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RESEARCH ARTICLE

Food-effect study on the pharmacokinetics of indapamide prolonged-release tablets

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Objective: A comparative study was performed to evaluate the food impact on the pharmacokinetics of indapamide 1.5 mg prolonged release tablets (SR).

Methods: The data evaluated were collected from 2 randomized, single dose, 2-way crossover bioequivalence studies with administration of indapamide to healthy Caucasian volunteers under fasting and fed conditions, respectively. Forty-four eligible subjects aged 19–39 years were enrolled in both studies: 22 subjects received indapamide under fasting (study 1) and the other 22 under fed (study 2) conditions. Blood samples were collected following the same schedule before and up to 96.0 hours after drug administration. Blood concentration of indapamide were quantified by a validated LC-MS/MS method. A non-compartmental analysis was used to calculate the pharmacokinetic parameters. Mathematical deconvolution was applied to assess indapamide absorption. Statistical significance for differences in key pharmacokinetic parameters was evaluated using an ANOVA test, with a significance threshold of $p < 0.05$.

Results: In total, 44 subjects were included in analysis. The outcomes demonstrated that ingestion of food independently reduced the mean of t_{max} by 4.64 h and increased the value of C_{max} by 19.7 ng/mL, while the AUC remained unchanged.

Conclusions: Notably, differences in drug absorption rate obtained after co-administration of indapamide with food had no significant influence in safety and efficacy of the drug.

Keywords: indapamide, food effect, pharmacokinetics, clinical study, bioequivalence

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Introduction

Hypertension remains a global challenge due to its high prevalence and the associated cardiovascular disease (CVD) risk, affects individuals of all ages, including young people [1-4]. Worldwide, an estimated 1.28 billion adults aged between 30–79 years are affected [2], with a sharply increase rate in the number of young and middle-aged patients over the past three decades [1]. Therapeutic management of hypertension is correlated with a decrease in the stroke risk of 35–40% and contributes to a 20–25% reduction in the risk of coronary heart disease (CHD) [4]. Lifelong treatment necessitates strict adherence, and therapeutic approaches often involve diuretics, either alone or in combination [5-7].

Indapamide, a sulfonamide derivative containing an indole ring exhibits pharmacological similarities to those of thiazide diuretics [8-10]. Its significant effect on blood pressure regulation positions it as a valuable therapeutic option in clinical practice for the treatment of mild to moderate hypertension [10,11]. The antihypertensive efficacy of indapamide is associated with improved arterial compliance and a reduction in both arteriolar and total peripheral resistance [8]. A dual mechanism of action has been considered: involving diuretic activity and direct vascular effects [10,12]. In well-controlled clinical trials lasting 12 to 52 weeks, indapamide SR 1.5 mg/day effectively reduced blood pressure, comparable to therapeutic dosages of other antihypertensive medications, such as amlodipine, candesartan, enalapril, hydrochlorothiazide or indapamide IR [4].

Two dosage forms are available on market, immediate release (IM) tablets 2.5 mg and modified-release (SR) tablets 1.5 mg [9,13,14]. Asmar et al. (1998) found that low-dose sustained-release (SR) indapamide (1.5 mg) achieved comparable antihypertensive efficacy to immediate-release (IR) indapamide (2.5 mg) while significantly reducing the number of individuals with side effects, such as hypokalemia [3].

Controlled-release formulations, such as SR tablets, are preferred due to their enhanced drug safety and reduced dosing frequency, leading to improved patient compliance [11,15]. For long-term antihypertensive treatment, gradual drug release ensures consistent blood pressure control, reducing complications associated with hypertension, such

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as heart attacks, strokes, and kidney diseases [3]. The low-dose SR, formulation based on a matrix system [8], maintains antihypertensive efficacy while offering a smoother pharmacokinetic profile [4]. It is characterized by a stable plasma concentration at steady state, exhibiting only minor fluctuations over a 24-hour period [16], serving as an effective candidate for monotherapy and a valuable component of multidrug antihypertensive regimens [4].

In terms of pharmacokinetic properties, the gastrointestinal absorption of indapamide is extremely fast and complete, possibly related to its high lipid solubility [10,12]. The peak concentration occur at 12 hours (for SR) [3] or 2-3 hours (for IR formulations) [12], while similar exposure is maintained [4]. Indapamide exhibits widespread distribution in the body, with extensive binding to specific sites, including red blood cells (80%) and carbonic acid anhydrase (98%) without inhibiting the enzyme. In plasma, it has a high binding affinity to plasma proteins (79%). Additionally, indapamide is significantly absorbed into the vascular wall, where it specifically binds to elastin. Due to its robust capacity of binding within the vascular compartment, indapamide has a relatively low apparent volume of distribution (approximately 60 L) [10]. With an 18-hour half-life (14 and 24 hours), indapamide allows once-daily dosing, an aspect appreciated by patients [3,10,12,16]. Both single-dose and multiple-dose pharmacokinetic data indicate that indapamide follows linear kinetics [10]. Steady-state concentrations are attained after 5-7 days, while optimal effect requires patience [8,13]. Indapamide is extensively metabolized in the liver and the elimination occurs in a biphasic manner, with approximately 70% excreted in the urine and 22% in the feces as inactive metabolites [8,10,16]. However, understanding its pharmacokinetics (PK) under different conditions, particularly food intake, is crucial.

This study aims to assess the effect of food on the pharmacokinetics of indapamide 1.5 mg prolonged-release tablets by exploring changes in pharmacokinetic parameters including maximum serum concentration (C_{max}), time to reach maximum concentration (t_{max}), and area under the curve (AUC) after single dose administration of indapamide under fasting and respectively fed conditions.

Methods

Ethical Considerations

The studies were designed and conducted in accordance with the relevant European Union (EU) [17] and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP) [18] guidelines. The study protocols were approved by National Ethics Committee, Romania and by the National Agency for Medicines and Medical Devices, Romania. Ethical standards outlined in the Declaration of Helsinki [17] were adhered to, and participants provided written informed consent before the study commenced. All relevant study aspects were discussed with each volunteer. The clinical trials carried out at the Center for Drug Evaluation, Antibiotice SA, Iași, Romania.

Study subjects

In each study were included healthy Caucasian subjects, aged 18 to 50 years, with a body mass index (BMI) from 18.5 to 30 kg/m². The main exclusion criteria were hypersensitivity to indapamide or any other inactive ingredient of the formulation, history or presence of digestive, renal, hepatic disease which could interfere with product pharmacokinetics, clinically significant abnormal findings on physical examination, 12 – lead electrocardiography, laboratory tests (hematology, blood biochemistry, urinalysis), pregnancy or breastfeeding. Other exclusion criteria were alcoholism, drug abuse, positive test results for hepatitis B or C, HIV, special diets or inability to consume the standard breakfast (study 2).

Drug products

Two formulations of indapamide 1.5 mg were administrated as a single oral dose of 3 mg (2 tablets) in fasted and fed studies:

- the test (T) product-Indapamide SR 1.5 mg prolonged-release tablets (T) developed by Antibiotice SA, Romania and
- the reference product (R)- Tertensif® SR 1.5 mg prolonged-release tablets, Servier Industries Ltd., Ireland.

Studies design

Both bioequivalence studies were randomized, open – label, single center, laboratory blind, single dose, 2 – way cross over studies, with drug administrations:

- Study 1: after 10 hours abstentions from food
- Study 2: 30 minutes after intake of a high fat, high calorie meal (range 800 – 1000 calories: 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat) [19,20].

Both bioequivalence studies followed the same methodology, except drug administration, as noted above.

In each period of the study, subjects were confined from at least 10 hours before drug administration until 24 hours post-dose. Subjects had to return for ambulatory visits 36-, 48-, 72-, and 96-hours post-dose.

Subjects enrolled were randomly assigned to one of the two treatment sequences (TR or RT) in a 1:1 ratio. A single oral dose of 3 mg indapamide (2 tablets) was administered in each period of the studies. Fluid and food intake was standardized: subjects remained fasted for 4 hours post-dose, and liquid consumption was restricted until 1 hour after drug administration.

Blood plasma samples collection

The blood sampling design was consistent for both the Reference and Test periods. Venous blood samples (5 ml each) were collected prior to drug administration (at 0 hours) and at specific time points post-dose, including 0.5,

1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 24.0, 36.0, 48.0, 72.0, and 96.0 hours. The collected samples were rapidly frozen until analysis at a temperature of (–70°C) ± 5°C.

Bioanalytical methodology

A high-throughput liquid chromatography tandem mass spectrometry method (LC/MS/MS) was developed and validated for concentrations ranging from 1 ng/ml to 50 ng/ml, utilizing Indapamide d3 as the internal standard. The bioanalytical method was specifically validated, in terms of linearity, accuracy, precision, selectivity, sensitivity, extraction recovery, and stability.

Pharmacokinetic analysis

Key PK parameters calculated were maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration–time curve from time zero to the last measurable concentration (AUC_{0-t}), and area under the curve from time zero to infinity ($AUC_{0-\infty}$). The elimination rate constant (k_{el}) was calculated using log-linear regression analysis. The half-life ($t_{½}$) was determined as $t_{½} = 0.693/k_{el}$. Additional parameters included apparent clearance (Cl_F) and apparent volume of distribution (Vd_F). In the realm of pharmacokinetics, deconvolution serves as a method to assess in vivo drug release and delivery. This approach relies on pharmacokinetic profile data and dosing information personalized to each individual profile [21]. Mathematical deconvolution was applied to analyze the results from plasma samples and obtain the mean cumulative amount and fraction of absorbed indapamide over time, focusing on absorption from the gastrointestinal tract. PK parameters were determined through non-compartmental pharmacokinetic analysis in Phoenix WinNonlin® 8.4 (Certara, PA, USA).

Statistical analysis

Statistical analysis was conducted using Phoenix WinNonlin® 8.4 (Certara, PA, USA). To compare plasma profiles of indapamide under fasted and fed conditions, Type III sum of squares from analysis of variance (ANOVA) were employed. A *p*-value less than 0.05 indicated statistically significant differences in pharmacokinetic parameters between study periods.

Results

In total, 44 subjects enrolled completed the study and were included in the analysis of the 2 bioequivalence studies of indapamide (Figure 1).

Subjects' characteristics

Two groups of healthy male / female Caucasian subjects, aged between 19-39 years (mean 24.04 ± 4.75) were included. Individual demographic data are summarised in table I.

Pharmacokinetic analysis

Bioequivalence data

The Test generic product Indapamide SR 1.5 mg prolonged-release tablets, developed by Antibiotice SA, Romania, was proved bioequivalent with Reference product with respect to the rate and extent of absorption, meeting the bioequivalence criteria, with a 90% Confidence Intervals (T/R) for C_{max}, for AUC_{0-t} and for $AUC_{0-\infty}$) (Table II).

Effect of food on indapamide PK

The mean plasma concentration-time profile of indapamide obtained from Reference data (study 1) and Test data (study 2), when administered under both fasted and respectively fed states is represented in Figure 2.

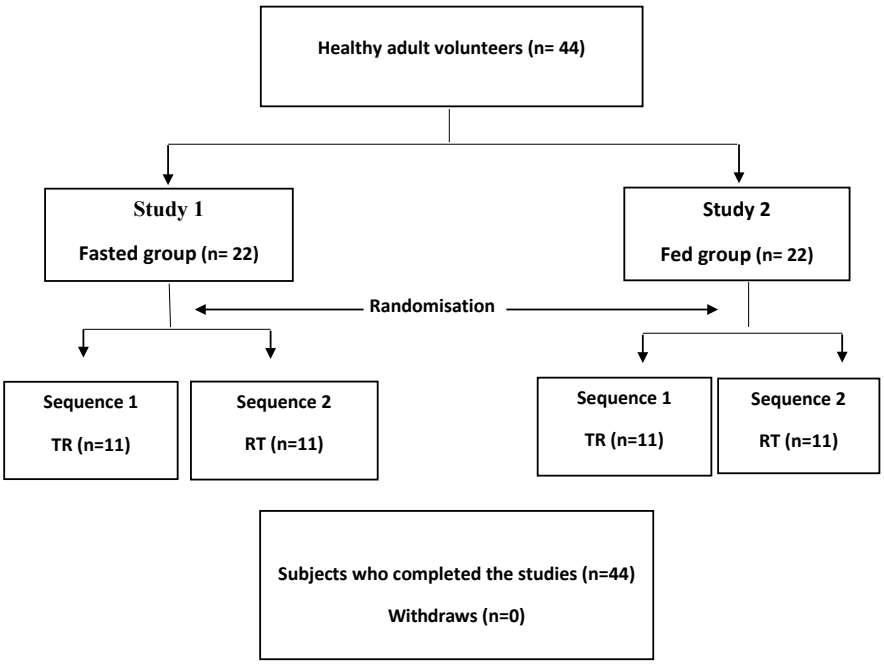

Fig. 1. Disposition of the subjects in the study

Table I. Demographic data summary of the subjects included in fasted and fed study

Characteristic	Study 1 (fasted state)	Study 2 (fed state)
Number of subjects	22	22
Gender (number) - Male	13	21
- Female	9	1
Age (years) – mean (SD*)	24.22 (5.14)	23.86 (4.43)
Range	19-36	20-39
BMI** (kg/m2) – mean (SD)	23.24 (3.35)	22.75 (3.01)
Range	19.27-29.3	18.83-28.41

*SD – standard deviation; **BMI – body mass index

Table II. Bioequivalence results

PK parameter	Units	Ratio (90% CI)	
		Fasted	Fed
C_{max}	ng/mL	87.95-103.34	80.54-96.08
AUC_{0-t}	ng*h/mL	91.47-104.82	91.82-100.72
$AUC_{0-\infty}$	ng*h/mL	91.82-104.93	91.78-100.50

Table III details the pharmacokinetic parameters and statistical analysis observed when the drug was administered to subjects under both fasted and fed states.

Using mathematical deconvolution, the mean cumulative amount and fraction absorbed over time were obtained. Figure 3 illustrates the profile of the mean cumulative amount of indapamide absorbed after administration of a single dose of 2x 1.5 mg indapamide for both fasting and fed state.

In our analysis, indapamide exposure was higher after food intake. There was noted a statistically significant increase for C_{max} approximately 31% (82.00 ± 20.38 ng/mL vs. 62.30 ± 17.55 ng/mL) ($p < 0.001$), while the time to reach peak plasma concentration (t_{max}) shortened from 11.07 ± 4.49 h (fasted state) to 6.43 ± 2.41 h (fed state) ($p < 0.001$). However, $AUC_{0-\infty}$ showed a non - significant increase of ~3% (2107.16 ± 481.06 ng*h/mL vs. 2180.50± 468.96 ng*h/mL) ($p = 0.4710$).

The absorption rate-time profiles of indapamide, administered under fasting and fed conditions is represented in Figure 4.

The time from administration to the beginning of absorption (t_{lag}) had a small but statistically significant increase after food intake (from 0.18± 0.27 h to 0.55 ± 0.43 h) ($p < 0.001$). The half-life ($t_{½}$) and the elimination constant (k_{el}) remained unchanged ($k_{el} = 0.05\ h^{-1}$), but there were statistically significant differences between mean residence time (MRT), probably correlated with t_{lag} differences in fasted and fed conditions.

Statistically, it has been demonstrated in this study that food affects the absorption rate of indapamide. Parameters such as C_{max}, t_{max}, and t_{lag} are influenced by food intake. Notably, since the AUC remains unaffected, this impact is limited to the absorption rate and not the overall extent of absorption.

Discussions

We evaluated the effect of food on the pharmacokinetic profile of indapamide sustained-release formulations in healthy participants of both genders, with a predominance of male subjects. This is particularly important to note because liver enzymes, especially CYP3A4, play a key role in the metabolism of most drugs and are generally expressed at higher levels and are more active in females compared to males [22-25]. Indapamide is primarily metabolized in the liver by CYP3A4, with additional metabolic contributions from CYP2C19 and CYP2C8 [26-29]. However, there is a lack of studies investigating the influence of gender on the metabolism of indapamide, highlighting the need for further studies in this area.

When administered after 10 hours abstention from food, median peak plasma concentration of indapamide 2 x 1.5 mg was 62.30 ng/mL and was reached in a mean

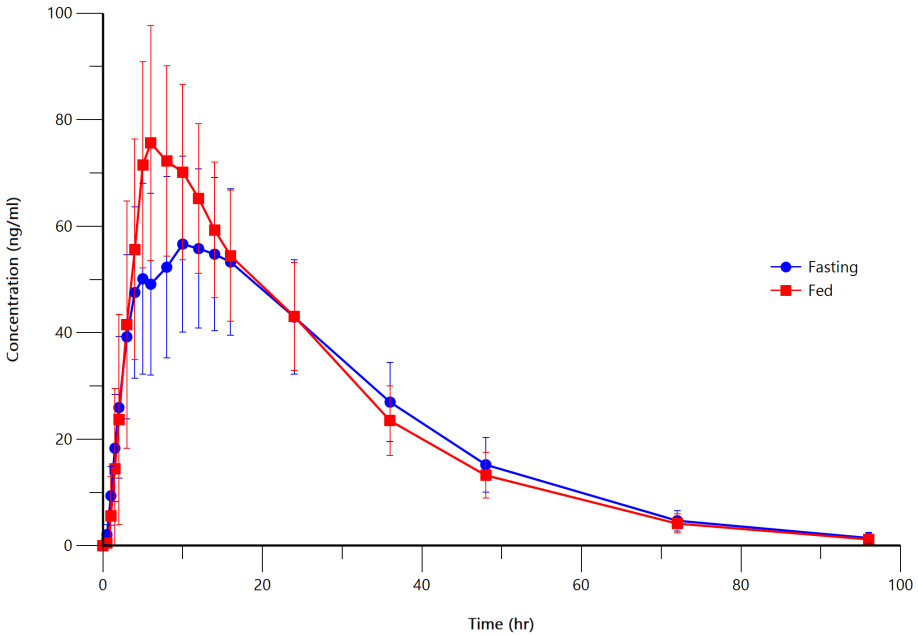

Fig. 2. Mean plasma concentration-time profiles of indapamide (2 x 1.5 mg, p.o) in fasted and fed states

Table III. Main pharmacokinetic (PK) parameters of indapamide after a single oral dose administration in subjects in fasted or fed conditions

PK parameter (units)	Study periods								Comparison of PK parameters fasted vs. fed state	
	Reference (fasted state)				Test (fed state)					
	Mean	SD	Median	CV%	Mean	SD	Median	CV%	F stat	p value*
C_{max} (ng/mL)	62.30	17.55	60.19	28.17	82.00	20.38	79.97	24.85	23.61	< 0.001
t_{max} (h)	11.07	4.49	12.00	40.61	6.43	2.41	6.00	37.40	36.39	< 0.001
AUC_{0-t} (ng*h/mL)	2099.16	484.58	2122.65	23.08	2170.51	475.35	2091.80	21.90	0.49	0.4876
$AUC_{0-\infty}$ (ng*h/mL)	2107.16	481.06	2122.65	22.83	2180.50	468.96	2106.73	21.51	0.52	0.4710
k_{el} (h^{-1})	0.05	0.01	0.05	15.55	0.05	0.01	0.05	12.38	0.05	0.8314
$t_{½}$ (h)	14.68	2.12	14.93	14.41	14.51	1.97	14.02	13.56	0.16	0.6909
t_{lag} (h)	0.18	0.27	0.00	146.37	0.55	0.43	0.50	78.63	22.84	< 0.001
MRT (h)	27.63	3.36	27.95	12.14	25.05	2.69	25.45	10.75	15.83	< 0.001
Cl_F (mL/h)	741.17	196.77	697.19	26.55	708.51	147.98	703.64	20.89	0.77	0.3814
Vd_F (mL)	15552.14	4432.20	14569.81	28.50	14785.15	3620.03	14092.61	24.48	0.79	0.3765

*p < 0.05 – statistically significant.

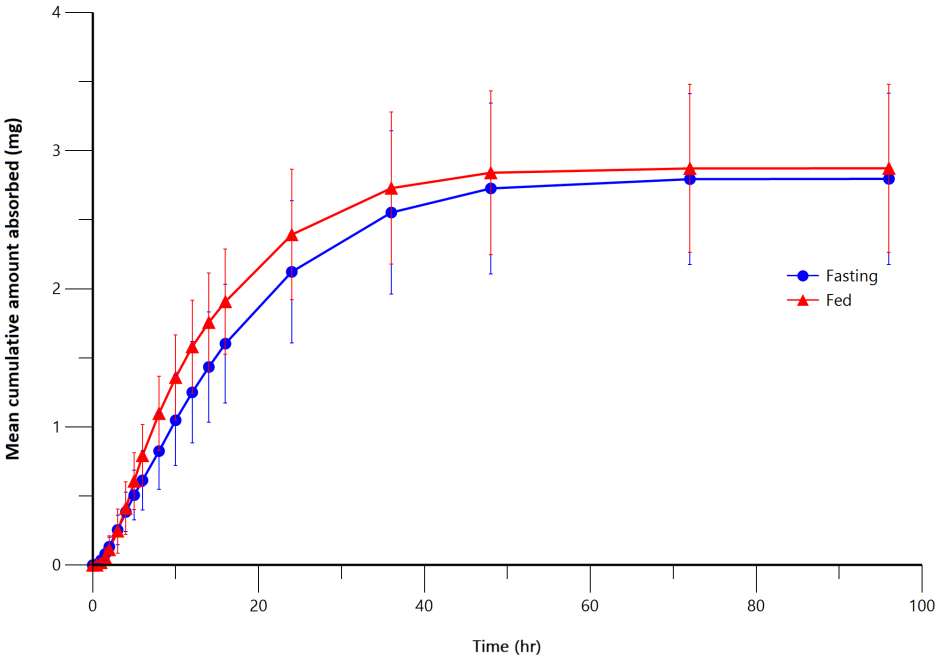

Fig. 3. Mean cumulative amount of indapamide absorbed after orally administration of a single dose of 2 x 1.5 mg in fasted and fed states

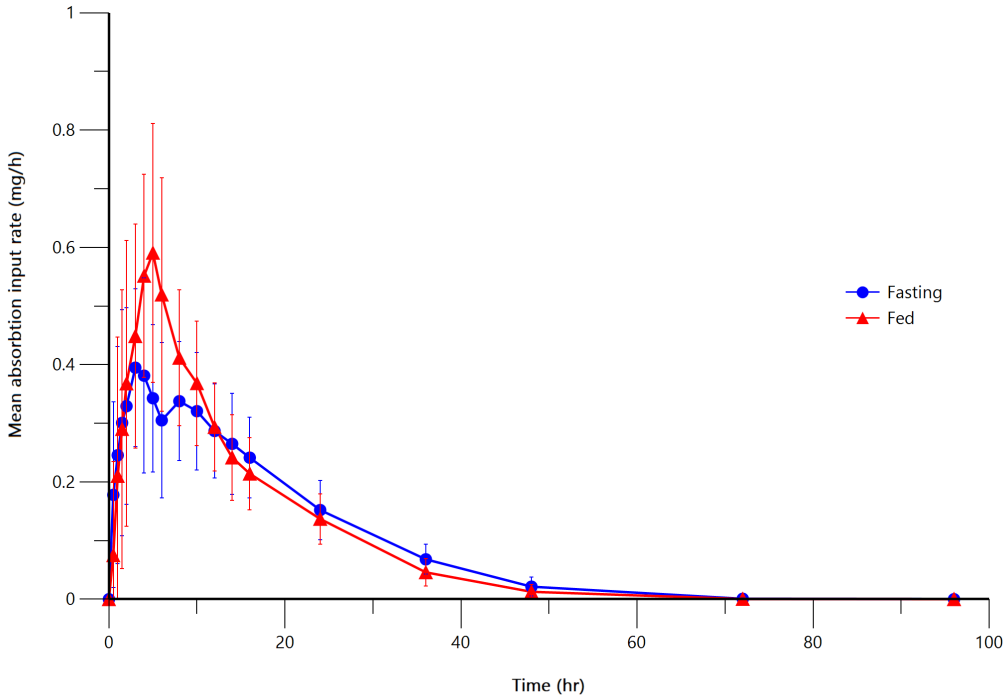

Fig. 4. Mean absorption rate-time profiles of indapamide (2 x 1.5 mg, p.o) in fasted and fed states

11 hours. When indapamide sustained release formulation was administered as a single dose of 1.5 mg, C_{max} was almost half of the value obtained in our study (32.3 – 32.9, 32.8-35.3) and was reached in almost 13 hours [30,31].

The results obtained in our analyses showed a decrease in fed state of t_{max} by 41.91% while C_{max} was increased by 31.62%. Based on the graphical representation (Figure 2), differences in C_{max} are observed within the approximately interval of 3 to 16 hours; beyond 16 hours, the concentration curves overlap.

Abbas et al (2023) noted similar findings for indapamide 1.5 mg sustained release formulation. They performed a study with 49 healthy subjects to investigate the impact of food and specific single nucleotide polymorphisms in the uridine diphosphate glucuronyl transferase (*UGT2B7*) gene on pharmacokinetics of indapamide and found a modest increase of C_{max} and decrease of t_{max} values [3].

The results obtained in our study for $AUC_{0-\infty}$ showed a small increase of ~3% after administration of indapamide in fed conditions, with no statistical significance in drug absorption. The observed variations in systemic exposure of certain drugs due to the presence of food may not be clinically significant when considering exposure-response data [19].

The term food effect, also referred to as food–drug interactions, commonly occurs with orally administered medications and encompasses changes in the rate or extent of drug absorption due to food intake [32]. Assessment of the food effect is an integral part of developing a new orally administered drug product [33] and is also critical for all modified-release formulations [34]. Despite the standard conditions for assessing the food effects, recent studies debate the potential interaction between food supplements (e.g. flavonoids, crucifers) and drug metabolism, particularly through the inhibition of the cytochrome P450 3A4 enzyme [26,35,36]. This pharmacological interaction can manifest as increased adverse effects and reduced drug efficacy, among other issues. Specific concerns are raised for the cardiovascular drugs prescribed for long -term treatment, including indapamide [26], which undergoes extensive liver metabolism, with less than 7% of the administered dose excreted unchanged in the urine [12]. Multiple metabolic pathways exist, primarily mediated by the enzyme CYP3A4, which facilitates key reactions such as hydroxylation, carboxylation, and dehydrogenation [28]. Considering the central role of CYP3A4, food components that modulate this enzyme's activity could significantly affect indapamide's metabolism and therapeutic outcomes when administered with food. However, the clinical relevance of this interaction within dietary contexts remains complex and multifaceted.

The Biopharmaceutics Drug Classification System can provide valuable insights for predicting the potential impact of food on both the oral drug absorption rate and extent [32].

Fisher et al. stated that drug-food interactions can be predicted using the Biopharmaceutics Classification System (BCS) [37] class. Class 1 drugs (high solubility/high permeability) are minimally affected by high-fat meals, while Class 2 drugs (low solubility/high permeability) experience increased bioavailability. Class 3 drugs (high solubility/low permeability) have decreased bioavailability with high-fat meals, and Class 4 drugs (low solubility/low permeability) are challenging to predict [38]. Gu CH et al. enhanced food effect predictions by considering drug solubility, permeability, and compound dose [38]. J. Deng et all. (2017) investigated in their study the impact of high-fat meals and standard meals on the rate and extent of oral drug absorption for 229 drugs. The results revealed that in 41.04% drugs the absorption was unaffected, while 46.28% experience absorption delayed and 12 % accelerated absorption [32].

Zou P. et all (2023) evaluated 136 orally administered extended-release (ER) drug products approved by the US FDA, and, it was observed that when the relative fasted bioavailability (BA) for the immediate-release (IR) drug product falls within the range of 80–125%, substantial food impact on the area under the curve (AUC) of the ER product are typically not anticipated, regardless of the drug substance's Biopharmaceutics Classification System (BCS) class [39].

Indapamide exhibits limited water solubility (75 mg/L). However, its apparent permeability coefficient is 7.0×10^{-5} cm/s, indicating efficient absorption in humans [40]. Characterized by low solubility and high permeability, is commonly classified as BCS Class 2. Its molecular structure features both polar and lipid-soluble groups at opposite ends, with a pKa of 8.8 and a logP value of 2.2 [40]. Interestingly, despite its water insolubility, there are conflicting reports regarding its classification. Some studies suggest it belongs to BCS Class 1 [11,41], due to rapid and nearly complete absorption after oral administration, while others maintain its BCS Class 2 status [40,42,43]. Overall, indapamide falls under BCS Type 2, emphasizing its permeability and solubility characteristics [37].

Class II drugs tend to experience increased bioavailability when administered with high-fat meals [32,38]. Existing literature suggests two mechanistic explanations for this phenomenon, either enhanced solubilization due to co-administered fat or reduced access to drug-metabolizing enzymes caused by inhibition of efflux transporters, resulting in decreased intestinal metabolism and increased bioavailability [32].

Other drugs with cardiovascular benefits, such as dapagliflozin, which is used for the management of heart failure and diabetes [44,45], demonstrate minimal impact from food intake on their overall bioavailability [46]. Dapagliflozin, in combination with indapamide, may be effective in the treatment of heart failure and hypertension, particularly in patients with multiple cardiovascular risk factors including diabetes or chronic kidney disease. Both drugs maintain their therapeutic efficacy regardless of food co-administration, making them reliable options for patients

with diverse dietary habits. Therefore, our results are in accordance with previously published studies, indicating that food does not significantly influence the bioavailability of drugs, either clinically or statistically. Overall exposure remains largely unaffected by food intake.

The SR formulations exhibit clear sustained release properties in comparison to the IR. The co-administration of food did not influence the dose-normalized area under the curve (AUC) for the SR formulations [47]. While the published literature suggests for indapamide no clinical significance resulting from the food effect, it is important to note that there are some pharmacokinetic changes.

Conclusion

In this study, co-administration of indapamide with food has a notable impact on the absorption rate of the drug following a single dose in healthy volunteers. Specifically, significant differences were observed in both C_{max} and T_{max}. Food reduces the T_{max} of indapamide by approximately 41.91% while increasing the C_{max} by 31.62%. Importantly, these modifications do not significantly impact safety or efficacy; they primarily affect the absorption rate without significant influence on the overall extent of absorption.

Authors' contribution

MC (Data collection, Pharmacokinetic analysis, Statistical analysis, Writing – original draft)
DI (Clinical study director, Validation, Data reporting)
MIO (Study design, Protocol development, Statistical evaluation, Writing – review & editing)
AMV (Data curation, Formal analysis, Software, Writing – original draft)
DMM (Data analysis, Visualization, Writing – review & editing)
LV (Data analysis, Software, Supervision, Visualization, Writing – review & editing)

Conflict of interest

This research study was supported by Antibiotice SA, Romania. MC, DI and MIO were employees of the Antibiotice SA, Romania during the conduct of this study. AMV, DMM and LV are full-time employees of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania and declare no conflict of interest.

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