Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 29s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Pharmacokinetics of Drug Absorption and Metabolism: Mechanisms, Influencing Factors, and Screening Strategies in Drug Development

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Cite this paper as: Wajihus Shams, Monika Acharya, Mrs. Rosmin Jacob, Riya Jaiswal, Renulata, Muhammad Murtaza, Chhavi Juyal, Akash Kumar, Shehu Yusuf, Mohd. Umar Azeem, Rajiv Roy, Hiba Parveen, (2025) Pharmacokinetics of Drug Absorption and Metabolism: Mechanisms, Influencing Factors, and Screening Strategies in Drug Development. *Journal of Neonatal Surgery*, 14 (29s), 574-581.

ABSTRACT

The pharmacokinetics of drug absorption and metabolism play a crucial role in determining therapeutic efficacy and safety. Drug absorption, primarily occurring in the small intestine, is influenced by various physicochemical and physiological factors, including solubility, particle size, gastrointestinal motility, and metabolic enzyme activity. The intestinal epithelium serves as both an absorption site and a barrier, impacting oral drug bioavailability through first-pass metabolism involving Phase I and Phase II reactions. Following absorption, drugs undergo distribution, metabolism, and excretion, with the liver being the primary site of biotransformation, largely mediated by the cytochrome P450 (CYP450) enzyme system. Understanding drug metabolism is critical for pharmaceutical development, particularly in predicting drug interactions and toxicity. This review explores key mechanisms, influencing factors, and screening strategies used in drug absorption and metabolism studies, emphasizing their significance in drug discovery and regulatory sciences.

Keywords: *Drug Absorption, Drug Metabolism, CYP450 Enzymes, Pharmacokinetics, Bioavailability*

1. INTRODUCTION

Pharmacokinetics (PK) is the quantitative examination of drug absorption, distribution, metabolism, and excretion (ADME), which refers to the manner in which the body processes a drug while it performs its actions. PK research includes a lot of different areas, such as looking into changes that happen in different physiological or pathologic conditions, how these changes happen, possible drug–drug interactions (DDI), and ways to make medication more precise, like adjusting the dose. Additionally, it includes studies on healthy subjects. In conjunction, these components of PK enable the personalization of drug dosage regimens to improve therapeutic results [1]. Because of this, a PK study is needed to figure out how the clinical benefits and activities of a drug are related to its underlying mechanisms. The information obtained is essential for the identification and optimization of leads in drug discovery, as well as the design and adjustment of dosage regimens in clinical practice. The accelerated advancements in molecular biology, biochemistry, computer science, and analytical chemistry have significantly contributed to the evolution of PK's complexity [2, 3]. There is a lot of information about the PK of many drugs,

and many technologies have been made to help with PK research. However, new studies have shown that there are new mechanisms that control the PK and the metabolism of drugs [4]. There are new computational modeling algorithms and experimental models that are being made to help us understand how important PK is in a whole-body system, but there are still many problems to solve [5].

Effective drug therapy necessitates the consideration of pharmacokinetic parameters such as absorption and metabolism. The small intestine absorbs many pharmaceuticals. The absorption of drugs is influenced by a variety of factors, such as particle size and drug solubility. The small intestinal epithelium is the main barrier that stops nutrients and xenobiotics that are eaten from being absorbed [6]. It also stops the absorbing surface from being permeable. The absorption of orally administered nutrients is regulated by the small intestinal epithelium, which serves as a primary barrier. It is also implicated in the first-pass metabolism of the pharmaceuticals, which encompasses both phase 1 and phase II reactions. If you take a drug by mouth, its effects depend on its chemical and physical makeup, as well as physiological factors like how fast your stomach empties, how fast your intestines move, their cell membranes, and the fluid that flows through them [7]. One of the most critical prerequisites for the efficacy of oral drug therapy is the adequate absorption of drugs from the digestive tract [8].

Additionally, the body distributes and metabolizes the substance after absorbing it through any route. The primary site of metabolism for the majority of xenobiotics is the liver. The majority of metabolism reactions are catalyzed by the CYP450 superfamily of enzymes [9]. Drug metabolism studies are crucial from both an industrial and fundamental research perspective, as they are employed to investigate drugs in the discovery and development process. Recently, the drugs terfenadine, astemizole, and cisapride were banned because they can cause serious heart rhythm problems when used with CYP450 inhibitors like ketoconazole and erythromycin. This shows how important metabolic studies are. The following are a few of the most frequently employed methods for screening drugs for absorption and metabolism [10].

2. ABSORPTION STUDIES

IN VITRO MODELS

Everted Gut Sac Model

Wilson and Wiseman introduced the first Everted intestinal GI sac model in 1954 to investigate nutrient transport. Subsequently, they altered the methodology to investigate drug transport through the intestine [10, 11]. Male Sprague-Dawley rats weighing between 250 and 300 g are employed. The small intestine of the animal that has been cut off is quickly taken out and put into Krebs-Henseleit bicarbonate buffer solution. The intestine is inverted and fastened at both ends using a glass rod to create an intestinal sac. Next, we use the blunt needle syringe to fill the reservoir with the physiological solution. Additionally, we inject a small air bubble to oxygenate the serosal side of the intestinal segment. The everted vesicle is then put in a container that has the compound of interest dissolved in a physiological saline solution that has a lot of oxygen. We quantify the drug's permeation through the intestinal tissues to the serosal side [12].

This model is capable of quantifying the absorption of test compounds at various locations within the intestine [13]. The model is also used to study efflux transporters, like the 'p' glycoprotein-mediated efflux of [PH] vinblastine, [C] doxorubicin, and verapamil, as well as pro-drug conversion in different parts of the intestine. Therefore, it can be demonstrated to be a critical instrument for the investigation of P-glycoprotein-mediated transport and putative P-glycoprotein substrate modifiers [14]. It is also beneficial for estimating the first-pass metabolism of substances in intestinal epithelial cells. One problem with this method is that it leaves behind the muscularis mucosa, which is usually not taken out of everted sac preparations, and the tissue is not very alive afterward. Consequently, the compound must penetrate all layers of the small intestine, including the musculature. In addition, the buildup of compounds may lead to transport saturation because there isn't much fluid on the serosal side, which is inside the sac. Alam et al. (2011) have recently conducted a review of this model [15]. The age of the animal, sex and species, pathological conditions, chronic therapy, and intestinal selectivity all influence this model. Several experimental factors affect the active transport in the animal's duodenal segments. These include pH, media, temperature, substrate-related factors (like how long it took to harvest the intestine and whether the animal was alive or dead), and the animal's state. This model is very helpful for studying how products change in different parts of the intestines, how drugs interact and move through the body, how excipients and formulations affect transport, and how drugs pass through different types of cells in different types of experiments.

Tissue Mounted in Ussing Chamber

The first drug absorption experiments were done by Ussing and Zerahn using intestinal tissue that was mounted in a Ussing chamber to look into how sodium moved through frog skin that was kept separate from other skin. Later, they modified it to explore the transportation of narcotics. In this system, the drug can expose either the mucosal side (apical side of enterocytes) or the serosal side (basolateral side of enterocytes). Jezyk et al. provide a detailed description of the procedure for conducting intestinal Ussing chamber investigations. They employ sixteen albino rats weighing between 225 and 275 g. We decapitate the animal after an overnight fast. After removing the small intestine, perform small sections of 2.5-3 cm in length. We open these sections along the mesenteric boundary. We affix the tissue in a Ussing chamber and then place it in a 37°C heating block. The block is aerated with 95% CO and 5% nitrous oxide and filled with 5 ml of buffer at 37°C and pH 7.4. After a

15-minute equilibration period, we replace the original buffer with a tepid, fresh buffer solution. We initiate the transport experiments by adding labeled and unlabeled drugs to either the apical or basolateral chamber. Samples of 500 µL are extracted from the receiver chamber every 30 minutes for a maximum of 120 minutes and replaced with a new tepid buffer of the same pH. The liquid scintillation counter is then employed to quantify the sample activity. In order to prevent excessive foaming during the production of buffer solutions containing surfactants or proteins, certain researchers have implemented a stirring rotor system in lieu of a gas lift [17].The utility of chambers in the study of intestinal transport has been acknowledged for a long time, and they have also been employed to investigate the intestinal metabolism of xenobiotics [18]. When equipped with the right electrodes, chambers are useful for studying how compounds affect the electrophysiological parameters of the intestinal barrier. Nevertheless, the integrity and viability of intestinal segments are crucial for the study of this effect. This is made possible by electrophysiological factors like transepithelial resistance (TEER), which protects tissue integrity, and short-circuit current (SSC), which shows the flow of ions across the membrane epithelium [19]. Mannitol and PEG 400 are examples of molecules that can be employed as markers to verify the integrity of intestinal segment cell layers.

Porcine Intestinal Tissue System

It has been shown that a new way of predicting how compounds with different chemical properties will be absorbed by human intestinal tissue that is mounted in an IntestineTM system and filled with biorelevant matrices is possible.estigate the effects of luminal factors on permeability and to investigate regional differences (duodenum, jejunum, and ileum) in compound permeability was also examined. The writers came to the conclusion that this system can be relied on to measure intestinal permeability, whether biorelevant samples are present or not [20].

Cell Culture Models

Cell culture models are based on the assumption that intestinal epithelium, in the form of monolayer of cells, is the main barrier for the drug molecules to reach the systemic circulation. These models are used to perform rapid screening of compounds for their absorption across the intestine. As enterocytes present in the intestinal epithelium play a major role in the absorptive functions, various immortalized tumor cells having intestinal epithelial cells are used to investigate the transport of drugs across the intestinal epithelium. One of the most commonly used cell lines for studying the drug absorption is Caco-2 cell line.

Caco-2 Cells

Caco-2 cells are derived from human colon carcinoma cells and exhibit similarities to intestinal enterocytes. Kim et al. [18] and Pauli-Magnus et al. [19] have recently described the feasibility of conducting drug transport investigations. Polarized monolayers of Caco-2 cells are propagated on semiporous filters.

During this time, these cells express P-glycoprotein on their apical surface. Vectorial transcellular transport, which includes moving from the basal to the apical and from the apical to the basal, can be studied better with these cells. Polycarbonate transwell cell culture insert plates are used to plate cells with a cell count of 2 x $10^{7'}$ cells/well, with passage numbers 33-50. We conduct transport experiments on the seventh day after plating. Approximately one hour before the experiment commences, we substitute the transport medium for the medium in each compartment. Subsequently, the test drug is introduced into either the apical or basolateral compartment for the transport experiments. The quantity of drug present in the opposing compartment (basal or apical) after 1, 2, 3, and 4 hours is quantified in 25 µl aliquots. When you take the apical-to-basal transport rate away from the basal-to-apical transport rate after 4 hours, you get the net basal-to-apical transport rate. We use the following equation to determine the permeability coefficient (P):

PdQ/dt 1/(AC) [cm/sec]

The initial concentrator in the donor chamber is C. (µmol/cm^3), the transport rate is dQ/dt (µmol/sec), and the surface area of the monolayer is A (cm^3).Sixteen We put the possible inhibitor into both compartments and check the same way to see if it stops P-glycoprotein from moving across Caco-2 cell monolayers that are joined together. The experiments are conducted exclusively in wells that exhibit a transepithelial electrical resistance (TEER) of over 350 ohms.After each transport experiment, we check the TEER in all wells to see what effect the test substance had on the monolayer's integrity.They also make transporter proteins and phase II conjugation enzymes, in addition to P-glycoproteins, to mimic a wide range of transcellular pathways and metabolic changes that test substances go through. In contrast to normal cells, Caco-2 cells do not express the cytochrome P450 isozyme, specifically CYP 3A4. Still, vitamin D3 can be used to treat Caco-2 cells chemically and cause the enzyme to work. Employing LCMS and LC-MS-MS in Caco-2 cell permeability assays allows for the simultaneous measurement of multiple compounds. Caco-2 cells are advantageous for the investigation of multiple pharmacokinetic parameters [21].Researchers discovered a similar permeability between the HT29-18-C1 colonic epithelial cell line and Caco-2. It was found that HT29-18-C1 monolayers can be used to study drug permeability at transepithelial electrical resistance (Rt) levels similar to those in the human intestine, without the need for Ca" chelation. Consequently, they provide a valuable alternative to Caco-2 for the simulation of intestinal drug absorption.

Other Cell Lines

Various other cell lines like Madin Darby Canine Kidney (MDCK) cells isolated from a dog kidney by Madin and Darby, Intestinal Epithelial Cell line (IEC) and Rat Intestinal Epithelial (RIE) cell line are also being used for drug intestinal absorption studies [22, 23, 24].

Advantages and Disadvantages of Cell Culture Models

Cell lines offer a variety of advantages:

- Easy to work with once cell culture conditions are established
- Less amount of test drug needed than in other systems
- Importance of different cell populations in absorption and metabolism of drugs can be studied by culturing specific cell types like enterocytes, crypt cells, etc.

Some of the disadvantages associated with the use of cell culture models include. Some are cancerous in origin, and thus, may not mimic the exact physiological features of normal intestinal cells

- Are not necessarily phenotypically stable and properties may differ with passage number
- Great expertise is needed in handling cell culture systems
- Molds, bacteria and fungi can infect the cultured cells and lead to erroneous results

IN SITU MODEL

***In Situ* Rat Gut Perfusion**

The in situ rat gut perfusion technique is a useful way to study intestinal transport because it is more like in vivo absorption experiments because it involves perfusing the intestinal segments in rats that have been put to sleep. The model offers a substantial advantage in that it eliminates biliary excretion and enterohepatic circulation, which enables the study of intestinal events in isolation.Male Wistar rodents, weighing between 225 and 275 g, are employed. Animals that have been fasted overnight are anesthetized with urethane 30 minutes prior to surgery. A midline longitudinal abdominal incision is used to expose the small intestine. After that, a silicon cannula is put into the duodenum, and an outlet cannula is put in just before the ileocecal junction. The intestine is subsequently purged with isotonic saline, and the remaining solution is removed by infusing air. We estimate the drug content of the effluent samples after infusing the drug solution, either with or without an inhibitor. The permeability coefficient of the drug across the small intestinal epithelium is determined by the quantity of the drug measured in the inlet and outlet cannula [25].

In-silico Model

For in-silico predictions of gastrointestinal drug absorption in pharmaceutical products development, SjÖrgen E et al. 2013 successfully developed a mechanistic absorption model. The GI-Sim deployed a compartmental gastrointestinal absorption and transit model as well as algorithms describing permeability, dissolution rate, salt effects, partitioning into micelles, particle and micelle drifting in aqueous boundary layer particle growth and amorphous or crystalline precipitation. The model's overall predictive performance was good in screening the selected APIs [26].

3. METABOLISM STUDIES

An overview of different in vitro models such as supersomes, microsomes, cytosol, S9 fraction cell lines, transgenic cell lines, primary hepatocytes, liver slices, isolated perfused liver with advantages, disadvantages and future prospectives is given by Brandon et al. 2003 [27]. For successful screening of drug candidate's selection of proper models and data interpretation are crucial. Methodologies for investigating drug metabolism at the early drug discovery stage and prediction of hepatic drug clearance and P450 contribution are reviewed by Emoto C et al. 2010. 26Recently, different in vitro and in vivo preclinical experimental models of drug metabolism and drug disposition in drug discovery and development are described in detail by Donglu et al. 2012 [28].

4. IN VITRO MODELS

A variety of in vitro models are employed to conduct drug metabolism investigations. These models assess the metabolism of the test compound using liver slices and hepatocytes. These models are helpful because they show the presence of drug-metabolizing enzymes like CYP450s, as well as other microsomal and cytosolic enzymes and cofactors that help with metabolism. Nevertheless, genetic variations in enzyme expression between individuals result in a variable rate of drug metabolism. *Lamba et al. 2002* [28] talk about these genetic differences that cause CYP 3A-mediated metabolism to be different in humans. These models also allow for the investigation of the compounds' hepatotoxic potential. Nevertheless, these cellular systems are not without their inherent drawbacks. For example, the cells and slices are difficult to freeze and

subsequently thaw for use in assays; the cell culture of hepatocytes is primary and cannot be passed on; and these cellular systems cannot be prepared from liver tissue that has been previously frozen. There is also an alternative method that uses a wide range of enzymes and simple homogenates of liver or other tissues. The homogenate-containing system contains all the enzymes, but it dilutes their cofactors.

Hepatocytes

Hepatocytes are functional elements of the liver, which is the primary site responsible for the metabolism of xenobiotics and drugs. Hepatocytes are isolated from a variety of laboratory animal species, including rat, mouse, dog, monkey, and human liver tissue. Hepatocytes can be used to study many parts of drug metabolism, including metabolite profiling, biotransformation pathway reaction phenotyping, metabolic drug-drug interactions, comparing xenobiotic metabolism to drug metabolism, and getting rid of harmful byproducts of xenobiotic metabolism. The collagenase perfusion method, which was initially devised using rat liver, is now employed to prepare hepatocytes from a variety of animal species. Collagenase perfusion is used because the liver's extracellular matrix is mostly made up of collagen (1 mg/g of wet weight in rodents and 5 mg/g in humans). This means that the liver has the most cells that can live.We obtain a liver and cannulate the portal vein to isolate hepatocytes from the rat liver. 20 to 40 ml/min of Krebs-Ringer bicarbonate buffer, Hanks balanced salt solution, or Dulbecco's phosphate buffered saline is pumped into the liver at 20 to 25 cm of HO to get rid of blood. This is done for 5–10 minutes. Shearing and anoxia, respectively, can cause liver tissue injury when perfusion rates are excessively high or low. The perfusion buffer can have EGTA (ethylene glycol bis ß-aminoethyl ether N, N, N, N tetra-acetic acid) added to it to make it easier to cut the hepatocytes. After adding collagenase to the reservoir, perfuse the liver for an additional 10-15 minutes or until visible softening is evident. Once you break or remove the liver capsule, gently caress the cell mass to separate the liver cells from each other. The cell suspension that results is filtered through a double layer of sterile cotton gauze or nylon mesh with a diameter of 50 to 250 µm. Centrifugation cleans the cells twice, throwing away the cloudy supernatant that has leftover collagenase, nonparenchymal cells, erythrocytes, nonviable hepatocytes, and cell debris. The hepatocytes were then centrifuged again through a porcell density gradient to get the most viable hepatocytes [29]. We then assess the hepatocytes' viability using the trypan blue exclusion assay. Desirable is a viability rate exceeding 90%. Following this, the cells are grown in 100-mm plates that are covered with 95–98% type I collagen at a density of 10' cells per ml of culture medium. We begin by growing hepatocytes in a 1:1 (v/v) solution of Ham's F12 and Williams' medium E. This solution has fetal calf serum, sodium bicarbonate, penicillin, streptomycin, ethanolamine, transferrin, insulin, dexamethasone, glucagon, linoleic acid, glucose, sodium pyruvate, ascorbic acid, and trace elements. Subsequently, they are cultured in serum-free medium in a humidified atmosphere of 5% CO_2/95% air at 37°C. Investigators investigate the drug's metabolism by placing it in distinct wells of the plate, both with and without an inhibitor. Shahi J et al. (2010) and Li, 2014 [32] recently talked about in vitro human hepatocyte-based experimental systems for testing how drugs work in humans, how they interact with each other, and how toxic drugs are.

Precision-cut Liver Slices

Precision-cut liver slices are frequently employed in in vitro metabolism investigations. Metabolism investigations can be conducted using liver slices from a wide range of laboratory animals, including humans. The liver samples are taken and put in Earle's Balanced Salt Solution (EBSS), which is an ice-cold culture medium with 25 mM of D-glucose, 50 µg/ml of gentamicin, and 2.5 µg/ml of fungizone, until the cutting process starts. The medium is pregassed with 95% O and 5% CO [33]. We prepare the tissue for segmentation in tissue cylinders using a motor river tissue coring instrument. 200-300 µm tissue segments are produced in well-oxygenated culture medium using a Krumdieck tissue slicer. After that, the tissue slices are put on steel mesh inserts and kept in polystyrene containers with culture medium at 37°C for 30 minutes in an atmosphere of 95% air and 5% CO. We rotate the roller system at 9 rpm. The ATP levels of the liver segments are restored through pre-incubation. Following this, the tissue is incubated with culture media that contain the test substance, and the medium is analyzed for metabolites [34]. Tissue sections cut with great accuracy from a range of species and organs can be used as great in vitro models for studying how chemicals can harm and change organs specifically [35]. They provide the benefit of preserving tissue architecture and preventing cell injury that may occur during cell isolation procedures. In addition, the technique for producing tissue slices is relatively straightforward and can be applied to tissue slices from a variety of species and organs [36, 37].

Microsomes

CYP3A4 enzymes metabolize most pharmaceuticals administered to humans in the liver. It is crucial to select an appropriate experimental system for the investigation of drug metabolism. In vitro, microsomes of diverse origins are employed. In Zuber et al. 2002, [38], they talk about the experiments that use cytochrome P450 in the context of the system that breaks down drugs. Overall, all of the common animal models used in experiments that study CYP1A-mediated pathways are good, except for the dog. Conversely, the canines are recommended for the modeling of processes that are dependent on CYP2D. The macaque (Maccacus rhesus) system is suggested as a good example of the CYP2C subfamily, which could be the biggest and most complicated. We recommend pig or minipig CYP3A29 as a suitable model for CYP3A. Microsomes are another in vitro way to look into how the test compound is broken down and changed by living things. The liver microsomes are

prepared by promptly removing the organs from the sacrificed animals and placing them in refrigeration. A mechanical meat grinder is used to break these up, and then a Potter Elvehjem homogenizer connected to a motor-driven Teflon pestle (2,500 rpm) is used to mix them in two volumes of 0.25 M sucrose and 0.05 M HEPES (pH 7.4). To get rid of the cell debris, nuclei, and mitochondria, the homogenate is spun at 10,000 g for 20 minutes after being diluted with 25% w/v buffered sucrose. The mitochondrial supernatant is once more centrifuged at 1,000,000 g for 45 minutes. This makes microsomal particles that are mixed with 0.15 M KCl and 0.02 M HEPES (pH 7.4) and then centrifuged at 192,000 g for 45 minutes. The buffered KCI is used to resuspend the cleansed pellet.35 We use the Lowry et al. method to estimate the protein content of the microsomal preparation. Thirty-nine the substrate is preincubated with 50 µg of microsomal protein, 30 mM MgCl, and 50 mM KH_2PO_4, pH 7.4, in a stirring water immersion at 37°C for 2 minutes in order to conduct metabolism experiments. The addition of 4.8 mM NADPH initiates the reaction, which is then incubated for an additional 5 minutes. The reaction is terminated after 5 minutes by the addition of 1.7 ml of ice-cold ethanol. The nature of the inhibition is determined by the incubation conducted in the presence of varying inhibitor concentrations [40].The microsomal preparations can be stored at -80°C or in liquid N for an extended period. Industries or other sources may provide human liver microsomes. The presence of various subfamilies of CYP450 is a drawback of human liver microsomes. The liver is usually thought of as the main source of enzymes, but other organs may also play a role in drug metabolism, depending on the enzyme and senobiotic [41].

Recombinant Systems

Due to the technical difficulties in isolating specific CYP450 enzymes from human liver and the lack of tissues, many recombinant systems expressing CYP450s have been made to make drug metabolism research easier. Several commercially available cell lines have been developed to express individual human CYP450s, such as the V79 Chinese hamster [42] and human lymphoblastoid cell lines. You can also get a lot of CYP450 to show up in yeast and insect cells [43] by using recombinant baculovirus41 and bacteria [44]. According to the activation and inactivation of chemotherapeutic drugs [45], the expression of P450 in mammalian cells is the best way to do toxicological research. One benefit of recombinant systems is that they make a lot of purified enzymes available for studies on drug metabolism. However, their high cost has made them less useful.

5. CONCLUSION

Understanding the pharmacokinetics of drug absorption and metabolism is essential for optimizing therapeutic efficacy and minimizing adverse effects. Drug absorption is influenced by physicochemical properties, gastrointestinal physiology, and metabolic enzymes, while metabolism, primarily occurring in the liver via CYP450 enzymes, determines drug clearance and potential drug interactions. Various in vitro, in vivo, and in silico models are employed to evaluate these processes, aiding in drug discovery and regulatory approval. Advancements in predictive models and precision medicine continue to improve drug development strategies. Future research should focus on personalized pharmacokinetics, enzyme variability, and novel screening technologies to enhance drug safety and effectiveness.

6. ACKNOWLEDGMENTS

I would like to thank all my co-authors for their timely contribution.

Conflict of Interest

No conflict of interest

REFERENCES

[1] Currie GM. Pharmacology, part 2: introduction to pharmacokinetics. Journal of nuclear medicine technology. 2018 Sep 1;46(3):221-30.

[2] Li Y, Meng Q, Yang M, Liu D, Hou X, Tang L, Wang X, Lyu Y, Chen X, Liu K, Yu AM. Current trends in drug metabolism and pharmacokinetics. Acta Pharmaceutica Sinica B. 2019 Nov 1;9(6):1113-44.

[3] Charles B. Population pharmacokinetics: an overview. Australian Prescriber. 2014 Dec 1;37(6).

[4] Heykants J, Van Peer A, Van de Velde V, Van Rooy P, Meuldermans W, Lavrijsen K, Woestenborghs R, Van Cutsem J, Cauwenbergh G. The clinical pharmacokinetics of itraconazole: an overview. mycoses. 1989 Nov;32:67-87.

[5] Wilson TH, Wiseman G. The use of sacs of everted small intestine for the study of the transferen of substances from the mucosal to the serosal surface. J Physiol 1954;123:116-25.

[6] Leppert PS, Fix JA. Use of everted intestinal rings for in vitro examination of oral absorptica potential. J Pharm Sci 1994;83:976-81.

[7] Hillgren KM, Kato A, Borchardt RT. In vitro systems for studying intestinal drug absorption. Med Res Rev 1995;15: 83-109.

[8] Chowhan ZT, Amaro AA. Everted rat intestinal sacs as an in vitro model for assessing absorptivity new drugs. J Pharm Sci 1977;66:1249-53.

[9] Carrreno Gomez B, Duncan R. Everted rat intestinal sacs: a new model for the quantification of P-glycoprotein mediated efflux of anticancer agents. Anticancer Res 2000:20:3157-61.

[10] Barthe L, et al 1998. An improved everted gut sac as a simple and accurate technique to measure paracellular transport across the small intestine. Eur J Drug Metab Pharmacokinet 1998:23(2):313-23.

[11] Alam MA, Al-Jenoobi FI, Abdullah MA. Everted gut sac model as a tool in pharmaceutical research: limitations and applications. J Pharm Pharmacol 2011;64:326-36.

[12] Ussing HH, Zerahn K. Active transport of sodium as the source of electric current in the short- circuited isolated frog skin. Acta Physiol Scand 1951:23:110-27.

[13] Jezyk N, Li C. Stewart BH, et al. Transport of pregabalin in rat intestine and Caco-2 monolayers. Pharm Res 1999;16:519-26.

[14] Ungell AL, Andreason A, Lundin K, Utter L. Effects of enzymatic inhibition and increased paracellular shunting on transport of vasopressin analogues in the rat J. Pharma Sci 1992:81:640-5.

[15] Soderholm JD, Hedman L. Artursson P, et al. Integrity and metabolism of human ileal mucosa in vitro in the Ussing chamber. Acta Physiol Scand 1998;162:47-56. Polentarutti Bl, Peterson AL, Sjoberg AK, Anderberg EKI., Utter LM, Ungell AL. Evaluation of viability of excised rat intestinal segments in the Ussing chamber:investigation of morphology, electrical parameters and permeability characteristics. Pharma Res 1999;16(3):446-54.

[16] Westerhout J, van de Steeq E, Grossouw D, et al. A new approach to predict human intestinal absorption using porcine intestinal tissue and biorelevant matrices. Eur J Pharm Sci 2014,63:167-77.

[17] Kim RB, Fromm MF, Wandel C, et al. The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors. J Clin Invest 1998;101:289-94.

[18] Pauli-Magnus C, von Richter O, Burk O, et al. Characterization of the major metabolites of verapamil as substrates and inhibitors of P-glycoprotein. J Pharmacol Exp Ther 2000;293:376- 82.

[19] Artursson P. Karlsson J. Correlation between oral absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. Biochem Biophys Res Commun 1991;175:880-5.

[20] van Breemen RB, Li Y. Caco-2 cell permeability assays to measure drug absorption. Expert Opin Drug Metab Toxicol 2005;1(2):175-85.

[21] Collet A. Sims E, Walker D, et al. Comparison of HT 29-18-C1 and Caco-2 cell lines as models for intestinal paracellular drug absorption. Pharm Res 1996;13(2):216-21.

[22] Gaush CR, Hard WL, Smith TF. Characterization of an established line of canine kidney cells (MDCK). Proc Soc Exp Biol Med 1966:122:931-5.

[23] Quaroni A, Beaulieu JF. Cell dynamics and differentiation of conditionally immortalized human intestinal epithelial cells. Gastroenterology 1997;113:1198-213.

[24] Blay J, Brown KD. Characterization of an epithelioid cell line derived from rat small intestine: demonstration of cytokeratin filaments. Cell Biol Int Rep 1984:8:551-60.

[25] Komiya 1, Park JY, Kamani A, et al. Quantitative mechanistic studies in simultaneously fluid flow and intestinal absorption using steroids as model solutes. Int J Pharm 1979;4:249-62.

[26] Doluisio JT, Billups NF, Dittert LW, et al. Drug absorption. I. An in situ rat gut technique yielding realistic absorption rates. J Pharm Sci 1969:58:1196-200.

[27] Sjogren E, Westergren 1, Grant L, et al. In silico predictions of gastrointestinal drug absorption in pharmaceutical product development: application of the mechanistic absorption model GI-Sim. Eur J Pharm Sci 2013;49(4):679-98.

[28] Brandon Esther FA, Raap Christiaan D, Meijerman I, et al. An update on in vitro test methods in human hepatic drug biotransformation research:pros and cons. Toxicol Applied Pharmacol 2003;189:233-46.

[29] Emoto C, Murayama N, Rostami-Hodjegan A, et al. Methodologies for investigating drug metabolism at the early drug discovery stage: prediction of hepatic drug clearance and P450 contribution. Current Drug Metab 2010;11(8):678-85.

[30] Zhang D, Luo G, Ding X, et al. Preclinical experimental models of drug metabolism and disposition in drug discovery and development. Acta Pharmaceutica Sinica B 2012;2(6):549-61.

[31] Lamba JK, Lin YS, Schuetz EG, et al. Genetic contribution to variable human CYP3A- mediated metabolism.

Adv Drug Deliv Rev 2002;54(10):1271-4.

[32] Bissell DM, Hammaker LE, Meyer UA. Parenchymal cells from adult rat liver in nonproliferating monolayer culture I Functional Studies. J Cell Biol 1973:59:722-34.

[33] Palma E, Doornebal EJ, Chokshi S. Precision-cut liver slices: a versatile tool to advance liver research. Hepatology international. 2019 Jan 15;13:51-7.

[34] Dewyse L, Reynaert H, van Grunsven LA. Best practices and progress in precision-cut liver slice cultures. International journal of molecular sciences. 2021 Jul 1;22(13):7137.

[35] Olinga P, Schuppan D. Precision-cut liver slices: a tool to model the liver ex vivo. Journal of hepatology. 2013 Jun;58(6):1252-3.

[36] Gandolfi AJ, Wijeweera J, Brendel K. Use of precision-cut liver slices as an in vitro tool for evaluating liver function. Toxicologic pathology. 1996 Jan;24(1):58-61.

[37] Van de Bovenkamp M, Groothuis GM, Meijer DK, Olinga P. Liver fibrosis in vitro: cell culture models and precision-cut liver slices. Toxicology in vitro. 2007 Jun 1;21(4):545-57.

[38] Hutchings SE, Sato GH. Growth and maintenance of HeLa cells in serum-free medium supplemented with hormones. Proc Natl Acad Sci USA 1978;75:901-4.

[39] Sahi J, Grepper S, Smith C. Hepatocytes as a tool in drug metabolism, transport and safety evaluations in drug discovery. Curr Drug Discov Technol 2010;7(3):188-98.

[40] Li AP. In vitro human hepatocyte-based experimental systems for the evaluation of human drug metabolism, drug-drug interactions, and drug toxicity in drug development. Curr Top Med Chem 2014;14(11):1325-38.

[41] Steensma A, Beamand JA, Walters DG, et al. Metabolism of coumarin and 7- ethoxycoumarin by rat, mouse, guinea pig, cynomolgus monkey and human precision-cut liver slices. Xenobiotica 1994:24:893-907.

[42] Zuber R, Anzenbacherova, Anzenbacher P. Cytochromes P450 and experimental models of drug metabolism. J Cell Mol Med 2002;6(2):189-98.

[43] Bend JR, Hook GE, Easterling RE, et al. A comparative study of the hepatic and pulmonary

[44] microsomal mixed-function oxidase systems in the rabbit. J Pharmacol Exp Ther 1972;183:206-

[45] 17. 36. Lowry OH, Rosebrough NJ, Farr AL., et al. Protein measurement and folin phenol reagent. J Biol Chem 1951;93:265-75.

[46] Kroemer HK, Echizen H, Heidemann H, et al. Predictability of the in vivo metabolism of verapamil from in vitro data: contribution of individual metabolic pathways and stereoselective aspects. I Pharmacol Exp Ther 1992:260:1052-7.

[47] Birkett DJ, Mackenize PI, Veronese ME, et al. In vitro approaches can predict human drug metabolism. Trends Pharmacol Sci 1993;4:292.

[48] Doehmer J. Oesch F. V79 Chinese hamster cells genetically engineered for stable expression of cytochrome P450. Methods Enzymol 1991;206:117-23.

[49] Gautier JC, Urban P, Beaune P, et al. Engineered yeast cells as model to study coupling between human xenobiotic metabolizing enzymes. Simulation of the two first steps on benzo[a]pyrene activation. Eur J Biochem 1993;211:63-72.

[50] Lee CA, Kadwell SH, Kost TA, et al. CYP3A4 expressed by insect cells infected with a recombinant baculovirus containing both CYP3A4 and human NADPH-cytochrome P450 reductase is catalytically similar to human liver microsomal CYP3A4. Arch Biochem Biophys 1995;319:157-67.

[51] Guengerich FP, Martin MV, Guo Z, et al. Purification of functional recombinant P450s from bacteria. Methods Enzymol 1996;272:35-44.

[52] Friedberg T, Tritchard MP, Bandera M, et al. Merits and limitations of recombinant models for the study of human P 450 mediated drug metabolism and toxicity:an inter laboratory comparison. Drug Metab Rev 1999;31(2):523-44