

Enhanced Drug Absorption with Food – Opportunities for Pharmaceutical Intervention

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ABSTRACT

Drug absorption after oral administration is crucial for achieving a therapeutic effect, and one of the most important external factors influencing this process is food intake. While some drugs are recommended to be taken on an empty stomach due to possible inhibition of absorption, for others – especially lipophilic and poorly soluble drugs – the presence of food, particularly high-fat meals, can significantly enhance bioavailability. This paper analyzes drugs from various therapeutic classes whose systemic exposure increases when taken with food, including antifungals, retinoids, antiretroviral drugs, antiviral agents for hepatitis C, antineoplastics, and antimalarials. A total of 16 drugs are presented, with reported absorption increases ranging from 1.5- to as much as 16-fold in the presence of food. Particular emphasis is placed on the role of pharmacists in identifying such drugs and counseling patients on the optimal timing of administration, type of meal, and the importance of consistency in therapy. Pharmaceutical intervention in this context includes patient education on proper drug administration, prevention of therapeutic failure, and improvement of therapeutic outcomes. The paper highlights the need to integrate nutritional recommendations into everyday pharmaceutical practice and to strengthen the pharmacist's role in therapy personalization.

Key words: drug absorption, food, pharmacist, bioavailability, lipophilic drugs

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INTRODUCTION

Absorption of medicinal products is an essential stage in the pharmacokinetic profile of any active substance administered orally. It is a process of the transition of a drug from the site of administration, most often from the digestive system, to the systemic circulation (1). The absorption efficiency directly determines the bioavailability of the drug, i.e., the proportion of the active substance that reaches the bloodstream unchanged and thus exerts a pharmacological effect. If absorption is

insufficient or highly variable, subtherapeutic plasma concentrations as well as therapeutic failure and, in the case of different groups of antimicrobials, the development of resistance may occur (2). Absorption mechanisms include primarily passive diffusion, which is the most common way for low-molecular weight lipophilic molecules to pass through biological membranes. In addition, some drugs utilize transport systems, including facilitated diffusion or active transport, using specific transporter proteins located in enterocytes.

Table 1. BCS class and food impact

BCS class	Solubility	Permeability	Example	Impact of food
I	High	High	Paracetamol	Minimal – good absorption in any case
II	rope	High	Itraconazole	Significant improvement in absorption with food
III	High	rope	Metformin	Possible reduction of side effects, but does not affect its importance to AUC
IV	rope	rope	Furosemide	Absorption is unpredictable – food can reduce or increase bioavailability

In rarer cases, such as large molecules or nanopreparations, endocytosis may occur as a mode of transmission. The ionization state of a molecule, which depends on its pKa value and the pH of the medium, also plays an important role, as it affects the solubility and ability for diffusion across lipid membranes (3). The absorption of a drug is determined by a number of factors that can be classified into several categories. The first set is the physicochemical properties of the active substance, where solubility and lipophilicity are of crucial importance. Drugs that dissociate poorly in aqueous media, and at the same time possess high membrane permeability, belong to the so-called class II according to the Biopharmaceutics Classification System (BCS) and are the most sensitive to external influences such as diet (4) (Table 1). Molecular weight and structure additionally affect the ability to cross the epithelial barrier, whereby drugs with higher molecular weights are more difficult to absorb.

In addition to the properties of the molecule, the formulation and pharmaceutical form also play an important role. Solutions and suspensions demonstrate faster and more complete absorption compared to solid forms such as tablets and capsules. Modified-release systems, such as gastro-resistant capsules or prolonged-acting preparations, further complicate the absorption process because they can target different parts of the digestive tract. Excipients used in the formulation, such as surfactants or complexants, can also promote the dissolution and absorption of the active substance (6). The physiological factors of the gastrointestinal system strongly affect the rate and extent of absorption. Primarily, the pH of the digestive system stands out, as it determines the ratio of the ionized and non-ionized form of the drug. Changes in pH, especially in the case of antacids or proton pump inhibitors, can significantly alter bioavailability. The motility and rate of gastric emptying also affect the retention time of the drug at the site of absorption and thus the

degree of absorption. Increased blood flow through the intestinal mucosa, for example after a meal, can further improve the transfer of the drug into the systemic circulation. Furthermore, enzymes and microbiota present in the gut may contribute to the presystemic metabolism of some drugs, which is another factor affecting bioavailability (7).

One of the most important external factors that modulates absorption is the presence of food (8). Food can increase the solubility of lipophilic drugs, stimulate the secretion of bile and pancreatic enzymes, prolong the retention of the drug in the stomach, and change the pH of gastric contents. Foods high in fat are particularly conducive to the absorption of drugs with low solubility, such as those from BCS class II (9). However, with some medications, food can have the opposite effect, for example by reducing absorption through chelation (as in the case of tetracyclines and fluoroquinolones) or by physically interfering with the contact of the active substance with the epithelium (10).

Absorption can also be altered by various pathological conditions. Diseases such as celiac disease, Crohn's disease, diarrhea, or vomiting impair the functionality of the intestinal mucosa, which can significantly reduce or completely prevent absorption (11, 12). Older adults often have reduced gastric acid secretion and changes in the composition of the microbiota, which can also affect pharmacokinetic parameters. Surgical procedures, especially gastric and intestinal resections, change the absorption surface and dynamics of the drug in the long term (13).

While many drugs emphasize the need to take them on an empty stomach to avoid a decrease in absorption, with certain pharmaceutical preparations, diet – especially one high in calories and rich in fatty macronutrients – significantly increases bioavailability. Such examples include drugs whose effectiveness is significantly related to food intake.

In the modern health care system, the role of pharmacists goes beyond the traditional boundaries of dispensing medicines and is

increasingly evolving toward clinically oriented and patient-centered care (14). Pharmaceutical counseling is a process in which the pharmacist provides the patient with professional information and recommendations with the aim of optimizing the use of drugs, improving adherence, and increasing therapeutic efficacy (15). In the context of drugs whose absorption is conditioned by nutritional status, educating patients about the correct time of intake, the type and amount of food, and potential interactions is of particular importance for achieving the desired pharmacotherapeutic effect (16).

Numerous studies confirm (17–19) that pharmacists have the most frequent and direct contact with patients, especially in the context of chronic therapy, where regular counseling and monitoring are crucial for the success of treatment. In such a model of care, pharmaceutical intervention includes a series of activities that can be preventive, corrective, or educational in nature. Preventive interventions include timely recognition of possible medication errors, such as taking the drug on an empty stomach when it is indicated to take it with a meal, which can prevent reduced absorption and therapeutic failure. Corrective interventions refer to the correction of errors in already started therapy, while educational interventions include a systematic explanation of the purpose, method of administration, duration of therapy, and importance of following dietary instructions (20).

In the case of drugs with pronounced food dependence, pharmaceutical consulting becomes necessary. Namely, patients are often unaware of the difference between the advice “take with food” and “take after meals”. The first implies the necessity of food to improve absorption, while the second is most often related to the reduction of gastrointestinal side effects. This seemingly simple difference has far-reaching consequences for the effectiveness of therapy. In this sense, the pharmacist must communicate clearly with each patient, using

concrete examples of food and situations from everyday life, to ensure the correct understanding and implementation of the instructions. Furthermore, the pharmacist must also take into account the patient's social circumstances – such as improper diet, loss of appetite, old age, or administration of multiple medications – as all these factors can further complicate the process of taking medication in accordance with dietary recommendations. An important aspect of pharmaceutical intervention is the monitoring of adherence, i.e., the degree to which the patient follows the agreed therapeutic regimen. In drugs with high absorption variability, such as many antifungals, antiretrovirals, and antineoplastics, non-adherence can have a direct impact on the outcome of treatment. The pharmacist can contribute to the detection of the cause of poor adherence, whether it is the complexity of the dosing regimen, or the side effects or erroneous beliefs of the patient, and offer solutions in the form of simplification of therapy, nutrition counseling, or referral for additional professional help.

In addition to working directly with patients, pharmaceutical interventions also involve collaboration with other health care professionals. The pharmacist can draw the doctor's attention to the need to change the pharmaceutical form (e.g., from capsule to solution for itraconazole), warn of a potential interaction between food and medication, or suggest educational materials for patients. In a team approach to the treatment of chronic diseases, the role of a pharmacist is indispensable and is based on expert assessment and an individualized approach to each patient. Pharmaceutical counseling and intervention are not only an addition to therapy, but an integral part of it. In the context of drugs in which food significantly affects absorption, the role of pharmacists in education, supervision, and the optimization of therapy has a direct impact on the outcome of treatment. The systematic and professional implementation of pharmaceutical interventions contributes to better patient

adherence and satisfaction of treatment outcomes.

OVERVIEW OF SELECTED DRUGS WITH IMPROVED ABSORPTION WITH FOOD

This chapter presents drugs whose absorption increases significantly in the presence of food, especially foods rich in fat. Most of these drugs belong to BCS class II, which means that they are poorly soluble but highly permeable, and their food intake improves dissolution and bioavailability (22). The effect on drug absorption is observed as the effect on the area under the curve (AUC) and peak maximum concentration (C_{max}). These are two basic pharmacokinetic parameters that are used to quantify the exposure of an organism to a drug after its administration. These indicators are utilized to assess the absorption, distribution, and elimination of a drug, and their interpretation is crucial in understanding the efficacy and safety of therapy, especially in drugs whose pharmacokinetics change significantly depending on the presence of food.

The term AUC refers to the area below the curve of the plasma concentration of a drug in relation to time. It represents the total systemic exposure to the drug over a period of time. AUC is expressed in concentration units multiplied by time (e.g., ng x h/ml), and the larger the area under the curve, the longer and more exposed the organism was to the active substance. AUC is particularly important when assessing the bioavailability of a drug and comparing different pharmaceutical forms, dosing regimens, or the effect of food on absorption. An increase in AUC in the presence of food indicates improved absorption and greater therapeutic potential of the drug (22).

C_{max} is the maximum concentration of the drug reached in plasma after administration. This parameter is often used to assess the rate of absorption, but also to evaluate possible toxic effects, since high concentrations of the drug are associated with an increased risk of

side effects. The C_{max} value depends on the rate of dissolution of the drug, its solubility, the presence of food, and the individual characteristics of the patient. Administration of the drug with food can delay the achievement of C_{max}, but also increase its absolute value, which is often the case with lipophilic and poorly soluble drugs. In such situations, a higher C_{max} value means more effective action, but also the need for careful monitoring of side effects (23).

In pharmaceutical practice, understanding and interpreting AUC and C_{max} helps in the correct choice of drug administration, the individualization of therapy, and the design of therapeutic regimens. When assessing the impact of food on a drug, AUC and C_{max} are used as objective indicators of improvement or decrease in absorption, thus becoming a direct tool in making recommendations for pharmaceutical intervention. Table 2 shows the selected medicinal products and their pharmacokinetic relationship with food.

Table 2. Selected drugs and the impact of food on their absorption

Drug	ATC code	Type of food	Absorption increase	Reference
Griseofulvin	D01BA01	Meal with high fat content	A significant increase	24
Isotretinoin	D10BA01	Meal with high fat content	1.5–2x	25
Itraconazole	J02AC02	Food in general	71%	26
Posaconazole	J02AC04	Meal with high fat content	4x AUC, a significant increase in C _{max} ; 51% AUC, 16% C _{max}	27, 28
Saquinavir	J05AE01	Meal with high fat content	3.3x AUC	29
Nelfinavir	J05AE04	Meal with high fat content	2–3x AUC	30
Lopinavir	J05AE06	Standard meal; meal with high fat content	48%–80% AUC, 23%–54% C _{max} ; 96%–130% AUC, 43%–56% C _{max}	31
Atazanavir	J05AE08	Light meal	33% AUC, 40% C _{max}	32
Tipranavir	J05AE11	Meal with high fat content	31% AUC, 16% C _{max}	33
Etravirine	J05AG04	Any meal	49% AUC	34
Rilpivirine	J05AG05	Standard meal	16% AUC	35
Boceprevir	J05AP01	Any meal	60% AUC	36
Telaprevir	J05AP02	Standard meal	235% AUC	37
Dolutegravir	J05AX12	Standard meal; high-fat meal	41% AUC; 66% AUC	38
Venetoclax	L01XX52	Meal with high fat content	5.1x AUC	39
Lumefantrine	P01BF01	Meal with high fat content	2.7–16x AUC	40

According to the classifications of the US Food and Drug Administration (FDA), there are differences in the terms “high-fat meal” and “standard meal”. A “high-fat meal” is one in which fat makes up 50% of the total caloric value, while a “high-calorie meal” is considered to be one containing between 800 and 1,000 kilocalories, distributed approximately to 150 kcal from protein, 250 kcal from carbohydrate, and 500 to 600 kcal from fat (41). For example, this is quite

important in the case of isotretinoin, as clinical trials that evaluated the efficacy and safety of isotretinoin were conducted under these conditions. However, in everyday practice, the situation is often different – many patients do not consume three meals a day, let alone one that meet the criteria of high fat and calorie intake. In such cases, the absorption of isotretinoin can be significantly reduced, which consequently leads to decreased effectiveness of the therapy. Of additional concern is the fact that many dermatologists do not provide patients with adequate

instructions on the nutritional requirements that accompany this therapy, further increasing the risk of a suboptimal therapeutic response. A moderately fat meal or standard meal refers to one that contains 500 to 682 kcal, of which 23% to 25% kcal comes from fat (42).

PHARMACEUTICAL INTERVENTION OPTIONS

Antifungals are a group of drugs whose systemic efficacy relies heavily on adequate absorption, especially in the case of oral administration. The antifungals reviewed here are poorly soluble in water, but highly permeable. Precisely because of this characteristic, their absorption is significantly improved when applied with foods, especially those rich in fat. Griseofulvin is used to treat dermatomycosis, and its oral bioavailability increases significantly when administered with a fatty meal. Clinical guidelines recommend taking the drug with foods containing at least 13 g of fat, such as full-fat milk, butter, cheese, or eggs (43). Pharmaceutical interventions are shown in the table below.

Itraconazole is a broad-spectrum azole antifungal. The oral absorption of itraconazole capsules increases by approximately 71% when administered with food, while the oral solution is better absorbed on an empty stomach (44). Posaconazole as an oral suspension shows a fourfold increase in AUC when taken with a high-fat meal, while a newer formulation of extended-release tablets demonstrates a more modest increase ($\approx 51\%$ AUC, 16% C_{max} with the same type of meal) (45).

Retinoids, derivatives of vitamin A, are used in the treatment of various dermatological conditions, and the most famous representative of this group is isotretinoin. It is a powerful systemic drug utilized in the treatment of severe forms of acne resistant to standard therapy. Isotretinoin is an extremely lipophilic drug with very low solubility in water, which is why its absorption in the gastrointestinal tract is strongly dependent on

the presence of fats in food (46). In randomized trials, it has been shown that the consumption of high-fat meals increases the absorption of isotretinoin by 1.5 to two times, compared to fasting (25). In addition, the form of the preparation also affects availability – traditional capsules require food, while newer formulations (e.g., isotretinoin in lipid capsules) may have less dependence on dietary conditions. A significant number of therapeutic failures and “weaker responses” to isotretinoin in clinical practice are actually a consequence of insufficient education on proper use. In this context, the pharmacist plays a key role in ensuring adequate exposure of the drug through individual consultation.

Protease inhibitors (PIs) represent a fundamental group of antiretroviral drugs in the treatment of HIV infection. They are characterized by pronounced interindividual pharmacokinetic variability, relatively low oral bioavailability, and strong dependence on the nutritional status of the patient.

The absorption of most PIs increases significantly with food intake, especially high-fat foods, resulting in better drug exposure, greater efficacy, and reduced resistance development (47). In clinical practice, it is important to recognize the differences between individual PI drugs, as the effect of food can vary from moderate to very pronounced.

In addition to protease inhibitors, other classes of drugs are increasingly used in antiretroviral therapy, including non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase inhibitors (INIs). Although the pharmacokinetics of these drugs are not always as food-dependent as PIs, certain NNRTIs and INIs show moderate to significant increases in absorption with food intake. Taking these drugs with a meal can increase therapeutic efficacy and reduce interindividual variability (48, 49).

Boceprevir and telaprevir belong to the group of HCV protease inhibitors, and were an integral part of early therapeutic regimens for the treatment of chronic hepatitis C genotype 1.

Table 3. Pharmaceutical interventions regarding nutrition in certain groups of drugs

Group	Drug	Pharmaceutical intervention
Antimycotics	Griseofulvin	<ul style="list-style-type: none"> advise patients to take the medicine during the main meal, recommendation of concrete examples of food, monitoring of therapeutic adherence and possible recurrences of infection.
	Itraconazole	<ul style="list-style-type: none"> educating patients about the difference between pharmaceutical forms (capsules vs. solution), indicating that the capsules are always taken with a full meal. advice to take the oral suspension with foods high in fat, e.g., full-fat yogurt, peanut butter, milk,
	Posaconazole	<ul style="list-style-type: none"> education on the importance of consistent use with food throughout treatment, identifying patients for whom the tablet is a better choice (e.g., those with difficulty eating).
Retinoids	Isotretinoin	<ul style="list-style-type: none"> clear advice to patients to always take the medication with a high-fat meal; recommendations may include foods such as eggs, avocado, cheese, butter, whole milk or nuts, education about the consequences of improper administration – suboptimal absorption can lead to ineffective therapy, delayed response, and longer duration of treatment, questions focused on the method of taking the medication at each refill, especially in adolescents, who often have irregular eating habits, collaboration with dermatologists in case of need for a change in the pharmaceutical form in patients with eating disorders or digestive disorders.
Protease inhibitors	Saquinavir	<ul style="list-style-type: none"> advice that the medicine should always be taken within 2 hours after a main meal rich in fat.
	Nelfinavir	<ul style="list-style-type: none"> recommendation to take the medicine with the main meal of the day (breakfast or lunch), avoid taking on an empty stomach.
	Lopinavir/ritonavir	<ul style="list-style-type: none"> in the case of solution – necessarily with food; with tablets – recommended should be taken with a meal for stability of exposure.
	Atazanavir	<ul style="list-style-type: none"> recommendation to take the medicine with food (e.g., toast with butter, yogurt), advise regularity of intake.
	Tipranavir	<ul style="list-style-type: none"> advice to patients to take the medicine with a meal, possibly with rich fats.
Nucleoside reverse transcriptase inhibitors Integrase inhibitors	Etravirine	<ul style="list-style-type: none"> emphasize that etravirine must be taken with any meal, ideally with breakfast or dinner, to avoid subtherapeutic concentration.
	Rilpivirine	<ul style="list-style-type: none"> advise patients on regular use of the product with at least 400 kcal of food (e.g., cheese and yogurt sandwich), especially in people with variable appetite or gastrointestinal symptoms.
	Dolutegravir	<ul style="list-style-type: none"> recommended with a meal, especially in polytherapy with other food-dependent medications.
Antiviral drugs for hepatitis C	Boceprevir	<ul style="list-style-type: none"> emphasize that the drug should not be taken on an empty stomach – it can be taken with any food, but regular use with a meal is crucial for the stability of concentration. strictly advise taking the drug with a standard or high-calorie meal, since absorption without food is insufficient,
	Telaprevir	<ul style="list-style-type: none"> education about foods high in fat (eggs, whole milk, cheese, avocados) is especially important.

Although today they have been largely replaced by modern direct-acting antiviral drugs (DAAs), their understanding remains relevant in the context of pharmacokinetics and the historical development of therapy. Both drugs are characterized by a strong

increase in absorption with food, which achieves significantly higher systemic exposure and reduces pharmacokinetic variability (50). Insufficient absorption, for example due to taking the drug on an empty stomach, can lead to subtherapeutic levels and

the development of resistance, which is particularly important in the treatment of viral diseases.

CONCLUSION

The absorption of drugs after oral administration is a key determinant of their therapeutic efficacy. A number of drugs, especially poorly soluble and lipophilic ones, show significant variability in absorption depending on the presence of food, as well as its quantity and composition. This study presented a group of drugs in which food, especially meals rich in fat, significantly increases bioavailability, which can multiply the outcome of therapy. Through a systematic analysis of 16 drugs from different therapeutic groups – including antifungals, retinoids, antiretrovirals, antivirals for hepatitis C, antineoplastics, and antimalarials – it was observed that absorption can increase from 1.5 times up to as much as 16 times in the presence of food. Such data are not only pharmacokinetically interesting, but also have direct clinical implications, especially in drugs with a narrow therapeutic range or in the treatment of chronic and resistant diseases.

In this context, pharmaceutical intervention is a key component of quality pharmacotherapy. A pharmacist, as an accessible and educated health professional, has the opportunity and obligation to:

- identify medicines whose absorption is dependent on food,
- provide clear and practical instructions on when and how to apply,
- monitor adherence and intervene in case of incorrect intake.

Counselling about taking the medicine with, for example, “full-fat yogurt” or “a meal containing at least 20 g of fat” can make the difference between therapeutic success and failure. Through an individual approach, continuous patient education, and clearly communicated instructions, pharmacists can

significantly contribute to the personalization of therapy, patient safety, and rational use of medications. Proper recognition and implementation of pharmaceutical interventions in the field of improved absorption of drugs with food is not only a professional duty, but also a powerful tool in optimizing therapeutic outcomes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Martin Kondža, Marija Banožić, Ivica Brizić, and Josipa Bukić designed the study. Martin Kondža and Marija Banožić designed the search strategies and performed the literature search. Ivica Brizić and Josipa Bukić reviewed the literature and extracted the available data. Martin Kondža and Josipa Bukić analyzed the data and wrote the paper. Ivica Brizić reviewed the written paper. All authors approved the submitted and final versions.

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Institutional review board statement: This review article does not require an ethics review, as it was based on published work found in a medical database. No identifiers or group of identifiers, which would allow the release of private information to an individual, were provided in the manuscript.

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