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KINETICS OF DAPAGLIFLOZIN 10 MG IMMEDIATE RELEASE TABLET IN HEALTHY CAUCASIAN VOLUNTEERS: DOES FOOD INTAKE AFFECT ITS DISPOSITION IN THE BODY?

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ABSTRACT. The aim of the current study was to investigate whether food intake alters the kinetics of dapaglliflozin, a modern anti-diabetic agent, after single-dose oral administration of a new 10 mg immediate release tablet. The evaluated formulation was developed and manufactured by Sun Pharmaceutical Industries Limited, India, and the studies were performed in healthy Caucasian subjects. The data obtained during the fasting and fed bioequivalence studies were analyzed to observe the influence of food on the bioavailability and disposition of the evaluated formulation. Although differences were observed between studies concerning some of the main parameters that describe dapagliflozin's disposition (maximum plasma concentration – C_{max}, and the time to reach it -T_{max}), they were proved bioequivalent. The 90% confidence intervals for the evaluated parameters were within the accepted range of 80.00-125.00% for bioequivalence conclusion, therefore the treatments are bioequivalent (dapagliflozin with/without food) and interchangeable. Hence, dapagliflozin can be administered regardless of food intake in diabetic patients.

Keywords: *dapagliflozin, kinetics, Caucasian volunteers, clinical trial, food intake*

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INTRODUCTION

Diabetes affects the lives of millions of people worldwide and represents a constant threat for people's health regardless of social class, region, or race. According to International Diabetes Federation (IDF) and World Health Organization (WHO) by 2045 is predicted that approximately 629.6 million people will be suffering from this condition. Along with cardiovascular disease and cancer, diabetes is one of the top 10 causes of global death [1-4].

In Europe, which according to IDF is the second region in deaths' prevalence caused by diabetes, around 700.000 deaths were reported before the age of 60 out of which 31.274 were recorded only in Romania [4]. In addition, it is estimated that there are more than 58 million people diagnosed with diabetes mellitus (DM) which represents 8.8% of the population from this region with age between 20-79 years old. However, the real silent threat is the alarming number of 22 million cases which remain undiagnosed. Another concern is that in Europe there are approximately 286.000 cases of type I diabetes (T1DM) in children and teenagers and almost 30.000 new cases are registered every year [4,5].

The sodium glucose co-transporter 2 (SGLT2) inhibitors represent a class of drugs which prevent glucose reabsorption from proximal tubules. Dapagliflozin along with canagliflozin and empagliflozin are the main representatives of the SGLT2 inhibitors class which improve both fasting and post-prandial plasma glucose levels [6-8]. These compounds decrease the blood sugar level by excretion of several grams of glucose in urine [9,10].

Dapagliflozin is known by its IUPAC name (2S,3R,4R,5S,6R)-2-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-6-(hydroxymethyl)oxane-3,4,5-triol. It was classified as a Class III molecule according to Biopharmaceutical Classification system (BCS) as it has a high solubility and low permeability for which the regulatory recommends the conduct of bioequivalence studies under fasting and fed conditions [8,11,12].

Bioavailability is one of the most important properties of a drug defined as the ability to release the active substance so that it reaches the site of action in a sufficient amount to elicit the desired therapeutic effect. More precisely, bioavailability is the rate and extent of absorption of a drug substance from the pharmaceutical form into the systemic circulation [13,14].

As the bioavailability of a drug may be affected by the food intake it is very important to know the drug-food interactions as to increase the efficacy and safety of therapies. It is well known that food may affect the absorption of drugs after oral administration and therefore the active substance's bioavailability and kinetics in the body (also known as disposition) might be affected [15-17]. The type and amount of meal is very important, therefore the regulatory established

standardized conditions for the test meal to be administered in fed clinical studies. More precisely, the test meal must be high-fat, high-calorie (approximately 800-1000 Kcal) [12].

The present study aimed to evaluate the food effect on dapagliflozin's disposition by comparing the results obtained in two bioequivalence studies conducted on healthy Caucasian subjects after administration of the tested drug under fasting and fed conditions.

RESULTS AND DISCUSSION

Subjects

The demographic data of the healthy volunteers who were selected for the bioequivalence studies are shown in Table 1.

Table 1. Demographic characteristics of the subjects included in the studies

Characteristics	Reference period (fasting state)	Test period (fed state)
Number of subjects	38	33
Gender (number) – Men	26	24
– Women	12	9
Age (years) – mean (SD)	29.9 (7.61)	25.9 (5.19)
– range	18-45	18-40
BMI (kg/m2) – mean (SD)**	23.85 (2.96)	23.28 (3.27)
– range	18.73-28.91	18.67-28.91

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

Kinetic analysis

Mean plasma concentration-time profiles of dapagliflozin from the reference product Farxiga® and from the test product developed by Sun Pharmaceutical Industries Limited, India, when given under fasting or fed state, are presented in Figure 1. For a better visual comparison of the bioavailability of dapagliflozin for reference and test product administered under fasting or fed condition of subjects, the mean plasma concentrations versus time profiles are depicted in Figures 2.

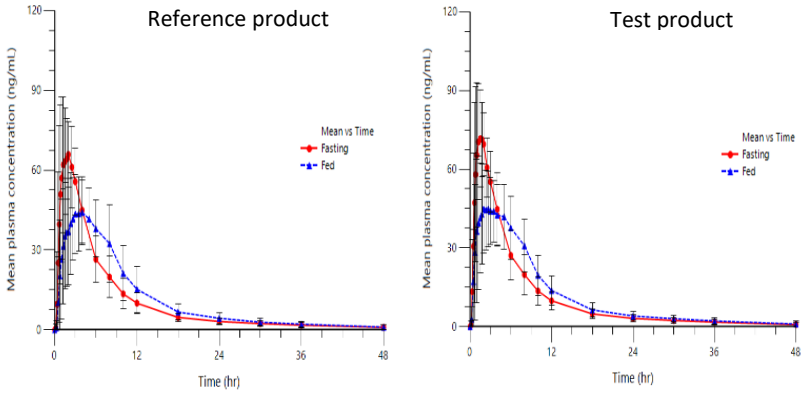

Figure 1. Mean ± standard deviation (SD) plasma concentration-time curves of dapagliflozin (10 mg, p.o.) administered in fasting state (n=38; represented with red line) or fed state (n=33; represented with blue line) of the reference product Farxiga® and of the test product developed by Sun Pharmaceutical Industries Limited, India

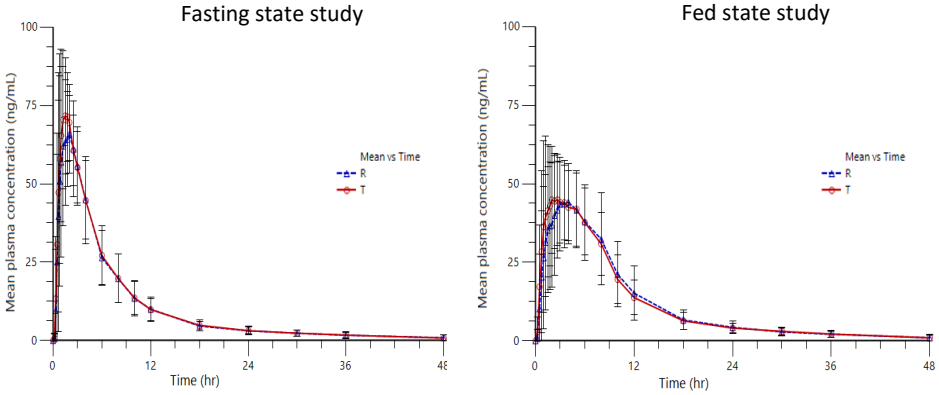

Figure 2. Mean plasma concentration profiles ± standard deviation (SD) of dapagliflozin after administration of a 10 mg single dose under fasting and fed condition of the reference product Farxiga® (with blue line) and of the test product developed by Sun Pharmaceutical Industries Limited, India (with red line)

Table 2 summarizes the main pharmacokinetic (PK) parameters of dapagliflozin, given with or without food in healthy subjects. These parameters describe in detail the kinetics of dapagliflozin given as a single dose by oral administration route. They describe the disposition of the active substance in the body, more precisely they characterize the processes of absorption, distribution, metabolism, and elimination (ADME processes) [18,19].

Table 2. Summary of pharmacokinetic (PK) parameters of dapagliflozin after a single dose of 10 mg p.o. administered under fasting or fed state of subjects

PK parameter* (units)	Study period							
	Reference (fasting state)				Test (fed state)			
	Mean	SD	Median	CV%	Mean	SD	Median	CV%
C_{max} (ng/mL)	83.56	28.85	77.32	30.93	59.53	15.59	56.76	26.19
T_{max} (hr)	1.72	0.72	1.75	41.91	3.38	2.13	2.83	62.97
AUC_{0-t} (ng*hr/mL)	488.02	122.39	461.02	25.08	522.01	145.57	501.16	27.89
$AUC_{0-\infty}$ (ng*hr/mL)	491.47	120.30	464.96	24.48	526.05	144.30	508.47	27.43
K_{el} (hr^{-1})	0.06	0.03	0.05	49.73	0.07	0.03	0.07	44.34
$T_{1/2}$ (hr)	15.32	8.19	14.40	53.45	12.85	6.25	10.63	48.62
MRT (hr)	11.76	4.48	11.21	38.12	12.84	3.86	12.33	30.04
Cl_F (L/hr)	20.43	4.93	20.77	24.13	19.41	4.91	18.47	25.28
Vd_F (L)	428.69	198.09	391.50	46.21	346.31	157.12	323.48	45.37

*where C_{max} – maximum plasma concentration; T_{max} – time to reach C_{max}; AUC_{0-t} – area under the plasma vs time curve from time 0 to last determined concentration; $AUC_{0-\infty}$ – area under the plasma vs time curve from time 0 to infinite; K_{el} – first order rate constant of elimination process; $T_{1/2}$ – half life time of given drug; MRT – mean residence time; Cl_F – apparent clearance; Vd_F – apparent volume of distribution

Statistical analysis

The bioequivalence analysis performed is summarized in Table 3. All evaluated pharmacokinetic parameters proved to be bioequivalent between fasting and fed study and therefore dapagliflozin can be administered regardless to food intake.

Table 3. Bioequivalence evaluation of the main PK parameters of dapagliflozin for the fasting and fed clinical trials

Study	Dependent	Units	Cl_90_Lower	Cl_90_Upper	Ratio_%Ref_	Bioequivalence conclusion*
Fasting	Ln(C_{max})	ng/mL	96.08	115.13	105.17	Bioequivalent
	Ln(AUC_{0-t})	ng*hr/mL	101.02	105.31	103.14	Bioequivalent
	Ln($AUC_{0-\infty}$)	ng*hr/mL	101.19	105.40	103.27	Bioequivalent
	T_{max}	hr	Non-parametric Friedman test			Bioequivalent
Fed	Ln(C_{max})	ng/mL	95.93	112.01	103.66	Bioequivalent
	Ln(AUC_{0-t})	ng*hr/mL	98.84	103.93	101.35	Bioequivalent
	Ln($AUC_{0-\infty}$)	ng*hr/mL	99.05	103.96	101.48	Bioequivalent
	T_{max}	hr	Non-parametric Friedman test			Bioequivalent

*Bioequivalent if Ratio_%Ref_ is in the range 80-125.

Table 4 presents the statistical analysis of the main pharmacokinetic parameters evaluated during both studies. The differences were assessed by using the analysis of variance (ANOVA test) and were considered statistically significant for *p* value less than 0.05 ($p<0.05$).

Table 4. Statistical analysis results of mean pharmacokinetic (PK) parameters comparison between Reference period (fasted state) and Test period (fed state) for dapagliflozin

PK parameter	Units	F_stat[a]	*p*_value[b]
C_{max}	ng/mL	57.47	<0.01
AUC_{0-t}	ng*hr/mL	2.18	0.142
$AUC_{0-\infty}$	ng*hr/mL	2.29	0.132
K_{el}	hr^{-1}	4.60	0.033
$T_{½}$	hr	4.60	0.033
MRT	hr	4.55	0.034
Cl_F	L/hr	1.58	0.211
Vd_F	L	8.96	0.003
T_{max}	hr	Friedman	NS[c]

[a]F_stat – statistic factor; [b]$p<0.05$ statistically significant; [c]NS – statistically non-significant

The adverse events reported by subjects during the bioequivalence clinical trials were carefully monitored and registered. They included increased triglycerides, increased aspartate aminotransferase (AST), increased total bilirubin, vaso-vagal reaction, diarrhea syndrome, and leukocyturia among other side effects. The summary of the adverse events by study period and treatment group are presented in Table 5. None of the reported adverse events posed a threat for the health of the volunteers, neither led to dropout events [15,16].

Table 5. Summary of adverse events reported during both clinical trials

Reported adverse events after dapagliflozin 10 mg administration p.o.	
Reference period (fasting state, 38 subjects)	**Test period (fed state, 33 subjects)**
- Increased triglycerides	- Vaso-vagal reaction
- Leukocyturia	- Diarrheal Syndrome
- Increased AST	- Vomiting
- Increased total bilirubin	- Increased triglycerides
- positive nitrites in urine	- Leukocyturia
- Decreased platelet.	- Urinary infection
- Leucocytosis	- Haematuria

Drug-food interactions, similar to kinetic drug-drug interaction, can modify a drug's disposition in the body [20-22]. If the later are evaluated as part of post-marketing safety evaluation, the first are investigated prior to market release [23-25]. Food intake may increase or decrease the rate of absorption of a drug product as the content of the meal and ingested amount can change the gastrointestinal transit time and permeability of the drug. The food influences the gastrointestinal motility, the digestive secretions and therefore modifies the bioavailability of the drugs, which can further influence the response to treatment [1,16,26]. Thus, the assessment of interaction between food and drugs represents an important part of development and manufacturing of orally administrated drugs [1,12,13,16,26,27].

Decreased absorption may reduce the efficacy of treatment as in the blood stream will arrive a lower amount from the active substance, while increased absorption may cause adverse reactions. On the other hand, in some cases, food may increase the rate and amount of absorption of an active substance; thus, certain drugs are indicated to be taken after food ingestion Therefore, it is important to establish the food-effect on the rate and extend of drugs' absorption before concluding the mode of administration [28-31].

The present research aimed to investigate the bioavailability of dapagliflozin and determine the pharmacokinetic parameters after oral administration of 10 mg immediate release formulation under fasting and fed conditions in healthy Caucasian subjects, males and females. The generic product was developed and manufactured by Terapia SA – a Sun Pharma Company and the clinical trials were conducted at the Clinical Pharmacology and Pharmacokinetics Department of Terapia SA, Cluj-Napoca, Romania.

After administration of test and reference product under fasting condition it was observed that the C_{max} (83.56 ± 28.85 ng/mL) was achieved within approximately 2 hours (T_{max}= 1.72 ± 0.72 hours). In comparison, after the administration of the two investigational medicinal products (IMP) under fed conditions the mean value for C_{max} was 59.53 ± 15.59 ng/mL and T_{max} was achieved within approximately 3 hours (3.38 ± 2.13 hours). After food ingestion, the C_{max} decreased with ~28%, whereas T_{max} increased with 96.5%, most probably due to prolonged gastrointestinal transit time. Also, the permeability of dapagliflozin might be affected by food composition, as it belongs to class III according to BCS. Its solubility is high, but the permeability along the gastro-intestinal tract is low and the administered food in the fed study was high-fat and high-calorie, as specified by regulatory agencies which validate the guidelines for this type of clinical trials [12]. However, the bioequivalence was concluded for both PK parameters, with parametric or non-parametric tests (see Table 3).

Even though the difference for T_{max} was statistically significant between studies (see Table 4), regulatory guidelines specify it is not clinically relevant [12].

After comparing the mean values obtained for AUC_{0-t} under fasting conditions (488.02 ± 122.39 ng*hr/mL) with the results obtained for AUC_{0-t} after administration of the IMP under fed conditions (522.01 ± 145.57 ng*hr/mL) it was noticed an increase of ~7% which resulted not statistically significant as the *p*-value was greater than 0.05 (*p*-value=0.142). A similar increase was observed for $AUC_{0-\infty}$, which also proved to be without statistical significance. Therefore, the bioequivalence was concluded for these PK parameters as well. The total area under the plasma concentration profile versus time is a good indicator of a patient's exposure to a given drug. In this case, the mean plasma concentration profiles of dapagliflozin after administration of a 10 mg single dose under fasting and fed condition of the reference product Farxiga® and of the test product developed by Sun Pharmaceutical Industries Limited, India, were almost superposable, with very small differences (see Figure 2), thus confirming the similar values obtained for AUC_{0-t} and $AUC_{0-\infty}$ in both clinical studies.

The other evaluated PK parameters displayed minor differences between fasting and fed studies. The ANOVA results indicated non-statistical significance of differences for K_{el}, $T_{1/2}$, MRT, Cl_F, and Vd_F (see Table 4). Also, the 90% confidence intervals for these parameters were within the accepted range for bioequivalence, which is 80.00-125.00% (see Table 3).

Similar to these results, no food effect was observed after oral administration of gliclazide, a sulfonylurea medicine also given in DM type 2 [1]. Bioequivalence was proved after statistical analysis of data obtained in two clinical trials conducted on healthy Caucasian subjects, under fasting and fed condition, in which the test product Gliclazide MR developed by Sun Pharmaceutical Industries, India, was evaluated in comparison with the reference product Diamicron MR (Servier, France) [32,33]. A decreased exposure to gliclazide after high-calorie, high-fat meal was observed, as the C_{max} registered a 14% decrease and the $AUC_{0-\infty}$ decreased with 17%. The T_{max} was shortened under fed conditions of subjects with approximately 2% and the K_{el} were comparable, regardless to food intake. However, the minor differences were not statistically significant, and the bioequivalence was concluded for gliclazide, administered with or without food, as in the case of dapagliflozin.

Generic drugs approved on the pharmaceutical market after bioequivalence clinical trials can ease the financial burden of diabetic patients, considering that other comorbidities are associated with DM type 2 which imply complex therapeutic approach with considerable costs.

CONCLUSIONS

The administration of immediate release formulation containing 10 mg dapagliflozin developed by Sun Pharmaceutical Industries, India, was proved bioequivalent with Farxiga®, AstraZeneca (reference product) in healthy adult Caucasian subjects, males and females, under fasting and fed conditions.

Differences were observed for certain PK parameters, but they were not statistically significant for the two investigational medicinal products and food intake did not affect the overall amount and rate of absorption of dapagliflozin. Therefore, the test and reference product were concluded to be interchangeable and can be administrated with or without food in diabetic patients.

EXPERIMENTAL SECTION

Subjects: The data obtained from two bioequivalence studies were considered for evaluation of food effect on the pharmacokinetic profile of dapagliflozin. In the first study were included 38 healthy volunteers and was performed under fasting condition, while in the second study was performed under fed condition, 33 healthy volunteers were selected. Therefore, the presented data correspond to 71 adult subjects, males and females, enrolled in both clinical trials [8,15,16].

The bioequivalence clinical trials were carried out in accordance with the Basic Principles defined in US 21 CFR Part 320, the ICH E6 (R1) (CPMP/ICH/135/95) 'Guideline for Good Clinical Practice' and the principles of the Declaration of Helsinki. The study protocols were approved by the National Agency for Medicines and Medical Devices and Bioethics National Committee of the Medicines and Medical Devices, Romania. Prior to any screening procedures, the volunteers gave their written informed consent for participation in studies. Only healthy subjects who filled all inclusion criteria were further admitted. The two clinical trials were carried out at Clinical Pharmacology and Pharmacokinetics Department of Terapia SA, Romania.

Study design and protocol*:* Both studies were designed as open-label, balanced, crossover, randomized, single-dose, with two periods. The test product (generic) was developed by Sun Pharmaceutical Industries Limited, India, and the reference product was Farxiga® (dapagliflozin) tablets

10 mg manufactured by AstraZeneca Pharmaceuticals, USA. It was defined as test data the results obtained in the fed bioequivalence study and as reference data the results obtained from the fasting study [8,15,16].

For both studies, the washout period between administration of reference and generic product was 7 days to ensure the complete elimination of drugs between study periods and to reduce the risk of carry over effect [15,16].

For the fasting study the blood samples were collected before the administration of drug and at 0.167, 0.33, 0.5, 0.66, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36 and 48 hours after drug administration [15].

For the fed study the blood samples were collected before the administration of drug and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36 and 48 hours post-dose [16].

Drug analysis from plasma samples: The total volume of blood collected from each subject during both studies did not exceed 260 mL, including the volume drawn at screening, at the end of study and additional blood collected due to out-of-range laboratory results [15,16].

The collected blood samples were centrifuged at 4000 rpm for 15 minutes under refrigeration at a set temperature of 4ºC. The separated plasma was kept at -50°C until analysis [15,16].

A validated HPLC-MS method was used to determine dapagliflozin plasma concentrations [8,15,16].

Pharmacokinetic and statistical analysis*:* The pharmacokinetic parameters of dapagliflozin during the performed studies were calculated by a non-compartmental analysis method, using Phoenix WinNonlin® version 6.3 (Certara, USA). The statistical analysis of differences registered for PK parameters from both clinical studies was performed with ANOVA test. In addition, the bioequivalence of dapagliflozin treatment given under fasted or fed state of subjects was assessed to highlight the influence of food-intake on the pharmacokinetic profile of the active substance. The analysis was performed as previously detailed [15,16].

Safety evaluation*:* Throughout both study periods of the fasting and fed bioequivalence studies the safety evaluation was performed, and the summary of adverse events reported are provided in Table 5.

REFERENCES

1. D. Pop; A.-M. Gheldiu; M. Oroian; A. Marcovici; S. Bhardwaj; A. Khuroo; R. Kochhar; L. Vlase; *Acta Med Marisiensis*, **2018**, *64*, 161-168.
2. M.B. Gomes; W. Rathmann; B. Charbonnel; K. Khunti; M. Kosiborod; A. Nicolucci; S.J. Pocock; M.V. Shestakova; I. Shimomura; F. Tang; H. Watada; H. Chen; J. Cid-Ruzafa; P. Fenici; N. Hammar; F. Surmont; L. Ji; *Diabetes Res Clin Pract*, **2019**, *151*, 20-32.
3. A.E. Caballero; *Front Endocrinol (Lausanne)*, **2018**, *9*, 479.
4. International Diabetes Federation (IDF) Diabetes Atlas, 10th edition, 2021. Available at: https://diabetesatlas.org/data/en/region/3/eur.html
5. Global Reports on Diabetes, World Health Organization, 2016, ISBN: 978 92 4 156525 7. Available at: https://www.who.int/publications/i/item/9789241565257
6. M.A. Abdul-Ghani; R.A. DeFronzo; *Expert Opin Pharmacother*, **2013**, *14*, 1695-1703.
7. M. Isaji; *Kidney Int*, **2011**, *79*, S14-S19.
8. M. Oroian; A. Marcovici; D. Pop; S. Bhardwaj; A. Khuroo; A.-M. Gheldiu; L. Vlase; *Studia UBB Chemia*, **2019**, *LXIV*, 297-308.
9. Y. Tamura; H. Miyagawa; T. Yoshida; H. Chuman; *Biochim Biophys Acta*, **2015**, *1848*, 2799-2804.
10. A. Tahara; T. Takasu; M. Yokono; M. Imamura; E. Kurosaki; *J Pharmacol Sci*, **2016**, *130*, 159-69.
11. R.Z.C. de Meira; A.B. Maciel; F.S. Murakami; P.R. de Oliveira; L.S. Bernardi; *Int J Anal Chem*, **2017**, *2017*, 2951529.
12. Guidance for industry. Food-effect Bioavailability and Fed Bioequivalence Studies. 2002. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070241.pdf
13. S.C. Chow; *Wiley Interdiscip Rev Comput Stat*, **2014**, *6*, 304-312.
14. A. Mateus; A. Treyer; C. Wegler; M. Karlgren; P. Matsson; P. Artursson; *Sci Rep*, **2017**, *7*, 43047.
15. M. Oroian; D.I. Pop; A.-M. Gheldiu; S. Bhardwaj; A. Marcovici; A. Khuroo; L. Vlase; *Acta Med Marisiensis*, **2020**, *66*, 30-34.
16. M. Oroian; D.I. Pop; A.-M. Gheldiu; S. Bhardwaj; A. Marcovici; A. Khuroo; L. Vlase; *Farmacia*, **2020**, *68*, 76-81.
17. D.I. Pop; A. Marcovici; M. Oroian; A.-M. Gheldiu; L. Vlase; *Studia UBB Chemia*, **2020**, *LXV*, 187-196.
18. A.-M. Gheldiu; A. Csavdari; M. Achim; L. Vlase; I. Tomuță; D. Muntean; *Studia UBB Chemia*, **2017**, *LXII*, 179-188.
19. A.-M. Gheldiu; D.M. Muntean; I. Cristea; I. Antonescu; R. Chira; C. Ureche; L. Vlase; *Rev Chim (Bucharest)*, **2016**, *67*, 702-705.
20. C. Briciu; M. Neag; D. Muntean; L. Vlase; C. Bocsan; A. Buzoianu; A.-M. Gheldiu; M. Achim; A. Popa; *J Clin Pharm Ther*, **2014**, *39*, 535–540.

21. A.-M. Gheldiu; A. Popa; M. Neag; D. Muntean; C. Bocsan; A. Buzoianu; L. Vlase; I. Tomuta; C. Briciu; *Pharmacology*, **2016**, *98*, 190-198.
22. I. Todor; A. Popa; M. Neag; D. Muntean; C. Bocsan; A. Buzoianu; L. Vlase; A.-M. Gheldiu; C. Briciu; *J Pharm Pharm Sci*, **2016**, *19*, 198-207.
23. A.-M. Gheldiu; L. Vlase; A. Popa; C. Briciu; D. Muntean; C. Bocsan; A. Buzoianu; M. Achim; I. Tomuta; I. Todor; D. Leucuta; M. Neag; *J Pharm Pharm Sci*, **2017**, *20*, 68-80.
24. A.-M. Gheldiu; D.M. Muntean; M. Neag; A. Popa; C. Briciu; L. Vlase; *Studia UBB Chemia*, **2019**, *LXIV*, 153-162.
25. A.-M. Gheldiu; A. Popa; M. Neag; D. Muntean; C. Bocsan; A. Buzoianu; L. Vlase; M. Achim; I. Todor; C. Briciu; *Farmacia*, **2015**, *63*, 453-459.
26. M. Koziolek; F. Carrière; C.J.H. Porter; *Pharm Res*, **2018**, *35*, 55.
27. P.G. Welling; *Annu Rev Nutr*, **1996**, *16*, 383-415.
28. M. Li; P. Zhao; Y. Pan; C. Wagner; *CPT Pharmacometrics Syst Pharmacol,* **2018**, *7*, 82-89.
29. Y. Kawai; Y. Fujii; F. Tabata; J. Ito; Y. Metsugi; A. Kameda; K. Akimotot; M. Takahashi; *Drug Metab Pharmacokinet*, **2011**, *25*, 180-191.
30. K. Sugano; M. Kataoka; C.C. Mathews; S. Yamashita; *Eur J Pharm Sci*, **2010**, *40*, 118-124.
31. A. Karim; M. Slater; D. Bradford D; L. Schwarts; A. Laurent; *J Clin Pharmacol*, **2007**, *47*, 48-55.
32. D.I. Pop; M. Oroian; S. Bhardwaj; A. Marcovici; A. Khuroo; R. Kochhar; L. Vlase; *Clin Pharmacol Drug Dev*, **2018**, *00*, 1-6.
33. D.I. Pop; M. Oroian; S. Bhardwaj; A. Marcovici; A. Khuroo; R. Kochhar; L. Vlase; *Farmacia*, **2018**, *66*, 597-601.