Identification of Omeprazole Metabolites in Human Urines and Investigation of Its Pharmacokinetic Variability

Alan Zhong*

Basis Independent Silicon Valley, Santa Clara, California, United States

Abstract: Omeprazole is a commonly prescribed drug used to treat gastroesophageal reflux diseases (e.g., heartburn). Metabolism is the chemical alteration of foods or drugs by the body's natural processes, and metabolites are the substances resulting from this metabolism. Drug metabolite identification is a means of profiling new chemical entities formed from the drug metabolism process. Although most metabolites are considered safe, some metabolites are associated with drug-induced toxicities. Legacy drugs such as omeprazole have not been thoroughly studied as many metabolites remain unknown. In this study, urine samples were used to reveal eight unknown metabolites and structures were tentatively proposed based on ultra-high performance liquid chromatography-mass spectrometry (UPLC-HRMS). Metabolites are not the only concern drugs pose as different drugs have varying interactions with the body based on the patient unique characteristics. Individualized medicine is the concept that different patients should have different dosing regimens as several factors may affect a patient's reaction to a drug, including age, organ function, and concurrent use of other medications. The pharmacokinetic parameters investigated in this study can provide evidence for the importance of individualized medicine which emphasizes that one dose does not fit all people. The different groups that were studied include: young healthy patients, elderly patients, renally impaired patients, and patients that were co-administered with other drugs. For instance, the clearance of renally-impaired patients was significantly decreased compared to other groups as they do not have complete renal function. The group on the other concurrent medication demonstrated drug-drug interactions of omeprazole with armodafinil, osilodrostat, and ritonavir.

1 INTRODUCTION

Metabolites are substances that result from the body's natural metabolic processes which alter the foods eaten or the drugs administered. The metabolites of drugs may have therapeutic or toxic effects which makes metabolite identification an important task in the early stages of drug development. Metabolite identification has been increasingly highlighted in the past few years by the pharmaceutical industry as well as regulatory authorities; however, metabolites of certain legacy drugs, such as omeprazole, have not been thoroughly studied. Omeprazole acts as a proton pump inhibitor that blocks the functioning of the H+/K+ ATPase proton pump in parietal cells to decrease the amount of gastric acid produced (Lorentzon et al., 1985). Omeprazole is a commonly prescribed drug for treating several gastrointestinal symptoms, such as heartburn, peptic ulcer disease, and gastroesophageal reflux disease (Mehraban et al., 2021). Common side effects of omeprazole include headaches, nausea, vomiting, abdominal pain, and increased intestinal gas. Some other rare but serious side effects include increased risk of bone fractures and also increased risk of pneumonia (Omeprazole 2022). Omeprazole has been shown to be metabolized by the family of enzymes, cytochrome P450, with two specific subclasses of CYP2C19 and CYP3A4 (Kanazawa et al., 2002). After oral administration of omeprazole, it is reported that about 80% of the metabolites are excreted through urine while the rest is primarily excreted through bile (Andersson et al., 1993).

Ultra-high performance liquid chromatography coupled with high-resolution mass spectrometry (UPLC-HRMS) was utilized to detect and profile omeprazole metabolites in human urine samples. Tandem Mass Spectrometry (MS/MS) was employed to elucidate novel omeprazole metabolites and the structures of which were proposed by analyzing the fragment ions present in the tandem mass spectra. The mass spectra were generated by an Orbitrap mass analyzer that measures the frequencies of axial oscillations of an ion, which is subsequently converted to the mass-to-charge ratios (m/z) of the corresponding ion through Fourier transformation.6 After the UPLC-HRMS data acquisition, data mining of omeprazole metabolites was carried out using Compound Discoverer 3.2.

The metabolites of a drug are not the only factor to be considered when viewing a drug's physiochemical properties, its pharmacokinetic profile should also be carefully considered. Pharmacokinetics is the study of the

* Corresponding author: alanzhong2006@gmail.com

fate of drugs upon administration to the body. A typical pharmacokinetic process consists of four phases: absorption, distribution, metabolism, and excretion (also known as ADME). Noncompartmental analysis (NCA) is a well-established model in the field of pharmacokinetic analysis. NCA is model-independent, and therefore it does not rely on models of the organ or tissue systems, but rather is built upon algebraic equations to estimate pharmacokinetic parameters.

2 EXPERIMENTAL

2.1 UPLC-HRMS

Due to limited access to scientific instrumentation, and for practical purposes, the UPLC-HRMS dataset was obtained from a case study provided by Thermo Fisher Scientific. Thermo Fisher Scientific reported that the urine samples collected were from 0-3, 3-5-, and 5-7-hours post-dose and were prepared using solid-phase extraction. These samples were then analyzed by a UPLC system, equipped with a 150 × 2.1, 1.9 µm Hypersil GOLD column. A gradient elution was used, as the composition of the mobile phase changes over the time course. Mobile phase A and B consisted of water and acetonitrile, respectively, containing 0.1% formic acid in both and a constant flow rate. The gradient utilized for chromatographic separation is visualized in Table 1.

Table 1 LC gradient used for metabolite separation

Time (min)	%A	%B	Flow (µL/min)
0.0	98	2	400
1.0	98	2	400
5.0	60	40	400
8.0	10	90	400
8.5	10	90	400
9.0	98	2	400
15.0	98	2	400

Following liquid chromatography, mass spectrometry was performed on a Q Exactive benchtop Orbitrap mass spectrometer. The mass spectrometer was operated in positive ionization mode. The ionization was carried out through Heated Electrospray Ionization (HESI) Probe using sheath gas and auxiliary gas of 40 and 15 respectively (arbitrary unit), and vaporizer temperature of 450 °C. The mass spectrometry analysis process is detailed as follows: first, solvated analytes are introduced to the mass spectrometer from liquid chromatography and these analytes were subsequently ionized to form positively charged species. These ions were then transferred through the ion optics via a quadrupole field which also allows for filtration of analyte ions with a specific m/z. The quadrupole field is generated from four cylindrical rods with two rods of similar charges facing one another. Each rod is equipped with a direct current voltage and a superimposed alternating current voltage. All full MS scans were followed by a MS^2 ion fragmentation scan to enable data-dependent acquisition (DDA). DDA mode allows the mass spectrometer to select ions with specific m/z from the first stage in tandem mass spectrometry and analyze the fragments of that specific ion, and this systematically assembles MS/MS data from all ions present in the initial scan. Passing the quadrupole field, the ions enter an Orbitrap mass analyzer which measures the m/z of the analyte ions. Specifically, the Orbitrap consists of a coaxial inner spindle-like electrode that has ionized compounds axially rotating around it with a barrel-like electrode cortex. The Orbitrap then measures the specific oscillation patterns of the ions, and through Fourier transformation, produces the m/z of the analyte ions.

2.2 Compound Discoverer 3.2

The application, Compound Discoverer 3.2, was used to analyze the mass spectra produced by UPLC-HRMS. The processing workflow is set to "MetID w Stats Expected and Unknown w Background Removal." For study factors and values, the time points of 0-3h, 3-5h, 5-7h, and 7-9h are inputted under categorical factors. All four samples will be kept under the label "Sample" under the "Sample Type" tab. In the "Generate Expected Compounds" node under the Workflows page, the target compound is set to omeprazole with the chemical formula of $C_{17}H_{19}N_3O_3S$, with dearylation set to "True," and All Phase I and Phase II transformation selected.

2.3 Pharmacokinetic Analysis

Datasets were collected from an online database, PK-DB, which provides open access to data collected from clinical studies and related meta-information including characteristics of the subjects (age, gender, smoking status, etc.), applied interventions (route of administration, dose level, substance, etc.), and time-course plasma concentrations of the test articles. As omeprazole is the focus of the present study, the studies involving omeprazole were filtered and the PK parameters obtained from the varying groups of individuals were examined. The studied patient groups include healthy young adults, elderly, renally impaired, and people who were on other medications - including armodafinil, osilodrostat, and ritonavir. Major PK parameters computed include: elimination rate constant = $-k_e$ (slope of the elimination phase), elimination half-life = $Ln[2]/-k_e$, AUC_{inf} (Area Under the Curve to infinity) = $AUC_{last} + Clast/k_e$, MRT (mean resonance time) = AUMC/AUC, clearance = $dose/AUC_{inf}$, volume of distribution = $dose/AUC_{inf}/k_e$, and oral bioavailability = dose-normalized AUC_{PO}/AUC_{IV}.

3 RESULTS

3.1 Detection and Identification of Omeprazole Metabolites

Table 2 shows the formula, m/z, retention times, and mass errors (provided for the parent ion only) of the protonated omeprazole metabolites as well as their corresponding fragmented ions.

Most of the metabolites produced were a result from phase I metabolism which includes reactions such as oxidation, reduction, and dealkylation. OME3, OME6, OME7 were all products from oxidation. OME3 first underwent oxidation reactions and were left with several possible structures for these metabolites which is shown by the number in the parentheses. OME6(1) and OME6(2) both represent possible structures based on the fragmentation pattern in the mass spectra. OME7 also has two possible structures. OME1 underwent a dealkylation reaction and then a reduction reaction. Phase II metabolites formed from conjugation reactions were also found, including OME8 and OME9. OME8 was a product of a sulfation reaction where a sulfone group was added; while OME9 was the result of a glucuronidation reaction which involves the addition of a glucuronic acid moiety.

Table 2 Summary of the MS/MS analysis. Metabolites with structure proposed are color-coded red which are shown in Figure 1.

Metabolite compound	Elemental Composition	m/z	Retention Time(min)	Δmass error (ppm)
Omeprazole	$C_{17}H_{20}N_3O_3S^+$	346.1232	5.004	-1.39
	$C_9H_{12}NO_2S^+$	198.0578		
	$C_8H_{10}NO_2^+$	152.0701		
	$C_8H_9N_2O^+$	149.0706		
	$C_8H_{10}NO^+$	136.0756		
	$C_8H_{11}N^+$	121.0886		
	$C_7H_8N^+$	106.0653		
OME1	$C_{16}H_{17}N_3O_2S^+$	316.1107	4.85	-1.25
	$C_8H_9N_2OS^+$	181.0425		
	$C_8H_{10}NOS^+$	168.0474		
	$C_8H_{12}NO_2^+$	154.0859		
	$C_8H_9N_2O^+$	149.0707		
	$C_8H_{11}NO^+$	137.0832		
	$C_7H_{10}N^+$	108.0811		
OME2	$C_{17}H_{18}N_3O_3S^+$	344.1052	4.939	-0.92
	$C_{16}H_{15}N_3O_3S^+$	329.0820		
	$C_{16}H_{13}N_3O_2S^+$	311.0719		
	$C_9H_{10}NO_2S^+$	196.0423		
	$C_8H_9N_2O^+$	149.0712		
	$C_8H_7N_2O^+$	147.0552		
OME3	$C_{17}H_{18}N_3O_4S^+$	360.1002	4.663	-1.30
	$C_{16}H_{13}N_3O_3S^+$	327.0672		
	$C_9H_{10}NO_3S^+$	212.0371		
	$C_9H_{10}NO_3^+$	180.0651		
	$C_8H_8NO_2^+$	150.0546		
	$C_8H_9N_2O^+$	149.0706		
OME4	$C_{17}H_{20}N_3O_3^+$	314.1490	4.794	-1.70
	$C_{16}H_{17}N_3O_3^+$	299.1257		
	$C_{16}H_{16}N_3O_3^+$	298.1177		
	$C_{16}H_{15}N_3O_2^+$	281.1150		
	$C_8H_7N_2O^+$	147.0548		
	$C_8H_{12}NO^+$	138.0912		
	$C_7H_9NO^+$	123.0682		

OME6	$C_{17}H_{20}N_3O_4S^+$	362.1091	4.909	-1.22
	$C_{17}H_{18}N_3O_3S^+$	344.1042		
	$C_9H_{12}NO_3S^+$	214.0527		
	$C_9H_{13}NO_2^+$	167.0937		
	$C_8H_{10}NO_2^+$	152.0702		
	$C_8H_9N_2O^+$	149.0706		
	$C_8H_{11}N^+$	121.0885		
	$C_8H_{10}N^+$	120.0807		
OME7	$C_{17}H_{20}N_3O_5S^+$	378.1106	5.507	-1.29
	$C_9H_{12}NO_4S^+$	320.0475		
	$C_8H_7N_2O_2S^+$	195.0218		
	$C_9H_{14}NO_3^+$	184.0964		
	$C_9H_{12}NO_2^+$	166.0858		
	$C_8H_{10}NO_2^+$	152.0701		
	$C_8H_9N_2O^+$	149.0705		
	$C_8H_{11}N^+$	121.0884		
OME8	$C_{17}H_{20}N_3O_6S_2^+$	426.0782	4.525	-1.23
	$C_{17}H_{20}N_3O_3S^+$	346.1209		
	$C_9H_{14}NO_2^+$	168.1015		
	$C_9H_{13}NO^+$	151.0987		
	$C_8H_{10}N^+$	120.0807		
	$C_7H_9^+$	93.07028		
OME9	$C_{23}H_{28}N_3O_9S^+$	522.1536	3.96	-0.87
	$C_{17}H_{20}N_3O_3S^+$	346.1211		
	$C_9H_{14}NO_2^+$	168.1015		
	$C_9H_{13}NO^+$	151.0987		
	$C_9H_{12}NO^+$	150.0911		
	$C_7H_7N_2O^+$	135.0552		
	$C_{18}H_{10}N^+$	120.0807		
	$C_7H_7N_2O^+$	93.0703		

Eight metabolites were detected and six of their structures were proposed based on the MS^2 fragmentation patterns:

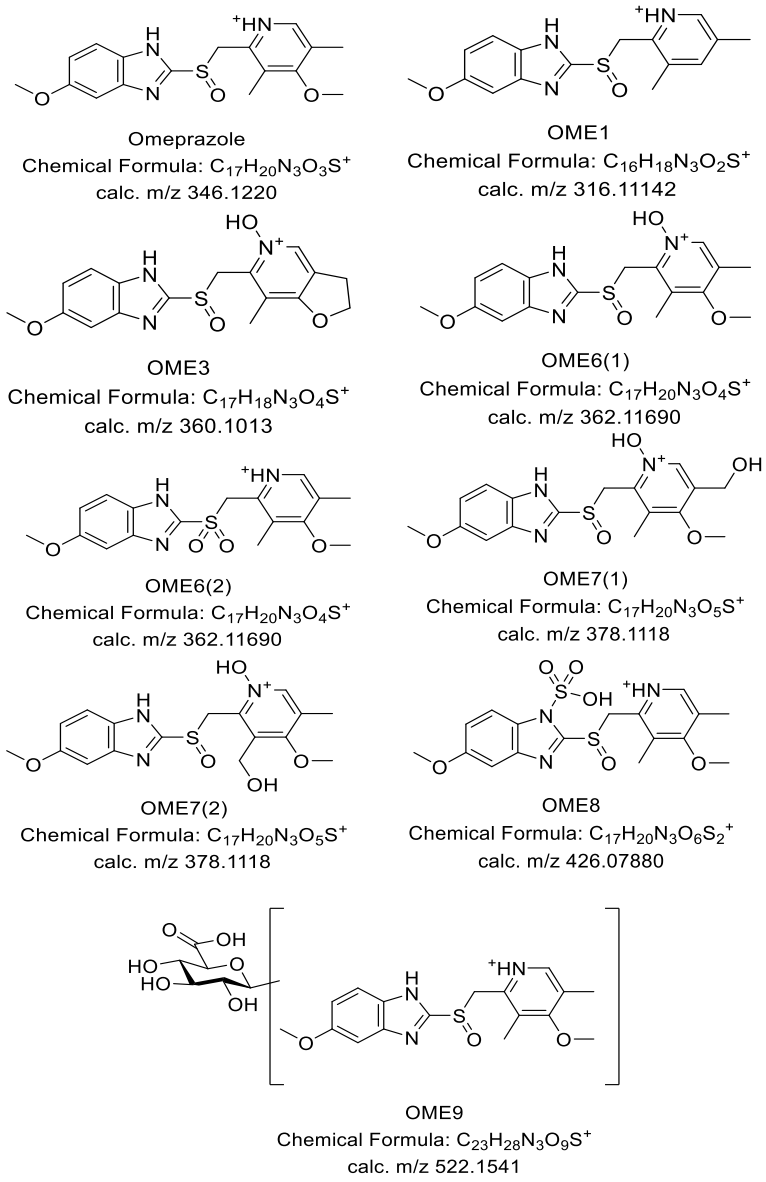

Figure1 Proposed structures of omeprazole metabolites

3.2 Pharmacokinetic Analysis

The following pharmacokinetic parameters were obtained using the formulated Excel sheet to compare the PK profiles of omeprazole in various groups of individuals. The groups of individuals include young, healthy, renally impaired, and as well as patients on concurrent medications such as ritonavir, osilodrostat, and armodafinil.

Table 3 Pharmacokinetic parameters of various groups after administration of omeprazole by IV or PO. OME: omeprazole, ZE = patients with Zollinger-Ellison syndrome

Data set	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	F% (PO only)	CL (L/hr, IV only)	Vd (L, IV only)
10 mg IV in ZE (Andersson et al., 1990)	26.79	39.06		3.66	4.44
10 mg PO in ZE (Andersson et al., 1990)	16.21	32.24	83%		
40 mg IV in ZE (Andersson et al., 1990)	55.25	100.51		5.69	13.60
40 mg PO in ZE (Andersson et al., 1990)	51.35	105.92	105%		
Young 10 mg IV (Regårdh 1986)	5.48	7.58		18.85	30.83

Elderly 20 mg IV (Landahl et al., 1992)	24.69	29.705		9.98	18.06
Renal-disease 20 mg IV (Landahl et al., 1992)	55.83	118.82		2.40	7.31
Young 20 mg PO (Landahl et al., 1992)	8.19	16.14	107%		
Elderly 40 mg PO (Landahl et al., 1992)	39.02	45.635	79%		
Renal-disease 40 mg PO (Landahl et al., 1992)	64.57	175.40	74%		
Healthy 40 mg OME (Darwish et al., 2008)	36.34	37.80			
Healthy 40 mg Armodafinil (Darwish et al., 2008)	46.75	48.05	127%		
20 mg OME (Armani et al., 2017)	17.99	18.04			
20 mg Osilodrostat (Armani et al., 2017)	10.10	10.28	57%		
Healthy 40 mg OME (2) (Dumond et al., 2010)	24.52	24.66			
40 mg with RTV (Dumond et al., 2010)	40.24	40.37	164%		
40 mg with RTV steady state (Dumond et al., 2010)	11.62	12.09	49%		

Clearance (CL) is the rate at which drugs are eliminated from the body. The studied groups had the following clearance measured in L/h: Young, 18.85; Elderly, 9.98; Renally impaired, 2.40. Clearance includes both renal clearance, removal by kidney function, and metabolic clearance, removal by metabolic processes. Older individuals have a lower clearance rate than younger individuals likely due to the decreased efficiency of renal or hepatic function. Meanwhile, renally impaired patients also had a significant decrease in clearance rate as some of their nephron functions were compromised, which significantly decreases the ability of the organ to remove drugs from their body.

Volume of distribution (V_d) measures the amount of drug diffused into the tissue from the plasma central compartment. It is calculated by measuring the dose and comparing it to the concentration of drug in the plasma, so a higher diffusion into tissues results in lower concentration and thus higher volume of distribution. Likewise, a higher concentration would represent lower diffusion into tissue and lower volume of distribution. The volume of distribution among the groups also varied and are as follows, measured in liters: Young, 30.83; Elderly, 18.06; Renally Impaired, 7.31. This result demonstrates that volume of distribution varies greatly among the several groups with decreased V_d in the elderly group compared to the young group. The renally impaired group also exhibited a decreased V_d. This would result in the greatest amount of drug diffusion into the tissues in the renally impaired group, followed by the elderly groups, and then the least diffusion in the young group. Also, dose level had a varying effect on the V_d measured in the ZE patient group, which was significantly increased from 4.44 L to 13.60 L when dose was increased from 10 mg to 40 mg. This would denote an increased diffusion of omeprazole from the blood plasma into tissues when given a higher dosage.

Absolute oral bioavailability (F) is the amount of drug that would reach the systemic circulation following oral administration compared to intravenous injection, which is defined as 100% bioavailable. Oral bioavailability can never exceed 100% because most drugs undergo first-pass metabolism by the liver and therefore only a fraction can eventually reach systemic circulation. The groups had the following bioavailability: Young healthy, 98.3%; Elderly, 81.5%; Renally impaired, 74%.

Relative bioavailability measures the relative amount of drug that reaches systemic circulation by a different route of administration (e.g. subcutaneous and oral) or the same route of administration under different circumstances (e.g. co-administration with other drugs to study the possible drug-drug interactions). Relative bioavailability can be greater than 100% as it is relative to the reference group. When comparing the relative bioavailability of dosing omeprazole alone and co-administration with other drugs, the relative bioavailability of omeprazole mildly increased to 127% and significantly increased to 164% when the patients were also taking armodafinil and ritonavir, respectively. On the other hand, the relative bioavailability decreased to 57% when the patients were on osilodrostat.

4 DISCUSSION AND CONCLUSION

In this study, eight novel metabolites were detected in human urines and six of their structures were proposed using a UPLC-HRMS system. These metabolites are the results of phase I and phase II metabolism reactions, which increases solubility and ultimately assists the excretion of these drugs by glomerular filtration. Phase I metabolism reactions include oxidation, reduction, and dealkylation which are all catalyzed by a group of enzymes known as cytochrome P450s. Involvement of CYP3A4 and CYP2C19 in the metabolism of omeprazole has been reported previously. CYP2C19 has been found

to catalyze a dealkylation reaction to convert omeprazole to 5-O-desmtylomeprazole (Kanazawa et al., 2002). CYP3A4 has been known to catalyze the conversion of omeprazole to 3-hydroxyomeprazole (Kanazawa et al., 2002). Phase II metabolism reactions also were present such as sulfation and glucuronidation reactions which are catalyzed respectively by sulfotransferases and UDP-glucuronosyltransferase, respectively.

The data produced regarding the PK parameters in the different groups of patients demonstrates the importance of individualized medicine. Individualized medicine is where doctors need to prescribe different drugs and different amounts of drugs to different patients depending on varying conditions which the patients face. These factors and conditions include, but not limited to, the patient's: age, kidney and liver health, other medications concurrently taken. For example, as demonstrated in this pharmacokinetic study of omeprazole, when dosing renally impaired and elderly patients, careful consideration should be given to the fact that the drug will likely stay in their system for a longer time as clearance rates are likely decreased. Prolonged exposure increases the possibility of overdose. Younger individuals also have higher plasma omeprazole concentration compared to older or renally impaired individuals. Drug-drug interactions remain as another important factor to consider when prescribing drugs. The relative bioavailability of omeprazole was 127% while armodafinil was co-administered. This suggests that omeprazole plasma concentration was 27% higher compared to administering omeprazole by itself. Co-administration of ritonavir resulted in an even more marked effect as the relative bioavailability was increased to be 164%. This increased relative bioavailability is likely caused by an interaction between the co-administered drug and the enzymes that metabolize omeprazole, namely CYP2C19 and CYP3A4. Armodafinil and ritonavir likely act as inhibitors of the cytochrome P450 enzymes which decreases the amount of enzymes available to metabolize omeprazole, and therefore, leads to greater omeprazole exposure. Co-administration of osilodrostat had the opposite effect as the relative bioavailability was lower, 57%, which suggests that osilodrostat likely acts as an inducer of the cytochrome P450 enzymes and results in a faster clearance of omeprazole by hepatic metabolism. This data provides insights on the drug-drug interactions between omeprazole and several other drugs which should be carefully considered when co-administered with omeprazole.

This study can benefit from improvements in some areas. For example, the AUC% extrapolated for several of these groups exceeds 20% of the AUC_{last} which could lead to an inaccurate estimation of AUC_{inf}. AUC_{inf} (AUC estimated to infinity) is calculated by using the elimination constant, k_e, and C_{last} to estimate the rest of the area under the curve that is not measured due to concentration falling below the limit of quantitation. In the data, some groups such as the Healthy 10 mg, 40 mg dosing and the renally impaired have extremely high percentage extrapolated which the average between IV and PO had a respective 40.57%, 48.28%, and 58.10% percent extrapolated. These numbers cannot provide accurate estimates of AUCinf as the recommended percent extrapolated is generally no more than 20% (Marzo et al., 1999). Greater percent extrapolated can be attributed to the premature ending of collecting data or inadequate sensitivity of the analytical tool. Ideally, concentration of no less than four half-lives should be accurately measured; however, in many of the studied cases, the concentration recorded ended at one or two half-lives because these studies were carried out when accurate analytical techniques such as LCMS were not available.

REFERENCES

1. ANDERSSON, T., MINERS, J. O., VERONESE, M. E., Tassaneeyakul, W., Tassaneeyakul, W., MEYER, U. A., & BIRKETT, D. J. (1993). Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. British journal of clinical pharmacology, 36(6), 521-530.
2. Andersson, T., Cederberg, C., Reg» rdh, C. G., & Sk» nberg, I. (1990). Pharmacokinetics of various single intravenous and oral doses of omeprazole. European journal of clinical pharmacology, 39, 195-197.
3. Armani, S., Ting, L., Sauter, N., Darstein, C., Tripathi, A. P., Wang, L., ... & Kulkarni, S. (2017). Drug interaction potential of osilodrostat (LCI699) based on its effect on the pharmacokinetics of probe drugs of cytochrome P450 enzymes in healthy adults. Clinical drug investigation, 37, 465-472.
4. Darwish, M., Kirby, M., Robertson, P., & Hellriegel, E. T. (2008). Interaction profile of armodafinil with medications metabolized by cytochrome P450 enzymes 1A2, 3A4 and 2C19 in healthy subjects. Clinical pharmacokinetics, 47, 61-74.
5. Dumond, J. B., Vourvahis, M., Rezk, N. L., Patterson, K. B., Tien, H. C., White, N., ... & Kashuba, A. D. M. (2010). A Phenotype–Genotype Approach to Predicting CYP450 and P-Glycoprotein Drug Interactions With the Mixed Inhibitor/Inducer Tipranavir/Ritonavir. Clinical Pharmacology & Therapeutics, 87(6), 735-742.
6. Foster, D. M., & Vicini, P. (2022). Noncompartmental and compartmental approaches to pharmacokinetic data analysis. In Atkinson's Principles of Clinical Pharmacology (pp. 113-135). Academic Press.
7. Kanazawa, H., Okada, A., Matsushima, Y., Yokota, H., Okubo, S., Mashige, F., & Nakahara, K. (2002). Determination of omeprazole and its metabolites in human plasma by liquid chromatography–mass spectrometry. Journal of Chromatography A, 949(1-2), 1-9.
8. Landahl, S., Andersson, T., Larsson, M., Lernfeldt, B., Lundborg, P., Regårdh, C. G., ... & Skånberg, I. (1992). Pharmacokinetic study of omeprazole in elderly healthy volunteers. Clinical pharmacokinetics, 23(6), 469-476.

9. Lorentzon, P., Eklundh, B., Brändström, A., & Wallmark, B. (1985). The mechanism for inhibition of gastric (H++ K+)-ATPase by omeprazole. Biochimica et Biophysica Acta (BBA)-Biomembranes, 817(1), 25-32.
10. Marzo, A., Ceppi Monti, N., & Vuksic, D. (1999). Experimental, extrapolated and truncated areas under the concentration–time curve in bioequivalence trials. European journal of clinical pharmacology, 55, 627-631.
11. Mehraban, M. S. A., Shirzad, M., Ahmadian-Attari, M. M., Shakeri, R., Kashani, L. M. T., Tabarrai, M., & Shirbeigi, L. (2021). Effect of rose oil on gastroesophageal reflux disease in comparison with omeprazole: a double-blind controlled trial. Complementary Therapies in Clinical Practice, 43, 101361.
12. Niessen, W. M., & Falck, D. (2015). Introduction to mass spectrometry, a tutorial. Analyzing biomolecular interactions by mass spectrometry, 1-54.
13. Omeprazole. In: Wikipedia.; 2021. Accessed January 6, 2022.https://en.wikipedia.org/w/index.php?title=Omeprazole&oldid=1059783996
14. Regårdh, C. G. (1986). Pharmacokinetics and metabolism of omeprazole in man. Scandinavian Journal of Gastroenterology, 21(sup118), 99-104.