Universidade de Lisboa

Faculdade de Farmácia

The effect of Proton Pump Inhibitors on the oral absorption of drugs

Rita Fuzeta da Ponte Nunes Capela

Monografia orientada pelo Professor Doutor Paulo Jorge Pereira Alves Paixão, Categoria de Professor Auxiliar.

Mestrado Integrado em Ciências Farmacêuticas

2024

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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2024

Acknowledgements

Em primeiro lugar gostaria de agradecer ao meu orientador, o Professor Doutor Paulo Paixão, pelo acompanhamento ao longo deste trabalho e, sobretudo pela sua disponibilidade, desde o início, para reunir comigo e esclarecer as minhas dúvidas. Agradecer também pelas palavras de motivação e apoio durante este processo.

Seguidamente, agradeço aos meus amigos também por todo o apoio durante a escrita deste trabalho e ao longo de todo o curso e ainda pelos conselhos e ajuda, principalmente nas fases mais difíceis e de maior trabalho.

Não posso deixar de agradecer à equipa incrível da Farmácia Sália, farmácia onde realizei o meu estágio curricular, por todo o apoio, carinho e ensinamentos que obviamente contribuíram para que fosse possível concretizar este trabalho em simultâneo com o estágio.

Agradecer ainda às pessoas mais importantes da minha vida: os meus pais, irmãs, cunhados, sobrinhos e namorado. Foram vocês quem mais aturaram os meus momentos de desespero em que tudo isto parecia um caminho sem fim e foram vocês quem mais me deram forças para continuar a lutar.

Obrigada a todos, mais uma etapa que se está a concluir e que no fim desta se abram muitas portas e janelas sempre convosco presentes na minha vida.

«A melhor preparação para amanhã é fazer o seu melhor hoje.»

(H. Jackson Brown JR)

Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

Os Inibidores das Bombas de Protões são uma classe de fármacos largamente prescrita por médicos em todo o mundo, sendo que existem também algumas formulações não sujeitas a receita médica, sendo, assim, mais facilitada a sua aquisição por parte dos doentes.

Estes fármacos são responsáveis pela supressão ácida do estômago e, consequentemente, pelo aumento do pH gástrico, estando descritas variadas interações com diferentes classes de fármacos.

Este trabalho foca-se nas interações de absorção existentes entre os Inibidores das Bombas de Protões e outros fármacos, quando ambos são tomados por via oral, verificando-se uma relação entre a classe biofarmacêutica dos fármacos e a ocorrência deste tipo de interações: os fármacos de classe biofarmacêutica II e IV são os que possuem maior predisposição para interagirem com os Inibidores das Bombas de Protões, por possuírem uma solubilidade baixa e várias vezes dependente do pH, estando o trabalho focado em fármacos destas duas classes.

Além disso, são também descritas as estratégias da tecnologia farmacêutica que nos permitem ultrapassar estes problemas, tais como a utilização de excipientes modificadores de pH e a utilização de dispersões sólidas amorfas.

No final do trabalho é realizada uma análise sobre os estudos de bioequivalência, mais concretamente sobre as condições em que estes normalmente são realizados, ou seja, em indivíduos saudáveis, e é discutida a relevância de realizar estudos adicionais de bioequivalência quando estamos perante populações que realizam tratamentos com agente antiácidos como os Inibidores das Bombas de Protões ou, por exemplo, em populações com acloridria, sendo que, em ambos os casos há que ter em conta que o pH gástrico difere dos seus valores fisiológicos.

Com este trabalho foi assim possível explorar e compreender os mecanismos adjacentes às interações de absorção oral entre Inibidores das Bombas de Protões e outros fármacos e concluir que os estudos de bioquivalência em indivíduos saudáveis podem não ser suficientes para garantir esta mesma bioequivalência em todos os indivíduos.

Palavras-chave: Inibidores das Bombas de Protões, Absorção Oral, Interações, Bioequivalência.

Abstract

Proton Pump Inhibitors are a class of drugs that are widely prescribed by doctors all over the world, and there are also some non-prescription formulations that make it easier for patients to acquire them.

These drugs are responsible for acid suppression in the stomach and, consequently, an increase in gastric pH, and various interactions with different classes of drugs have been described.

This study focuses on the absorption interactions between Proton Pump Inhibitors and other drugs, when both are taken orally. There is a relationship between the biopharmaceutical class of the drugs and the occurrence of this type of interaction: biopharmaceutical class II and IV drugs are the most likely to interact with Proton Pump Inhibitors, as they have low solubility and are often pH-dependent, and the study focuses on drugs from these two classes.

Strategies in pharmaceutical technology that allow us to overcome these problems are also described, such as the use of pH-modifying excipients and the use of amorphous solid dispersions.

At the end of the paper, an analysis is made of bioequivalence studies, more specifically the conditions under which they are normally carried out, i.e. in healthy individuals, and the relevance of carrying out additional bioequivalence studies is discussed when we are dealing with populations undergoing treatment with antacid agents such as Proton Pump Inhibitors or, for example, in populations with achlorhydria, since in both cases it must be taken into account that gastric pH differs from their physiological values.

This work has therefore made it possible to explore and understand the mechanisms involved in oral absorption interactions between Proton Pump Inhibitors and other drugs and to conclude that bioequivalence studies in healthy individuals may not be sufficient to guarantee the same bioequivalence in all individuals.

Keywords: Proton Pump Inhibitors, Oral Absorption, Interactions, Bioequivalence.

Abbreviations

Ae	Urinary Excretion
AIDS	Acquired Immunodeficiency Syndrome
ATV/c	Atazanavir/cobicistat
ATV/r	Atazanavir/ritonavir
AUC	Area under the plasmic concentration curve
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
CL	Clearance
CR	Prolonged release
Cmax	Maximal plasma concentration
CYP450	Cytochrome P450
CYP4A4	Cytochrome P4A4
CYP2C19	Cytochrome P2C19
CYP3A4	Cytochrome P3A4
CYP2C9	Cytochrome P2C9
CYP3A5	Cytochrome P3A5
CYP2J2	Cytochrome P2J2
CYP2D6	Cytochrome P2D6
CYP1A1	Cytochrome P1A1
DDI	Drug-drug interaction
EMA	European Medicines Agency
FDA	Food and Drug Administration
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HME	Hot Melt Extrusion

HPLC	High-performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HPMCAS	Hydroxypropyl methylcellulose acetate succinate
ICH	Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LG	L grade
MMF	Mycophenolate Mofetil
MPA	Mycophenolic Acid
OROS	Oral push-pull osmotic system
PBPK	Physiologically based pharmacokinetic
PPI	Proton Pump Inhibitor
TKI	Tyrosine Kinase Inhibitors
Tmax	Time to maximal plasma concentration
V	Apparent volume of distribution
T1/2	Elimination half-life

Table of contents:

1 Introduction: Characterisation of Proton Pump Inhibitors....10
1.1 What are Proton Pump Inhibitors and how do they work?....10
1.2 What are the limitations of Proton Pump Inhibitors? 11
1.3 Pharmacokinetics and pharmacodynamics of Proton Pump inhibitors....12
2 Oral Absorption of drugs 16
2.1 Oral absorption of Proton Pump Inhibitors....18
3 Biopharmaceutical classification and the effect on the PPIs interactions with other drugs....20
3.1 Mechanisms of interactions between PPIs and other drugs....21
3.1.1 Mycophenolate mofetil....22
3.1.2 Digoxin 24
3.1.3 Nifedipine 25
3.1.4 Bismuth....26
3.1.5 Protease Inhibitors 27
3.1.6 Itraconazole....28
3.1.7 Tyrosine Kinase Inhibitors....28
3.2 Pharmaceutical technology strategies to overcome absorption problems ...29
3.3 Interaction studies: when is it necessary? 34
3.4 Drug-drug interaction design study....35
4 Bioequivalence....37
5 Conclusion 43
Bibliography 44

Figure Index:

Figure 1.1 Mechanisms of transport of drugs through GI epithelium. 12
Figure 4.1 In vitro dissolution profiles of the reference levothyroxine tablet (a) and capsule (b), and the reference (c) and test (d) nifedipine CR formulation extracted from the literatue....36
Figure 4.2 Simulated and observed plasma levothyroxine concentration profiles for the reference tablet (a) and test capsule (b) of levothyroxine in healthy volunteers. Observed plasma levothyroxine concentration profiles for the reference and test formulations in healthy volunteers after the intravenous administration of esomeprazole (c). Simulated plasma levothyroxine concentration profiles for the reference and test formulations in virtual healthy volunteers using gastric pH 5.0 (d), pH 6.0 €, and pH 7.0 (f). The plasma levothyroxine concentrations were baseline-adjusted.....36
Figure 4.3 Simulated and observed plasma nifedipine concentration profiles for the reference (a) and test (b) nifedipine CR formulations in healthy volunteers under fasted state. Simulated and observed plasma nifedipine concentration profiles for the reference and test formulations in healthy volunteers under fed state (c). Simulated plasma nifedipine concentration profiles for the reference and test formulations in Japanese achlorhydric elderly (d)……37

Table Index:

Table 1.1 Pharmacokinetcis Property of PPIs.....10
Table 3.1 BCS classification. 17
Table 3.2 Drugs that have their absorption rate altered due to their interaction with PPIs 19
Table 3.3 Disposition of bismuth after a single oral dose of tripotassium dicitrato bismuthate (240mg). 23
Table 3.4 Physicochemical properties of pH midifying agents. 29

1 Introduction: Characterisation of Proton Pump Inhibitors

1.1 What are Proton Pump Inhibitors and how do they work?

Proton Pump Inhibitors are benzimidazole derivatives drugs and weak bases with pka1 between 3.9 and 4.9 and have a strong inhibitory effect on gastric acid secretion in parietal cells of the stomach (1).

These drugs are the most prescribed drugs for people with gastric acid related disorders like gastric and duodenal ulcer and reflux oesophagitis or in polymedicated patients (1).

PPIs are prodrugs and it means that they need to be activated, in this case, by acidic conditions and they are only effective after this protonation reaction.

The protonation reaction forms the thiophilic drug that reacts with luminally accessed cysteines on the acid pump enzyme. It means that the presence of acid conditions is necessary for action of PPIs, because without this protonation PPIs can't be activated and they won't work.

It is very important to note that these drugs need to be administered 30 minutes before a meal to ensure that the pumps are active when peak concentrations of the PPIs are present in the blood. In other words, this fact supports the affirmation above: PPIs need acid conditions to work (2). Also, since their effect is systemic, they need to be protected for the gastric pH in order to be absorbed, being administered orally as gastroresistant products.

Their mechanism of action centers on inhibition, by covalent binding, of the H+/K+ ATPase enzyme in gastric mucosal parietal cells, which is responsible for hydrogen ion secretion in exchange for potassium ions in the gastric lumen.(3)

Currently, PPIs are divided into two generations: first-generation PPIs and second-generation PPIs.

First-generation PPIs include omeprazole, lansoprazole and pantoprazole. Second-generation PPIs include rabeprazole and esomeprazole.

In the second generation, we find advantages over the first generation, which should be listed: they have a shorter onset time and greater efficacy, because they stablish a more stable covalent bond and their plasma concentration is not strongly influenced by CYP2C19 hepatic enzyme activities; they can maintain acid suppression for 24 hours; they have fewer individual differences and even fewer systemic interactions with other drugs; they don't have the NAB effect (nocturnal acid breakthrough) (4,5).

This NAB effect is defined as the presence of at least 60 continuous minutes in which the gastric pH drops below 4 during the night (considered to be between 10 p.m. and 6 a.m.), in patients being treated with PPIs twice a day, before meals.(6)

1.2 What are the limitations of Proton Pump Inhibitors?

Today, it is very common for people to take PPIs every day and for a long time, especially older, polymedicated people.

However, some studies have shown that when people take PPIs in high doses (twice a day) and/or for a long time (more than one year), the risk of hip, wrist and spinal fractures increases.

In 2010, the FDA obliged industries to revise their labels to include a warning about the possibility of these fractures when taking PPIs as described above.(3)

This adverse effect is more important in older people, because of osteoporosis and like said above, older people are the larger group that take PPIs in high doses and/or for a long period of time.

It should be added that some studies have also shown that this excessive and prolonged use of PPIs can be associated with deficiencies in magnesium and vitamin B12 levels, although there are yet no recommendations to supplement patients in a preventative manner. This may be of particular concern for special patients populations, like bariatric ones.

In addition to the elderly, this effect is also more noticeable in people with nutritional problems and in patients undergoing haemodialysis treatments concurrently with taking PPIs.

Reducing inappropriate prescriptions of PPIs by doctors could reduce this potential risk of vitamin and mineral deficiency (3).

Many people think that PPIs are an inoffensive drug and may use it freely as over-the-counter drugs, but as we can see, we need to take caution in some cases and it is very important to study the interactions between these drugs and other drugs, especially in polymedicated people.

1.3 Pharmacokinetics and pharmacodynamics of Proton Pump inhibitors

Metabolism of PPIs is dependent on the cytochrome P450 system. CYP2C19 and CYP3A4 are the major components for this. All PPIs have an elimination half-life of about 1 hour in healthy subjects (omeprazole, esomeprazole, rabeprazole, lansoprazole and pantoprazole), but in the other parameters, PPIs have differences, and we can see these differences in the table below (2).

Table 1. Pharmacokinetics property of PPIs(2,7–12)

Parameter	Omeprazole 20mg	Lansoprazole 30mg	Pantoprazole 40mg
Bioavailability (%)	30 – 40	80 – 90	77
T_{max} (h)	1 - 4	1.2 – 2.1	2 - 4
C_{max} (µmol/L)	0.23 – 23.2	1.62 – 3.25	2.87 – 8.61
AUC (µmol.h/L)	0.58 – 3.47	4.6 – 13.5	5.22 – 13.04
V (L/Kg)	0.13 – 0.35	0.4	0.15
CL /mL/min)	400 - 620	400 - 650	90 - 225
$T_{1/2}$ (h)	0.5 – 1.2	0.9 – 2.1	0.8 – 2.0
Route of elimination	77% of the dose is eliminated in urine as at least six different metabolites. The remainder of the dose was found in the feces. This suggests significant biliary excretion of omeprazole metabolites.	A reported 14-23% of a lansoprazole is eliminated in the urine with this percentage range including both conjugated and unconjugated hydroxylated metabolites.	About 71% of the dose was excreted in the urine, with 18% excreted in the feces by biliary excretion.

Table 1. Continued

Parameter	Rabeprazole 20mg	Esomeprazole 30mg
Bioavailability (%)	52	64-90
T_{max} (h)	3.5	1.0 – 3.5
C_{max} (μmol/L)	1.14	2.1 – 2.4
AUC (μmol.h/L)	2.22	4.2
V (L/Kg)	NA	0.22 – 0.26
CL /mL/min)	NA	160 - 330
$T_{1/2}$ (h)	0.6 – 1.4	1.3 – 1.6
Route of elimination	90% of the drug is eliminated in the urine.	Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

NA – Not Applicable

As we can see, all PPIs have similar elimination half-life and the most are eliminated in urine as metabolites.

Although their elimination half-life is short, this factor has almost no influence on their pharmacodynamic properties, because the covalent binding to the H+, K+ -ATPase enzyme predominately influences the duration of antisecretory action. The covalent binding to the cysteine residues leads a duration of action that is substantially longer than would be predicted based strictly on the plasma concentration profile (9).

The oral drugs are formulated as enteric-coated delayed-release prodrugs that are extensively absorbed in the small bowel. The bioavailability of omeprazole and esomeprazole after oral administration increases over the first 5 days of therapy.

These increases in area under the concentration-time curve (AUC) and bioavailability result from a decrease in first-pass extraction, which likely is due to a decrease in acid degradation in the gastric lumen as gastric pH rises over the first few days of therapy, and inhibition of the drug's own metabolism (9).

When therapy with a PPI begins, the active pumps are not inhibited all at once, and their degree of inhibition increases as the days of therapy go by, because PPIs only inhibit active proton pumps.

So, on the first day, and after a stimulus like food, about 80% of proton pumps are active and they are available to be inactivated by PPIs.

After the first administration and before the second, new pumps will be synthesized and, finally, the remaining 20% of pumps that were not inhibited the first day are available to be inhibited. Of the newly synthesized pumps, we will once again have around 80% of these pumps active and therefore available to be inhibited.

So, this process is repeated until pharmacodynamic steady state is reached in which the number of pumps inhibited each day equals the number of new pumps generated each day.

In some cases, the patient can take PPIs twice a day (before breakfast and before evening meal) to reduce the time that it needs to get sufficient acid suppression (9).

2 Oral Absorption of drugs

To understand all the processes of oral absorption of drugs, we needly first understand what oral absorption of drugs is.

So, absorption is a process where chemical substances suffer transference from the GI tract to the bloodstream and lymphatic stream.

In this process we have two main mechanisms of drugs' movement through the GI epithelium: by transcellular and paracellular routes. The transcellular route is the movement of drugs through the cells themselves and the paracellular route is the movement of drugs through the between cells connecting spaces.

Beyond this, the transcellular movement is divided into 3 other mechanisms: simple passive diffusion, carrier-mediated diffusion and endocytosis. In the figure below we can see clearly these different mechanisms of transport (13).

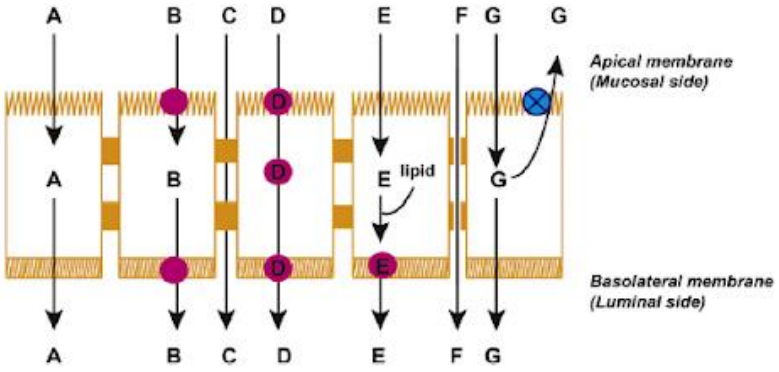

Figura.1 Mechanisms of transport of drugs through GI epithelium(13)

A: transcellular passive diffusion;

B: carrier-mediated transcellular diffusion;

C: paracellular diffusion;

D: transcellular diffusion by endocytosis;

E: transcellular diffusion and incorporation into lipid particles;

F: paracellular diffusion with a modulator of tight junctions;

G: transcellular diffusion modified by a polarizes efflux mechanism.

Oral administration of drugs is often the preferred route of administration for patients, due to its simplicity, and is also the most economical in terms of the drug manufacturing process.

However, as we have seen from what has been described above, the process of oral absorption is a complex one and is affected by factors not only of the active substance itself, such as its physicochemical characteristics, but also by factors associated with the pharmaceutical form in question (tablets, capsules, solutions, suspensions) and also by factors of our own body, such as the physiology of the GI tract, through pH variations and variations in intestinal transit.

Other factors like food, GI diseases and the patient's age can also affect the absorption of drugs.

The interaction between food and drugs is complex and it can result in an increased absorption, decreased absorption, delayed absorption or unaffected absorption. Why? Because this interaction can produce variations in pH of GI tract, differences in gastric emptying time and in intestinal transit time too.

Studies have shown that fatty meals result in a variable gastric pH and in an increase of extent and duration of pH gastric buffering.(14)

Patient’s age is other factor that contributes to an altered absorption of drugs, because the incidence of hypochlorhydria (reduced acid secretion) or achlorhydria (absence of acid secretion) is approximately 10–20% in older subjects (>70 years) compared to less than 1% in young individuals (<40 years).

In addition, patients with upper GI diseases may show different gastric acidity compared to healthy subjects. To exemplify: patients with oesophageal or duodenal ulcers exhibit a lower gastric pH and patients with gastric ulcer or gastric cancer show a higher gastric pH, always when compared to healthy subjects.

Weakly basic drugs and weakly acid drugs are usually pH dependents drugs and, obviously, the more affected drugs with the pH differences within the GI tract. The pKa value of the molecule corresponds to the pH value at which the drug is 50% ionized and 50% non-ionized.

When the pH of the GI tract is higher than the pKa of the drug, we can say that the non-ionized form of weak base predominates and, in the case of a weak acid, we can say that the ionized form predominates.

As such, basic drugs (with pka > 5 - 6) have a rapid dissolution in acidic environment, like gastric environment, and have a low solubility in basic environment, like small intestine.

In the other hand, acid drugs (with pka < 5- 6) have a minimal dissolution in stomach and maximum in basic environments like small intestine.(13,14)

On the other side, biological membranes are lipophilic and favor the transport of molecules in their non-ionized form, making the overall absorption process a complex pH dependent process in itself.

Due to its physiology, it is not only the GI tract that is considered a barrier to drug bioavailability.

The liver can also be considered another barrier, but in a different way. This organ is a more uniform region when compared to the stomach, but it has other particularities: it contains numerous metabolizing enzymes, which inactivate lipophilic substances that have escaped intestinal metabolism.

Among these enzymes, we can consider phase I enzymes, which belong to the large cytochrome P450 family and produce metabolites that can subsequently be conjugated by phase II enzymes into hydrophilic molecules. These hydrophilic metabolites are then excreted in the bile or transported to the kidneys for elimination.(13)

2.1 Oral absorption of Proton Pump Inhibitors

Proton Pump Inhibitors are extremely unstable in the gastrointestinal environment, so, there aren't many studies on the mechanism of absorption of PPIs, because it is difficult to study this.

However, an in situ perfusion study conducted by Tianxiang Shen *et al* with male and female rats, studied the absorption process of ilaprazole, ilaprazole sodium and rabeprazole sodium, by obtaining the average value of drug concentration in the collected blood samples and in the in situ perfusate at different time points.

This study was developed with a modified rat model of in situ absorption where the temperature was controlled to ensure an enough stability of PPIs, because in traditional

intestinal absorption experiments, the perfusate is usually kept at physiological temperature (37º), but PPIs are so unstable at physiological temperature that they undergo fast degradation and, like we said above, the absorption studies are a big challenge with these medicines.

The results described that the duodenum could be the best site of oral absorption for the PPIs in the whole gastrointestinal tract and ilaprazole and ilaprazole sodium exhibited significantly higher absorption efficiency compared to rabeprazole sodium by analysing the apparent permeability coefficients in the in situ perfusate and steady-state plasma concentrations of the PPIs after the perfusion in all gastrointestinal tract. Between ilaprazole and ilaprazole sodium, ilaprazole has a more stable absorption behaviour in all gastrointestinal tract. (4)

Proton Pump Inhibitors are small molecules, so they cross the membranes through passive diffusion.(7)

Gastro resistant PPIs pass through the stomach unaltered and then into the small intestine, where their enteric coating is dissolved. After this, PPIs are absorbed into the blood where they have a relatively short plasma half-life.

Gastrin is the hormone that stimulates parietal cells to release gastric acid. When PPI inhibits the acid production in the stomach, gastrin release is increased to compensate for the low acidity of the stomach.

Several studies have suggested that when patients stop the therapy with PPIs, our organism continues to produce gastrin at above pre-treatment levels, causing an effect referred to as a rebound acid secretion.(15)

This pH increases in the stomach by PPIs action results in many interactions between PPIs and other drugs, which we will see in the next chapter.

3 Biopharmaceutical classification and the effect on the PPIs interactions with other drugs

PPIs are responsible for increasing gastric pH to help patients in different conditions. However, this increase in pH causes problems, especially in terms of the absorption of other drugs.

The dissolution of weak acids is increased, while the dissolution of weak bases is decreased.

To better understand this relationship, it is important to analyse the Biopharmaceutical Classification System (BCS) of drugs.

BCS is a classification system that allows the in vivo pharmacokinetic behaviour of a drug to be predicted from in vitro studies. (14)

This system classifies drugs into four different categories, based on their intestinal permeability and solubility, and these parameters obviously influence the absorption rate of the drug, depending on the category it is in.

The different categories are summarized in Table 3.1.

Table 3.1 BCS Classification (16)

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Class I drugs have maximum absorption rates, class II drugs have limited solubility, class III drugs have limited permeability and class IV drugs have very low absorption rates. (16) Thus, the low dissolution of weak bases, due to the increase in pH caused by PPIs, is particularly worrying for BCS class II drugs and especially those with low pka values (like posaconazole), because for these, an acidic environment is essential for their good absorption in vivo.

In this chapter we will mainly study BCS class II and class IV drugs, as these are the two classes of drugs with pH-dependent absorption, calling into question their concomitant use with PPIs.(14,16)

3.1 Mechanisms of interactions between PPIs and other drugs

Drug-drug interactions of Proton Pump Inhibitors can be divided into two main categories: pharmacokinetic interactions and pharmacodynamic interactions. Into the pharmacokinetic categories we have mechanisms that cause the alteration of drug absorption, mechanisms that cause the alteration of hepatic drug metabolism and also mechanisms that cause the alteration of drugs renal elimination.(1)

For our study, we will focus on the mechanisms that cause changes in absorption.

So, relative to changes in absorption we have two main mechanisms: elevation of gastric pH and interaction with Efflux Transporter or Intestinal Cytochrome P450 Enzymes.

About the increase in gastric pH, we know that a change in this parameter can affect the solubility of weakly basic and acidic drugs. In other words, an interaction between PPIs and other drugs, due to this effect, will result in an expectable decrease (for bases) or increase (for acids) in the AUC of the victim drug (1).

Regarding the other mechanisms mentioned, it should be remembered that PPIs are metabolised by CYP450, specifically CYP4A4 and CYP2C19 polymorphism are major components for this. In the small intestine, CYP3A4 has been observed to be the most abundant CYP enzyme, followed by CYP2C9 and CYP3A5 and as the third most common enzymes we have CYP2C19, CYP2J2, CYP2D6 and CYP1A1 (2,17,18).

Omeprazole, lansoprazole and pantoprazole are substrates for P-glycoprotein, which means that drugs that are substrates for this glycoprotein may have their exposure increased because they may compete to bind to its receptor (18).

In table 3.2, we show some classes and drugs that have their absorption rate altered due to their interaction with PPIs, and we will then explain the mechanisms involved in these interactions, but only for drugs that need dose adjustment and/or which monitoring is required and/or which have clinical relevance, because in the other ones, the interaction with PPIs is not clinically relevant.

Table 3.2 Drugs that have their absorption rate altered due to their interaction with PPIs (1,16,19–23)

Drug class	Drug	BCS class	PPI	Dose adjustment
Immunosuppressant	Mycophenolate Mofetil	II	Omperazole and Pantoprazole	Monitoring required
Digitalis	Digoxin	IV	Omeprazole and Rabeprazole	Monitoring required
Calcium channel blockers	Nifedipine	II	Omeprazole	NA
Bismuth compounds	Bismuth	II	Omeprazole	Dose reduction
HIV protéase inhibitors	Atazanavir	II	Omeprazole and Lansoprazole	Dose increase
	Atazanavir/Ritonavir	II e IV	Omeprazole	Dose increase
	Raltegravir	II	Omeprazole	Dose reduction
Triazole antifungals	Itraconazole	II	Omeprazole	Dose increase
Tyrosine kinase inhibitors		II	Omeprazole	Dose increase

3.1.1 Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an immunosuppressant and a prodrug of mycophenolic acid (MPA), which is widely used in transplant situations (24).

Transplant patients often experience gastrointestinal adverse effects, making it relatively common for MMF to be used together with PPIs for a prolonged period of time(24,25).

The interaction between PPIs and MMF is becoming increasingly important as it has been discovered that PPIs can reduce the exposure of the active form of MMF(24).

This interaction occurs because MMF is cleaved in the acidic environment of the gastric compartment, i.e. it needs an acidic environment to be absorbed properly. Since PPIs suppress stomach acid, they prevent MMF from being absorbed properly.

The solubility of MMF is around 4mg/L at pH 4, 0.24mg/L at pH 5.2 and 0.04mg/L at pH 7, so its solubility decreases with increasing pH.

This interaction could be extremely important, since exposure to inadequate levels of MMF could lead to rejection of the transplanted organ (26).

A study by Kiberd *et al* shows that the pharmacokinetics of MPA are not affected when the dose of MMF is increased when used with PPIs (instead of 1.0g twice a day, it is 1.5g twice a day) (24).

Kofler *et al* carried out a study on 33 patients who had undergone heart transplantation to assess the impact of coadministration of PPIs on the plasma concentration of MPA.

All the patients in the study received the same therapy: tacrolimus and mycophenolate mofetil.

Pantoprazole 40mg/day was administered to 21 patients and no PPI was administered to the remaining 12.

The plasma concentration of MPA was assessed and determined in all patients using the mini-AUC equation, with blood samples taken 30 min before the administration of MMF, 1 hour and 2 hours after its administration.

The results showed that the plasma concentration of MPA was significantly higher in the control group (17.9 +/- 11.5, 7.6 +/- 4.2 and 13.8 +/- 9.1 mg/L, at 30 min, 1 hour and 2 hours, respectively), when compared to the group that received the PPI (6.7 +/- 4.6 mg/L, 5.0 +/- 2.8 mg/L and 7.7 +/- 4.1 mg/L, at 30 min, 1 hour and 2 hours, respectively).

This again demonstrates that MPA absorption is markedly reduced by PPIs, in this case pantoprazole. (27)

Another study, by David-Neto *et al*, revealed that the mean $AUC_{0\text{-}12h}$ of MPA was at the lower limit of the therapeutic window on day 7 post-transplant in patients also taking omeprazole. However, there was an increase on days 14 and beyond, with most patients being at a comfortable value, i.e. within the therapeutic window, after day 7.

It should be noted that when patients are adequately exposed to MPA in the first week after transplantation, the likelihood of rejection is greatly reduced.

Therefore, given that on day 7 after transplantation we find patients at the lower limit of the therapeutic window, MPA levels should be carefully monitored, specifically during these first 7 days, in order to prevent rejection (24,25).

However, PPIs decrease the absorption of MMF, but not enteric-coated mycophenolate sodium (a formulation that is therapeutically equivalent to MMF), indicating that the decrease in MMF absorption with PPIs is the result of incomplete dissolution of MMF in the stomach at high pH.

As such, this formulation, being therapeutically equivalent, is seen as an alternative to MMF when it is necessary to carry out joint therapy with PPIs (24).

3.1.2 Digoxin

Digoxin is a medicine used to treat various heart conditions like heart failure and atrial fibrillation (28,29).

Omeprazole can induce increased absorption and serum levels of digoxin and impairs the clearance by P-glycoprotein inhibition, leading to digoxin toxicity (24).

So, omeprazole induces increased gastric permeability to digoxin, enhancing its absorption and inhibit the P-glycoprotein-mediated clearance of digoxin, reducing its elimination.

All patients who are taking digoxin and have a concomitant treatment with PPIs should be monitored to make sure that these interactions don’t occur (30).

We have an example of a 65 year old Caucasian woman that was treated with digoxin at a dose of 0.625 mg daily for 6 years. She started concomitant therapy with

omeprazole and after three months, her serum digoxin level jumped for 1.1 to 3.9 ng/mL with normal hepatic and renal function.

It is important to note that the usual digoxin therapeutic range is 0.8–2 ng/mL (24).

Oosterhuis *et al*. reported that, after 8 days of taking 20mg omeprazole once daily, the maximum plasma concentration and AUC for a single dose of digoxin were increased 10%. Since digoxin is a Narrow Therapeutic Index drug, this increase may be considered clinically relevant.

But it is not just omeprazole that interact with digoxin: coadministration of 20mg/day rabeprazole with 0,25mg/day digoxin for 2 weeks results in a 19% increase in the AUC and a 22% rise in trough digoxin levels in normal volunteers (31).

3.1.3 Nifedipine

Nifedipine is a calcium channel blocker indicated for the treatment of angina and hypertension.

Nifedipine is completely absorbed after oral administration and is extensively metabolised by CYP3A4 and CYP3A5.

It is a BCS class II drug and therefore has low solubility and this solubility is pH-dependent: as the pH increases, the solubility of nifedipine decreases. It is available on the market in immediate-release and extended-release forms. For the latter form, there are osmotic pump-based formulations, i.e. the drug is released over time in a constant and pH-independent manner, while the other form, i.e. matrix-based formulations, have a pH-dependent release profile.

Several studies have shown that there is in fact an increase in the systemic exposure of nifedipine in individuals undergoing treatment with PPIs, particularly with omeprazole.

Although this interaction is true and does exist, its mechanism is not yet well explained, since this interaction may be since PPIs increase gastric pH and/or may be mediated by inhibition of the CYP3A4 enzyme.

However, there are already studies which report that the impact of pH elevation is minimal and that CYP3A4 mediation plays the biggest role in this interaction (32).

Omeprazole inhibits CYP3A4 activity and CYP3A4-mediated oxidation is the main route of metabolism of nifedipine, thus explaining the increase in systemic exposure of this drug when used concomitantly with omeprazole (33).

This interaction can be overcome easily, since if we switch PPIs, specifically from omeprazole to pantoprazole, this reaction will no longer occur (18).

3.1.4 Bismuth

Bismuth compounds are used as medicines to treat gastrointestinal conditions. These compounds have gastroprotective effects and can eradicate *H. pylori*.

In addition, they have antimicrobial, anti-leishmanial and anti-cancer properties (34).

As we know and as has already been mentioned, omeprazole is used to eradicate *H. pylori*.

However, tripotassium dicitrato bismuthate is used concomitantly in these patients because it prevents ulcer recurrence when *H. pylori* is eradicated.

Therefore, given that these drugs are used simultaneously, it is extremely important to study their interactions, especially because tripotassium dicitrato bismuthate solubility is known to be pH dependent.

Gerhard Treiber *et al* conducted a study where six healthy volunteers received daily oral doses of 40 mg omeprazole for 1 week and a single oral dose of 240 mg tripotassium dicitrato bismuthate. Plasma concentration-time profiles (AUC) and urinary excretion (Ae) of bismuth were measured by atomic absorption spectrophotometry and plasma levels of omeprazole by HPLC. In addition, intragastric pH values were monitored for 8 hours.

The results of this study are shown in the table below and demonstrate that omeprazole, by increasing gastric pH, greatly increases the systemic bioavailability of bismuth.

Table 3.3 Disposition of bismuth after a single oral dose of tripotassium dicitrato bismuthate (240 mg) (35)

Parameter*	Control	Plus Omeprazole
Cmax (µg/L)	36,7 +/- 29,7	86,7 +/- 81,8
tmax (hr)	0,42 +/- 0,20	0,68 +/- 0,26
AUC (µg/L . hr)	46 +/- 33	172 +/- 158
Ae (µg/ 8 hr)	0,27 +/- 0,28	1,88 +/- 2,00
CL (mL/min)	65 +/- 50	91 +/- 40

*Mean + SD (n=6)

Therefore, if this combination of drugs is used, the author of this study says that the dose of bismuth salts should be reduced by at least half (35).

3.1.5 Protease Inhibitors

Protease Inhibitors (PIs) are a class of antiretroviral drugs used to treat and manage patients with human immunodeficiency virus (HIV).

Drugs in this class are usually used in combination to enhance their virological and immunological properties and to prevent resistance to these antiretroviral drugs (36).

Protease inhibitors lose their solubility with an increase of gastric pH. So, this is important because, as we know, PPIs increase the gastric pH and obviously affect the solubility and absorption of protease inhibitors.

Omeprazole and lansoprazole can significantly reduce the plasma concentrations of certain PIs, including atazanavir, fosamprenavir, indinavir, and nelfinavir, by 76-98%, 2-9%, 10-50%, and 36%, respectively (37).

Atazanavir loses its solubility at a higher pH (atazanavir solubility is 1.1mg/mL at pH 0,8 and reduces to 0.002 mg/mL at pH 5.4) and it is the PI more sensitive to pH changes caused by PPIs (1,37).

Omeprazole 40mg administered once a day in concomitant therapy with atazanavir can cause a decrease in the exposure of this drug between 75% and 94% (24,38).

A single dose of lansoprazole (60mg) with atazanavir reduces the Cmax of atazanavir by more than 90% (1).

A guideline from Clinical Info HIV (database that offers access to the latest, federally approved HIV/AIDS medical practice guidelines) refer that atazanavir shouldn't to be coadministered with omeprazole and shows that the combination of atazanavir/ritonavir (ATV/r) and atazanavir/cobicistat (ATV/c) with omeprazole 40mg cause a decrease of 76% in the AUC of atazanavir, but when omeprazole 20mg is given 12 hours before atazanavir/ritonavir and atazanavir/cobicistat the AUC of atazanavir decrease 42%, showing that PPIs should be administered at least 12 hours before ATV/c or ATV/r and PPI dose should not exceed a dose equivalent to omeprazole 20 mg daily (38).

3.1.6 Itraconazole

Itraconazole is a broad-spectrum triazole antifungal agent used to treat various fungal infections such as blastomycosis and onychomycosis (39).

Itraconazole is a lipophilic weak base with pKa = 3.7, so it is nearly insoluble at pH > 4 and association of this drug with a PPI causes a significant decrease in the AUC.

However, Johnson et al discovered that when omeprazole is administered with itraconazole oral solution, the AUC of itraconazole does not change, demonstrating that the increase in gastric pH interferes with the dissolution and, consequently, absorption (1,40).

With the example of this drug, we can see that when we administer itraconazole in solution, the problem of dissolution is already solved and therefore there is no change in its absorption.

3.1.7 Tyrosine Kinase Inhibitors

The tyrosine kinase inhibitors are commonly used as anticancer drugs and have significantly improved outcomes in chronic myelogenous leukaemia and other diseases like idiopathic pulmonary fibrosis.

They can disrupt the signal transduction pathways of protein kinases by several modes of inhibition and examples of TKIs include imatinib, gefitinib, erlotinib, and sunitinib (41,42).

Many cancer patients develop gastrointestinal conditions such as gastro-oesophageal reflux. Therefore, these patients need to be treated with antacids such as PPIs.

However, the combined use of TKIs with PPIs has shown a significant decrease in the AUC of TKIs (erlotinib 46%, nilotinib 34%, gefitinib 44%, bosutinib 26%, lapatinib

26%, neratinib 65%, nilotinib 34% and pazopanib 40%), leaving a great concern that these drugs may not be able to reach the plasma concentration necessary to exert their therapeutic activity. Since TKIs are weak bases (pKa of erlotinib 5.4, nilotinib 5.4, gefitinib 7.2, lapatinib 7.3, neratinib 7.7) and their solubility highly dependent of the solution pH, this bioavailability decrease my be, in fact, due to the elevated gastric pH.

Therefore, the use of PPIs with TKIs should be avoided and, if necessary, TKI levels should be closely monitored to ensure their therapeutic efficacy (43).

3.2 Pharmaceutical technology strategies to overcome absorption problems

As we have seen so far, a large part of the interactions between PPIs and other drugs are because the latter increase gastric pH, which causes changes in the absorption of drugs, especially those classified as BC class II and as weak bases, as their solubility decreases with the increase in pH (44–46).

Many patients take drugs that fall into these categories, and it is essential to look for and discover strategies to obtain formulations in which their dissolution profile is less dependent of pH (45).

The most studied strategies involve including some pharmaceutical excipients in the formulations, such as specific salts and pH-stabilizing excipients, to improve the dissolution and bioavailability of this type of drug by manipulating their own solubility and dissolution rates (47,48).

We can therefore divide these strategies into three main ways:

- We can adjust the pH of the matrix microenvironment to a constant lower pH value with the addition of pH modifiers.

  It should be noted that the pH of the microenvironment is a crucial parameter for achieving a pH-independent profile.

  The pH modifiers mentioned here are acidic pH modifiers that allow us to obtain a uniform release of weakly basic drugs from matrix-type dosage forms such as tablets and pellets. The most commonly used acids are fumaric acid, citric acid, succinic acid, ascorbic acid, adipic acid, sorbic acid, glutaric acid, tartaric acid and finally malic acid (45,47,48). Other compounds also used as pH modifiers are meglumine, sodium carbonate, Neusilin S2 and betaine chloride (45–48).

The effect of these pH modifiers on the dissolution of the drugs investigated is influenced by factors related to the drugs themselves (solubility, molecular weight and pKa), the composition of the dosage forms and the physicochemical characteristics of the acid added (chemical structure, molecular weight and solubility).

Since the pH of the microenvironment is such an important factor in the development of formulations whose dissolution is independent of pH, how can we determine and control this parameter?

a) Through invasive methods:

   These methods include incorporating pH-indicating colouring substances into the structure of the tablet or a contact pH electrode to determine the internal pH of the tablet.

b) Non-invasive methods:

   Measurement of the pH of the surface of the outer layer by a contact pH electrode, using confocal laser scanning microscopy, which is a sophisticated method that uses pH-sensitive fluorescent dyes and electron paramagnetic resonance, which also provides information on micro viscosity and micro polarity (45).

   However, the inclusion of these pH modifiers also has disadvantages that must be considered: a formulation with a large amount of active substance requires a large amount of pH modifying agents inside the formulation, which can affect its stability (46,47).

- In addition, the use of solid dispersions has been the most studied method, as it is low-cost and highly viable.

  The main function of these solid dispersions is to transform the drug into an amorphous state from a crystalline state, while recrystallization is constantly prevented, and the solubility of the drug is improved by increasing its wettability and reducing its particle size.

  Various methods can be used to formulate these amorphous solid dispersions, with the hot melt extrusion (HME) method having the most advantages and being the most widely used: it is a method that does not use solvents; it has few

processing steps; it is inexpensive; it is feasible to transpose to an industrial scale; it is suitable for processing drugs with high melting points and viscous materials.

HPMCAS LG (hydroxypropyl methylcellulose acetate succinate L grade) has shown great efficiency in preventing recrystallization and improving the solubility of drugs at high gastric pH (46,47).

- For modified-release formulations, we can aim at an increase in the bioavailability of the dosage form by incorporating polymers with pH-dependent solubility that are able to compensate for the low solubility of the drugs in question. These polymers include alginates or enteric polymers such as Eudragits ® and are applied as matrix former, sub coating or as part of the extended-release coating.

Having already seen the most common and effective strategies for overcoming absorption problems at a high gastric pH, let's now look at some studies that actually prove these results.

Makoto Kataoka *et al*, from Faculty of Pharmaceutical Sciences, Setsunan University, Japan, published a study in which DNT (dantrolene) was used as a model of a weak acid drug with a pKa (7.5) higher than that of intestinal fluid.

This study was divided into two branches: an in vivo study and an in vitro study with a dissolution/permeation system to evaluate the oral absorption of DNT for a formulation with and without an enteric coating polymer under normal and high gastric pH, in rats and humans respectively.

A salt form of DNT was then used with an amorphous solid dispersion with HPMC, and there were two forms of HPMC: a solid dispersion of simple HPMC and a solid dispersion of HPMC with succinate acetate (enteric-coated form).

At the end of the study, the simple form of HPMC showed greater absorption at high gastric pH than at gastric pH at physiological levels.

However, HPMC with succinate acetate was able to attenuate the differences in absorption between high gastric pH and physiological pH, significantly improving absorption, thus proving the efficacy and usefulness of using this polymer (46).

Ahmed Almotairy *et al* published another study in which the aim was to investigate the effect of an amorphous solid dispersion generated by hot melt extrusion and the addition of pH modifiers on the stability and solubility of telmisartan.

HPMC L grade was the polymeric carrier and recrystallization inhibitor used and meglumine and sodium carbonate were incorporated as pH modifiers to achieve a desirable microenvironment pH.

Using methods such as differential scanning calorimetry, powder X-ray diffraction and Fourier transform infrared spectroscopy, it was possible to obtain the characteristics of the amorphous and crystalline state of telmisartan.

The results confirmed that telmisartan was partially transformed into an amorphous state, and subsequently an in vitro release study showed that this drug in its amorphous state increased its dissolution by two times compared to the pure drug and up to five times when pH modifiers were incorporated (47).

Niloufar Salehi *et al* developed a hierarchical mass transport model to predict the dissolution of drugs under different pH conditions, obviously including high gastric pH.

This model considered the effect of the physical and chemical properties of the drug and the pH modifier, such as pKa, solubility, and particle size distribution.

It is also important to note that the effect of physiological conditions was also considered, such as the rate of gastric emptying, the rate of acid secretion, and the length of stay in the gastrointestinal tract.

After evaluating various drugs with different pH modifiers, some important conclusions could be drawn.

Phosphoric acid proved to be very effective in improving drug dissolution at high gastric pH because it has a low molecular weight and its triprotic structure allows it to buffer over a wide pH range. However, phosphoric acid causes skin irritation and it should not be used for patient safety.

Succinic acid, on the other hand, showed excellent efficacy for drugs with pKa values above 9, as did adipic acid.

Tartaric acid was more effective for drugs with a pKa of less than 8, and ascorbic acid was the least effective pH modifier, regardless of the drug's pKa.

Finally, malic and citric acids did not show good efficacy for pKa lower than 7 and fumaric acid had the best results at a high gastric pH (48).

To support these facts we can look at table 3.4.

Table 3.4 Physicochemical properties of pH modifying agents (48,49)

pH modifier	**pKa (37ºC)**	**Solubility (g/100mL)**	**Included in the FDA inactive ingredient list**	**Acceptable Daily Intake**
Adipic acid	4,45 - 5,42	1,4	Yes	5 mg/kg body weight
Ascorbic acid	4,20 - 11,60	33	Yes	not specified
Betaine Chloride	1,94	60	No	90 mg/kg body weight
Citric acid	4,39	160,8	Yes	not limited
Fumaric acid	2,74 - 4,17	0,63	Yes	not specified
Malic acid	3,26 - 4,77	55,8	Yes	not specified
Phosphoric acid	6,69	548	Yes	40 mg/kg body weight - cause skin irritation
Succinic acid	3,93 - 5,30	5,8	Yes	not specified
Tartaric acid	2,90 - 4,03	21	Yes	240 mg/kg body weight

Although betaine chloride is also used in some studies, this compound is not on the list of active ingredients authorized by the FDA and cannot be used.

With all the above in mind, it is possible to conclude that there are already several strategies for obtaining drugs with a pH-independent dissolution profile and that this is a field that is increasingly studied and of greater interest, but which involves many

variables such as the characteristics of the drug itself and should be studied on a case-by-case basis.

3.3 Interaction studies: when is it necessary?

We have seen so far that PPIs have a wide profile of interactions and, for this reason, it is important to understand when interaction studies should be carried out between a drug" X" and PPIs.

We have seen that drugs classified as BCS class II and IV are the most at risk for potential pH-dependent interactions, as they have low solubility.

To see how important this is, we must mention that around 30% of the drugs on the market belong to BCS class II, and these are drugs as common and well-known as NSAIDs, ezetimibe and folic acid.

As for class IV, around 10% of medicines belong to this class, such as furosemide and bifonazole (50).

How do you know if it's necessary to carry out interaction studies with PPIs?

There is an algorithm developed by the FDA for weak basic drugs that lets you know which drugs should be studied, and all you must do is answer a set of questions below:

1. Does the drug we are investigating have pH-dependent solubility in a pH range between 1 and 6.8?

If yes -> question 2

2. Is the solubility of the therapeutic dose of this drug in 250mL at a pH between 6 and 6.8 less than the dose divided by 250?

If yes -> We have a possible interaction with PPIs and an interaction study is required.

This algorithm is also applicable to other antacid agents, with PPIs representing the worst-case scenario and providing guidance for studies with other antacids.

If there is an interaction with PPIs, the concomitant use of these two drugs should be avoided, but the interaction should be assessed with a lower dose of PPI or another study should be conducted with other antacid agents such as H2 blockers.

For weak acid drugs, FDA has less experience and, although expecting less relevant pH absorption effects, the need for DDI studies should be considered in a case-by-case approach (50,51).

3.4 Drug-drug interaction design study

After concluding that an interaction study with PPIs is necessary, the study needs to be designed.

To do this, there is already a design described by the FDA for this type of study, which is based on the following aspects:

- The study population can be made up of healthy volunteers;

- The sample size must allow for a reliable estimate of the magnitude and variability of the interaction in question;

- A crossover design with a fixed or randomized sequence is preferable.

However, for drugs with a long half-life, a parallel rather than crossover design may be acceptable (50,51).

To clarify, in a parallel study we have trials where the different arms of the study receive different treatments and are evaluated simultaneously, without ever crossing over.

In cross-over studies, the different arms of the study receive different treatments and at a certain point the groups cross over, each receiving the treatment previously assigned to the other.

In addition, to minimize the carryover effect, it is more common to use a fixed sequence, with the PPI being administered in the last period of the study. This fixed sequence tells us that the study design remains unchanged during the study and is defined before the study begins (50–52).

The carryover effect describes the transfer of unwanted material from one container to another, i.e. it describes the influence of one sample on the next (53).

It is recommended that a single dose of the test article be administered on an empty stomach, with the dose of this product and the PPI administered at the maximum

recommended therapeutic dose (40mg esomeprazole, 40mg omeprazole, 40mg pantoprazole) (50,51).

For PPIS, it should be noted that there should be pre-treatment for 4 to 7 days, which is the period needed to reach steady state, before administering the study drug (51).

At the end of the study, to be able to draw a conclusion about the effect of the PPI on the test article, a comparison of pharmacokinetic parameters such as AUC, C_{max} and t_{max} should be made between the group in which the PPI was administered and the group in which it wasn't (50,51).

It is generally said that an observed interaction effect between a drug and an acid-reducing agent can be extrapolated to other antacids of the same class. For example, if we observe an effect with a PPI, we can extrapolate this same effect to other PPIs (51).

However, in the specific case of PPIs, it is crucial to understand that there are class reactions and non-class reactions. Non-class reactions are characterized by the fact that not all PPIs cause the same interaction reaction. A clear example of this is the interaction between clopidogrel and omeprazole and esomeprazole, due to the affinity of these two PPIs for CYP2C19.

However, other PPIs, such as pantoprazole and lansoprazole, do not have this affinity with this CYP, and thus do not have this interaction.

Therefore, we conclude that not all interaction reactions can be extrapolated to all PPIs, as they have different characteristics (18).

4 Bioequivalence

The EMA's definition for bioequivalence is: "When two medicines release the same active ingredient into the body at the same rate and to the same extent under similar conditions" (54).

The FDA definition is: "Two products are considered to be bioequivalent when they are equal in the rate and extent to which the active pharmaceutical ingredient (API) becomes available at the site(s) of drug action" (55).

Bioequivalence studies should be carried out, for example, when a sponsor proposes the production of a generic medicine or, for example, when we have an original medicine already on the market and that same medicine undergoes a change in its pharmaceutical form or composition, particularly in terms of excipients, in such a way as to cause differences, particularly in its dissolution and absorption rates, which is what we have been focusing on in this work (44,55).

So, to have a bioequivalence study, it is always necessary to have a comparator drug, which is the drug accepted by the regulatory agencies that can be used to compare with the drug under study.

It is advisable to investigate more than one batch of the comparator product and the test product used in the bioequivalence study must be representative of the product to be marketed.

The test product batches used in the study must provide a high level of assurance that the product will be viable on a commercial scale.

These studies should be carried out under certain conditions that minimize variability to improve the detection of potential pharmacokinetic differences between the two medicines.

For solid oral forms, single-dose studies carried out in the fasting state usually generate greater discrimination between the pharmacokinetic profiles of the two drugs.

Fasting conditions are at least 10 hours without food or drink before the drug is administered, and drinking water is permitted except 1 hour before taking the drug. It should be taken with a standardized dose of water, between 150 and 250mL of water.

However, food can have an impact on the absorption of high-risk substances, preventing the extrapolation of bioequivalence under fasting conditions to feeding conditions.

High-risk products are products in which the complexity of their formulation design leads to a greater likelihood of their in vivo performance being affected by variable gastrointestinal conditions between fasting and feeding states.

Medicines containing low-solubility active substances (such as class II BCS) usually have these more complex formulations, as explained above, due to the incorporation of amorphous solid dispersions, microemulsions, nanotechnology, etc., which ensure sufficient solubility and manage the impact of food (44).

ICH Guideline M13A on bioequivalence for immediate release solid oral dosage forms say that when there are qualitative or quantitative differences in the pH-stabilizing excipients, the manufacturing process or the salt form in relation to the comparator product or when we have patients taking antacid agents or patients taking medicines that their solubility are pH dependent, the bioequivalence study under fasting conditions between the two products may not guarantee bioequivalence in a situation of altered gastric pH, as is the case with PPIs. In such a situation, an additional BE study with concomitant treatment of a pH-modifying drug product would generally be necessary to demonstrate BE (44,56).

Now, we are going to look for some studies to think about the information of ICH: Are additional bioequivalence studies necessary under these conditions?

We start with a study conducted by Corinne Seng Yue *et al* where they showed that bioequivalence in healthy volunteers may not translate to bioequivalence in patients.

In this study they compared the pharmacokinetics of levothyroxine capsules and tablets, two formulations deemed bioequivalence in healthy volunteers under fasting conditions, when taken with or without esomeprazole. To do this, they conducted two studies in healthy volunteers given single dose levothyroxine (600 mg) with a 45-day washout period:

- Study 1 (parallel design/two-way crossover):

  Sixteen subjects received either levothyroxine capsules (final n = 8) or tablets (final n = 6), each group with or without prior administration of esomeprazole.

- Study 2(two-way crossover):

Sixteen subjects received both capsules or tablets after esomeprazole (final n = 15).

Blood samples were collected pre-dose and up to 24 hours post-dose, within baseline-adjusted pharmacokinetics parameters were calculated: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-6} and AUC_{0-12}.

The results showed that, in study 1, esomeprazole caused a great decrease in levothyroxine exposure of tablets vs capsules (13% vs 6% for Cmax and 10% vs. 8% for AUC_{0-t}). In study 2, a difference was also detected between capsules and tablets, as in study 1, with a 16% smaller levothyroxine exposure with tablets vs. capsules.

So, although the number of subjects in both studies is low, these studies highlight that, although both formulations are considered "bioequivalent" in healthy volunteers, they may not necessarily be bioequivalent in patients with impaired gastric pH conditions or taking PPIs. This highlights also the need for considering additional BE studies when drugs have pH dependent dissolution, as is the case of levothyroxine (57).

Another study by K. Doki et al evaluated the differences in bioequivalence studies for levothyroxine and controlled-release nifedipine when there are situations of achlorhydria, using a physiologically based pharmacokinetic (PBPK) modelling framework.

Dissolution profiles at neutral pH in vivo were incorporated into the PBPK to mimic achlorhydria and this model effectively reproduced the results of bioequivalence studies in healthy volunteers under normal conditions, as well as under conditions of achlorhydria, induced by PPIs.

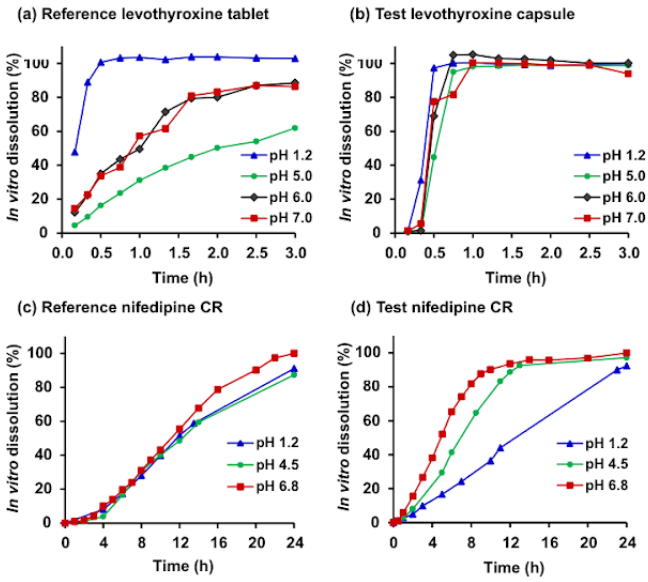

Figure 4.1 In vitro dissolution profiles of the reference levothyroxine tablet (a) and capsule (b), and the reference (c) and test (d) nifedipine CR formulation extracted from the literature (58)

The above graphs, taken from the study in question and with data from the literature, show that when we have levothyroxine in tablets, it has a slower dissolution profile at neutral and weakly acidic pH, when compared to a very acidic pH, such as the physiological pH of the stomach.

However, when we look at the dissolution profile of levothyroxine capsules, which are soft capsules in which the active substance is dissolved in glycerine, we see that its dissolution profile is consistent, i.e. it is not pH-dependent, and there is a big difference between these formulations of the same active substance.

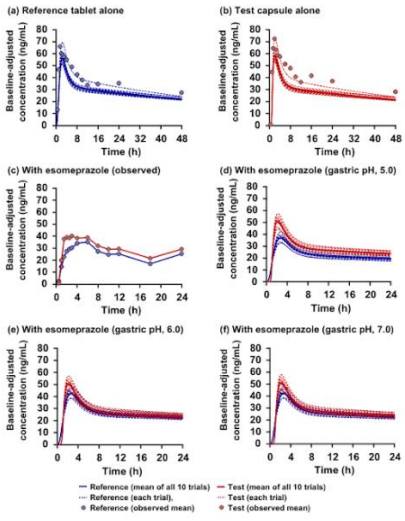

Figure 4.2 Simulated and observed plasma levothyroxine concentration profiles for the reference tablet (a) and test capsule (b) of levothyroxine in healthy volunteers. Observed plasma levothyroxine concentration profiles for the reference and test formulations in healthy volunteers after the intravenous administration of esomeprazole (c). Simulated plasma levothyroxine concentration profiles for the reference and test formulations in virtual healthy volunteers using gastric pH 5.0 (d), pH 6.0 €, and pH 7.0 (f). The plasma levothyroxine concentrations were baseline-adjusted (58)

In these last graphs, we can see the concentrations reached by levothyroxine tablets and capsules and compare them when there is concomitant administration of a PPI, in this case esomeprazole.

In all cases we can see that, although from around 4 hours onwards the peak concentration starts to decrease and a steady state begins to be absorbed, we can also see that the capsules always reach a higher peak concentration and that, even in the steady state, they also manage to maintain a higher concentration, regardless of the pH we find.

Once again, this information reinforces the benefits that soft gelatine capsules can have over levothyroxine tablets.

Regarding the other substance under study, nifedipine, this is marketed in the form of prolonged release (CR), however, this release system can differ from one another, with the oral push-pull osmotic system (OROS) and hydrophilic matrix tablets.

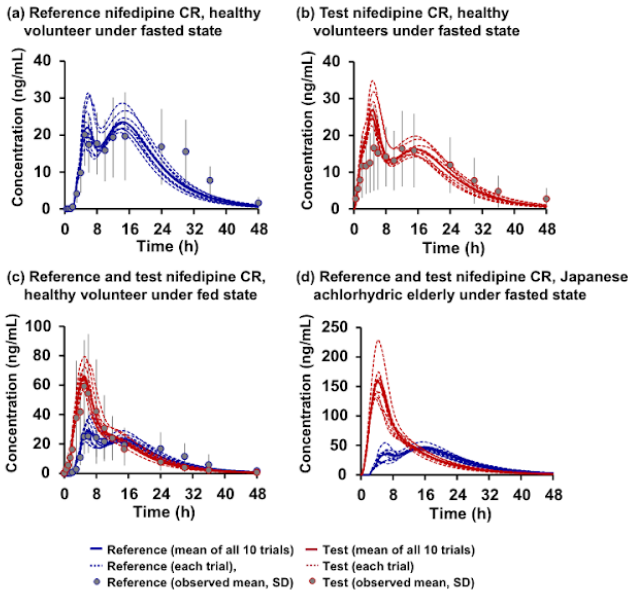

Figure 4.3 Simulated and observed plasma nifedipine concentration profiles for the reference (a) and test (b) nifedipine CR formulations in healthy volunteers

under fasted state. Simulated and observed plasma nifedipine concentration profiles for the reference and test formulations in healthy volunteers under fed state (c). Simulated plasma nifedipine concentration profiles for the reference and test formulations in Japanese achlorhydric elderly (d) (58)

Before we interpret these graphs for the nifedipine formulations, it should be noted that our reference formulation is the OROS extended-release formulation, while our test product is the extended-release formulation with the hydrophilic matrix.

That said, the OROS formulations have pH-independent dissolution profiles, while the hydrophilic matrix tablet shows a clear dependence on pH in its dissolution.

Once again, this study also raises questions about the possibility that bioequivalence cannot be assumed in the same way in a population of healthy individuals as in a population of individuals with achlorhydria or taking antacid agents, as is the case with PPIs.

Therefore, looking at all the above, what the ICH says is confirmed, i.e. a normal bioequivalence study carried out in a fasting situation and in healthy volunteers may not, in certain situations, guarantee that this bioequivalence is also valid in patients with a high gastric pH, different from the normal physiological pH (44,58).

5 Conclusion

Throughout this work, PPIs have been studied and, most importantly, the interactions between PPIs and other drugs have been addressed, enabling us to understand which drugs/class of drugs are most likely to interact with PPIs.

This is extremely important because many drugs that are marketed and are likely to interact with PPIs, such as BCS class II and IV drugs, have low and pH-dependent solubility, making them at risk of interacting with antacid agents because they increase the pH of the stomach to a level different from the normal physiological pH.

To overcome these solubility problems and therefore these interactions, it has been studied that there are various strategies for making the dissolution profile of some drugs independent of pH.

The inclusion of pH-modifying excipients, as well as the use of amorphous solid dispersions, are the most widely used strategies that show the best results.

We have also seen that bioequivalence studies are usually carried out in fasting conditions and with healthy volunteers.

These conditions, that are considered sufficient for demonstrating therapeutic equivalence for most of the drugs, may not guarantee bioequivalence in populations who are medicated with PPIs and other agents that alter the pH of the stomach, as well as in other populations, such as patients with achlorhydria.

Therefore, for these drugs that are expected to interact with PPIs and for formulations that contain, for example, pH-modifying excipients that help make their dissolution profile pH-independent, it is necessary to consider the need for carry out bioequivalence studies with the concomitant administration of a pH-modifying drug so that bioequivalence can be guaranteed for all populations.

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