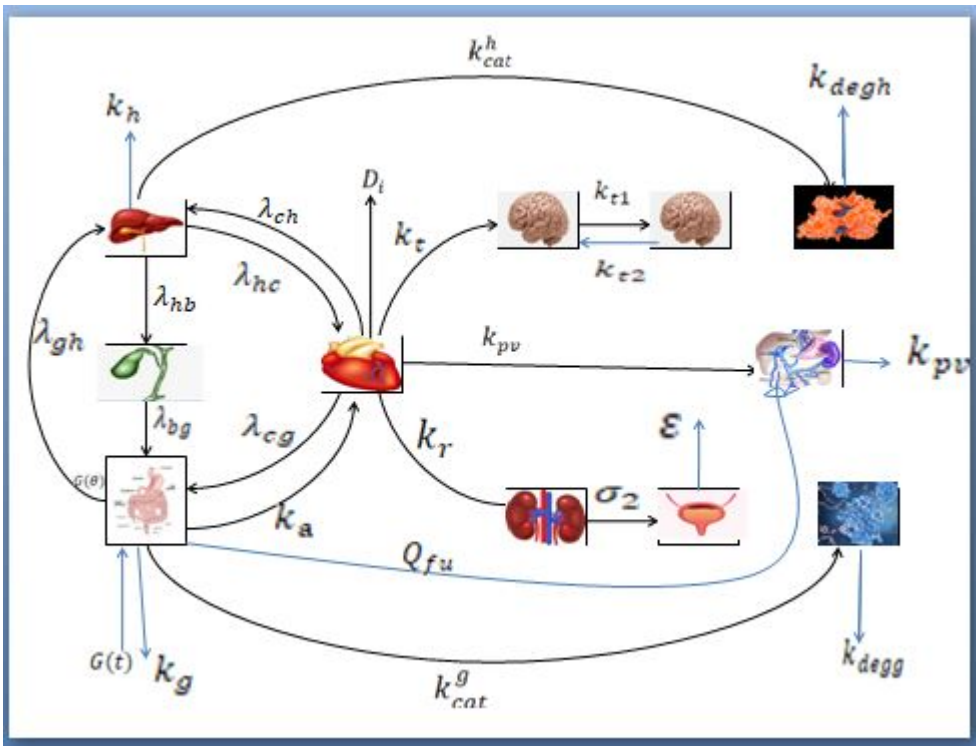


Figure 3.1: Schematic Representation of the Model

VARIABLES	DESCRIPTION
A_c	Amount of drug in central compartment
A_h	Amount of drug in hepatocyte compartment
A_g	Amount of drug in Gut Compartment
A_b	Amount of drug in Gallbladder compartment
E_g	Amount of drug saturated by Enzymes in Gut
E_h	Amount of drug saturated in hepatocytes
A_{pv}	Amount of drug of drug in portal Vein
A_k	Amount of drug in kidney
A_u	Amount of drug in urine
A_{t1}	Amount of drug in vascular space of tissue
A_{t2}	Amount of drug in interstitial space of tissue

Table 3.1: Description of State variables of EHC model

Parameters	Description
k_a	drug absorption from the gut to central compartment
$k_{g,deg}$	elimination by gut
$k_{h,deg}$	elimination by hepatocyte
$k_{g,b}$	binding rate and dissociation from gut
$k_{h,b}$	binding rate and dissociation from hepatocyte
ϕ	Residual bile rate
a_1	maximum transport rate
k_{mg}	Michealis constant of half v_{maxg}
k_{mh}	Michealis constant of half v_{maxh}
Q_g	membrane permeability of the drug
v_{maxh}	velocity of drug elimination from the hepatocyte
v_{maxg}	maximum velocity of drug elimination from the gut
f_{ug}	fraction of unbound drug in gut
f_{uh}	fraction of unbound drug in hepatocyte
F_a	fraction of dose absorbed from lumen
τ_1, τ_2	pathological defect parameters
$f(\theta)$	gallbladder emptying rate
$G(\theta_1)$	force of oral administration
D	drug dose
k_t	flow rate of drug from central to fluid compartment
k_{t1}	rate of drug flow from fluid to tissue
k_{t2}	rate of drug flow from tissue to fluid

Table 3.2: Description of Paramters of EHC Model

3.1 MODEL ANALYSIS

It is imperative to investigate the robustness of the model before simulation. This is attainable by carrying out some qualitative analysis on system one as follows.

Lemma 3.1 *: The close set*

$$\delta = \{(A_c, A_h, A_b, A_g, A_{t1}, A_{t2}, A_{pv}, A_k, A_u, E_h, E_g)\, \varepsilon R_+^{11} : A_c + A_h +$$

$$A_b + A_g + A_{t1} + A_{t2} + A_{pv} + A_k + A_u + E_h + E_g \leq \frac{F_a D k_a e^{-k_a \theta_1}}{K_T}\}$$

is positively invariant and attracting with respect to the model.

Proof.

Adding all the equations in the model gives

$$\frac{dA_T}{dt} = F_a D k_a e^{-k_a\theta_1} - k_t A_T \tag{3.2}$$

Where A_T = total amount of drug, k_t=total elimination rate of drug

$$A_T(t) = \frac{F_a D k_a e^{-k_a t}}{k_t} + Ae^{-k_t t} \tag{3.3}$$

Further simplification of (**??**) with initial condition $A_T(t_0) = A_T(0)$,implies

$$A_T(t) = \frac{F_a D k_a e^{-k_a\theta_1}}{k_t}(1 - e^{-k_t t}) + A_t(0)e^{-k_t t} \tag{3.4}$$

$A_T(t) \leq \frac{F_a D k_a e^{-k_a\theta_1}}{k_t}$ if $A_t(0) \leq \frac{F_a D k_a e^{-k_a\theta_1}}{k_t}$, thus δ is positively invariant. Further, if $A_T(t) > \frac{F_a D k_a e^{-k_a\theta_1}}{k_t}$,then either the solution enters δ in a finite time or $A_T(t)$ approaches $\frac{F_a D k_a e^{-k_a\theta_1}}{k_t}$ and the variables $A_c, A_h, A_b, A_g, A_{t1}, A_{t2}, A_{pv}, A_k, A_u, E_h, E_g$ approaches zero. Hence, δ is attracting that is all solution in R_+^{11} eventually enters δ. Thus, the model is well posed mathematically. Hence, the model is sufficient to study the pharmacokinetic of drug *reabsorption with compartment delay and nonlinear kinetics effect.*

3.1.1 Existence and Stability Of Equilibria.

In view of model (**??**), the stability of trajectories is analyze on three steady state. The drug free state(DFE), Toxic Equilibrium (TEE), Drug Saturation Equilibrium(DSE) and Drug Reabsorption Free equilibrium (DRFE).

3.1.1.1 Drug free equilibrium (DFE).

When the drug is administered orally, its residence rate at GIT tract is $\frac{F_a D k_a e^{-k_a\theta_1}}{K_T}$, as $t \to \infty$,for $k_T > 0$, the drug feasile out of the body, leaving each compartment with no drug.Hence the steady state becomes

$$\pi^o = (A_c, A_h, A_b, A_g, A_{t1}, A_{t2}, A_{pv}, A_k, A_u, E_h, E_g) = (0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$$

The next generation matrix operator method proposed by Van den Driessche and Watmough (2002) can be used to ascertain the linear stability of system (**??**). The matrices V (for drug transference) and F (drug toxicity)

$$V = \begin{bmatrix} k_1 & 0 & 0 & -k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -k_t & 0 & 0 & 0 & k_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & k_6 & 0 & 0 & 0 & 0 & 0 \\ -k_{pv} & 0 & 0 & -L_1 & 0 & 0 & k_7 & 0 & 0 & 0 & 0 \\ -k_r & 0 & 0 & 0 & 0 & 0 & 0 & k_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\sigma_2 & k_9 & 0 & 0 \\ 0 & -L_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{10} & 0 \\ 0 & 0 & 0 & -L_3 & 0 & 0 & 0 & 0 & 0 & 0 & k_{11} \end{bmatrix};$$

$$F = \begin{bmatrix} 0 & v_{hc}f_{hc} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & v_{gh}f_{gh} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & v_{hb}f_{hb} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix};$$

$$\chi_d = \rho(FV^{-1}) = \frac{f_{hc}f_{ch}v_{ch}v_{hc}k_3k_4 + \sqrt{k_3k_4(H_1 + H_2)}}{k_1k_2k_3k_4}$$

Where $k_1 = k_r + k_{pv} + k_t$, $k_2 = k_h + \frac{k_{cat} f_{uh}}{k_{mh}}$, $k_3 = f(\theta)v_{bg} - \phi$, $k_4 = k_a + k_g + \frac{k_{cat} f_{ug}}{k_{mg}}$,.

$H_1 = 4f_{bg}f_{gh}f_{hb}k_1^2 k_2 f(\theta)v_{bg}v_{gh}v_{hb}$

$H_2 = 4f_{cg}f_{gh}f_{hc}k_1 k_2 k_3 v_{cg}v_{gh}v_{hc} + f_{hc}^2 f_{ch}^2 k_3 k_4 v_{ch}^2 v_{hc}^2$

ρ = Spectral radius.

Next,compute the determinant of the system at DFE,gives

$$k_1 k_2 k_3 k_4 k_5 k_6 k_7 k_8 k_9 k_{10} k_{11}(1 - \chi_d) \tag{3.5}$$

: The drug free equilibrium is locally and asymptotically stable if χ_d and unstable if χ_d>1. The threshold χ_d is the drug reabsorption number. It is the potential secondary toxicity in the systemic circulation when a drug is administered orally or intravenously. The pharmacological implication of **??** is that drug toxicity induced by drug saturation in the absence of pathological defect can be effectively managed (or eliminated) from the body ($\chi_d < 1$) if the initial dose of drug of the model are in the basin of attraction . Beyond the initial dose of the drug in the compartmental model, drug toxicity can be effectively controlled.

Theorem 3.1 *Drug free equilibrium (π^o), of the model* (**??**) *is globally asymptotically stable if* $\chi_d < 1$.

Proof

Consider the Lyapunov function

$$V(t) = A_c(t) + Q_1 A_h(t) + Q_2 A_b(t) + Q_3 A_g(t) \tag{3.6}$$

where

$$Q_1 = \frac{(l_{hc} + l_{hb})k_1}{k_2 l_{ch}}$$

$$Q_2 = \frac{\chi_d k_1}{l_{ch}}$$

$$Q_3 = \frac{\chi_d k_1}{l_{ch}}$$

Next, differentiate (**??**) with respect to time(t),

$$\frac{dV(t)}{dt} = \frac{dA_c}{dt} + Q_1\frac{dA_h}{dt} + Q_2\frac{dA_b}{dt} + Q_3\frac{dA_g}{dt}$$

$$\frac{dV(t)}{dt} = k_a A_g + l_{hc}A_h - k_1 A_c + \frac{(l_{hc}+l_{hb})k_1}{k_2 l_{ch}}(l_{ch}A_c + l_{bg}A_g - k_2 A_h)$$
$$+ \frac{\chi_d k_1}{l_{ch}}(l_{hb}A_h - k_3 A_b) + \frac{\chi_d k_1}{l_{ch}}(l_{cg}A_c + k_3 A_b - k_4 A_g)$$

$$= k_a A_g - k_4 A_g\frac{k_1}{l_{ch}} + l_{hc}A_h + \frac{k_1\chi_d l_{hb}}{l_{ch}}A_h + \frac{k_1}{l_{ch}}l_{cg}A_c - k_1 A_c \tag{3.7}$$

Simplifying (**??**),gives

$$\frac{dV(t)}{dt} = (1-\frac{k_4 k_1}{k_a l_{ch}}\chi_d)k_a A_g + (1+\frac{k_1 l_{hb}}{l_{ch}l_{hc}}\chi_d)l_{hc}A_h + (\frac{k_1 l_{cg}}{k_1 l_{ch}}\chi_d - 1)k_1 A_c \tag{3.8}$$

applying the ratio test condition,drug transference from central compartment to hepatocyte $\frac{l_{ch}}{k_1} = 1$,also from central compartment to gut $\frac{l_{cg}}{k_1} = 1$, $\frac{l_{hb}}{l_{hc}} = -1$,since total efflux rate k_2 is not defined. Substitute into (11),gives

$$\frac{dV(t)}{dt} \leq (\chi_d - 1)k_a A_g + (\chi_d - 1)l_{hc}A_h - (\chi_d - 1)k_1 A_c$$

$$\frac{dV(t)}{dt} \leq (\chi_d - 1)[k_a A_g + l_{hc}A_h - k_1 A_c] \tag{3.9}$$

by definition

$$\dot{A_c}(t) = k_a A_g + l_{hc}A_h - k_1 A_c$$

substitute into (**??**),gives

$$\frac{dV(t)}{dt} \leq (1-\chi_d)\dot{A_c}(t) \tag{3.10}$$

If $\chi_d \leq 1$, $V(t) \leq 0$, with $V(t) = 0$, iff $A_g = A_h = A_c = A_b = 0$. One can deduce from the LaSalle's Invariance Principle (Gumel, (2015)), that every solution to the equations in (**??**) with initial conditions in δ converge to π^o as $t \to \infty$.Hence $(A_g, A_h, A_c, A_b) \to (0, 0, 0, 0)$ .so that the DFE, χ_d is GAS in δ if $\chi_d \leq 1$ as $t \to \infty$.The pharmacological implication is that $\chi_d \leq 1$, is a necessary and sufficient condition for the elimination of drug or control of drug reabsorption.

3.1.2 Toxicity Equilibrium (TES)

At the drug toxicity state it is assumed that the force of circular influx of EHC drug are of equal magnitude in EHC compartment, that is $\lambda_{gh} = \lambda_{hb} = \lambda_{bg} = \lambda_{hc} = \lambda_{EHC}$. Hence system (**??**), re-cast into

$$\begin{aligned}
\frac{dA_c}{dt} &= k_a A_g + \lambda_{EHC} A_h - k_1 A_c.. \\
\frac{dA_h}{dt} &= \lambda_{CT} A_c + \lambda_{EHC} A_g - k_2 A_h \\
\frac{dA_b}{dt} &= \lambda_{EHC} A_h - k_3 A_b \\
\frac{dA_g}{dt} &= \lambda_{CT} A_c + \lambda_{EHC} A_b - k_4 A_g + G(\theta_1) \\
\frac{dA_{t1}}{dt} &= k_t A_c - k_{t1} A_{t1} + l_{t2} A_{t2} \\
\frac{dA_{t2}}{dt} &= l_{t1} A_{t1} - k_{t2} A_{t2} \qquad (3.11) \\
\frac{dA_{pv}}{dt} &= k_{pv}(A_c - A_{pv}) + \tilde{Q} f_u A_g \\
\frac{dA_k}{dt} &= k_r A_c - \sigma_2 A_k \\
\frac{dA_u}{dt} &= \sigma_2 A_k - \varepsilon A_u \\
\frac{dE_h}{dt} &= \frac{k_{cath} f_u^h A_h}{k_{m1}} - k_{degh} E_h \\
\frac{dE_g}{dt} &= \frac{k_{catg} f_u^g A_g}{k_{m2}} - k_{degg} E_g.
\end{aligned}$$

Solving system (**??**),setting the derivatives to zero,gives

$$A_c^{**} = \frac{F_a k_2 k_3}{(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)}$$

$$A_h^{**} = \frac{\lambda_{CT} F_a k_3}{(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)} -$$

$$\frac{\lambda_{EHC} F_a k_3 (\lambda_{EHC}\lambda_{CT} - k_1 k_2)}{(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)}$$

$$A_b^{**} = \frac{\lambda_{EHC}\lambda_{CT} F_a}{(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)} -$$

$$\frac{\lambda_{EHC}^2 F_a (\lambda_{EHC}\lambda_{CT} - k_1 k_2)}{(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)}$$

$$A_g^{**} = \frac{F_a k_2 k_3 (\lambda_{EHC}\lambda_{CT} - k_1 k_2)}{(k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2) - (\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2)}$$

$$A_u^{**} = \frac{F_a k_2 k_3 k_r}{[(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)]k_9$$

$$A_k^{**} = \frac{F_a k_2 k_3 k_r}{[(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)]k_8$$

$$E_h^{**} = \frac{k_{cat} f_u^h}{k_{m1} k_{10}} [\frac{\lambda_{EHC} F_a k_3 (\lambda_{EHC}\lambda_{CT} - k_1 k_2)}{(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda^2}$$

$$\frac{\lambda_{EHC} F_a k_3 (\lambda_{EHC}\lambda_{CT} - k_1 k_2)}{(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)}]$$

$$E_g^{**} = \frac{k_{cat} f_u^g}{k_{m2} k_{11}} [\frac{F_a k_2 k_3 (\lambda_{EHC}\lambda_{CT} - k_1 k_2)}{(k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2) - (\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} -$$

$$A_{pv}^{**} = \frac{1}{k_7} [\frac{F_a k_2 k_3 k_{pv}}{(\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2) - (k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2)}$$

$$\frac{Q f_u F_a k_2 k_3 (\lambda_{EHC}\lambda_{CT} - k_1 k_2)}{(k_2 k_3 \lambda_{CT} + \lambda_{CT}\lambda_{EHC}^2)(k_a k_2 + \lambda_{EHC}^2) - (\lambda_{EHC}^3 - k_2 k_3 k_4)(\lambda_{EHC}\lambda_{CT} - k_1 k_2)}]$$

.

Next,we investigate the existence of Drug saturation equilibrium point with respect to drug reabsorption incidence function ,using the the ratio condition for toxicity,

$$\frac{A_c}{A_c^{**} + A_h^{**} + A_b^{**} + A_g^{**}} = \chi_d \tag{3.12}$$

Simplifying (**??**),gives

$$\lambda_{EHC}^2 - \lambda_{EHC} k_3 - k_2 k_3 + (1 - \chi_d)\frac{k_3}{k_1} = 0 \tag{3.13}$$

$$\lambda_{EHC}^3 + \lambda_{EHC}^2 \alpha_1 - \lambda_{EHC}\alpha_2 + \alpha_3 = 0 \tag{3.14}$$

Equation (**??**) and (**??**) defines the existence of drug saturation equilibrium without and with hepatic uptake respectively.

3.1.3 Drug Reabsorption Free equilibrium point(DRFEP).

$$A_c^{**} = \frac{F_a k_2 k_3}{(k_2 k_3 k_4)(k_1 k_2) - (k_2 k_3 \lambda_{CT})(k_a k_2)}$$

$$A_h^{**} = \frac{\lambda_{CT} F_a k_3}{(k_2 k_3 k_4)(k_1 k_2) - (k_2 k_3 \lambda_{CT})(k_a k_2)}$$

$$A_b^{**} = 0$$

$$A_g^{**} = \frac{F_a k_2 k_3 (k_1 k_2)}{(k_2 k_3 \lambda_{CT})(k_a k_2) - (k_2 k_3 k_4)(k_1 k_2)}$$

$$
\begin{aligned}
A_u^{**} &= \frac{F_a k_2 k_3 k_r}{[(k_2k_3k_4)(k_1k_2) - (k_2k_3\lambda_{CT})(k_ak_2)]k_9} \\
A_k^{**} &= \frac{F_a k_2 k_3 k_r}{[(\lambda_{EHC}^3 - k_2k_3k_4)(\lambda_{EHC}\lambda_{CT} - k_1k_2) - (k_2k_3\lambda_{CT})(k_ak_2)]k_8} \\
E_h^{**} &= \frac{\lambda_{CT} F_a k_3}{(k_2k_3k_4)(k_1k_2) - (k_2k_3\lambda_{CT})(k_ak_2)} \\
E_g^{**} &= \frac{k_{cat} f_u^g}{k_{m2} k_{11}} [\frac{F_a k_2 k_3 (k_1k_2)}{(k_2k_3\lambda_{CT})(k_ak_2) - (k_2k_3k_4)(k_1k_2)}] \\
A_{pv}^{**} &= \frac{1}{k_7} [\frac{F_a k_2 k_3 k_{pv}}{(k_2k_3k_4)(k_1k_2) - (k_2k_3\lambda_{CT})(k_ak_2)} \\
&\quad + \frac{Q f_u F_a k_2 k_3 (k_1k_2)}{(k_2k_3\lambda_{CT})(k_ak_2) - k_2k_3k_4k_1k_2)}]
\end{aligned}
$$

3.1.4 Existence Drug Saturation Equibrium point (DSEP)

At drug saturation equilibrium point the drug kinetics changes from Michealis Menten function to zero order kinetics .Hence the model(**??**) becomes

$$
\begin{aligned}
\frac{dA_c}{dt} &= k_a A_g + \lambda_{EHC} - k_1 A_c.. \\
\frac{dA_h}{dt} &= \lambda_{CT} + \lambda_{EHC} - k_2 A_h \\
\frac{dA_b}{dt} &= \lambda_{EHC} - k_3 A_b \\
\frac{dA_g}{dt} &= \lambda_{CT} + \lambda_{EHC} - k_4 A_g + G(\theta_1) \\
\frac{dA_{t1}}{dt} &= k_t A_c - k_{t1} A_{t1} + l_{t2} A_{t2} \\
\frac{dA_{t2}}{dt} &= l_{t1} A_{t1} - k_{t2} A_{t2}
\end{aligned} \tag{3.15}
$$

Let $\pi^d = (A_c^{**}, A_h^{**}, A_b^{**}, A_g^{**}, A_{t1}^{**}, A_{t2}^{**}, A_{pv}^{**}, A_k^{**}, A_u^{**}, E_h^{**}, E_g^{**})$. Solving (18) at steady state gives

$$A_g^{**} = \frac{\lambda_{CT} + \lambda_{EHC} + G(D,\theta_1)}{k_4}$$
$$A_b^{**} = \frac{\lambda_{EHC}}{k_3}$$
$$A_c^{**} = \frac{k_a(G(D,\theta_1) + \lambda_{CT} + \lambda_{EHC})}{k_1 k_4} + \frac{\lambda_{EHC}}{k_1}$$
$$A_h^{**} = \frac{\lambda_{CT} + \lambda_{EHC}}{k_2}$$
$$A_{pv}^{**} = \frac{k_{pv}(k_a(G(D,\theta_1) + \lambda_{CT} + \lambda_{EHC})}{k_7 k_1 k_4} + \frac{\lambda_{EHC}}{k_7 k_1} + \frac{Q_g}{Q_{pv}} \frac{(\lambda_{CT} + \lambda_{EHC} + G(D,\theta_1))}{k_4 k_7}$$
$$A_k^{**} = \frac{k_r}{k_8}[\frac{k_a(G(D,\theta_1) + \lambda_{CT} + \lambda_{EHC})}{k_1 k_4} + \frac{\lambda_{EHC}}{k_1}]$$
$$A_u^{**} = \frac{\sigma_2}{k_9}[\frac{k_a(G(D,\theta_1) + \lambda_{CT} + \lambda_{EHC})}{k_1 k_4} + \frac{\lambda_{EHC}}{k_1}]$$
$$A_{t1}^{**} = \frac{k_{t1}}{(k_{t1} - \alpha)}(\frac{k_a(G(D,\theta_1) + \lambda_{CT} + \lambda_{EHC})}{k_1 k_4} + \frac{\lambda_{EHC}}{k_1})$$
$$A_{t2}^{**} = \frac{\alpha k_{t1}}{(k_{t1} - \alpha)}(\frac{k_a(G(D,\theta_1) + \lambda_{CT} + \lambda_{EHC})}{k_1 k_4} + \frac{\lambda_{EHC}}{k_1})$$
$$E_g^{**} = \frac{k_{catg} f_{ug}}{k_{mg} k_{degg}}(\frac{\lambda_{CT} + \lambda_{EHC} + G(D,\theta_1)}{k_4})$$
$$E_h^{**} = \frac{k_{cath} f_{uh}}{k_{mh} k_{degh}}(\frac{\lambda_{CT} + \lambda_{EHC}}{k_2})$$

3.2 Local stability of toxic equilibrium point without pathological parameters

Theorem 3.2 *Consider the model* (**??**) *with* $\tau_1 = \tau_2 = 0$. *The unique toxic equilibrium of the model (4), denoted by* $\tilde{\pi^d} = \pi^d$, *is LAS if* $\tilde{\chi_d} = \chi_d > 1$.

proof:

Firstly we apply the theory of series on (1) at the vicinity $y_1 = A_c - A_c^{**}$, $y_2 = A_h - A_h^{**}$, $y_3 = A_b - A_b^{**}$, $y_4 = A_g - A_g^{**}$, $y_5 = A_{t1} - A_{t1}^{**}$, $y_6 = A_{t2} - A_{t2}^{**}$, $y_7 = A_{pv} - A_{pv}^{**}$,

$y_8 = A_k - A_k^{**}$, $y_9 = A_c - A_c^{**}$, $y_{10} = E_g - E_g^{**}$, $y_{11} = E_h - E_h^{**}$. Next, we simplify (**??**) at the neighborhood:

$$\frac{dA_c}{dt} = k_a A_g\left(t-\tau_1\right) - A_g^{**} + V_m^{hc} f_u^{hc}[\frac{A_h^{**}}{k_m^{hc} + f_u^{hc} A_h^{**}} + \frac{k_m^{hc}(A_h - A_h^{**})}{\left(k_m^{hc} + f_u^{hc} A_h^{**}\right)^2}$$
$$- \frac{k_m^{hc}\left(A_h - A_h^{**}\right)^2}{\left(k_m^{hc} + f_u^{hc} A_h^{**}\right)^3}] - .$$
$$V_m^{ch} f_u^{ch}[\frac{A_c^{**}}{k_m^{ch} + f_u^{ch} A_c^{**}} + \frac{k_m^{hc}(A_c - A_c^{**})}{\left(k_m^{ch} + f_u^{ch} A_c^{**}\right)^2} - \frac{k_m^{hc}\left(A_c - A_c^{**}\right)^2}{\left(k_m^{ch} + f_u^{ch} A_c^{**}\right)^3}]-$$

$$- V_m^{cg} f_u^{cg}[\frac{A_c^{**}}{k_m^{cg} + f_u^{cg} A_c^{**}} + \frac{k_m^{cg}(A_c - A_c^{**})}{\left(k_m^{cg} + f_u^{cg} A_c^{**}\right)^2} - \frac{k_m^{cg}\left(A_c - A_c^{**}\right)^2}{\left(k_m^{cg} + f_u^{cg} A_c^{**}\right)^3}]$$
$$- (k_r + k_{pv}) + k_t)(A_c - A_c^{**})$$
$$\frac{dA_h}{dt} = V_m^{ch} f_u^{ch}[\frac{A_c^{**}}{k_m^{ch} + f_u^{ch} A_c^{**}} + \frac{k_m^{hc}(A_c - A_c^{**})}{\left(k_m^{ch} + f_u^{ch} A_c^{**}\right)^2} - \frac{k_m^{hc}\left(A_c - A_c^{**}\right)^2}{\left(k_m^{ch} + f_u^{ch} A_c^{**}\right)^3}] + ...$$
$$V_m^{gh} f_u^{gh}[\frac{A_g^{**}}{k_m^{gh} + f_u^{gh} A_g^{**}} + \frac{k_m^{gh}(A_g - A_g^{**})}{\left(k_m^{gh} + f_u^{gh} A_g^{**}\right)^2} - \frac{k_m^{hc}\left(A_g - A_g^{**}\right)^2}{\left(k_m^{gh} + f_u^{gh} A_g^{**}\right)^3}]$$

$$-V_m^{hc} f_u^{hc}[\frac{A_h^{**}}{k_m^{hc} + f_u^{hc} A_h^{**}} + \frac{k_m^{hc}(A_h - A_h^{**})}{\left(k_m^{hc} + f_u^{hc} A_h^{**}\right)^2} - \frac{k_m^{hc}\left(A_h - A_h^{**}\right)^2}{\left(k_m^{hc} + f_u^{hc} A_h^{**}\right)^3}]- \quad (3.16)$$

$$V_m^{hb} f_u^{hb}[\frac{A_h^{**}}{k_m^{hb} + f_u^{hb} A_h^{**}} + \frac{k_m^{hb}(A_h\left(t-\tau_2\right) - A_h^{**})}{\left(k_m^{hb} + f_u^{hb} A_h^{**}\right)^2} - \frac{k_m^{hb}\left(A_h\left(t-\tau_2\right) - A_h^{**}\right)^2}{\left(k_m^{hb} + f_u^{hb} A_h^{**}\right)^3}]$$
$$- (k_h + \frac{k_{cath} f_u^h}{k_{m1}})(A_h - A_h^{**})$$
$$\frac{dA_b}{dt} = V_m^{hb} f_u^{hb}[\frac{A_h^{**}}{k_m^{hb} + f_u^{hb} A_h^{**}} + \frac{k_m^{hb}(A_h\left(t-\tau_2\right) - A_h^{**})}{\left(k_m^{hb} + f_u^{hb} A_h^{**}\right)^2} - \frac{k_m^{hb}\left(A_h\left(t-\tau_2\right) - A_h^{**}\right)^2}{\left(k_m^{hb} + f_u^{hb} A_h^{**}\right)^3}]$$
$$- (\frac{V_m^{bg} f_u^{bg} A_b}{k_m^{bg} + f_u^{bg} A_b} f(t) - \phi) * A_b$$

$$- V_m^{bg} f_u^{bg} \left(\frac{A_b^{**}}{k_m^{bg} + f_u^{bg} A_b^{**}} + \frac{k_m^{bg}(A_b - A_b^{**})}{\left(k_m^{bg} + f_u^{bg} A_b^{**}\right)^2} - \frac{k_m^{bg}\left(A_b - A_b^{**}\right)^2}{\left(k_m^{bg} + f_u^{bg} A_b^{**}\right)^3}\right) f(t) + \phi(A_b - A_b^{**})$$

$$\frac{dA_g}{dt} = -V_m^{cg} f_u^{cg} \left[\frac{A_c^{**}}{k_m^{cg} + f_u^{cg} A_c^{**}} + \frac{k_m^{cg}(A_c - A_c^{**})}{\left(k_m^{cg} + f_u^{cg} A_c^{**}\right)^2} - \frac{k_m^{cg}\left(A_c - A_c^{**}\right)^2}{\left(k_m^{cg} + f_u^{cg} A_c^{**}\right)^3}\right] -$$

$$V_m^{gh} f_u^{gh} \left[\frac{A_g^{**}}{k_m^{gh} + f_u^{gh} A_g^{**}} + \frac{k_m^{gh}(A_g - A_g^{**})}{\left(k_m^{gh} + f_u^{gh} A_g^{**}\right)^2} - \frac{k_m^{hc}\left(A_g - A_g^{**}\right)^2}{\left(k_m^{gh} + f_u^{gh} A_g^{**}\right)^3}\right] - \left(k_a A_g\left(t - \tau_1\right) - A_g^{**}\right)$$

$$\left(k_g + \frac{k_{catg} f_u^g}{k_{m2}} + \tilde{Q} f_u\right)(A_g - A_g^{**}) + F_a D_i k_a e^{-k_a t} +$$

$$V_m^{bg} f_u^{bg} \left(\frac{A_b^{**}}{k_m^{bg} + f_u^{bg} A_b^{**}} + \frac{k_m^{bg}(A_b - A_b^{**})}{\left(k_m^{bg} + f_u^{bg} A_b^{**}\right)^2} - \frac{k_m^{bg}\left(A_b - A_b^{**}\right)^2}{\left(k_m^{bg} + f_u^{bg} A_b^{**}\right)^3}\right) f(t)$$

$$\frac{dA_{t1}}{dt} = k_t(A_c - A_{t1}) - a_1 \left(\frac{A_{t1}^{**}}{b_1 + A_{t1}^{**}} + \frac{b_1(A_{t1} - A_{t1}^{**})}{\left(b_1 + A_{t1}^{**}\right)^2} + \frac{b_1\left(A_{t1} - A_{t1}^{**}\right)^2}{\left(k_m^{bg} + f_u^{bg} A_b^{**}\right)^3}\right) +$$

$$+ a_1 \left(\frac{A_{t2}^{**}}{b_1 + A_{t2}^{**}} + \frac{Rb_1(A_{t2} - A_{t2}^{**})}{\left(b_1 + A_{t2}^{**}\right)^2} + \frac{Rb_1\left(A_{t2} - A_{t2}^{**}\right)^2}{\left(Rb_1 - A_{t2}^{**}\right)^3}\right)$$

$$\frac{dA_{t2}}{dt} = a_1 \left(\frac{A_{t1}^{**}}{b_1 + A_{t1}^{**}} + \frac{b_1(A_{t1} - A_{t1}^{**})}{\left(b_1 + A_{t1}^{**}\right)^2} + \frac{b_1\left(A_{t1} - A_{t1}^{**}\right)^2}{\left(k_m^{bg} + f_u^{bg} A_b^{**}\right)^3}\right) -$$

$$a_1 \left(\frac{A_{t2}^{**}}{b_1 + A_{t2}^{**}} + \frac{Rb_1(A_{t2} - A_{t2}^{**})}{\left(b_1 + A_{t2}^{**}\right)^2} + \frac{Rb_1\left(A_{t2} - A_{t2}^{**}\right)^2}{\left(Rb_1 - A_{t2}^{**}\right)^3}\right.$$

$$\frac{dA_{pv}}{dt} = k_{pv}(A_c - A_c^{**}) - k_{pv}(A_{pv} - A_{pv}^{**}) + \tilde{Q} f_u (A_g - A_g^{**})$$

$$\begin{aligned}
\frac{dA_k}{dt} &= k_r(A_c - A_c^{**}) - \sigma_2 A_k \\
\frac{dA_u}{dt} &= \sigma_2 A_k - \varepsilon A_u \\
\frac{dE_h}{dt} &= \frac{k_{cath} f_u^h (A_h - A_h^{**})}{k_{m1}} - k_{degh}(E_h - E_h^{**}) \\
\frac{dE_g}{dt} &= \frac{k_{catg} f_u^g (A_g - A_g^{**})}{k_{m2}} - k_{degg}(E_g - E_g^{**})
\end{aligned}$$

$$\frac{dy_1}{dt} = k_a y_4 + V_m^{hc} f_u^{hc}[\frac{A_h^{**}}{k_m^{hc} + f_u^{hc} A_h^{**}} + \frac{k_m^{hc}(y_2)}{(k_m^{hc} + f_u^{hc} A_h^{**})^2}]$$

$$-V_m^{ch} f_u^{ch}[\frac{A_c^{**}}{k_m^{ch} + f_u^{ch} A_c^{**}} + \frac{k_m^{hc}(y_1)}{(k_m^{ch} + f_u^{ch} A_c^{**})^2}] - .$$

$$-V_m^{cg} f_u^{cg}[\frac{A_c^{**}}{k_m^{cg} + f_u^{cg} A_c^{**}} + \frac{k_m^{cg}(y_1)}{(k_m^{cg} + f_u^{cg} A_c^{**})^2}] - (k_r + k_{pv} + k_t)(y_1)$$

$$\frac{dy_2}{dt} = V_m^{ch} f_u^{ch}[\frac{A_c^{**}}{k_m^{ch} + f_u^{ch} A_c^{**}} + \frac{k_m^{hc}(y_1)}{(k_m^{ch} + f_u^{ch} A_c^{**})^2}]$$

$$+V_m^{gh} f_u^{gh}[\frac{A_g^{**}}{k_m^{gh} + f_u^{gh} A_g^{**}} + \frac{k_m^{gh}(y_4)}{\left(k_m^{gh} + f_u^{gh} A_g^{**}\right)^2}] - ...$$

$$-V_m^{hc} f_u^{hc}[\frac{A_h^{**}}{k_m^{hc} + f_u^{hc} A_h^{**}} + \frac{k_m^{hc}(y_2)}{(k_m^{hc} + f_u^{hc} A_h^{**})^2}] \tag{3.17}$$

$$-V_m^{hb} f_u^{hb}[\frac{A_h^{**}}{k_m^{hb} + f_u^{hb} A_h^{**}} + \frac{k_m^{hb}(y_2)}{(k_m^{hb} + f_u^{hb} A_h^{**})^2}]$$

$$-(k_h + \frac{k_{cath} f_u^h}{k_{m1}})(y_2)$$

$$\frac{dy_3}{dt} = V_m^{hb} f_u^{hb}[\frac{A_h^{**}}{k_m^{hb} + f_u^{hb} A_h^{**}} + \frac{k_m^{hb}(y_2)}{(k_m^{hb} + f_u^{hb} A_h^{**})^2}] - ...$$

$$-V_m^{bg} f_u^{bg}(\frac{A_b^{**}}{k_m^{bg} + f_u^{bg} A_b^{**}} + \frac{k_m^{bg}(y_3)}{\left(k_m^{bg} + f_u^{bg} A_b^{**}\right)^2}) f(t) + \phi(y_3)$$

$$\frac{dy_4}{dt} = -V_m^{cg} f_u^{cg}[\frac{A_c^{**}}{k_m^{cg} + f_u^{cg} A_c^{**}} + \frac{k_m^{cg}(y_1)}{(k_m^{cg} + f_u^{cg} A_c^{**})^2}] - V_m^{gh} f_u^{gh}[\frac{A_g^{**}}{k_m^{gh} + f_u^{gh} A_g^{**}}$$

$$+\frac{k_m^{gh}(y_4)}{\left(k_m^{gh} + f_u^{gh} A_g^{**}\right)^2}] - (k_a y_4) - (k_g + \frac{k_{catg} f_u^g}{k_{m2}} + \tilde{Q} f_u)(y_4)$$

$$F_a D_i k_a e^{-k_a t} + V_m^{bg} f_u^{bg} \left(\frac{A_b^{**}}{k_m^{bg} + f_u^{bg} A_b^{**}} + \frac{k_m^{bg}(y_3)}{\left(k_m^{bg} + f_u^{bg} A_b^{**}\right)^2}\right) f(t)$$

$$\frac{dy_5}{dt} = k_t(y_1 - y_5) - a_1\left(\frac{A_{t1}^{**}}{b_1 + A_{t1}^{**}} + \frac{b_1(y_5)}{(b_1 + A_{t1}^{**})^2}\right) +$$

$$+ a_1\left(\frac{A_{t2}^{**}}{b_1 + A_{t2}^{**}} + \frac{R b_1(y_6)}{(b_1 + A_{t2}^{**})^2}\right)$$

$$\frac{dy_6}{dt} = a_1\left(\frac{A_{t1}^{**}}{b_1 + A_{t1}^{**}} + \frac{b_1(y_5)}{(b_1 + A_{t1}^{**})^2}\right) - a_1\left(\frac{A_{t2}^{**}}{b_1 + A_{t2}^{**}} + \frac{R b_1(y_6)}{(b_1 + A_{t2}^{**})^2}\right)$$

$$\frac{dy_7}{dt} = k_{pv}(y_1) - k_{pv}(y_7) + \tilde{Q} f_u(y_4)$$

$$\frac{dy_8}{dt} = k_r(y_1) - \sigma_2 y_8$$

$$\frac{dy_9}{dt} = \sigma_2 y_8 - \varepsilon y_9$$

$$\frac{dy_{10}}{dt} = \frac{k_{cath} f_u^h(y_2)}{k_{m1}} - k_{degh}(y_{10})$$

$$\frac{dy_{11}}{dt} = \frac{k_{catg} f_u^g(y_4)}{k_{m2}} - k_{degg}(y_{11})$$

Compute the Jacobian matrix at $\tilde{\pi^d}$

$$J_n(\pi^d) = \begin{bmatrix} -L_1 & L_{hc} & 0 & k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ L_{ch} & -L_2 & 0 & L_{gh} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & L_{hb} & -L_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ L_{cg} & 0 & \phi & -L_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ k_{t1} & 0 & 0 & 0 & -L_5 & L_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & L_5 & -L_6 & 0 & 0 & 0 & 0 & 0 \\ k_{pv} & 0 & 0 & Q f_{ug} & 0 & 0 & -L_7 & 0 & 0 & 0 & 0 \\ k_r & 0 & 0 & 0 & 0 & 0 & 0 & -L_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_2 & -L_9 & 0 & 0 \\ 0 & \frac{k_{cat} f_{uh}}{km1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -L_{10} & 0 \\ 0 & 0 & 0 & \frac{k_{cat} f_{ug}}{km2} & 0 & 0 & 0 & 0 & 0 & 0 & -L_{11} \end{bmatrix};$$

Next,we establish theorem 3.2, using the Krosnoselskii sub-linearity trick (Oyovwevvotu, 2021). System (**??**) has solution of the form

$$Z(t) = Z_0 e^{wt} \tag{3.18}$$

with $Z_0 = (Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11})$ and $w,\ Z_i \in \mathbb{C}$(i=1,2,...11). Substitue (**??**) into (**??**),

$$\begin{aligned}
wZ_1 &= L_{hc}Z_2 + k_a Z_4 - \alpha_1 Z_1 \\
wZ_2 &= L_{ch}Z_1 + L_{gh}Z_4 - \alpha_2 Z_2 \\
wZ_3 &= L_{hb}Z_2 - \alpha_3 Z_3 \\
wZ_4 &= L_{cg}Z_1 + L_{bg}Z_3 - \alpha_4 Z_4 \\
wZ_5 &= k_{t1}Z_1 + L_6 Z_6 - \alpha_5 Z_5 \\
wZ_6 &= L_5 Z_5 - \alpha_5 Z_6
\end{aligned}$$

$$wZ_7 = k_{pv}Z_1 + Qf_{ug}Z_4 - \alpha_7 Z_7 \tag{3.19}$$

$$\begin{aligned}
wZ_8 &= k_r Z_1 - \alpha_8 Z_8 \\
wZ_9 &= \sigma_2 Z_8 - \alpha_9 Z_9 \\
wZ_{10} &= \frac{k_{ct} f_{uh}}{km1} Z_2 - \alpha_{10} Z_{10} \\
wZ_{11} &= \frac{k_{ct} f_{uh}}{km2} Z_4 - \alpha_{11} Z_{11}
\end{aligned}$$

The system (**??**) is simplified by first of all moving the negative terms in the last equation (**??**) to their respective right hand sides. The resulting equation are then rewritten in terms of Z_i, and all other negative terms are moved to the right hand side. These simplification gives

$$\left[F_1(w) + 1\right] Z_1 = (MZ)_1$$

$$\left[F_2(w) + 1\right] Z_2 = (MZ)_2$$

$$\left[F_3(w) + 1\right] Z_3 = (MZ)_3$$

$$[F_4(w)+1]\,Z_4 = (MZ)_4$$

$$[F_5(w)+1]\,Z_5 = (MZ)_5 \tag{3.20}$$

$$[F_6(w)+1]\,Z_6 = (MZ)_6$$

$$[F_7(w)+1]\,Z_7 = (MZ)_7$$

$$[F_8(w)+1]\,Z_8 = (MZ)_9$$

$$[F_9(w)+1]\,Z_9 = (MZ)_9$$

$$[F_{10}(w)+1]\,Z_{10} = (MZ)_{10}$$

$$[F_{11}(w)+1]\,Z_{11} = (MZ)_{11}$$

where,

$$F_1(w) = \frac{w}{\alpha_1}, F_2(w) = \frac{w}{\alpha_2}, F_3(w) = \frac{w}{\alpha_3}, F_4(w) = \frac{w}{\alpha_4}, F_5(w) = \frac{w}{\alpha_5}, F_6(w) = \frac{w}{\alpha_6}, F_7(w) =$$

$$F_8(w) = \frac{w}{\alpha_8}, F_9(w) = \frac{w}{\alpha_9}, F_{10}(w) = \frac{w}{\alpha_{10}}, F_{11}(w) = \frac{w}{\alpha_{11}}$$

with

$$M = \begin{bmatrix} 0 & \frac{L_{hc}}{\alpha_1} & 0 & \frac{k_a}{\alpha_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{L_{ch}}{\alpha_2} & 0 & 0 & \frac{L_{gh}}{\alpha_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{L_{hb}}{\alpha_3} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{L_{cg}}{\alpha_4} & 0 & \frac{L_{bg}}{\alpha_4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{k_{t1}}{\alpha_5} & 0 & 0 & 0 & 0 & \frac{L_6}{\alpha_5} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{L_5}{\alpha_6} & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{k_{pv}}{\alpha_7} & 0 & 0 & \frac{Qf_{ug}}{\alpha_7} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{k_r}{\alpha_8} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\sigma_2}{\alpha_9} & 0 & 0 & 0 \\ 0 & \frac{k_{cath}f_{uh}}{\alpha_{10}k_{m1}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{k_{catg}f_{ug}}{\alpha_{11}k_{m2}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

The toxic equilibrium point $\pi^d = (A_c^{**}, A_h^{**}, A_b^{**}, A_g^{**}, A_{t1}^{**}, A_{t2}^{**}, A_{pv}^{**}, A_k^{**}, A_u^{**}, E_h^{**}, E_g^{**})$,satisfy $\pi^d = M\pi^d$, and the matrix of M, has non-negative entries, .If Z is a solution of (**??**), then it is possible to find a minimal positive real number, r, such that

$$/Z/ \leq r\tilde{\pi^d} \tag{3.21}$$

The main goal is to show that $Re(w) < 0$. Assume, by contradiction, that $Re(w) \geq 0$. There are two cases to consider as below.

Case 1 $w = 0$

The determinant of the system $\Omega = (\tilde{\chi_d} - 1)\alpha_1\alpha_2\alpha_3, \alpha_4, \alpha_7, \alpha_8, \alpha_9, \alpha_{10}\alpha_{11}(L_{t1}\alpha_5 + \alpha_5\alpha_6)$. The determinant is negative whenever $\tilde{\chi_d} < 1$,since the determinant is negative, it follows that the system has a unique solution given by $Z = 0$,which correspond to toxic free equilibrium.

Case 2 $w \neq 0$

Since $Re(w) > 0$,then $/1 + F_i(w)/ > 1$ $i = 1, 2...11$. Define $F(w) = min/1 + F_i(w)/$,then $F(w) > 1$ and $r > \frac{r}{F(w)}$

by definition r is the minimum number such that $//Z// \leq r\tilde{\pi^d}$, then

$$//Z// > \frac{\tilde{\pi^d} r}{F(w)} \tag{3.22}$$

Taking the norm of (25)

$$F(w)\,\|Z_2\| \leq |1 + F_2(w)|\,\|Z_2\|$$

$$\|(MZ)_2\| \leq M\,\|Z_2\| \leq rM(\tilde{\pi^d})_2$$

$$= r\left(\tilde{\pi^d}\right)_2 = rA_h^{**} \tag{3.23}$$

It follows from (26) that $\|Z_2\| \leq \frac{r}{F(w)}A_h^{**}$,which contradict (**??**), $Re(w) < 0$. Thus, all eigenvalues of the characteristic equation associated with the linearized system (**??**) will have negative real part, so that toxic equilibrium, $\tilde{\pi^d}$ is locally asymptotically stable whenever $\tilde{\chi_d} > 1$. The pharmacological implication of Theorem 3.2 is that drug toxicity will persist in the compartment thus enhancing drug reabsorbtion .

3.2.1 Centre Manifold Theorem Depending on Parameters

Theorem 3.3 *Consider the compact system of $n \times n$ nonlinear defined below*

$$\dot{x} = Ax + f(x, y, \mu)$$

$$\dot{y} = By + g(x, y, \mu) \tag{3.24}$$

Where;

$(x, y, \mu) \in \mathbb{R}^c \times \mathbb{R}^s \times \mathbb{R}^p$.

$A = c \times c$ *matrix of real numbers with zero eigenvalue*

$B = s \times s$ *matrix of real numbers having negative real part and f and g are nonlinear function with atleast second order terms, satisfying the following properties*

$f(0, 0, 0) = 0 \quad Df(0, 0, 0) = 0$

$g(0, 0, 0) = 0 \quad Dg(0, 0, 0) = 0$

We can approximate the centre manifold of (**??**), using the first tangency condition as follows

$$y = h(x, \mu)$$

$$0 = D_x h(x,\mu)\dot{x} - \dot{y} \tag{3.25}$$

Substitue (**??**) into (**??**),

$$0 = D_x h(x,\mu)[Ax + f(x,h(x,\mu),\mu)] - Bh(x,\mu) - g(x,h(x,\mu),\mu) \tag{3.26}$$

Equation (**??**) defines the coefficient of the centre manifold .The dynamics of the centre manifold is given by

$$\dot{u} = Au + f(x,h(u,\mu),\mu) \qquad u \in \mathbb{R}^c \tag{3.27}$$

$$\dot{\mu} = 0$$

Theorem 3.4 *There exist a centre manifold of* $(x,y) = (0,0)$ *for (28),whose dynamics is restricted to* $\dot{u} = Au + f(x,h(u,\mu),\mu) \qquad u \in \mathbb{R}^c$.

Theorem 3.5 *Suppose that the zero solution of* (**??**) *is stable(asymptotically stable) or unstable ,then the zero solution of* (**??**) *is also stable(asymptotically stable) or unstable.(ii)Suppose that the zero solution of (24) is stable . Then if* $(x(t),y(t))$ *is a solution of* (**??**) *with* $(x(0),y(0))$*,then there is a solution* $u(t)$ *of* (**??**) *such that* $t \to \infty$

$$x(t) = u(t) + O(e^{-\lambda t})$$

$$y(t) = h(u(t)) + O(e^{-\lambda t}) \quad \lambda > 0$$

is a constant.

apply Theorem 3.3 and Theorem 3.4 to the model as follows

firstly,consider the linearized matrix of the model about the toxic free equilibrium $\pi^0 = (A_c^{**}, A_h^{**}, A_b^{**}, A_g^{**}, A_{t1}^{**}, A_{t2}^{**}, A_{pv}^{**}, A_k^{**}, A_u^{**}, E_h^{**}, E_g^{**}) \to (0,0,0,0,0,0,0,0,0,0,0)$

$$\begin{pmatrix} \dot{y_1} \\ \dot{y_2} \\ \dot{y_3} \\ \dot{y_4} \\ \dot{y_5} \\ \dot{y_6} \\ \dot{y_7} \\ \dot{y_8} \\ \dot{y_9} \\ \dot{y_{10}} \\ \dot{y_{11}} \end{pmatrix} = \begin{bmatrix} -k_1 & 0 & 0 & k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ k_t & 0 & 0 & 0 & -k_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & L_{t1} & -k_6 & 0 & 0 & 0 & 0 & 0 \\ k_{pv} & 0 & 0 & L_1 & 0 & 0 & -k_7 & 0 & 0 & 0 & 0 \\ k_r & 0 & 0 & 0 & 0 & 0 & 0 & -k_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_2 & -k_9 & 0 & 0 \\ 0 & L_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{10} & 0 \\ 0 & 0 & 0 & L_3 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{11} \end{bmatrix} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \\ y_7 \\ y_8 \\ y_9 \\ y_{10} \\ y_{11} \end{pmatrix}$$

It is seen that the linearized system is not in its compact form (**??**).

Hence we generate a transition matrix ,for the standard normal form of the linearized system as follows. Firstly,

eigen value of the the linearized matrix gives

$$0, -k_1, -k_{10}, -k_{11}, -k_2, -k_3, -k_4, -(k_5 + k_6), -k_7, -k_8, -k_9$$

suggesting that ,our system consist of one centre manifold ($W^c(0)$) and ten stable manifold (W^s_{10}).

Next,we compute the transition matrix

$$T = \begin{bmatrix} 0 & g_1 & 0 & 0 & 0 & g_2 & g_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & g_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & g_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & g_6 & g_7 & 0 & 0 & 0 & 0 \\ g_8 & -g_9 & 0 & 0 & 0 & g_{10} & g_{11} & 0 & 0 & 0 & 0 \\ 1 & g_{12} & 0 & 0 & 0 & g_{13} & g_{14} & 1 & 0 & 0 & 0 \\ 0 & g_{15} & 0 & 0 & 0 & g_{16} & g_{17} & 0 & 1 & 0 & 0 \\ 0 & g_{18} & 0 & 0 & 0 & g_{19} & g_{20} & 0 & 0 & g_{21} & 0 \\ 0 & 1 & 0 & 0 & 0 & g_{22} & g_{23} & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \end{bmatrix};$$

$g_1 = \frac{(k_1 - k_8)(k_1 - k_9)}{k_r k_8}$,

$g_3 = \frac{k_a k_{11} - k_a k_4}{L_3(k_1 - k_4)}$,
$g_6 = \frac{k_{11} - k_3}{L_3}$,
$g_8 = \frac{k_6}{k_5}$,
$g_9 = \frac{(k_1 - k_6)(k_1 - k_9)(k_{t1} k_1 - k_{t1} k_8)}{k_r k_1 k_8 (k_1 - k_5 - k_6) k_8}$,
$g_{12} = \frac{(k_1 - k_9)(k_{t1} k_1 k_5 - k_{t1} k_5 k_8)(k_1 - k_9)}{k_1 k_r (k_1 - k_5 - k_6) k_8}$

$g_2 = \frac{k_a k_{11} - k_a k_3}{L_3(k_1 - k_3)}$,
$g_4 = \frac{k_{10} - k_2}{L_2}$, $g_5 = \frac{(k_3 - k_{11})(k_3 - k_4)}{L_3 k_3}$,
$g_7 = \frac{k_{11} - k_4}{L_3}$,
$g_{10} = \frac{k_{t1}(-k_a k_{11} + k_a k_3)(k_3 - k_6)}{L_3(k_1 - k_3)(k_3 - k_5 - k_6) k_3}$,
$g_{11} = \frac{k_{t1}(-k_a k_{11} + k_a k_4)(k_4 - k_6)}{L_3(k_1 - k_3)(k_3 - k_5 - k_6) k_3}$
$g_{13} = \frac{k_{t1}(k_a k_{11} - k_a k_3) k_5}{L_3(k_1 - k_3)(k_3 - k_5 - k_6) k_3}$,
$g_{14} = \frac{k_{t1}(k_a k_{11} - k_a k_4) k_5}{L_3(k_1 - k_4)(k_4 - k_5 - k_6) k_4}$,
$g_{15} = \frac{k_{pv}(k_1 - k_8)}{k_r(k_1 - k_7) k_r}$, $g_{16} = \frac{k_a k_{pv} k_{11} + L_1 k_1 k_{11} + k_a k_{pv} k_r + L_1 k_{11} k_3 - L_1 k_3 k_3}{L_3(k_3 - k_1)(k_3 - k_7)}$

$g_{17} = \frac{k_a k_{pv} k_{11} + L_1 k_1 k_{11} - k_a k_{pv} k_4 - L_1 k_1 k_4 - L_1 k_{11} k_4 + L_1 k_4 k_4}{L_3(k_3 - k_1)(k_3 - k_7)}$,
$g_{18} = \frac{k_9 - k_1}{k_8}$, $g_{19} = \frac{k_a k_r k_3 + k_a k_r k_{11}}{L_3(k_3 - k_1)(k_3 - k_8)}$,
$g_{20} = \frac{k_a k_r k_4 - k_a k_r k_{11}}{L_3(k_3 - k_1)(k_4 - k_8)}$
,$g_{22} = \frac{k_a k_r k_{11} k_8 - k_a k_r k_4 k_8}{L_3(k_1 - k_4)(k_4 - k_8)(k_4 - k_9)}$,
$g_{23} = \frac{k_a k_r k_{11} k_8 - k_a k_r k_4 k_8}{L_3(k_1 - k_4)(k_4 - k_8)(k_4 - k_9)}$,
$g_{21} = \frac{k_9 - k_8}{k_8}$

$$\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \\ y_7 \\ y_8 \\ y_9 \\ y_{10} \\ y_{11} \end{pmatrix} = T \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \\ u_6 \\ u_7 \\ u_8 \\ u_9 \\ u_{10} \\ u_{11} \end{pmatrix} \rightarrow \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \\ u_6 \\ u_7 \\ u_8 \\ u_9 \\ u_{10} \\ u_{11} \end{pmatrix} = T^{-1} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \\ y_7 \\ y_8 \\ y_9 \\ y_{10} \\ y_{11} \end{pmatrix} =$$

$$\begin{bmatrix} \frac{g_9-g_{12}}{g_1+g_1g_8} & 0 & z_6 & z_8 & \frac{1}{1+g_8} & \frac{1}{1+g_8} & 0 & 0 & 0 & 0 & 0 \\ \frac{1}{g1} & 0 & \frac{g_3g_6-g_2g_7}{g_1g_5g_7} & \frac{-g_3}{g_1g_7} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{-1}{g4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & \frac{g_6-g_7}{g_5g_7} & \frac{-1}{g_7} & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & \frac{1}{g_4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{g5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{-g_6}{g_5g_7} & \frac{1}{g_7} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{g_9-g_{12}g_8}{g_1+g_1g_8} & 0 & z_1 & z_4 & \frac{-1}{1+g_{18}} & \frac{g_8}{1+g_8} & 0 & 0 & 0 & 0 & 0 \\ -\frac{g15}{g1} & 0 & z_3 & \frac{g_{15}g_3-g_1g_{17}}{g_1g_7} & 0 & 0 & 1 & 0 & 0 & 0 & 01 \\ \frac{g_{18}}{g_1g_{21}} & 0 & z_5 & \frac{g_{18}g_3-g_{11}g_{20}}{g_1g_{21}g_7} & 0 & 0 & 0 & \frac{1}{g_{21}} & 0 & 0 & 0 \\ \frac{g_{18}}{g1} & 0 & z_2 & z_7 & 0 & 0 & 0 & \frac{-1}{g_{21}} & 0 & 0 & 0 \end{bmatrix}$$

$$\begin{pmatrix} \dot{u_1} \\ \dot{u_2} \\ \dot{u_3} \\ \dot{u_4} \\ \dot{u_5} \\ \dot{u_6} \\ \dot{u_7} \\ \dot{u_8} \\ \dot{u_9} \\ \dot{u_{10}} \\ \dot{u_{11}} \end{pmatrix} = T^{-1}AT \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \\ u_6 \\ u_7 \\ u_8 \\ u_9 \\ u_{10} \\ u_{11} \end{pmatrix} + T^{-1} \begin{pmatrix} c_1 \\ c_2 \\ 0 \\ c_3 \\ c_4 \\ c_5 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$\begin{pmatrix} \dot{u_1} \\ \dot{u_2} \\ \dot{u_3} \\ \dot{u_4} \\ \dot{u_5} \\ \dot{u_6} \\ \dot{u_7} \\ \dot{u_8} \\ \dot{u_9} \\ \dot{u_{10}} \\ \dot{u_{11}} \end{pmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_{10} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_{11} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -k_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -k_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -k_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -(k_5+k_6) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_7 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_8 & 0 \\ 0 & h_1 & 0 & 0 & 0 & h_3 & 0 & 0 & 0 & h_2 & -k_9 \end{bmatrix} + \begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \\ w_6 \\ w_7 \\ w_8 \\ w_9 \\ w_{10} \\ w_{11} \end{pmatrix} \tag{3.28}$$

$$z_1 = \frac{g_1(-g_6g_{11} + g_{10}g_7 + g_{14}g_6g_8 - g_{13}g_7g_8) - (g_3g_6 - g_2g_7)g_7 - (g_3g_6 - g_2g_7)(g_{12}g_8 + g_9)}{g_1g_5g_7(1 + g_8)}$$

$$z_2 = \frac{(g_{18} - g_{21})(g_3 g_6 - g_2 g_7) + g_1(-g_{20} g_6 + g_{21} g_{23} g_6 + g_{19} g_7 - g_{21} g_{22} g_7)}{g_1 g_{21} g_5 g_7}$$

$$z_3 = \frac{g_1 g_{17} g_6 - g_{15} g_3 g_6 - g_1 g_{16} g_7 + g_{15} g_2 g_7}{g_1 g_5 g_7}$$

$$z_4 = \frac{g_1 g_{11} - g_1 g_{14} g_8 + g_{12} g_3 g_8 + g_3 g_9}{g_1 g_7 + g_1 g_7 g_8}$$

$$h_1 = \frac{(k_2 - k_8)(k_1 - k_9)}{k_8}$$

$$h_2 = \frac{(-k_2 + k_8)(k_8 - k_9)}{k_8}$$

$$h_3 = \frac{k_a k_r (k_3 - k_4)(k_2 - k_8)}{L_3 (k_1 - k_4)(k_1 - k_8)}$$

$$z_5 = \frac{g_1 g_{20} g_6 - g_{18} g_3 g_6 - g_1 g_{19} g_7 + g_{18} g_2 g_7}{g_1 g_5 g_7}$$

$$z_6 = \frac{g_1(g_{11} + g_{14}) g_6 - g_1(g_{10} + g_{13}) g_7 - (g_3 g_6 - g_2 g_7)(g_{12} - g_9)}{g_1 g_5 g_7 (1 + g_8)}$$

$$z_7 = \frac{g_1 g_{20} - g_1 g_{21} g_{23} - g_{18} g_3 + g_{21} g_3}{g_1 g_{21} g_7}$$

$$z_8 = \frac{g_3 g_9 - g_{12} g_3 - g_1 g_{11} + g_1 g_4}{g_1 g_7 + g_1 g_7 g_8}$$

$$c_1 = (g_1^2u_2^2 - 2g_1g_3u_2u_7 + g_3^2u_7^2)(l_{ch} + l_{cg})$$

$$c_2 = -l_{ch}(g_1^2u_2^2 - 2g_1g_3u_2u_7 + g_3^2u_7^2) + l_{gh}g_7^2u_7^2$$

$$c_3 = -l_{cg}(g_1^2u_2^2 - 2g_1g_3u_2u_7 + g_3^2u_7^2) - l_{gh}g_7^2u_7^2$$

$$c_4 = l_{t1}(g_8^2u_2^2-2g_8g_9u_2u_1+g_9^2u_2^2+2g_8g_{11}u_7u_1+g_{11}^2u_7^2)-l_{t2}(u_1^2+2g_{12}u_1u_2+g_{14}^2u_7^2-2g_{14}u_1u_7+g_{13}u_{14}u_7)$$

$$c_5 = l_{t2}(u_1^2+2g_{12}u_1u_2+g_{14}^2u_7^2-2g_{14}u_1u_7+g_{13}u_{14}u_7)-l_{t1}(g_8^2u_2^2-2g_8g_9u_2u_1+g_9^2u_2^2+2g_8g_{11}u_7u_1+g_{11}^2u_7^2)$$

$$w_1 = \frac{k_{t1}(-k_a(L_{cg}(g_1^2u_2^2 + u_7(2g_1g_3u_2 + (g_3^2 + g_7^2L_{gh})u_7) + (L_{cg} + L_{ch})(g_1u_2 - g_3u_7)^2k_5}{k_1k_4(k_5 + k_6)}$$

$w_2 > 0,\ w_3 > 0,$

$$w_4 > 0, w_5 > 0, w_6 > 0, /]w_7 > 0, w_8 > 0, w_9 > 0, w_{10} > 0, w_{11} > 0.$$

system (**??**) is the normal form known as the block form.Next,we compute the centre manifold as follows

let $\bar{X} = (u)$,$\bar{Y} = (u_2, u_3, u_4, u_5, u_6, u_7, u_8, u_9, u_{10}, u_{11})$

$$\bar{Y} = h(\bar{X}) = h_i(u, k_3)\forall i = 2, 3...11.$$

$$h_1(u, k_3) = \rho_1u_1^2 + \rho_2u_1k_3 + \rho_3k_1^2$$

$$h_2(u, k_3) = \delta_1u_1^2 + \delta_2u_1k_3 + \delta_3k_1^2$$

$$h_3(u,k_3) = \vartheta_1 u_1^2 + \vartheta_2 u_1 k_3 + \vartheta_3 k_1^2$$

$$h_4(u,k_3) = \varrho_1 u_1^2 + \varrho_2 u_1 k_3 + \varrho_3 k_1^2 \tag{3.29}$$

$$h_5(u,k_3) = \zeta_1 u_1^2 + \zeta_2 u_1 k_3 + \zeta_3 k_1^2$$

$$h_6(u,k_3) = \sigma_1 u_1^2 + \sigma_2 u_1 k_3 + \sigma_3 k_1^2$$

$$h_7(u,k_3) = \varphi_1 u_1^2 + \varphi_2 u_1 k_3 + \varphi_3 k_1^2$$

$$h_8(u,k_3) = \varsigma_1 u_1^2 + \varsigma_2 u_1 k_3 + \varsigma_3 k_1^2$$

$$h_9(u,k_3) = \Omega_1 u_1^2 + \Omega_2 u_1 k_3 + \Omega_3 k_1^2$$

$$h_{10}(u,k_3) = d_1 u_1^2 + d_2 u_1 k_3 + d_3 k_1^2$$

applying the first tangency condition

$$\frac{\partial h_i}{\partial u_1} \dot{u_1} - \dot{u_{i+1}} \doteq 0 \tag{3.30}$$

applying (**??**) on (**??**) , we obtain the coefficient below

$$\rho_1 = \frac{l_{ch}}{k_2 + l_{hb} + l_{hc} - 2k_1}, \rho_2 = 0, \rho_3 = 0. \delta_1 = -\frac{l_{hb} l_{ch}}{k_2 + l_{hb} + l_{hc} + l_{ch} - 2k_1}, \delta_2 = 0, \delta_3 = 0.$$

$$\vartheta_1 = -\frac{l_{cg}}{2k_1}, \vartheta_2 = 0, \vartheta_3 = 0. \varrho_1 = 0, \varrho_1 = 0, \varrho_1 = 0$$

$$\sigma_1 = \frac{-Q f_u l_{cg}}{2k_1(k_{pv} - 2k_1)}, \sigma_2 = 0, \sigma_3 = 0. \varphi_1 = 0, \varphi_2 = 0, \varphi_3 = 0. \varsigma_1 = 0, \varsigma_2 = 0, \varsigma_3 = 0.$$

$$\Omega_1 = \frac{k_{cat} f_u^h l_{ch}}{k_{m2}(k_2 + l_{hb} + l_{hc} + l_{ch} - 2k_1)}, \Omega_2 = 0, \Omega_3 = 0. d_1 = 0, d_2 = 0, d_3 = 0. \zeta_1 = 0, \zeta_2 = 0, \zeta_3 = 0$$

.

Next,we invoke the second tangency condition (**??**),to establish the dynamics of centre manifold .

$$\dot{u} = Au + f(x, h_i(u, \mu), \mu) \tag{3.31}$$

With much rigorous exercise we obtained the dynamics as

$$\dot{u} = (1 - \chi_d)\lambda_0 - \lambda_1 u_1 + \lambda_2 u_1^2$$

3.2.2 Hoph Bifurcation Analysis

In this section, we investigate the stability of the system in the presence of pathological defect. This is attainable using the Hoph Bifurcation analysis. Hoph Bifurcation occurs when the eigen values of the system are conjugate pair of purely immaginary roots and the conjugate pair must cross the immaginary axis with nonzero speed (transversality condition). Firstly, we transform the model (3.1) in its compact form:

$$\frac{dY(t)}{dt} = F(D,t) + J_n Y(t) + J_{d1} Y(t - \tau_1) + J_{d2} Y(t - \tau_2) \tag{3.32}$$

where

$$J_n = \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ k_t & 0 & 0 & 0 & -k_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & L_{t1} & -k_6 & 0 & 0 & 0 & 0 & 0 \\ k_{pv} & 0 & 0 & L_1 & 0 & 0 & -k_7 & 0 & 0 & 0 & 0 \\ k_r & 0 & 0 & 0 & 0 & 0 & 0 & -k_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_2 & -k_9 & 0 & 0 \\ 0 & L_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{10} & 0 \\ 0 & 0 & 0 & L_3 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{11} \end{bmatrix}$$

$$J_{d2} = \begin{bmatrix} 0 & 0 & 0 & k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} e^{-\lambda\tau_1}$$

$$J_{d2} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -L_{hb} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & L_{hb} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} e^{-\lambda\tau_2}$$

$$F(D,t) = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & F_a D k_a e^{-k_a t} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\frac{d}{dt}\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \\ y_7 \\ y_8 \\ y_9 \\ y_{10} \\ y_{11} \end{bmatrix} = j_n^* \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \\ y_7 \\ y_8 \\ y_9 \\ y_{10} \\ y_{11} \end{bmatrix} + j_{d1}^* \begin{bmatrix} y_1(t-\tau_1) \\ y_2(t-\tau_1) \\ y_3(t-\tau_1) \\ y_4(t-\tau_1) \\ y_5(t-\tau_1) \\ y_6(t-\tau_1) \\ y_7(t-\tau_1) \\ y_8(t-\tau_1) \\ y_9(t-\tau_1) \\ y_{10}(t-\tau_1) \\ y_{11}(t-\tau_1) \end{bmatrix} + j_{d2}^* \begin{bmatrix} y_1(t-\tau_2) \\ y_2(t-\tau_2) \\ y_3(t-\tau_2) \\ y_4(t-\tau_2) \\ y_5(t-\tau_2) \\ y_6(t-\tau_2) \\ y_7(t-\tau_2) \\ y_8(t-\tau_2) \\ y_9(t-\tau_2) \\ y_{10}(t-\tau_2) \\ y_{11}(t-\tau_2) \end{bmatrix}$$

Since the trajectory of (**??**) is satisfied by decay solution $y(t) = e^{-St}$. Equation (**??**), gives

$$SI - F(D,t)e^{-St} - J_n - e^{-S\tau_1}J_{d1} - e^{-S\tau_2}J_{d2} = 0$$

The characteristics polynomial gives

$$F(S) = P_1(S,\beta_i)[P_2(S,\alpha_i)+$$

$$e^{-S\tau_2}P_3(S,v_i)+e^{-S\tau_1}P_4(S,\eta_i)+e^{-S(\tau_1+\tau_2)}P_5(S,m_i)] \tag{3.33}$$

Where

$$P_1(S,\beta_i)=S^7+\beta_6S^6+\beta_5S^5+\beta_4S^4+\beta_3S^3+$$

$$\beta_2S^2+\beta_1S$$

$$P_2(S,\alpha_i)=S^4+\alpha_3S^3+\alpha_2S^2+\alpha_2S+\alpha_0$$

$$P_3(S,v_i)=v_3S^3+v_2S^2+v_1S+v_0$$

$$P_4(S,\eta_i)=\eta_3S^3+\eta_2S^2+\eta_2S+\eta_0$$

$$P_5(S,m_i)=m_2S^2+m_1S+m_0$$

$$\beta_6=k_{10}+k_{11}+k_5+k_6+k_7+k_8$$

$$\beta_5=k_{10}k_{11}+k_{11}k_5+k_5k_{11}+k_6k_{10}+k_{11}k_6+k_7k_{10}$$

$$k_5k_7+k_5k_8+k_{11}k_8+k_{10}k_8+k_6k_7+k_{11}k_7+$$

$$+k_6k_8+k_8k_7+k_{11}k_9+k_{10}k_9+k_6k_9+k_9k_7.$$

$$\beta_4=k_{10}k_{11}k_5+k_{10}k_{11}k_6+k_{10}k_{11}k_7+k_{10}k_8k_5+$$

$$k_{10}k_{11}k_8++k_5k_7k_9+k_{11}k_6k_7+k_{10}k_6k_8+k_6k_{11}k_8$$

$$+k_{10}k_6k_7+k_{11}k_5k_7+k_{10}k_7k_5+k_{11}k_5k_8+k_5k_8k_9$$

$$+k_{10}k_7k_8+k_{11}k_7k_8+k_5k_7k_8+k_{10}k_5k_9+k_{10}k_{11}k_9$$

$$+k_6k_7k_8+k_{11}k_9k_5+k_{10}k_6k_9+k_{11}k_6k_9+k_{10}k_7k_9$$

$$+k_{11}k_8k_9+k_{10}k_8k_9+k_6k_7k_9+k_6k_8k_9+k_7k_8k_9$$

$$\beta_3=k_{10}k_{11}k_5k_7+k_{10}k_{11}k_6k_7+k_{10}k_5k_7k_8+k_{10}k_{11}k_7k_8+$$

$$k_{11}k_6k_7k_8+k_{10}k_6k_7k_8+k_{11}k_5k_8k_7+k_{10}k_{11}k_5k_9+$$

$$k_{10}k_{11}k_6k_9+k_{10}k_{11}k_7k_9+k_{10}k_5k_7k_9+$$

$$k_{10}k_5k_8k_9+k_{11}k_8k_8k_9+k_6k_7k_8k_9+k_5k_7k_8k_9$$

$$\beta_2=k_{11}k_6k_7k_8k_9+k_{10}k_6k_7k_8k_9+k_{11}k_5k_7k_8k_9+$$

$$k_{10}k_5k_7k_8k_9+$$

$$k_{10}k_{11}k_7k_8k_9 + k_{10}k_{11}k_6k_8k_9 + k_{10}k_{11}k_5k_8$$

$$+k_9k_{10}k_{11}k_6k_7k_9 + k_{10}k_{11}k_5k_7k_8 + k_{10}k_{11}k_6k_7k_8.$$

$$\beta_1 = k_{10}k_{11}k_6k_7k_8k_9 + k_{10}k_{11}k_5k_7k_8k_9$$

$$\alpha_3 = k_2 + k_4 - G\theta$$

$$\alpha_2 = 1 + k_2(k_4 - G\theta) + (k_1 + k_3)(k_4 - G\theta) + ((k_1 + k_3)k_2$$

$$+k_1k_3$$

$$\alpha_1 = k_3l_{hc}l_{ch} + (k_1 + k_3)(k_4 - G\theta) + k_1k_3(k_4 - G\theta)+$$

$$k_1k_2k_3l_{gh}l_{hb}$$

$$\alpha_0 = l_{ch}l_{hc}k_3k_4 - k_1k_3l_{hb}l_{gh} - k_3G\theta l_{ch}l_{hc}$$

$$v_3 = l_{hb}$$

$$v_2 = l_{hb}(k_4 - G\theta) + (k_1 + k_3)l_{hb} + k_3l_{hb}$$

$$v_1 = k_1k_3l_{hb} + (k_1 + k_3)l_{hb} - l_{gh}k_3l_{hb}$$

$$v_0 = k_1k_3l_{hb}(k_4 - G\theta) + k_3l_{hb} - k_1l_{gh}k_3l_{hb}$$

$$\eta_3 = k_a$$

$$\eta_2 = k_2k_a + (k_1 + k_3)k_a$$

$$\eta_1 = l_{ch}k_al_{hc} + l_{ch}l_{hc}k_ak_3 + k_1k_3k_a + (k_1 + k_3)k_2k_a$$

$$\eta_0 = l_{ch}l_{hc}k_ak_3 - k_3l_{ch}l_{hc}k_a + k_1k_3k_2k_a$$

$$m_2 = l_{hb}k_a$$

$$m_1 = l_{hb}(k_1 + k_3)k_a$$

$$m_0 = k_3k_1l_{hb}k_a.$$

The trivial equilibrium π^0 is locally asymptotically stable for sufficiently small values of $\tau_1+\tau_2 > 0$, whenever $G(\theta) = 0$. At drug free equilibrium π^0=(0,0,0,0,0,0,0,0,0,0,0),$G(t) =$ 0,Simplifying (18) gives

$$\eta_0 + v_0 + m_0 + \alpha_0 = (1 - \chi_d)\alpha_3(l_{12} + l_{hc}) > 0 \tag{3.34}$$

and the $Lim_{S\mapsto\infty}F(S) = +\infty$. It shows that all eigenvalues of $F(s) = 0$,have negative real parts.Hence the system is asymptotically stable. The pharmacological implication is that mild pathological defect is not a sufficient condition for drug reabsorption in the physiological compartments,even when the drug toxicity number is greater than one,drug will feasile out as $t \mapsto \infty$.

Lemma 3.2 *:In the presence of pathological defects (Mild Case), the trivial equilibrium* π^0 *remains asymptotically with* $\tau_1 + \tau_2 < \frac{v_2+2m_2}{\eta_2} = T$.

Firstly, we noticed that the condition for asymptotic stability of the drug free equilibrium π^0 are given by

$$ImF(i\omega_0) > 0 \tag{3.35}$$

$$ReF(i\omega_0) = 0 \tag{3.36}$$

where $F(S)$ is defined by (**??**). Next,we implement (**??**) on (**??**):

$$\omega^4 - \omega^3(v_3 sin\omega\tau_2 + \eta_3 sin\omega\tau_1) - ...$$

$$-\omega^2(\alpha_2 + v_2 cos\omega\tau_2 + \eta_2 cos\omega\tau_1 + (cos\omega\tau_1 cos\omega\tau_2 - sin\omega\tau_1 sin\omega\tau_2))$$

$$-\omega((cos\omega\tau_1 sin\omega\tau_2 - sin\omega\tau_1 cos\omega\tau_2) - v_1 sin\omega\tau_2)$$

$$+\alpha_0 + v_0 cos\omega\tau_2 + \eta_3 cos\omega\tau_1 + (cos\omega\tau_1 cos\omega\tau_2 - sin\omega\tau_1 sin\omega\tau_2) = 0.$$

The inequality (**??**) is satisfied when we invoke (**??**) on (**??**),

$$\phi(\tau_1, \tau_2, \omega_0) > \varphi(\tau_1, \tau_2, \omega_0) \tag{3.37}$$

where

$$\phi(\tau_1, \tau_2, \omega_0) = \omega^2 v_2 sin\omega\tau_2 + (cos\omega\tau_1 sin\omega\tau_2 - sin\omega\tau_1 cos\omega\tau_2)m_2\omega^2 \tag{3.38}$$

$$\varphi(\tau_1, \tau_2, \omega_0) = -\eta_2\omega^2 sin\omega\tau_1. \tag{3.39}$$

Next,we find $\phi(\tau_1, \tau_2)$ and $\varphi(\tau_1, \tau_2)$ such that

$$\frac{\phi(\tau_1, \tau_2, \omega_0)}{(\tau_1 + \tau_2)\omega^2} \geq \phi(\tau_1, \tau_2) > \varphi(\tau_1, \tau_2) \geq \frac{\varphi(\tau_1, \tau_2, \omega_0)}{(\tau_1 + \tau_2)\omega^2} \tag{3.40}$$

From (**??**), we have that

$$\frac{\varphi(\tau_1, \tau_2, \omega_0)}{(\tau_1 + \tau_2)\omega^2} \leq |\eta_2| \tag{3.41}$$

Hence we choose $\varphi(\tau_1, \tau_2) = |\eta_2|$,where $\tau_1 + \tau_2 < T$ and $0\omega_0 < \omega_+$.

$$\frac{\phi(\tau_1, \tau_2, \omega_0)}{(\tau_1 + \tau_2)\omega^2} = \frac{v_2 + 2m_2}{\tau_2 + \tau_1} \tag{3.42}$$

By the two inequality (**??**), (**??**) ,gives

$$\tau_1 + \tau_2 < \frac{v_2 + 2m_2}{\eta_2} = T \tag{3.43}$$

$\tau_1 + \tau_2$is the upper bound for which the equilibrium state π^0 remains asymptotically stable.The pharmacological implication is that defect in physiological compartment progresses from mild to acute condition when pathological defect parameters exceed the threshold i.e $\tau_1 + \tau_2 > \frac{v_2+2m_2}{\eta_2}$.

Case1:$\tau_1 \in [0, \tau_{10}^{**}]$ for $\tau_2 > 0$.We analyze the effect of pathological defect from Gastrointesinal tract. Eqaution (33) reduces to

$$F(S, \beta_i, \alpha, v_i, \eta_i, m_i, \tau_2) = P_1(S, \beta_i)[P_{2,4}(S, \alpha_i + \eta_i) + \tag{3.44}$$

$$e^{-S\tau_2} P_{3,5}(S, v_i + m_i)]$$

simplify (**??**) when $F(S) = 0$, and $s = iw$ gives

$$w^4 - (\alpha_3 + \eta_3)iw^3 - (\alpha_2 + \eta_2)w^2 + (\alpha_0 + \eta_0) - (cosw\tau_2 - isinw\tau_2)v_3 iw^3$$

$$-(cosw\tau_2 - isinw\tau_2)(v_2 + m_2)w^2 + (v_1 + m_1)iw(cosw\tau_2 - isinw\tau_2) + \tag{3.45}$$

$$(v_0 + m_0)iw(cosw\tau_2 - isinw\tau_2) = 0$$

separate real from imaginary in (**??**),gives

$$w^4 - (\alpha_2 + \eta_2)w^2 + (\alpha_0 + \eta_0) = -cosw\tau_2 v_3 + cosw\tau_2(v_2 + m_2)w^2 - \tag{3.46}$$

$$-sinw\tau_2(v_1 + m_1)w - cosw\tau_2(v_0 + m_0)$$

$$-(\alpha_3 + \eta_3)w^3 = v_3 sinw\tau_2 - sinw\tau_2(v_2 + m_2)w^2 - \tag{3.47}$$

$$cosw\tau_2(v_1 + m_1)w + sinw\tau_2(v_0 + m_0)$$

By the help of (**??**) and (**??**), we obtained the polynomial of the angular frequency as follows

$$w^8 + ((\alpha_3 + \eta_3)^2 - 2(\alpha_2 + \eta_2))w^6 + ((2(\alpha_0 + \eta_0) +$$

$$(\alpha_2 + \eta_2) - (v_2 + \eta_2))w^4 -$$

$$(-(\alpha_0 + \eta_0)(\alpha_2 + \eta_2) - (v_2 + \eta_2))w^2 + (\alpha_0 + \eta_0)^2 - v_3^2 = 0 \tag{3.48}$$

.Solving (**??**) and (**??**),gives

$$cosw\tau_2 = \frac{D}{D_1}$$

$$\tau_{2j} = \frac{1}{\omega} cos^{-1}(\frac{D}{D_1}) + \frac{2\pi j}{\omega}$$

$j = 0, 1, ...H(42)$

$$D = (w^4 - (\alpha_2 + \eta_2)w^2 + (\alpha_0 + \eta_0))(v_3 - (v_2 + \eta_2)w^2$$

$$+(v_0 + m_0)) - (\alpha_3 + \eta_3)(v_1 + m_1)w^3$$

$$D_1 = v_3(v_3 - (v_2 + \eta_2)w^2 + (v_0 + m_0)) + (v_2 + m_2)(v_3 - (v_2 + \eta_2)w^2 +$$

$$+(v_0+m_0))-(v_0+m_0)(v_3-(v_2+\eta_2)w^2+(v_0+m_0))-(v_1+m_1)^2w^2$$

Let $\lambda(\tau)=\alpha(\tau)+iw(\tau)$, be a purely imaginary roots of (**??**), such that $\alpha(\tau_{2j})=0, \quad w(\tau_{2j})=w$. Next,we establish the transversality condition by differentiating (33),with respect to τ_2.

$$[\frac{ds}{d\tau_2}]^{-1}=\frac{-se^{-s\tau_2}[p_1^1(s,\beta_i)p_{2,4}(s,\alpha_i+\eta_i)+p_{2,4}^1(s,\alpha_i+\eta_i)p_1(s,\beta_i)]}{p_1(s,\beta_i)p_{3,5}(s,v_i+m_i)}+$$

$$\frac{s[p_1^1(s,\beta_i)p_{3,5}(s,v_i+m_i)+p_1(s,\beta_i)p_{3,5}^1(s,v_i+m_i)]}{p_1(s,\beta_i)p_{3,5}(s,v_i+m_i)}+ \tag{3.49}$$

$$+\frac{\tau_2}{s}$$

Substitute $s=iw$ into (**??**). Further simplification gives

$$[\frac{dRe(s)}{d\tau_2}]_{s=iw}^{-1}=\frac{Q_1(\omega,\beta_i,\alpha_i+m_i)+Q_2(\omega,\beta_i,\alpha_i+m_i)}{Q_3(\omega,\beta_i,\alpha_i+m_i)}\neq 0 \tag{3.50}$$

(**??**), satisfy the transverse condition. The implication is that the imaginary root crosses the LHS of the S-plane with a nonzero speed. The pharmacological implication is that pathological defect from the Gastrointestinal tract only, can effect drug reabsorption. Drug saturation equilibrium is locally asymptotically stable if $\tau_2\varepsilon[0,\tau_2^*)$, the model undergo Hoph bifurcation at drug saturation equilibrium when $\tau_2=\tau_2^*$,and a family of periodic solution $\tau_2>\tau_2^*$. Case2 $\tau_1=\tau_2=\tau$

Using same approach in (**??**),equation (**??**) becomes

$$F(S)=P_1(S,\beta_i)[P_2(S,\alpha_i)+e^{-S\tau}P_{3,4}(S,v_i+\eta_i)+e^{-2S\tau}P_5(S,m_i)] \tag{3.51}$$

Simplifying (**??**),gives

$$P_2(S,\alpha_i)+e^{-s\tau}((v_3+\eta_3)s^3+(v_2+\eta_2)+(v_1+\eta_1)s+(v_0+\eta_0))+e^{-2S\tau}(m_2s^2+m_1s+m_0)=0 \tag{3.52}$$

substitute $s=iw$ into (**??**),

$$w^4(cosw\tau+isinw\tau)-iw^3\alpha_3(cosw\tau+isinw\tau)-(cosw\tau+isinw\tau)\alpha_2w^2+...$$

$$(cosw\tau+isinw\tau)\alpha_1iw+(cosw\tau+isinw\tau)\alpha_0++(cosw\tau+isinw\tau)\alpha_2-(v_3+\eta_3)iw^3$$

$$-(v_2+\eta_2)w^2+(v_1+\eta_1)w+(v_0+\eta_0)-(cosw\tau-isinw\tau)m_2w^2+... \tag{3.53}$$

$$+iw(coswτ - isinwτ)m_1 + (coswτ - isinwτ)m_0 = 0$$

Seperate real from imaginary in (**??**), gives

$$v_0 + \eta_0 - (v_2 + \eta_2)w^2 = -w^4 coswτ - \alpha_3 w^3 sinwτ + \alpha_2 coswτ + \alpha_1 wsinwτ...$$

$$-\alpha_0 coswτ + m_2 w^2 coswτ - wm_1 sinwτ - m_0 coswτ \tag{3.54}$$

$$-(v_3 + \eta_3)w^3 + (v_1 + \eta_1)w = -w^4 sinwτ + \alpha_3 w^3 coswτ + \alpha_2 sinwτ - \alpha_1 wcoswτ - ...$$

$$\alpha_0 sinwτ - m_2 w^2 sinwτ - m_2 w^2 sinwτ - wm_1 coswτ + m_0 sinwτ = 0 \tag{3.55}$$

Solving (**??**) and (**??**). We obtained the angular frequency equations as follows

$$w^8 - ((v_3 + \eta_3)^2 + \beta_3^2)w^6 + (m_2^2 + 2(v_3 + \eta_3)(v_1 + \eta_1) -$$

$$(v_1 + \eta_1)^2)w^2 + m_0^2 + \beta_2^2 - (v_0 + \eta_0)^2 = 0 \tag{3.56}$$

There exist atleast a positive root in (**??**). Next, we solve the threshold condition for which Hoph bifurcation exist for (**??**). Our result is defined below;

$$\begin{aligned}
coswτ &= [\frac{(v_0 + \eta_0 - (v_3 + \eta_3)w^2)(-w^4 + \alpha_2 - \alpha_0 - m_2 w^2 + m_2)}{F_1} \\
&\quad \frac{(-\alpha_3 w^3 + \alpha_1 w - m_1)(-(v_3 + \eta_3)w^3 + (v_1 + \eta_1)w)}{F_2}] \\
\tau^* &= \frac{1}{w} cos^{-1}[\frac{(v_0 + \eta_0 - (v_3 + \eta_3)w^2)(-w^4 + \alpha_2 - \alpha_0 - m_2 w^2 + m_2)}{F_1} \\
&\quad \frac{(-\alpha_3 w^3 + \alpha_1 w - m_1)(-(v_3 + \eta_3)w^3 + (v_1 + \eta_1)w)}{F_2}] \\
F_1 &= (-w^4 + \alpha_2 - \alpha_0 - m_2 w^2 + m_2)^2 + \\
&\quad (-\alpha_3 w^3 + \alpha_1 w - m_1)(-\alpha_1 w + \alpha_3 w^3 + m_1 w) \\
F_2 &= (-w^4 + \alpha_2 - \alpha_0 - m_2 w^2 + m_2)^2 + \\
&\quad (-\alpha_3 w^3 + \alpha_1 w - m_1)(-\alpha_1 w + \alpha_3 w^3 + m_1 w)
\end{aligned}$$

Next,investigate the transverse condition $[\frac{ds}{d\tau}]^{-1}$,from (**??**),gives

$$[\frac{d(s)}{d\tau}]^{-1} = \frac{s(P_1^1(s,\beta_i)P_2(s,\alpha_1)e^{s\tau} + P_2^1(s,\alpha_1)P_1(s,\beta_i)e^{s\tau})s}{P_1(s,\beta_i)P_{3,4}(s,v_i + \eta_1) + P_1(s,\beta_i)P_5(s,m_i)e^{-s\tau}} + \frac{\tau}{s} +$$

$$\frac{s(P_1(s,\beta_i)P_{3,4}(s,v_i + \eta_i)e^{s\tau} + P_1(s,\beta_i)P_{3,4}(s,v_i + \eta_1))}{P_1(s,\beta_i)P_{3,4}(s,v_i + \eta_1) + P_1(s,\beta_i)P_5(s,m_i)e^{-s\tau}} +$$

$$+\frac{s(P_1^1(s,\beta_i)P_5(s,m_i)e^{-s\tau})}{P_1(s,\beta_i)P_{3,4}(s,v_i+\eta_1)+P_1(s,\beta_i)P_5(s,m_i)e^{-s\tau}} \tag{3.57}$$

Substitue $s = iw$ into (**??**). Further simplication gives

$$[\frac{dRe(s)}{d\tau}]^{-1}_{s=iw} = \frac{Q_4(\omega,\beta_i,v_i+\eta_i)w[Q_5(\omega,\beta_i,m_i)-Q_6(\omega,\beta_i,\alpha_1)}{Q_3(\omega,\beta_i,\alpha_i+m_i)}+$$

$$\frac{-Q_7(\omega,\beta_i,\alpha_1)-Q_8(\omega,\beta_i,v_i+\eta_i)-2Q_5(\omega,\beta_i,m_i)}{(Q_4(\omega,\beta_i,v_i+\eta_i))^2+4\,(Q_5(\omega,\beta_i,m_i))^2} \neq 0 \tag{3.58}$$

(**??**), satisfy the transverse condition.The implication is that the imaginary root crosses the LHS of the S-plane with a nonzero speed. The pharmacological implication is that pathological defect from the Gastrointestinal tract only,can effect drug reabsorption. Theorem4: The model incorporated with pathological defect **parameters under condition** (**??**), **h**as its drug saturation to be locally asymptotically stable, when $\tau\varepsilon[0,\tau^*)$, its undergo Hoph bifurcation at drug saturation equilibrium when $\tau = \tau^*$, and a familiy of periodic solution at the drug saturation equilibrium when $\tau > \tau^*$.

3.2.3 Direction of Stability

In this section , a thorough analysis on the hoph bifurcation properties shall be discussed. This is attainable by employing the centre manifold theorem and normal form theorem. Let $t = s\tau$,

$A_c(t) = y_1(s\tau)$, $A_h(t) = y_2(s\tau)$, $A_b(t) = y_3(s\tau)$, $A_g(t) = y_4(s\tau)$, $A_{t1}(t) = y_5(s\tau)$, $A_{t2}(t) = y_6(s\tau)$, $A_{pv}(t) = y_7(s\tau)$, $A_k(t) = y_8(s\tau)$, $A_u(t) = y_9(s\tau)$, $E_g(t) = y_{10}(s\tau)$, $E_h(t) = y_{11}(s\tau)$

and $\tau = \tau_2^{**} + \Omega$, where τ_2^{**} is the threshold value for holph bifurcation, $\Omega\varepsilon lR$,assume that $\tau_1^{**} < \tau_2^{**}$,where $\tau_1^{**}\varepsilon(0,\tau_{10})$.The system is transformed into the following FDE in $C([-1,0],lR^{11})$.

$$\dot{u(t)} = L_\mu(u_t) + F(\mu,u_t) \tag{3.59}$$

Where

$$L_\mu : C \to lR^{11} and F : lR \times C \longrightarrow lR^{11}$$

are defined respectively , by

$$L_\mu\phi = \tau_{20}^{**}(X_{1max}\phi(0) + X_{2max}\phi(-\frac{\tau_1^{**}}{\tau_2^{**}}) + X_{3max}\phi(-1) \tag{3.60}$$

$$F(\mu,\phi) = \begin{pmatrix} -l_{hc}\phi_2^2(0) + l_{ch}\phi_1^2(0) + l_{cg}\phi_1^2(0) \\ -l_{ch}\phi_1^2(0) - l_{gh}\phi_4^2(0) + l_{hc}\phi_2^2(0) + l_{hb}\phi_2^2(-\tau_2) \\ -l_{hb}\phi_2^2(-\tau_2) \\ -l_{cg}\phi_1^2(0) - l_{gh}\phi_4^2(0) \\ l_{t1}\phi_5^2(0) - l_{t2}\phi_6^2(0) \\ l_{t2}\phi_6^2(0) - l_{t1}\phi_5^2(0) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$X_{1max} = \begin{bmatrix} -k_1 & l_{max}^{hc} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ l_{max}^{ch} & -k_2 & 0 & l_{max}^{gh} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & l_{max}^{hb} & -k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ l_{max}^{cg} & 0 & l_{max}^{bg} & -k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ k_{t1} & 0 & 0 & 0 & -k_5 & k_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & l_{t1} & k_6 & 0 & 0 & 0 & 0 & 0 \\ k_{pv} & 0 & 0 & 0 & 0 & 0 & -k_7 & 0 & 0 & 0 & 0 \\ k_r & 0 & 0 & 0 & 0 & 0 & 0 & -k_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma 2 & -k_9 & 0 & 0 \\ 0 & l_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{10} & 0 \\ 0 & 0 & 0 & l_3 & 0 & 0 & 0 & 0 & 0 & 0 & -k11 \end{bmatrix}$$

$$X_{2max} = \begin{bmatrix} 0 & 0 & 0 & k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$X_{3max} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -l_{hb} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & l_{hb} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix};$$

By the Reisz representation theorem there exist a matrix function $\eta(\theta, \mu)$ of bounded variation for $\theta\varepsilon[-1, 0]$.

$$L_u\phi = \int_{-1}^{0} d\eta(\theta, \mu)\phi(\theta) \tag{3.61}$$

The matrix function is satisfield for the following condition

$$\eta(\theta, \mu) = \begin{cases} (\tau_{2*} + \mu)(X_{1max} + X_{2max} + X_{3max}), & \theta = 0 \\ (\tau_{2*} + \mu)(X_{1max} + X_{2max}), & \theta\varepsilon[\frac{\tau_{1*}}{\tau_{2*}}, 0) \\ (\tau_{2*} + \mu)(X_{3max}) & \theta\varepsilon(-1, -\frac{\tau_{1*}}{\tau_{2*}}) \\ 0 & \theta = -1 \end{cases}$$

for $\phi \in C([-1, 0], \mathbb{R}^{11})$ define

$$A(\mu)\phi = \begin{cases} \frac{d\phi(\theta)}{d\theta} & -1 \leq \theta \prec 0 \\ \int_{-1}^{0} d\eta(\theta, \mu) & \theta = 0 \end{cases}$$

$$R(\mu)\phi = \begin{cases} 0 & -1 \leq \theta \prec 0 \\ F(\mu, \theta) & \theta = 0 \end{cases}$$

The system (**??**) is equivalent to

$$\dot{u} = A(\mu)u_t + R(\mu)u_t \tag{3.62}$$

where $u_t = u(t + \theta)$

The adjoint operator $A^*(\mu)$ of $A(\mu)$ is defined by

$$A^*\Psi(s) = \begin{cases} \frac{d\Psi(s)}{d\theta} & 0 < s \leq 1 \\ \int_{-1}^{0} d\eta^T(s, 0)\Psi(-s), & s = 0 \end{cases}$$

for $\Psi\varepsilon C([-1, 0], \mathbb{R}^{11})$, $\phi\varepsilon C([-1, 0], \mathbb{R}^{11})$

defined

$$< \Psi(s), \phi(\theta) >= \Psi\bar{(}0)\phi(0) - \int_{\theta=1}^{0} \int_{\xi=0}^{\theta} \bar{\Psi}(\xi - \theta) d\eta \phi(\varepsilon) d\xi$$

$$< \Psi(s), \phi(\theta) >= \Psi\bar{(}0)\phi(0) - \bar{D} \int_{\theta=1}^{0} \int_{\xi=0}^{\theta} e^{-i(\xi-\theta)w\tau} d\eta \phi(\xi) d\xi \tag{3.63}$$

From (**??**) it can be seen that $\pm\, i\tau_2\omega_{2*}$ are the eigenvalues of $A\,(0)$, so $\pm\, i\tau_2\omega_{2*}$ are also the eigenvalues of $A^*\,(0)$, suppose that $q(\theta) = (1, q_2 ... q_i)^T\, e^{i\tau_2\omega_{2*}\theta}$ and $q^*(s) = (1, q_2 ... q_i)^T\, e^{i\tau_2\omega_{2*}s}$ be the eigenvectors for $A\,(0)$ and $A^*\,(0)$ corresponding to $+i\tau_2\omega_{2*}$ and - $i\tau_2\omega_{2*}$ respectively. Then, obtained the vectors as follows

$$A\,(0)\, q(\theta) = iwq(\theta), A^*\,(0)\, q^*(s) = iwq^*(s) \tag{3.64}$$

We compute (**??**) with

$$q(\theta) = q(0)e^{i\omega_{2*}\theta}, q^*(s) = q^*(0)e^{i\omega_{2*}s},$$

$$\begin{bmatrix} -k_1 & l_{max}^{hc} & 0 & k_a e^{-i\omega_{2*}\tau_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ l_{max}^{ch} & -k_2 - l_{hb}e^{-i\omega_{2*}\tau_2} & 0 & l_{max}^{gh} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & l_{hb}e^{-i\omega_{2*}\tau_2} & -k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ l_{max}^{ccg} & 0 & l_{max}^{bg} & -k_4 - k_a e^{-i\omega_{2*}\tau_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ kt1 & 0 & 0 & 0 & -k_5 & k_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & l_{t1} & -k_6 & 0 & 0 & 0 & 0 & 0 \\ k_{pv} & 0 & 0 & 0 & 0 & 0 & -k_7 & 0 & 0 & 0 & 0 \\ k_r & 0 & 0 & 0 & 0 & 0 & 0 & -k_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_2 & -k_9 & 0 & 0 \\ 0 & l_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{10} & 0 \\ 0 & 0 & 0 & l_3 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{11} \end{bmatrix} \begin{pmatrix} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \end{pmatrix}$$

$$i\omega_{2*} \begin{pmatrix} 1 \\ q_2 \\ q_3 \\ q_4 \\ q_5 \\ q_6 \\ q_7 \\ q_8 \\ q_9 \\ q_{10} \\ q_{11} \end{pmatrix}$$

Solving (59) using the matrix above,gives

$$q_2 = \frac{(i\omega_2 + k_1)(l_m^{hc} l_m^{gh} + k_2 k_2 k_1 e^{-i\omega_2\tau_1} + l_m^{hb} e^{-i\omega_2\tau_1} e^{-i\omega_2\tau_2} + l_m^{hc} i\omega_2 k_a e^{-i\omega_2\tau_1})}{l_m^{hc}(l_m^{hc} l_m^{gh} + k_2 k_2 k_1 e^{-i\omega_2\tau_1} + l_m^{hb} e^{-i\omega_2\tau_1} e^{-i\omega_2\tau_2} + l_m^{hc} i\omega_2 k_a e^{-i\omega_2\tau_1})}$$

$$q_3 = \frac{(k_4 + k_a e^{-i\omega_2\tau_1} + w_2)}{l_m^{hc}(l_m^{hc} l_m^{gh} + k_2 k_2 k_1 e^{-i\omega_2\tau_1} + l_m^{hb} e^{-i\omega_2\tau_1} e^{-i\omega_2\tau_2} + l_m^{hc} i\omega_2 k_a e^{-i\omega_2\tau_1})} q_2$$

$$q_4 = \frac{k_2 i w_2 + k_2 k_1 - w^2 l_m^{hc} + l_m^{hc} i w_2 k_1}{(l_m^{hc} l_m^{gh} + k_2 k_2 k_1 e^{-i\omega_2\tau_1} + l_m^{hb} e^{-i\omega_2\tau_1} e^{-i\omega_2\tau_2} + l_m^{hc} i\omega_2 k_a e^{-i\omega_2\tau_1})} +$$
$$\frac{e^{-iw_2\tau_2}(l_{hb} i w_2 + k_1 l_{hb}) - w_2^2 l_m^{hc} + l_m^{hc} i w_2 k_1}{(l_m^{hc} l_m^{gh} + k_2 k_2 k_1 e^{-i\omega_2\tau_1} + l_m^{hb} e^{-i\omega_2\tau_1} e^{-i\omega_2\tau_2} + l_m^{hc} i\omega_2 k_a e^{-i\omega_2\tau_1})}$$

$$q_6 = \frac{k_{t1} l_{t1}}{(k_6 + i w_2)(i w_2 + k_5) - l_{t1} k_6}$$

$$q_5 = \frac{k_{t1} + k_6 q_6}{i w_2 + k_5}$$

$$q_7 = \frac{k_{pv}}{i w_2 + k_7}$$

$$q_8 = \frac{k_r}{i w_2 + k_8}$$

$$q_9 = \frac{\sigma_2 k_r}{(i w_2 + k_8)(i w_2 + k_9)}$$

$$q_{10} = \frac{l_2 q_2}{i w_2 + k_8}$$

$$q_{11} = \frac{l_3 q_4}{i w_2 + k_{11}}$$

$$q_2^* = \frac{(k_a e^{-iw_2\tau_1} l_m^{bg} l_{hb} + l_m^{hc} e^{-iw_2\tau_2}) l_{hb} e^{-iw_2\tau_2}}{l_{hb}[i w_2 + (k_4 + e^{-iw_2\tau_1})(i w_2 + k_3)(i w_2 + k_2 + l_{hb} e^{-iw_2\tau_2} - l_m^{bg} l_m^{gh}}$$

$$q_4^* = \frac{k_a e^{-iw_2\tau_1} + l_m^{gh} q_2^*}{i w_2 + (k_4 + e^{-iw_2\tau_1})}$$

$$q_3^* = \frac{l_m^{bg} q_4^*}{i w_2 + k_3}$$

$$q_5^* = q_6^* = q_7^* = q_8^* = q_9^* = q_{10}^* = q_{11}^* =$$

$$< \Psi(s), \phi(\theta) >= \bar{\Psi(}0)\phi(0) - \bar{D} \int_{\theta=-1}^{0} e^{-i(\xi-\theta)w\tau}(1,,\bar{q_i^*})d\eta(\theta)e^{i\xi w\tau}(1,q_i)^T d\xi$$

$$< \Psi(s), \phi(\theta) >= \bar{\Psi(}0)\phi(0) - \bar{D} \int_{\theta=-1}^{0} e^{i\theta w\tau}(1,\bar{q_i^*})d\eta(\theta)(1,q_i)^T\theta$$

$$= \bar{\Psi(}0)\phi(0) + \bar{D} \int_{\theta=-1}^{0} (1,\bar{q_i^*})e^{-iw\tau}d\eta(\theta)(1,q_i)^T$$

$$= \bar{\Psi}(0)\phi(0) + \bar{D}(1,\bar{q_i^*})X_{2max}(1,q_i)^T + \bar{D}(1,\bar{q_i^*})X_{3max}(1,q_i)^T$$

$$= \bar{D}(1+q_i^*q_i) + \bar{D}(k_aq_3 - k_aq_3q_3^*)e^{-iw\tau_1}\tau_1 + \bar{D}(l_{hb}q_1q_2^* - l_{hb}q_1q_1^*)e^{-iw\tau_2}\tau_2 \quad (3.65)$$

Further simplification of (**??**) gives

$$\bar{D} = \frac{1}{1+q_i^*q_i + (k_aq_3 - k_aq_3q_3^*)e^{-iw\tau_1}\tau_1 + (l_{hb}q_1q_2^* - l_{hb}q_1q_1^*)e^{-iw\tau_2}\tau_2} \quad (3.66)$$

Next, we compute the coordinates to describe the centre manifold C_0 at $\mu = 0$. Let $u_t \varepsilon C$ be the solution of system (**??**) and defined

$$z(t) =< q^*, u_t >, \quad W(t,\theta) = u_t(\theta) - z(t)q(\theta) - \bar{z}\bar{q}(\theta) \quad (3.67)$$

where z and $\bar{z}$ are local coordinate for the centre manifold C_0 in the direction of q^* and $\bar{q^*}$.

On the centre manifold

$$W(t,\theta) = W(z(t),\bar{z}(t),\theta)$$

$$W(z,\bar{z},\theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} \quad (3.68)$$

The existence of (**??**) enables us to reduce (**??**) to an ODE on C_0. When $\mu = 0$.

$$\dot{z}(t) =< q^*, \dot{u_t} > \quad (3.69)$$

$$\dot{z}(t) =< q^*, A(\mu)u_t + R(\mu)u_t > \quad (3.70)$$

$$\dot{z}(t) =< q^*A^*, u_t > + < q^*, R(u_t) > \quad (3.71)$$

$$\dot{z}(t) = iw\tau z(t) + \bar{q^*}(0).f(0,u_t) \quad (3.72)$$

with

$$\bar{q^*}(0).f(0,u_t) \doteq g(z,\bar{z})$$

Thus (**??**), becomes

$$\dot{z}(t) = iw\tau z(t) + g(z,\bar{z}) \tag{3.73}$$

where

$$g(z,\bar{z}) = g_{20}(\theta)\frac{z^2}{2} + g_{11}(\theta)z\bar{z} + g_{02}(\theta)\frac{\bar{z}^2}{2} + g_{21}(\theta)z^2\frac{\bar{z}}{2} + ...$$

by definition

$$u_t(\theta) = u(t+\theta) = W(t,\theta) + 2Re\{z(t), q(t)\}.$$
$$u_t(\theta) = u(t+\theta) = W(t,\theta) + 2Re\{z(t), q(t)\}$$

$$u_t(\theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + (1,q_i)^T e^{iw_0\tau\theta}z + (1,\bar{q_i})^T e^{-iw_0\tau\theta}\bar{z} \tag{3.74}$$

$$F(0,u_t) = \begin{pmatrix} -l_{hc}u_2^2(t) + l_{ch}u_1^2(t) + l_{cg}u_1^2(t) \\ -l_{ch}u_1^2(t) - l_{gh}u_4^2(t) + l_{hc}u_2^2(t) + l_{hb}u_2^2(t-\tau_2) \\ -l_{hb}u_2^2(t-\tau_2) \\ l_{cg}u_1^2(t) + l_{gh}u_4^2(t) \\ l_{t1}u_5^2(t) - l_{t2}u_6^2(t) \\ l_{t2}u_6^2(t) - l_{t1}u_5^2(t) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

Simplify (**??**),gives

$$u_1(t) = z + \bar{z} + W_{20}^1(0)\frac{z^2}{2} + W_{11}^1(0)z\bar{z} + W_{02}^1(0)\frac{\bar{z}^2}{2}$$
$$u_2(t) = zq_2 + \bar{z}\bar{q_2} + W_{20}^2(0)\frac{z^2}{2} + W_{11}^2(0)z\bar{z} + W_{02}^2(0)\frac{\bar{z}^2}{2}$$
$$u_3(t) = zq_3 + \bar{z}\bar{q_3} + W_{20}^3(0)\frac{z^2}{2} + W_{11}^3(0)z\bar{z} + W_{02}^3(0)\frac{\bar{z}^2}{2}$$
$$u_4(t) = zq_4 + \bar{z}\bar{q_4} + W_{20}^4(0)\frac{z^2}{2} + W_{11}^4(0)z\bar{z} + W_{02}^4(0)\frac{\bar{z}^2}{2}$$
$$u_5(t) = zq_5 + \bar{z}\bar{q_5} + W_{20}^5(0)\frac{z^2}{2} + W_{11}^5(0)z\bar{z} + W_{02}^5(0)\frac{\bar{z}^2}{2}$$
$$u_6(t) = zq_6 + \bar{z}\bar{q_6} + W_{20}^6(0)\frac{z^2}{2} + W_{11}^6(0)z\bar{z} + W_{02}^6(0)\frac{\bar{z}^2}{2}$$
$$u_7(t) = zq_7 + \bar{z}\bar{q_7} + W_{20}^7(0)\frac{z^2}{2} + W_{11}^7(0)z\bar{z} + W_{02}^7(0)\frac{\bar{z}^2}{2}$$
$$u_8(t) = zq_8 + \bar{z}\bar{q_8} + W_{20}^8(0)\frac{z^2}{2} + W_{11}^8(0)z\bar{z} + W_{02}^8(0)\frac{\bar{z}^2}{2}$$
$$u_9(t) = zq_9 + \bar{z}\bar{q_9} + W_{20}^9(0)\frac{z^2}{2} + W_{11}^9(0)z\bar{z} + W_{02}^9(0)\frac{\bar{z}^2}{2}$$
$$u_{10}(t) = zq_{10} + \bar{z}\bar{q_{10}} + W_{20}^{10}(0)\frac{z^2}{2} + W_{11}^{10}(0)z\bar{z} + W_{02}^{10}(0)\frac{\bar{z}^2}{2}$$
$$u_{11}(t) = zq_{11} + \bar{z}\bar{q_{11}} + W_{20}^{11}(0)\frac{z^2}{2} + W_{11}^{11}(0)z\bar{z} + W_{02}^{11}(0)\frac{\bar{z}^2}{2}$$
$$u_4(t-\tau_1) = zq_4e^{-iw\tau_1} + \bar{z}\bar{q_4}e^{iw\tau_1} + W_{02}^4(-1)\frac{z^2}{2} + W_{11}^4(-1)z\bar{z} + W_{02}^4(-1)\frac{\bar{z}^2}{2}$$
$$u_2(t-\tau_2) = zq_2e^{-iw\tau_2} + \bar{z}\bar{q_2}e^{iw\tau_2} + W_{02}^2(-2)\frac{z^2}{2} + W_{11}^2(-2)z\bar{z} + W_{02}^2(-2)\frac{\bar{z}^2}{2}$$

Obtain the coefficient

$$g_{20} = q_1(l_{ch}+l_{cg})+q_1(l_{ch}+l_{cg})W_{20}^{(1)}(0)-q_1l_{hc}q_2^2-q_1l_{hc}q_2^2W_{20}^{(1)}(0)-q_2l_{hch}-q_2l_{hch}W_{20}^{(1)}(0)$$

$$-q_2l_{gh}q_4^2-q_2l_{gh}W_{20}^{(1)}(0)q_4^2+l_{hc}q_2q_2^2+l_{hc}q_2q_2^2W_{20}^{(2)}(0)+l_{hb}q_2q_2^2e^{-2iw\tau_2}+l_{hb}q_2q_2^2W_{20}^{(2)}(-2)e^{-2iw\tau_2}$$

$$-l_{hb}q_3q_2^2e^{-2iw\tau_2}-l_{hb}q_3q_2^2W_{20}^{(2)}(-2)e^{-2iw\tau_2}+q_4l_{cg}+q_4l_{cg}W_{20}^{(1)}(0)+q_4l_{gh}q_4^2+q_4l_{gh}q_4^2W_{20}^{(4)}(0)$$

$$+l_{t1}q_5q_5^2+l_{t1}q_5q_5^2W_{20}^{(5)}(0)-l_{t2}q_5q_6^2-l_{t2}q_5q_6^2W_{20}^{(6)}(0)-l_{t1}q_6q_5^2-l_{t1}q_6q_5^2W_{20}^{(5)}+l_{t2}q_6q_6^2+l_{t2}q_6q_6^2W_{20}^{(6)}(0)$$

$$g_{11} = 2q_1(l_{ch}+l_{cg})-l_{hc}q_1\bar{q_2}-l_{ch}q_2-l_{gh}q_2\bar{q_4}+l_{hc}q_2\bar{q_2}+l_{hb}\left(\bar{q_2}\right)^2 q_2-2l_{hb}q_3\bar{q_2}+2q_4l_{cg}+2q_4\bar{q_4}$$

$$+2l_{t1}q_5\bar{q_5}-2l_{t2}q_5\bar{q_6}+2l_{t2}q_6\bar{q_6}-2l_{t2}q_6\bar{q_5}$$

$$g_{02} = q_1(l_{ch}+l_{cg})-l_{hc}q_1\left(\bar{q_2}\right)^2-l_{ch}q_2-l_{gh}q_2\left(\bar{q_4}\right)^2+l_{hc}q_2\bar{q_2}+l_{hb}q_2\left(\bar{q_2}\right)^2 e^{2iw\tau_2}$$

$$-l_{hb}q_3\left(\bar{q_2}\right)^2 e^{2iw\tau_2}+q_4l_{cg}+q_4l_{gh}\left(\bar{q_4}\right)^2+l_{t1}q_5\left(\bar{q_5}\right)^2-l_{t2}q_5\left(\bar{q_6}\right)^2+l_{t2}q_6\left(\bar{q_6}\right)^2-l_{t1}q_6\left(\bar{q_5}\right)^2$$

$$g_{21} = q_1(l_{ch}+l_{cg})+W_{11}^{(1)}(0)(l_{ch}+l_{cg})q_1-q_1l_{hc}\left(q_2\right)^2\bar{q_2}+\bar{q_2}\left(q_2\right)^2 q_1W_1^{(2)}(0)-2l_{ch}q_2W_{20}^{(1)}(0)$$

$$-q_2l_{ch}W_{11}^{(1)}(0)-2l_{gh}q_2\left(q_4\right)^2\bar{q_4}W_{20}^{(4)}(0)-l_{gh}q_2\left(q_4\right)^2\bar{q_4}W_{11}^{(4)}(0)+2l_{hc}q_2\left(q_2\right)^2\bar{q_2}W_{20}^{(2)}(0)$$

$$+l_{hc}q_2\left(q_2\right)^2\bar{q_2}W_{11}^{(2)}(0)+2l_{hb}q_2\left(q_2\right)^2\bar{q_2}W_{20}^{(2)}(-2)e^{-iw\tau_2}+l_{hb}q_2\left(q_2\right)^2\bar{q_2}W_{11}^{(2)}(-2)e^{-iw\tau_2}$$

$$-2l_{hb}q_3\left(q_2\right)^2\bar{q_2}W_{20}^{(2)}(-2)e^{-iw\tau_2}-l_{hb}q_3\left(q_2\right)^2\bar{q_2}W_{11}^{(2)}(-2)e^{-iw\tau_2}+q_4l_{cg}2W_{20}^{(1)}(0)+q_4l_{cg}2W_{11}^{(1)}(0)$$

$$+2q_4l_{gh}\left(q_4\right)^2\bar{q_4}W_{20}^{(4)}(0)+q_4l_{gh}\left(q_4\right)^2\bar{q_4}W_{11}^{(4)}(0)+2l_{t1}q_5\left(q_5\right)^2\bar{q_5}W_{20}^{(5)}(0)+l_{t1}q_5\left(q_5\right)^2\bar{q_5}W_{11}^{(1)}(0)$$

$$-2l_{t2}q_5\left(q_6\right)^2\bar{q_6}W_{20}^{(6)}(0)-l_{t2}q_5\left(q_6\right)^2\bar{q_6}W_{11}^{(6)}(0)+2l_{t2}q_6\left(q_6\right)^2\bar{q_6}W_{20}^{(6)}(0)+l_{t2}q_6\left(q_6\right)^2\bar{q_6}W_{11}^{(6)}(0)$$

$$-2l_{t1}q_6\left(q_5\right)^2\bar{q_5}W_{20}^{(5)}(0)-l_{t1}q_6\left(q_5\right)^2\bar{q_5}W_{11}^{(5)}(0)$$

with

$$W_{20}(\theta) = \frac{ig_{20}q(0)}{\tau_2^*\omega_2}e^{\tau_2^*\omega_2\theta} + \frac{iq(\bar{0})\bar{g_{02}}}{3\tau_2^*\omega_2}e^{-\tau_2^*\omega_2\theta} + E_1 e^{2\tau_2^*\omega_2\theta}$$

$$W_{11}(\theta) = \frac{ig_{11}q(0)}{\tau_2^*\omega_2}e^{\tau_2^*\omega_2\theta} + \frac{iq(\bar{0})\bar{g_{11}}}{\tau_2^*\omega_2}e^{-\tau_2^*\omega_2\theta} + E_1$$

$$E_1 = 2\begin{bmatrix} k_1^* & 0 & 0 & -k_a e^{-2i\tau_1\omega_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_2^* & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -l_{hb}e^{-2i\tau_2\omega_2} & k_3^* & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -v_{mbg} & k_4^* & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -kt1 & 0 & 0 & 0 & k_5^* & -k_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -l_{t1} & k_6^* & 0 & 0 & 0 & 0 & 0 \\ -k_{pv} & 0 & 0 & 0 & 0 & 0 & k_7^* & 0 & 0 & 0 & 0 \\ -k_r & 0 & 0 & 0 & 0 & 0 & 0 & k_8^* & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\sigma_2 & k_9^* & 0 & 0 \\ 0 & -l_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{10}^* & 0 \\ 0 & 0 & 0 & -l_3 & 0 & 0 & 0 & 0 & 0 & 0 & k_{11}^* \end{bmatrix} \times$$

$$\begin{pmatrix} (l_{ch}+l_{cg})q_1^2 - l_{hc}q_2^2 \\ -l_{ch}q_1^2 - l_{gh}q_4^2 + l_{hc}q_2^2 + l_{hb}q_2^2 \\ -l_{hb}q_2^2 \\ -l_{cg}q_1^2 - l_{gh}q_4^2 \\ l_{t1} - l_{t2} \\ l_{t2} - l_{t1} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$E_2 = 2\begin{bmatrix} -k_1 & 0 & 0 & k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_2 + l_{hb} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & l_{hb} & -k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & v_{mbg} & -k_4 + k_a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ kt1 & 0 & 0 & 0 & -k_5 & k_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & l_{t1} & -k_6 & 0 & 0 & 0 & 0 & 0 \\ k_{pv} & 0 & 0 & 0 & 0 & 0 & -k_7 & 0 & 0 & 0 & 0 \\ k_r & 0 & 0 & 0 & 0 & 0 & 0 & -k_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_2 & -k_9 & 0 & 0 \\ 0 & l_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{10} & 0 \\ 0 & 0 & 0 & l_3 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{11} \end{bmatrix} \times$$

$$\begin{pmatrix} (l_{ch}+l_{cg})(q_1^2+(\bar{q_1})^2)-l_{hc}(q_2^2+(\bar{q_2})^2) \\ -l_{ch}(q_1^2+(\bar{q_1})^2)+l_{gh}(q_4^2+(\bar{q_4})^2)+(l_{hc}+l_{hb})(q_2^2+(\bar{q_2})^2) \\ -l_{hb}(q_2^2+(\bar{q_2})^2) \\ -l_{cg}(q_1^2+(\bar{q_1})^2)-l_{gh}(q_4^2+(\bar{q_4})^2) \\ l_{t1}-l_{t2} \\ l_{t2}-l_{t1} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$\begin{aligned}
k_1^* &= 2i\omega_2 + k_1 \\
k_2^* &= 2i\omega_2 + k_2 - l_{hb}e^{-2i\tau_2\omega_2} \\
k_3^* &= 2i\omega_2 + k_3 \\
k_4^* &= 2i\omega_2 + k_4 - k_a e^{-2i\tau_1\omega_2} \\
k_5^* &= 2i\omega_2 + k_5 \\
k_6^* &= 2i\omega_2 + k_6 \\
k_7^* &= 2i\omega_2 + k_7 \\
k_8^* &= 2i\omega_2 + k_8 \\
k_9^* &= 2i\omega_2 + k_9 \\
k_{10}^* &= 2i\omega_2 + k_{10} \\
k_{11}^* &= 2i\omega_2 + k_{11}
\end{aligned}$$

Thus, we have

$$\begin{aligned}
C_1(0) &= \frac{i}{2\tau_{2*}\omega_2}(g_{11}g_{20} - 2\left|g_{11}\right|^2 - \frac{\left|g_{02}\right|^2}{3}) + \frac{g_{21}}{2}, \\
\mu_2 &= \frac{Re\left\{C_1(0)\right\}}{\left\{S'(\tau_2*)\right\}} \\
\beta_2 &= 2Re\left\{C_1(0)\right\} \\
T_2 &= \frac{Im\left\{C_1(0)\right\} + \mu_2 Im\left\{S'(\tau_2*)\right\}}{\tau_{2*}\omega_2*}
\end{aligned} \tag{3.75}$$

Theorem 3.6 *For system (1), if $\mu_2 > 0$ ($\mu_2 < 0$),then the Hoph bifurcation is supercritical, if ($\beta_2 > 0$), then the bifurcating periodic solutions are stable(unstable);if $T_2 > 0, (T_2 < 0)$,then the periodic solutions increases (decreases).*

3.3 Derivation of Pharmacokinetic Parameters.

3.3.0.1 Drug Clearance

In order to ascertain the impact of hepatobiliary on drug clearance,which is defined as the elimination of drug from the systemic compartment,we established equations for drug clearance for each compartment as follows

$$
\begin{aligned}
CL &= V_c k_r \\
&\quad + V_c[\frac{k_a k_2 f_u^{hc} f_u^{ch} f_u^{cg} + V_{max}^{hc} k_4 f_u^{ch} f_u^{cg} + V_{max}^{ch} k_4 f_u^{hc} f_u^{cg} f_u^{ch} + V_{max}^{cg} k_4 k_2 f_u^{hc} f_u^{ch} f_u^{cg}}{k_4 k_2 f_u^{hc} f_u^{ch} f_u^{cg}}] \\
CL_h &= V_c[\frac{k_a(k_h k_{m1} + k_{cat}^h + V_{max}^{hb}) f_u^{hc} f_u^{ch} f_u^{cg}}{k_4 k_2 f_u^{hc} f_u^{ch} f_u^{cg} k_{m1}}] \\
CL_g &= [\frac{\left(k_g k_{m2} + k_{cat}^g + V_{max}^{gh}\right)\left(V_{max}^{hc} f_u^{ch} f_u^{cg} + V_{max}^{ch} f_u^{hc} f_u^{cg} f_u^{ch}\right)}{k_4 k_2 f_u^{hc} f_u^{ch} f_u^{cg}}]
\end{aligned}
$$

3.3.1 Volume of Distribution

The volume of distribution of drug is the ratio of the total amount of drug in the system to the plasma concentration of the drug ,i.e

$$V_{ss} = \frac{\sum_{i=1}^{i=n} A_i}{C_c} \tag{3.76}$$

Simplify (**??**),gives

$$
\begin{aligned}
V_{ss} &= V_c[(\frac{(k_{t1}-\alpha)k_4 k_8 Q_{pv} k_m^g k_{deg}^g + 2k_a(k_{t1}-\alpha)k_4 k_8 Q_{pv} k_m^g k_{deg}^g}{(k_{t1}-\alpha)k_1 k_4 k_8 Q_{pv} k_m^g k_{deg}^g} \\
&\quad + \frac{Q_r k_h \sigma_2 k_8 k_4 Q_{pv}(k_{t1}-\alpha)k_m^g k_{deg}^g + Q_g k_a k_1 k_8 (k_{t1}-\alpha) k_m^g k_{deg}^g}{(k_{t1}-\alpha)k_1 k_4 k_8 Q_{pv} k_m^g k_{deg}^g} \\
&\quad + \frac{2k_{t1} k_a k_4 k_8 Q_{pv} k_m^g k_{deg}^g + k_{cat}^g f_u^g (k_{t1}-\alpha) k_m^g k_{deg}^g k_1 k_8 Q_{pv}}{(k_{t1}-\alpha)k_1 k_4 k_8 Q_{pv} k_m^g k_{deg}^g}) \\
&\quad (\frac{V_{max}^{cg} + V_{max}^{bg} - V_{max}^{gh} + F_a D_i k_a e^{-k_a t}}{k_4}) \\
&\quad + (2 + \frac{Q_r k_a \epsilon(k_{t1}-\alpha) + \sigma_2 Q_r k_a (k_{t1}-\alpha) + 2k_{t1}\epsilon k_8}{(k_{t1}-\alpha)k_1 \epsilon})(V_{max}^{hc} + V_{max}^{ch} - V_{max}^{cg}) \\
&\quad + (\frac{k_m^h k_{deg}^h + k_{cat}^h f_u^h}{k_m^h k_{deg}^h k_2})(V_{max}^{ch} + V_{max}^{gh} - V_{max}^{hc} + V_{max}^{hb}) \\
&\quad \frac{(V_{max}^{hb} + V_{max}^{bg} - V_{max}^{gh} sin(wt))}{k_3}]
\end{aligned}
$$

3.3.1.1 Bioavailability of Drug

Bioavailibilty of EHC drug is define as the ratio of drug amount in urine when it is administered orally to the drug amount in urine when administered intraveneously[Stefan Horkovic-Kovats]. Invoke this definition into model,we obtained bioavailililibility formula as follow

$$B = \frac{F_a(k_3(k_a k_2 + v_{gh} v_{hc})}{(v_{gh} v_{hb} v_{bg} - k_2 k_3 k_4)}$$

Chapter 4

NUMERICAL SIMULATION

This chapter focuses on numerical simulation of physiological based pharmacokinetic model of Enterohepatic drugs that captures nonlinear kinetics and pathological defect.The effect of EHC on pharmacokinetic parameters such as Bioavailabilty and Clearance of the drug are investigated.

Table 4.1: Baseline values, units, ranges, and references for parameters of EHC

Parameter	Baseline value / Units	Range	Reference
k_r	$0.015(h^{-1})$	fixed	Leyanis R.V. (2023)
k_a	$0.995((h^{-1})$	fixed	Alpizar et al.
v_{ch}	$20.05(mgh^{-1})$	fixed	Saganuwan (2021)
v_{bg}	$8.01(mgh^{-1})$	fixed	Saganuwan (2021)
f_{bg}	0.6 (dimensionless)	fixed	Saganuwan (2021)
k_{bg}	4.01 (mgL^{-1})	fixed	Assumed
f_{ch}	0.85 (dimensionless)	fixed	Assumed
k_{ch}	$10.01(mgL^{-1})$	fixed	Assumed
v_{hc}	$11.20(mgh^{-1})$	fixed	Saganuwan (2021)
f_{hc}	0.75 (dimensionless)	fixed	Assumed
k_{hc}	$5.41(mgL^{-1})$	fixed	Assumed
v_{cg}	$17.20mgh^{-1}$	(0, 1]	Assumed
f_{cg}	0.85	(0, 1]	Saganuwan (2021)
k_{cg}	$8.405mgL^{-1}$	fixed	Assumed
q_k	$0.57mgh^{-1}$	fixed	Saganuwan (2021)
q_{pv}	0.6209	(0, 1]	Assumed
v_{gh}	$1.08h^{-1}$	(0, 1]	Manuel (2020)
f_{gh}	0.8	(0, 1]	Manuel (2020)
k_{gh}	5.47	(0, 1]	Leyanis R.V. (2023)
v_{hb}	8.0	(0, 1]	Manuel (2020)
f_{hb}	0.8	(0, 1]	Assumed
τ_2	1	(0, 10]	Assumed
w	varied	(0, 180]	Assumed
ρ_1	varied	1, 6, 18, 48	Assumed
τ_1	0.5	(0, 10)	Assumed
θ	varied	(0, 180]	Assumed
f_a	0.04051	(0, 1]	Assumed
D	300mg	(100, 700)	Saganuwan (2021)
k_{mg}	0.067	fixed	Assumed
k_{catg}	$0.0068h^{-1}$	fixed	Saganuwan (2021)
f_u	0.75	(0, 1]	Assumed
q_g	$0.00101h^{-1}$	(0, 1]	Manuel (2020)
Q_g	$0.2h^{-1}$	(0, 1]	Manuel (2020)
Q_{pv}	$0.8760h^{-1}$	(0, 1]	Manuel (2020)
q_2	$0.108h^{-1}$	(0, 1]	Manuel (2020)
ε	$0.0065h^{-1}$	(0, 1]	Assumed
k_{degh}	$0.25h^{-1}$	(0, 1]	Saganuwan (2021)
k_{degh}	$0.15h^{-1}$	(0, 1]	Saganuwan (2021)
ϕ	$1.5h^{-1}$	(0, 1]	Assumed
τ_1	0.5	(0,10)	Assumed

4.1 Impact of EHC on Drug Clearance

$$CL = V_c k_r + V_c[\frac{k_a k_2 f_u^{hc} f_u^{ch} f_u^{cg} + V_{max}^{hc} k_4 f_u^{ch} f_u^{cg} + V_{max}^{ch} k_4 f_u^{hc} f_u^{cg} f_u^{ch} + V_{max}^{cg} k_4 k_2 f_u^{hc} f_u^{ch} f_u^{cg}}{k_4 k_2 f_u^{hc} f_u^{ch} f_u^{cg}}] \quad (4.1)$$

Taking the second partial of (**??**) with respect to EHC parameter gives

$$\frac{\partial^2 CL}{\partial v_{gh}^2} = \frac{f_{ch} f_{hc} f_{cg} k_a k_g + k_r}{f_{ch} f_{hc} f_{cg} k_1 v_{gh}^3} > 0 \quad (4.2)$$

The second partial derivatives of (**??**),is positive.This suggest that EHC processes atenuate drug clearance.

Drug Clearance CL with EHC	Drug Clearance CL without EHC
0.0984382	0.101076

Table 4.2: Data of CL (with/without EHC). Further validates the claim in (**??**) numerically.

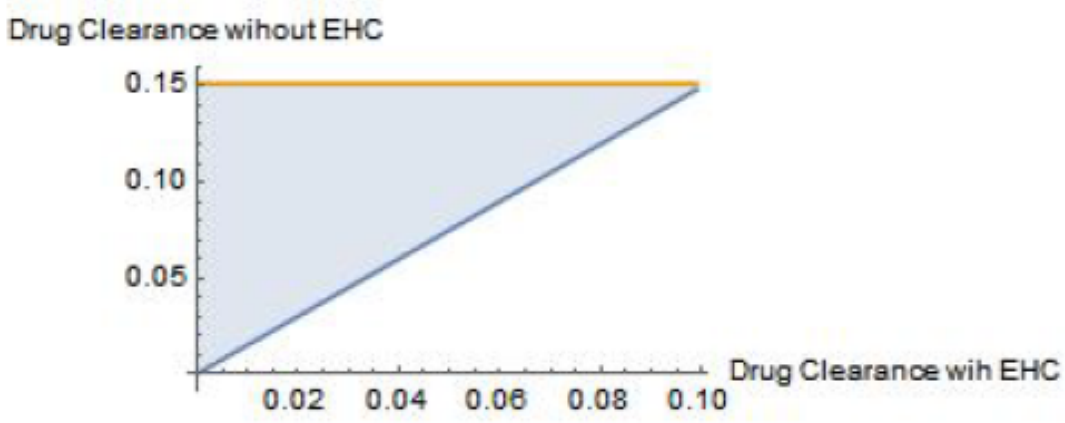


Figure 4.1: Numerical Simulation of CL(with/without EHC)

The figure **??** above shows the simulation of (**??**) with and withouth EHC parameter.The yellow line (drug clearance without EHC parameter),suppresses the blue line(drug clearance with EHC parameter)

4.2 Impact of EHC on Bioavailibility

$$B = \frac{F_a(k_3(k_a k_2 + v_{gh} v_{hc})}{(v_{gh} v_{hb} v_{bg} - k_2 k_3 k_4)} \quad (4.3)$$

Taking the second partial of (**??**) with respect to EHC parameter gives

$$\frac{\partial^2 B}{\partial v_{gh}^2} = -\frac{2F k_2 k_3 v_{bg} v_{hb}(k_a v_{bg} v_{hb} + k_3 k_4 v_{hc})}{(k_2 k_3 k_4 - v_{gh} v_{hb} v_{bg})^3} < 0 \quad (4.4)$$

Bioavailibility without EHC	Bioavailibility with EHC
25.4895	60.8163

Table 4.3: Computed data of Bioavailibility(with/without EHC)

The second partial derivative of (**??**), suggest that EHC process increases bioavailibility.

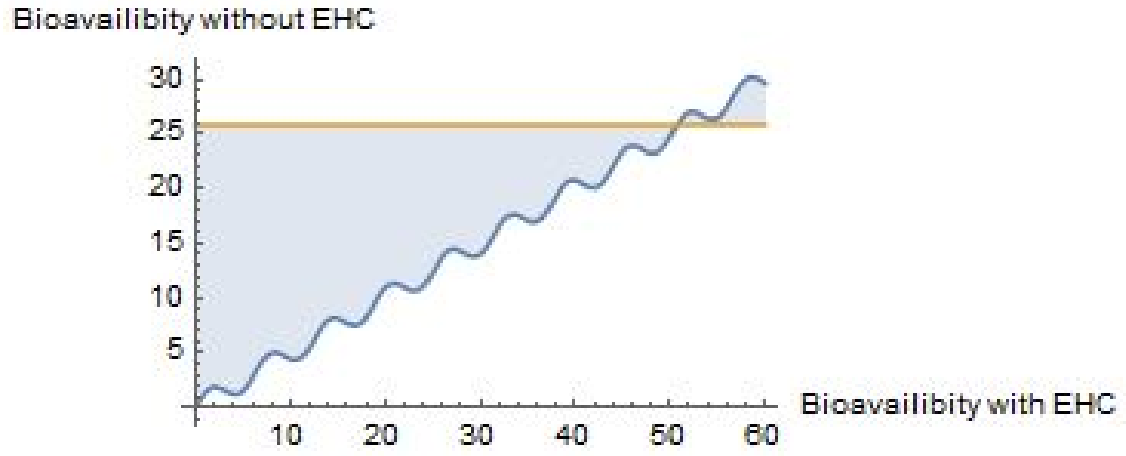


Figure 4.2: Numerical Simulation of Bioavailibility(with/without EHC)

The figure **??** above shows the simulation of (**??**) with and withouth EHC parameter.The blue line (drug bioavailibility with EHC) dorminate the yellow line (drug bioavailibility without EHC parameter).Which validate the claim in (**??**).

4.2.1 Effect of Bile Delay on Drug Reabsorption Number

In this section,we shall investigate numerically the effect of pathological defect on drug reabsorption number in the presence of meal intake.

Bile Delay Parameter(τ_2)	Period of Meal Intake(ρ_1)	Drug ReabsorptionNumber(χ_d)
0.5	1	1.09103
0.5	6	1.11522
0.5	17	0.448162
0.5	30	0.438665
0.5	48	0.517033

Table 4.4: The effect of bile delay is induced as a result of pathological defects (e.g., liver injury, mild case).

Bile Delay Parameter (τ_2)	Period of Meal Intake (ρ_1)	Drug Reabsorption Number (χ_d)
6	1	266.967
6	6	169.167
6	17	109.662
6	30	107.338
6	48	126.514

Table 4.5: Effect of bile delay on the drug reabsorption number (χ_d). The effect of bile delay arises from pathological defects (e.g., severe liver injury or acute gallbladder dysfunction).

	V_{ss} (L/kg)	CL $(L/kg \cdot hr)$	AUC $(mg \cdot kg \cdot hr/L)$
Computed Values	0.821679	0.107387	2793.63
Standard Values	0.75	0.12	2937.3

Table 4.6: Comparison of pharmacokinetic parameters with experimental values.

Parameter Description	**Symbol**	**Sensitivity Index Value**	**Effect Type**	
Fraction in hepatobiliary system	f_{hb}	+10	Positive	
Absorption rate constant	k_a	+20	Positive	
Michaelis–Menten constant (GIT)	k_{mcg}	-320	Strong Negative	Major neg
Bile volume flow rate	v_{hb}	-50	Negative	
Recycling coefficient	ϕ	-40	Negative	
Catalytic rate constant	k_{cath}	≈ 0	Neutral	
Hepatic elimination constant	k_h	≈ 0	Neutral	
Volume of central compartment	v_{cg}	≈ 0	Neutral	

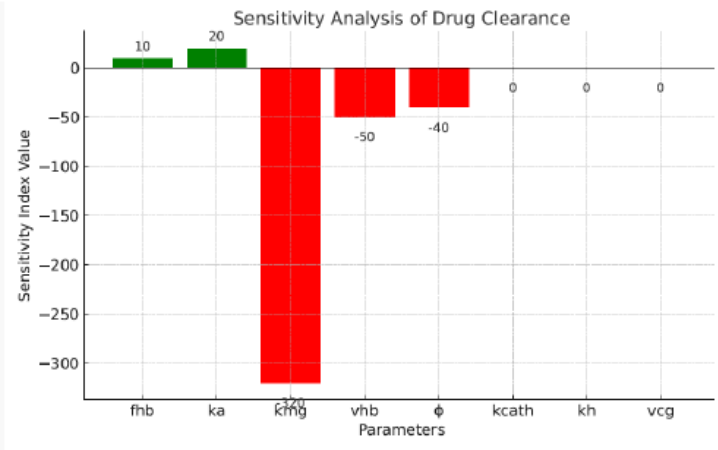


Figure 4.3: Sensitivity Analysis

Figure **??** provides insight into how different pharmacokinetic parameters influence the overall clearance of the drug within the enterohepatic circulation model. Each bar in the plot represents how strongly a parameter affects the rate at which the drug is eliminated from the body. kmg (the Michaelis–Menten constant for gastrointestinal metabolism) shows the largest negative influence on clearance. This means that as kmg increases, drug clearance slows down significantly. In practical terms, a higher kmg reduces the efficiency of metabolic enzymes in the gastrointestinal tract, allowing the drug to remain longer in circulation. This observation agrees with the earlier nonlinear kinetic patterns, where enzyme saturation limited metabolism and prolonged the drug's presence in the system. In contrast, parameters such as ka (absorption rate constant) and fhb (fraction bound in the hepatobiliary system) show small positive effects. A higher ka enhances drug absorption into the bloodstream, which can lead to more efficient elimination, but the impact remains modest compared to the dominant effect of kmg. The bile flow rate (v_{hb}) and the biliary recycling constant ϕ also have noticeable negative effects. When these parameters increase, more of the drug is reabsorbed into the gastrointestinal tract rather than being fully cleared, resulting in delayed elimination and possible re-exposure of the system to the drug. Other parameters such as kcath, kh, and vcg have very small or negligible sensitivity indices, suggesting that their direct effect on clearance is minimal under the current model conditions.

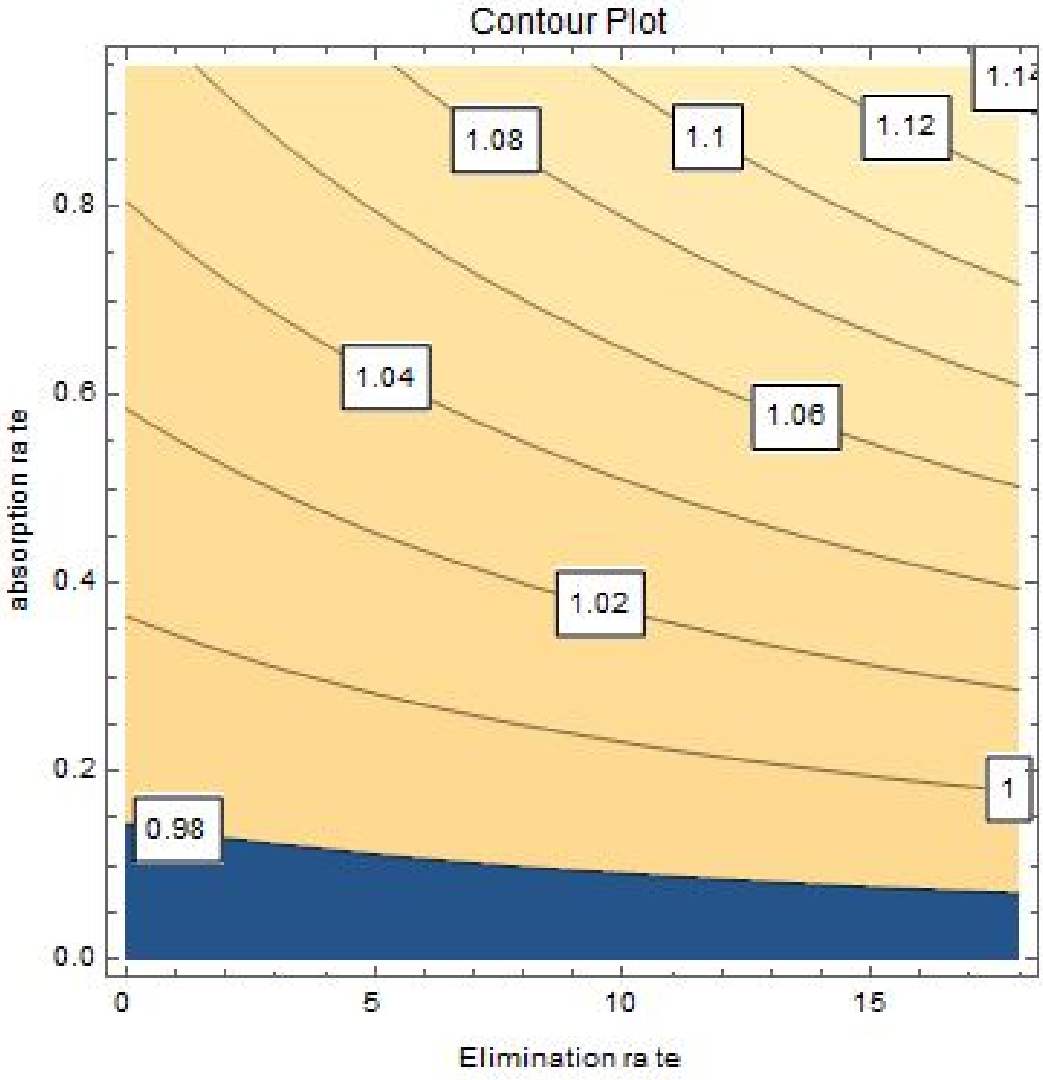


Figure 4.4: Elimination rate

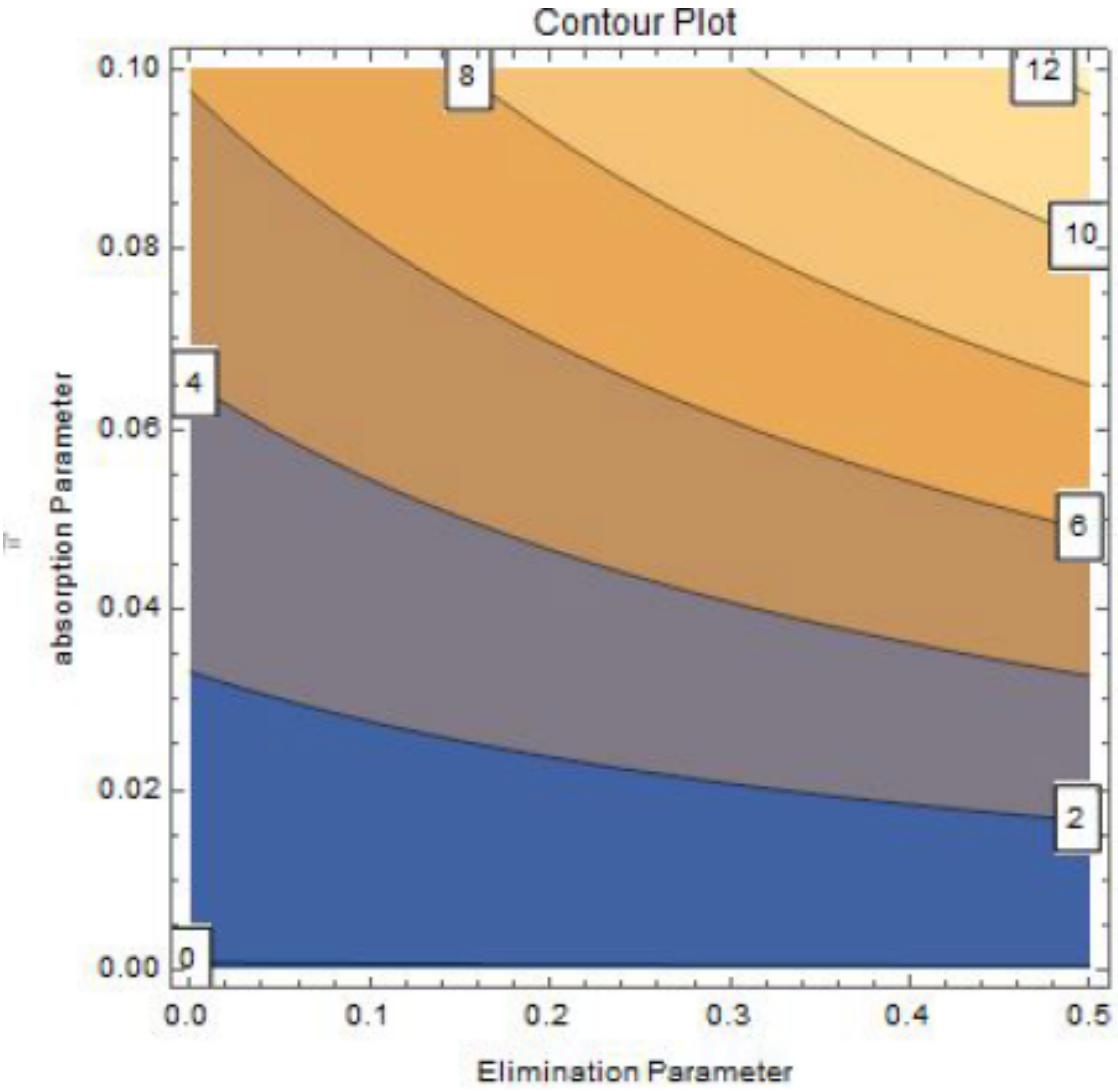
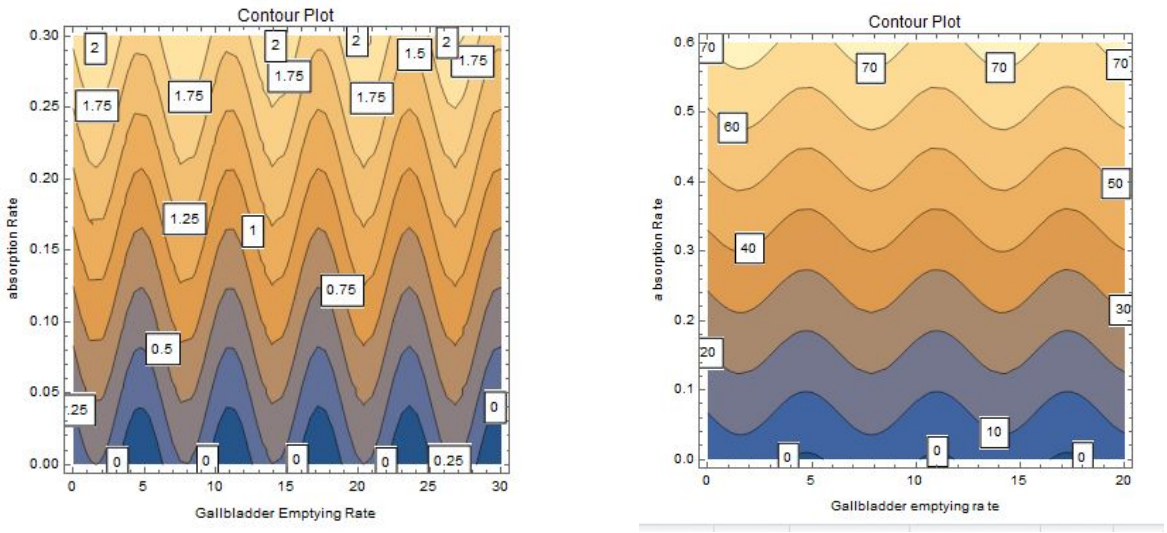


Figure 4.5: Elimination Parameter

At lower elimination rates, the toxicity values of figure **??** stay close to 1.0, meaning that the drug is relatively safe under those conditions. However, as both absorption and elimination increase, the toxicity value rises slightly above 1.1. This suggests that when the drug is absorbed quickly and not eliminated as efficiently, more of it accumulates in the body, leading to a mild increase in toxicity.

Figure **??** also compares absorption and elimination, but this time the contour values range from 0 to 12, showing a wider span of toxicity levels. At the lower end—where both absorption and elimination are small—the toxicity values are very low, between 0 and 2. As both parameters increase, the toxicity gradually rises, reaching the highest levels around 12.

Figure **??** show how toxicity is related to absorption and elimination rates, the wave-



(a) Contour plot(Toxicity Number) **(b)** Contour plot

Figure 4.6: Drug Reabsorption number with Bile delay effect

like contours suggest that the drug does not simply decline over time but instead goes through repeated cycles of reabsorption. This happens because, after being metabolized by the liver, part of the drug isot.

Figure **??** shows toxicity in relation to the gallbladder emptying rate and absorption rate, also reflects this cyclical behavior. Each "wave" represents a phase of drug re-entry into the bloodstream following bile release from the gallbladder. As the gallbladder empties faster or as the absorption rate increases, more drug is reabsorbed, leading to higher toxicity values in those regions. released into the bile, stored in the gallbladder, and later emptied into the intestine. From there, some of the drug is reabsorbed into the bloodstream, causing secondary increases in drug levels.

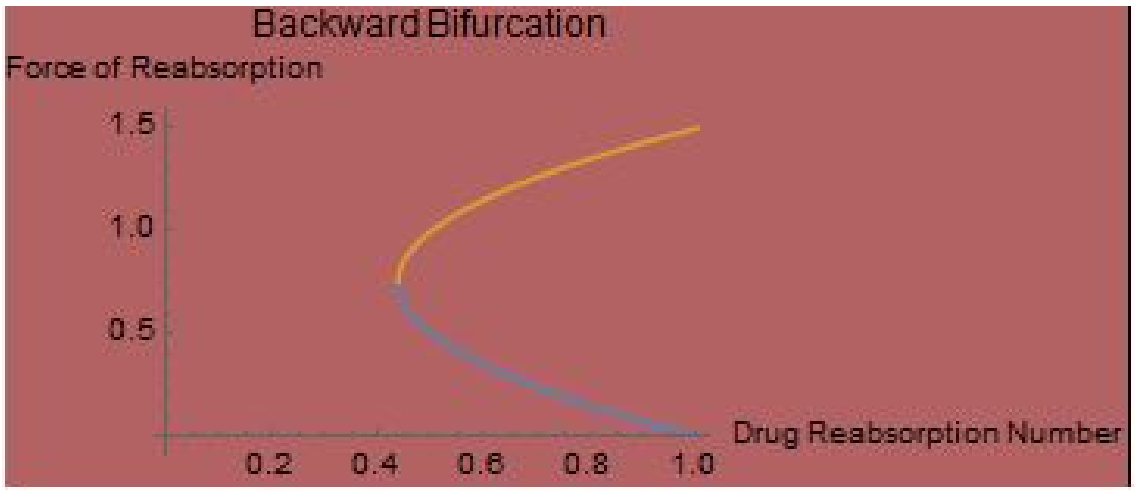
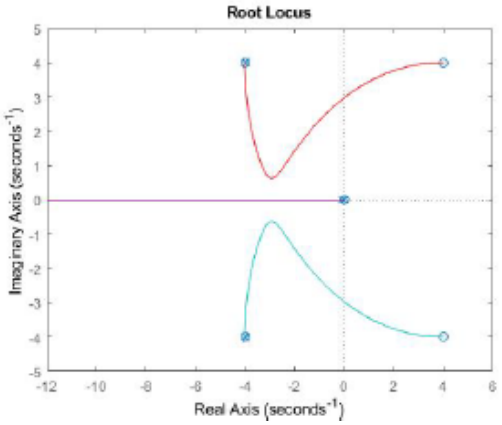
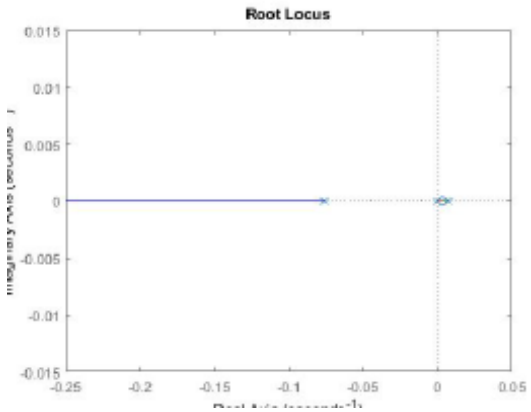


Figure 4.7: Bifurcation Diagram

Figure **??** shows that $\chi_d < 1$ is not a sufficient condition for toxic free state at [0.4 1),this suggest that there exist stable region(grey) for toxicity and unstable region(yellow).



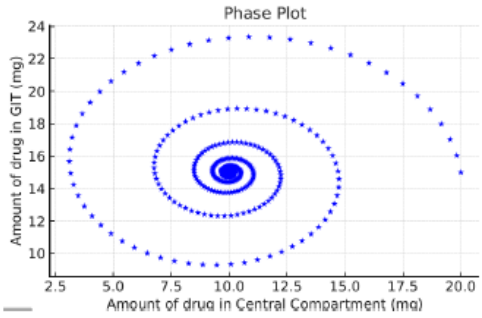
(a) Contour plot(Toxicity Number)



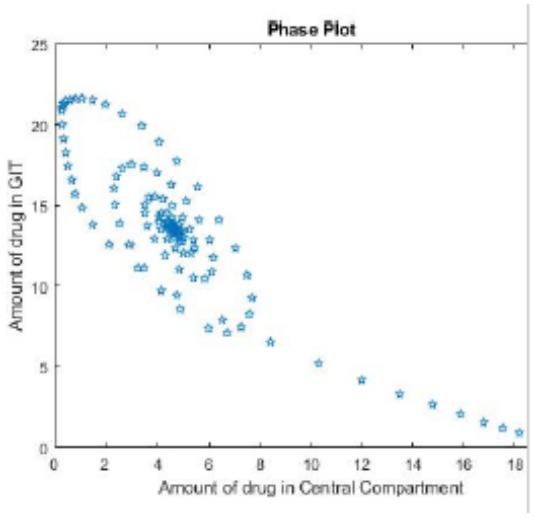
(b) Contour plot

Figure 4.8: Drug Reabsorption number with Bile delay effect

Figure **??** shows the stability plot in the presence and absence of pathological parameters. Figure(**??**) depict the transverse condition as pathological parameters crosses the immaginary plane with non zero speed. The physiological implication is that a patient with systemic disease shouldn't be administered EHC drug, becauses pathological parameters increases drug reabsorption. Thus increases the chances of systemic exposure to the disease.



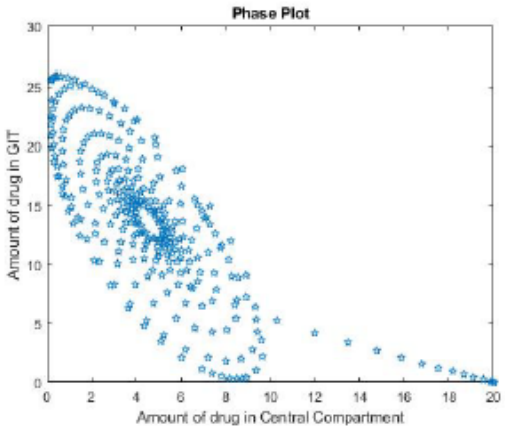
(a) Contour plot(Toxicity Number)



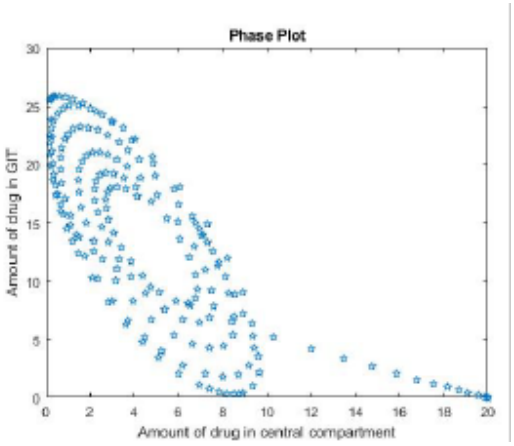
(b) Contour plot

Figure 4.9: Phase Portrait

The spiral plot in figure **??** and **??** establishes the existence of Hoph bification suggesting drug reabsortion in physiological model when $\tau = \tau^*$.



(a) Contour plot(Toxicity Number)



(b) Contour plot

Figure 4.10: Phase Portrait

Figure**??** and **??** define limit circle(familiy of periodic solution) when $\tau > \tau^*$.The pharmacological implication is that pathological defect transit from mild to worse case.

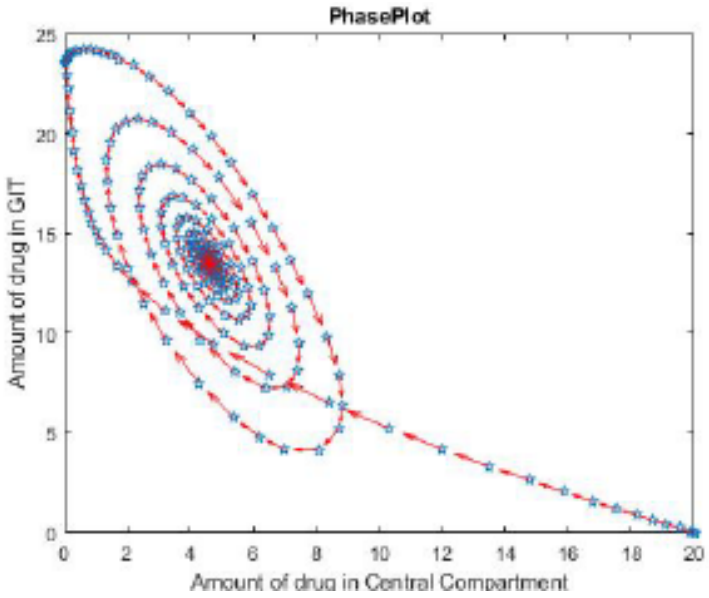
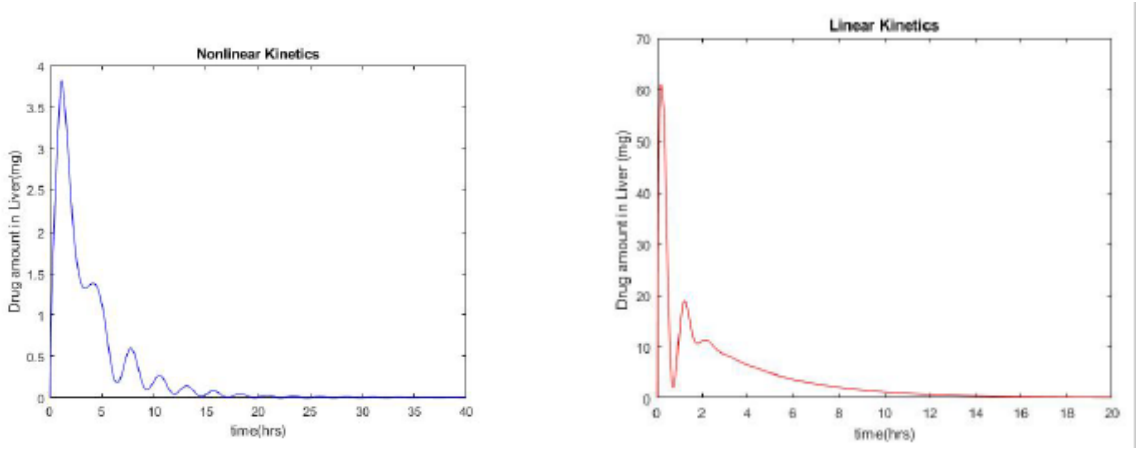


Figure 4.11: Sink spiral of the system at toxicity steady state

Figure **??** represent sink spiral of the system when it is investigated at toxic equilibria. Hence the system is stable at toxic equilibrium



(a) liver nonlinear

(b) Simulation of Liver Compartment(linear Kinetics)

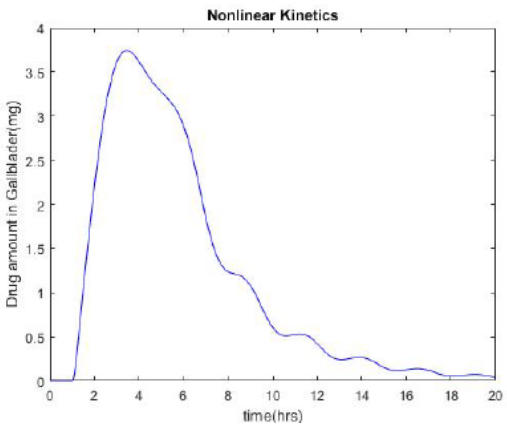
Figure 4.12: Simulation of Liver Compartment

Figure **??** show how the drug behaves in the liver under both linear and nonlinear conditions, highlighting the role of enzyme activity in drug metabolism.

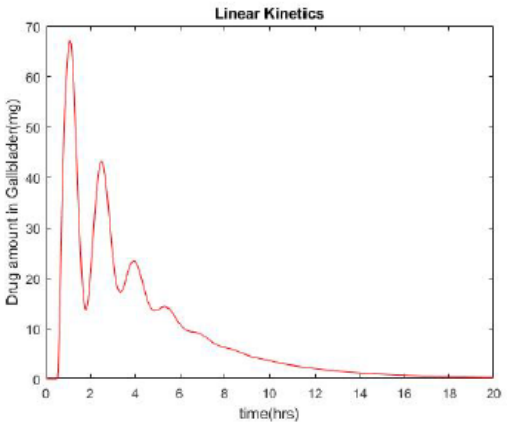
In the figure **??**, the amount of drug in the liver rises and falls repeatedly over time, forming several peaks before it gradually decreases. This fluctuation suggests that the drug is continuously being taken up and metabolized by the liver, possibly with some recycling between the liver and other organs. The gradual reduction in peak height shows that the drug is being cleared at a steady rate, meaning the

enzymes are not saturated and the elimination process stays proportional to the concentration of the drug.

In figure **??**, in the nonlinear kinetics plot, the drug level increases quickly, reaching a single peak of about 0.6 mg at around the fifth hour, then slowly declines. This pattern suggests enzyme saturation — when the enzymes responsible for metabolism are working at full capacity and can't process the drug any faster. As a result, the drug stays longer in the liver before it's fully eliminated.



(a) Nonlinear

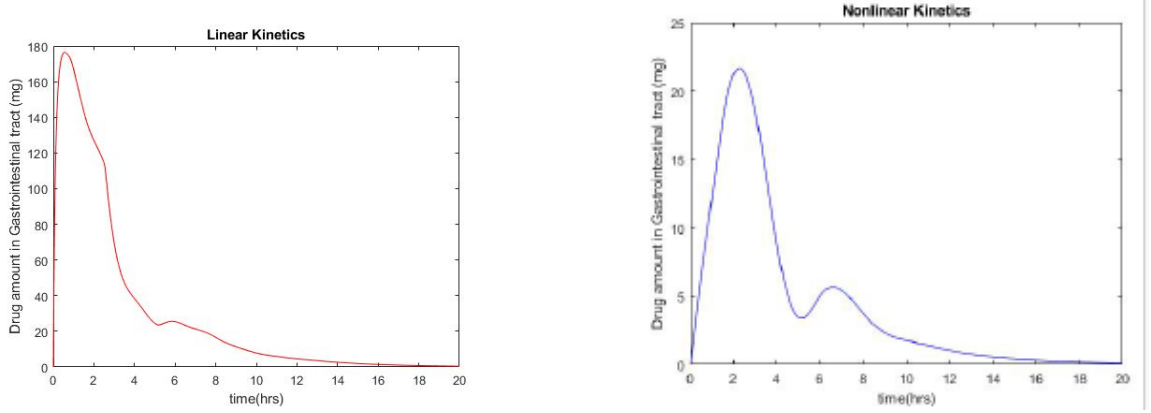


(b) linear plot

Figure 4.13: Simulation of Gallblader Compartment

Figure **??**, shows that the drug level in the gallbladder increases more smoothly to a smaller peak of about 3.5–4 mg around four hours, then declines gradually with only slight fluctuations. The absence of strong multiple peaks means that the recycling process is less active here. This likely happens because the enzymes or transporters responsible for moving the drug into the bile become saturated at higher concentrations. Once these systems reach their limit, less of the drug can enter the bile, and the recycling effect becomes weaker. Figure **??**, shows that the amount of drug in the gallbladder rises sharply to about 65 mg within the first two hours and then shows several smaller peaks that gradually decrease over time. These repeating rises and falls suggest that the drug is being released and reabsorbed in cycles. This pattern is typical of enterohepatic circulation, where the liver sends the drug into the bile, it collects in the gallbladder, and after bile is released into the intestine, part of the drug is absorbed again into the bloodstream. Each small rise on the graph reflects one of these recycling events. Although the overall level of the drug decreases with time, the recycling process slows down its complete elimination from the body.

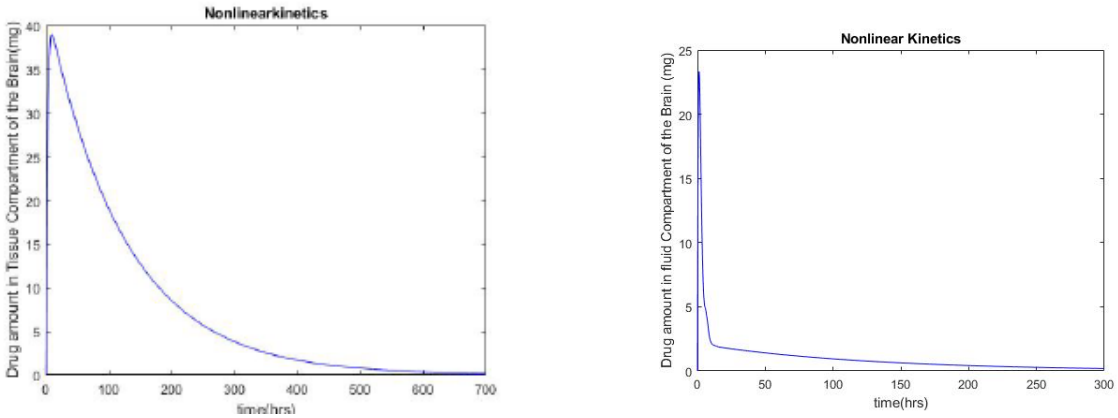
Figure **??**, the amount of drug interacting with enzymes in the gastrointestinal tract rises quickly to about 25 mg within the first five hours, then gradually decreases



(a) git linear **(b)** Git Nonlinear

Figure 4.14: Simulation of GIT Compartment(linear Kinetics

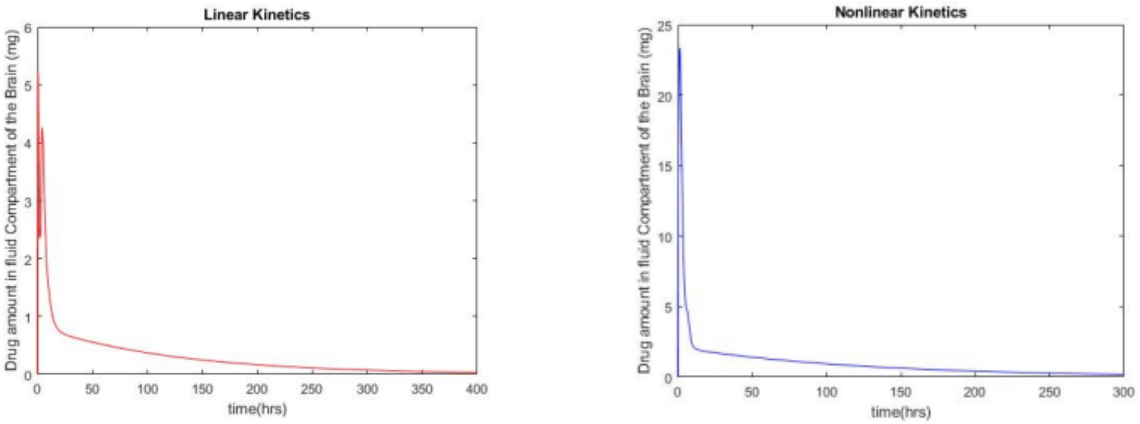
over time. This pattern shows that the drug binds to the enzymes in a steady and predictable way — as more drug is present, more enzymes become occupied, and as the concentration drops, the enzymes are slowly freed again. The smooth rise and fall of the curve indicate that the body's metabolic system is working normally without becoming overloaded. This is typical of a situation where the rate of metabolism depends directly on how much drug is available, meaning the enzymes are not saturated.Figure **??**, the drug reaches a smaller peak of about 4.5 mg at around the same time and then declines gradually. The lower peak suggests that the enzymes in the gut become saturated quite early, so even when more drug is available, the metabolism cannot speed up any further. This happens when the enzyme capacity is limited — once all active sites are occupied, the system cannot process the drug any faster. As a result, the curve shows a short plateau before the decline begins.



(a) linear kinetics **(b)** Nonlinear kinetics

Figure 4.15: Simulation of Fluid Compartment of the Brain

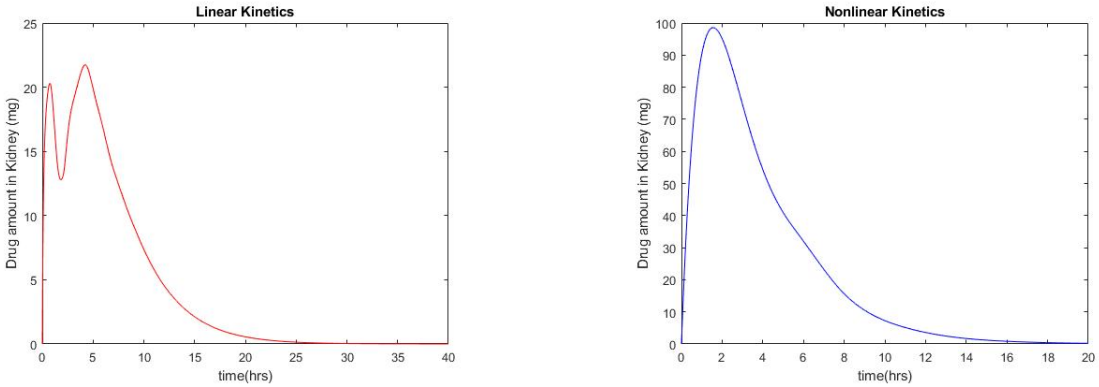
Figure **??**, the amount of drug in the brain fluid compartment rises quickly to a small peak of around 4–5 mg and then decreases sharply during the first few hours. After this initial drop, the decline becomes much slower, extending over several hundred hours. This pattern indicates that the drug enters the brain fairly quickly but leaves it gradually, following a steady first-order process where the rate of elimination depends on the drug's concentration. The smooth decline suggests that there is no saturation of the transport or metabolic processes involved. This behavior is typical of EHC drugs that cross the blood–brain barrier easily and are cleared slowly, without strong binding or accumulation inside brain tissue. Figure **??**, the curve starts much higher, around 25 mg, and then falls very rapidly within the first 10 hours before continuing to decline slowly over time. The sharp initial drop reflects a situation where the brain's elimination mechanisms—such as active transporters or metabolic enzymes—become saturated at high concentrations. Once the drug level drops below that saturation point, the elimination becomes more regular and follows a slower, more proportional decline. The long tail in the graph shows that some of the drug remains in the brain for a long time, likely due to storage or binding within brain tissues.



(a) tissue linear **(b)** Tissue Nonlinear

Figure 4.16: Simulation of Tissue Compartment of the Brain

Figure **??**, the drug amount rises quickly compare to figure **??**, meaning it is absorbed and distributed into the brain almost immediately after administration. After reaching a peak, the amount of drug steadily decreases over time. This slow, smooth decline shows how the drug is gradually broken down and removed from the body.



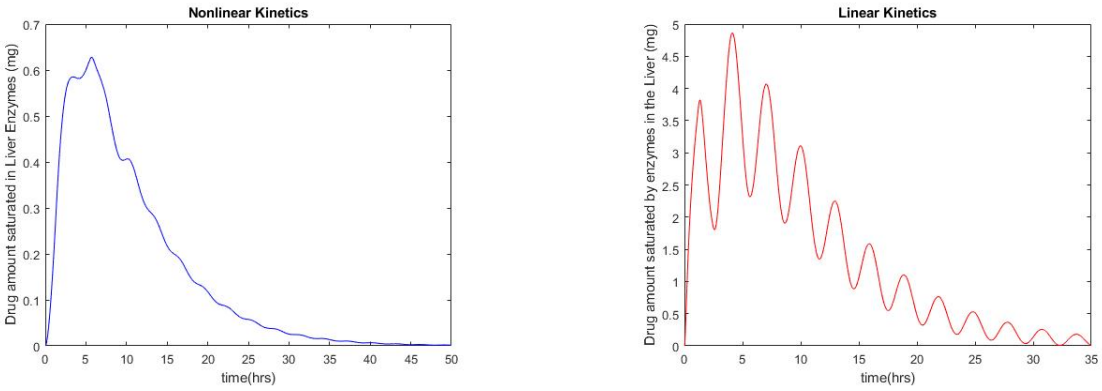
(a) Kidney Linear **(b)** kidney Nonlinear

Figure 4.17: Simulation of kidney Compartment

The plots (figure **??**) show how the drug behaves in the kidney under both linear and nonlinear kinetics.

In figure **??**, the drug amount in the kidney rises quickly, reaching a high peak of about 95 mg around the second hour. This sharp increase suggests that the kidney absorbs the drug rapidly, likely due to enzyme or transporter saturation at higher concentrations. After reaching the peak, the amount of drug decreases gradually as the elimination process begins to dominate.

Figure **??**, the pattern is much smoother and less intense. The drug concentration increases steadily, peaking at around 22 mg near the fourth hour, before slowly declining. The absence of saturation effects means that the rate of elimination remains proportional to the drug concentration throughout the process.

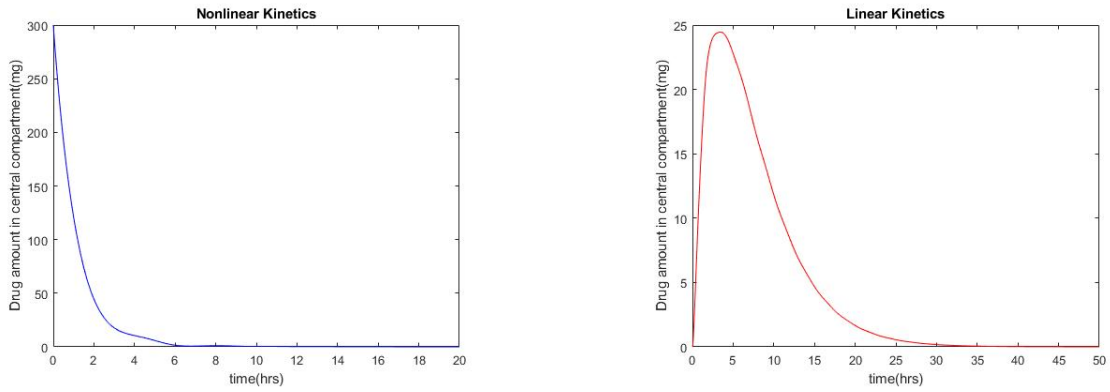


(a) liver enzymes nonlinear

(b) Liver Enzymes linear

Figure 4.18: Simulation of Enzyme Compartment in Liver

Figure **??**, the drug reaches a smaller peak of about 4.5 mg at around the same time and then declines gradually. The lower peak suggests that the enzymes in the gut become saturated quite early, so even when more drug is available, the metabolism cannot speed up any further. This happens when the enzyme capacity is limited — once all active sites are occupied, the system cannot process the drug any faster. As a result, the curve shows a short plateau before the decline begins. In figure **??**, the amount of drug interacting with enzymes in the hepatocyte rises quickly to about 4.8 mg within the first five to ten hours, then gradually decreases over time. This pattern shows that the drug binds to the enzymes in a steady and predictable way — as more drug is present, more enzymes become occupied, and as the concentration drops, the enzymes are slowly freed again. The smooth rise and fall of the curve indicate that the body's metabolic system is working normally without becoming overloaded. This is typical of a situation where the rate of metabolism depends directly on how much drug is available, meaning the enzymes are not saturated.



(a) Nonlinear kinetics

(b) linear kinetics

Figure 4.19: Drug Reabsorption number with Bile delay effect

Figure **??** represents the behavior of the drug under linear kinetics. The curve rises quickly to a peak value of about 25 mg within the first few hours and then declines gradually over time. This pattern suggests that the drug is absorbed rapidly into the central compartment and eliminated at a constant rate that depends on its concentration. In other words, the body clears the drug in proportion to how much of it is present. This kind of response usually occurs when the metabolic and excretory systems are not saturated, which is typical for drugs given at low or moderate doses. Figure **??**, the drug amount starts very high—around 300 mg—and drops sharply within the first few hours. After that, the decline slows down, and there is a small secondary rise or shoulder in the curve around five to six hours. This behavior indicates that the elimination processes have become saturated; the body cannot clear the drug as quickly once certain enzymes or transport systems are working at full capacity. The small secondary rise suggests that some of the drug is being reabsorbed into the bloodstream after biliary excretion, a process known as enterohepatic recirculation.

Chapter 5

SUMMARY AND CONCLUSION

5.1 summary

Enterohepatic circulation (EHC) is one of the major causes of systemic diseases in human with pathological defect which are spurred by drug saturation that has the potency of inducing toxicity in the systemic circulation.It involves influx circulation of synthesize drug(Bile Acids) from the liver to the Gallbladder where it is excreted into the Gastrointestinal tract and subsequently reabsorbed into the liver. Mudra et al., 2011, asserted that cholestasis reduces biliary secretion by seventy to ninety percent in human compartment. This is due to disorder of eneterohepatic circulation process. We present physiological base delay differential equation that consider physiological conditions in the presence and absence of pathological defect.The model is rigorously analyzed on Drug Free Equilibria, Drug Saturation Equilibria, Toxicity Equilibria and Drug Reabsorption Equilibrium. Qualitative analysis such as Local and global stability of the model in the absence of pathological defect is considered. Also, Hoph bifurcation analysis for the model in the presence of Pathological parameter is investigated for which there exist a trans from spiral to periodic phase. The direction of Stability(super critical and sub critical) was thoroughly analyzed.Secondary data is sourced for the model and parameters are fitted using MATLAB software (dde23).

5.2 FINDINGS

The findings of the study are as follows;

1. The drug free equilibrium of EHC model in the absence of pathological defect parameters was locally and globally asymptotically stable when $\chi_d \leq 1$. However,for small values of pathological parameters, EHC model is stable. Also, there exist a unique equilibrium in EHC model in the absence of drug reabsorption free equilibrium.These equilibrium is locally asymptotically stable in the presence of drug forcing function. First and second tangency condition for backward bifurcation is satisfied if reabsorption parameters and pathological paramters are set to zero.

2. There exist condition for which which pathological defect progresses from mild to acute $\tau_1 + \tau_2 > \frac{v_2+2m_2}{\eta_2}$. Also, Pathological defect from the Gastrointestinal tract only, can effect drug reabsorption when $\tau^* = \tau$

3. Drug reabsorption number is a consequence of drug toxicity when $\chi_d \geq 1$.When $\chi_d \leq 1$.It implies that drug reabsorption can be effectively controlled. Drug toxicity decreases with increase in gallbladder emptying and renal elimination, hence reduces chances for systemic diseases such as gallstone, hepatotoxicity, cholelithiasis and bile duct cancer.

4. Sensitivity analysis of the parameters showed that drug clearance decreases with k_m^{cg}(low value) and residual bile volume(ϕ).But increases with absorption of the drug k_a,indicating enzymes saturation.Also,volume of distribution at steady state is attenuated by fraction of unbound drug(f_{hb})and increases by residual bile volume(ϕ),suggesting high binding effect of enzymes with drug decreases v_{ss}.

5. Numerical simulation result showed that nonlinear kinetics initiate oscillation despite the absence of pathological parameters and linear kinetics induces oscillation if and only if pathological parameters are captured in the model.

5.3 Contribution to Knowledge

The study has contributed to knowledge in the following ways;

1. A novel mathematical model for enterohepatic circulation with bile delay effect that captures nonlinear kinetics of drug was formulated.

2. Patients with pathological defect under the administration of EHC drugs are easily exposed to drug toxicity.

3. Drug toxicity can be easily manage in patient without pathological defect.

5.4 Concluding Remarks

A formulated physiological mathematical models consisting of system of nonlinear delay differential equation are used to investigate the dynamics of enterohepatic process and suggest homeostatic mechanism that can disrupt the process. In particular, two special case for the physiological model are thoroughly discussed : pathological defect (Bile delay and Gastrointestinal disorder) and non pathological defect.
The analysis of the model at the drug free equilibria revealed that the model in the absence of pathological defect parameters was locally and globally asymptotically stable when $\chi_d \leq 1$. However,for small values of pathological parameters, EHC model is locally and asymptotically stable. Also, there exist a unique equilibrium in EHC model in the absence of drug reabsorption free equilibrium. These equilibrium is locally asymptotically stable in the presence of drug forcing function. First and second tangency condition for backward bifurcation is satisfied if reabsorption parameters and pathological parameters are set to zero. Analysis of the model with pathological parameters(bile delay and Gastrointestinal disorder) revealed that there exist condition for which which pathological defect progresses from mild to acute $\tau_1 + \tau_2 > \frac{v_2+2m_2}{\eta_2}$. Also, Pathological defect from the Gastrointestinal tract only, can effect drug reabsorption when $\tau^* = \tau$. Sensitivity analysis of the parameters showed that drug clearance decreases with k_m^{cg} (low value) and residual bile volume (ϕ). But increases with absorption of the drug k_a,indicating enzymes saturation. Also, volume of distribution at steady state is attenuated by fraction of unbound drug (f_{hb}) and increases by residual bile volume(ϕ), suggesting high binding effect of enzymes with drug decreases v_{ss}. Numerical simulation result showed that nonlinear kinetics initiate oscillation despite the absence of pathological parameters and linear kinetics induces oscillation if and only if pathological parameters are captured in the model.

Overall, this research provides a solid theoretical foundation for understanding how bile circulation affects drug toxicity. The results can help in designing safer drugs, improving dosage planning, and guiding clinical decisions for patients with liver or bile-related disorders.

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