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ORIGINAL PAPER

EVALUATION OF THE INFLUENCE OF A *β*-LACTAM ANTIBIOTIC ON THE ABSORPTION PROCESS OF Mg^{2+} IONS FROM SOLID DISPERSIONS CONTAINING NICOTINATE MAGNESIUM SALTS

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Abstract

Magnesium belongs to the group of bioelements indispensable for the proper functioning of a human body. Many years of studies on the role of this element in the living system have revelaed its exact function in numerous, essential processes and metabolic transformation. According to previous studies, associations of magnesium with organic ligands enhance the absorption of magnesium ions. Interesting directions in the research are those that explain the problems of the loss of magnesium and interactions with other drugs. The subject of the study was to investigate the interaction between administered drugs and an antibiotic. This work is a continuation of the research into the influence of a *β*-lactam antibiotic on the absorption of Mg^{2+} ions from magnesium salts modified by such amino acids as glycine or arginine. The aim of the study was to evaluate the effect of penicillin G on the degree of the absorption of Mg^{2+} ions from nicotinate magnesium salts and its derivatives with glycine or arginine as well as from solid dispersions containing these salts. The process of the absorption of Mg^{2+} ions was examined *in vitro* on a model of the rat's small intestine. The results showed that an additional ligand (glycine or arginine) in the structure of nicotinate magnesium significantly decreased values of the kinetic parameters measuring absorption of Mg^{2+} ions from solid dispersions containing magnesium salts. The addition of a phosphatidylcholine carrier (PC45) to solid dispersions containing nicotine magnesium salts has significantly decreased the rate of absorption of Mg^{2+} ions from these formulations. Moreover, the results of the experiments indicate that penicillin G inhibits the process of Mg^{2+} ion absorption from the examined solid dispersions in the small intestine.

Keywords: nicotinate magnesium salts, glycine, arginine, penicillin G, solid dispersion, absorption.

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INTRODUCTION

Interesting research trends are the ones that allow one to explain the problems of the loss of magnesium and interaction with other drugs. An effective method of leveling and preventing magnesium deficiency in the body is supplementation. Previous studies have shown that many drugs given concomitantly with antibiotics can cause pharmacokinetic or pharmacodynamics interactions, often leading to adverse effects or increasing the toxicity of the drugs used. A very important element of therapy is the interaction between antibiotics and other medications that the patient receives. Interactions can lower or increase the blood levels of the drug, and even prolong the absorption of the drug or cause an adverse effect on the body. A special group of patients are elderly patients. Organ damage, diabetes, circulatory insufficiency, thirst disorders and hypovolemia increase the risk of adverse and even toxic effects. Another important group of patients are newborns and young children, in whom biological barriers are insufficiently developed and mature, hence the difference between toxic and therapeutic concentrations is small. The interactions between some drugs and magnesium preparations affect the Mg^{2+} homeostasis causing hypo- or hypermagnesaemia (Condray et al. 2005, Lameris et al. 2012, Morais et al. 2017). Factors that reduce the absorption of Mg^{2+} from the digestive tract are phosphates, oxalates, tannins and free fatty acids (Bohn 2008, Schuchardt, Hahn 2017) Moreover, antibiotic therapy affects the reduction of Mg in the body (Kostka-Trąbka, Woroń 2011, Donnarumma et al. 2018).

Interactions between magnesium and antibiotics may vary, depending on the type of antibiotics (Bolhuis et al. 2011). Administration of the formulations of magnesium together with antibiotics from the group of fluoroquinolones, tetracyclines and oral anticoagulants, as well as formulations containing phosphates, iron compounds and calcium leads to a reciprocal reduction of absorption from the gastrointestinal tract (Rodriguez 1991). When used, aminoglycosides increased magnesium excretion in the kidney. The most likely mechanism explaining the inhibitory activity of the tetracyclines rely on the chelation of divalent ions Ca^{2+} and Mg^{2+} (Guz, Bugla-Płoskońska 2007). Singh et al. (2012) investigated the interaction of the fluoroquinolone enrofloxacin with Ompf porin *Escherichia coli* in the presence $MgCl_2$. Using molecular modeling, the authors determined the most probable mechanism of interaction limiting the rate of antibiotic penetration. They showed that enrofloxacin in the presence of $MgCl_2$ has completely different binding kinetics for the OmpF channel. Based on simulations, it was found that Mg^{2+} ion directly interacts with two oxygen molecules of protein and four molecules of water.

β-lactam antibiotics are antimicrobial agents which are most often used in clinical practice. Penicillin G, a natural antibiotic from the group of *β*-lactams, was among the first medications to be effective against many

bacterial infections caused by *Staphylococci* and *Streptococci*. Lactam antibiotics significantly affect the process of methylation of the carboxyl groups in the protein, lowering the ascorbic acid (vitamin C) content (Rodriguez et al. 1991).

Administered formulations in combination with magnesium β-lactam antibiotics leads to a reciprocal reduction in absorption from the gastrointestinal tract. Based on the previous study, we found that antibiotics interacted with other medicines (Marcoin, Szulc-Musioł 2015). Solid dispersions are systems which allow one to control release of a therapeutic substance, and it is one the methods used to ensure optimal pharmaceutical availability of drug. According to Sareen et al. (2012), Mesallati et al. (2017), this technique is an effective way to improve the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. Numerous publications in the pharmaceutical literature confirm that molecular dispersions have been used to increase the bioavailability of medical preparations (Javed et al. 2011, Singh et al. 2011, Jagadeesan, Radbiakrishnan 2013).

The aim of this study was to evaluate the effect of a β-lactam antibiotic of penicillin G on the absorption of Mg^{2+} ions *in vitro* through the intestinal membrane from solid dispersions containing magnesium nicotinate salts as well as their derivatives with the ligands arginine and glycine. The solid dispersions containing magnesium salts used in this study ensured easy dosing and improved bioavailability. In addition, the influence of phosphatidylcholine (PC 45) on the release of magnesium ions from prepared dispersions containing magnesium nicotinate salts in the presence of penicillin G was evaluated.

MATERIALS AND METHODS

The following were subject of the experiment:

– magnesium nicotinate – $Mg(Nic)_2$, $Mg(C_6H_4O_2N)_2$, mol.wt.268.31;
– magnesium glycine – nicotinate – Mg(Nic-Gly), $Mg(C_8H_8O_4N)_2$, mol. wt. 284.31;
– magnesium arginine-nicotinate – Mg(Nic-Arg), $Mg(C_{12}H_{18}O_4N)_2$, mol. wt. 320.43;
– penicillin G benzathine salt – Sigma Chemical Co. (St. Louis, USA) Sigma-Aldrich.
– phosphatidylcholine 45% (PC 45) was purchased, Lucas Meyer, Ltd

All the chemicals were of the analytical reagent grade. The nicotinate magnesium salts were obtained using the method described by Marcoin and Ryszka (1991).

The synthesis of magnesium glycine-nicotinate Mg(Nic-Gly) and magnesium arginine-nicotinate Mg(Nic-Arg) was carried according to the procedure previously described by Marcoin and Winiarski (2006). The content of magne-

sium in the salts was measured by atomic absorption spectrophotometry (Carl Zeiss Jena model AAF 3) at the wavelength of 258.2 nm.

Solid dispersions containing the magnesium salts were prepared by FP XI. After previous micronization, each magnesium salt was mixed with the selected carrier (PC 45) in a molar ratio of 1:10 and dissolved in ethanol. The solvent was then evaporated in a vacuum dryer at 333 K to constant mass. The dried mass was pulverized, passed through a 30 mesh screen, stored in a vacuum desiccator, and passed through a 60 mesh screen, and then transferred to an amber colored, airtight container. Solid dispersions containing modified magnesium salts with the selected carrier PC 45 were obtained with a method similar to the one described in previous research (Marcoin and Szulc-Musioł 2015).

The absorption of Mg^{2+} ions from the examined magnesium salts with PC 45 was carried out in an *in vitro* model according to the method described previously (Marcoin, Szulc 2002), in which the absorption area was the small intestine (the ileum) of a rat.

The experiments were carried out on mature male Wistar rats fed a standard diet *at libitum*. The rats were obtained from the Center of Experimental Medicine, Medical University of Silesia, Katowice, Poland. The procedure of the experiments on animals was approved by the Local Ethics Commission, Katowice, Poland (permit number 37/2008). The animals were fasted for 24 hours prior to the experiment while having free access to water. Their weight ranged between 200 and 250 g. The rats were anesthetized with ether before the experiment; the intestine was isolated, and then the animals were sacrificed by cervical dislocation. The intestine was quickly excised, stripped of adhering tissue and flushed several times with 0.9% NaCl. Then, it was cut into small sacs of 5 cm in length, everted, and hanged in a glass chamber containing 30 ml of the studied drug dissolution in 0.9% NaCl. The apparatus was incubated at 37±0.5°C. Aqueous 0.9% NaCl solution was pumped with a peristaltic pump through the intestine sac at a constant rate of 1.2 ml min^{-1}. Samples were withdrawn at the same times and the magnesium concentration in the outlet perfusate solution was assayed by atomic absorption spectrophotometry (Carl Zeiss Jena model AAF 3) at the wavelength 285.2 nm. A similar procedure was carried out to study the absorption of Mg^{2+} ions from solid dispersions containing magnesium salts with addition of PC 45 carrier in the presence of penicillin G (50 mg).

The constant rate of absorption (k) and absorption half time ($t_{50\%}$) were also calculated. The AUC (an area under concentration – a time curve) has been calculated as the area under the curve of magnesium concentration changes in the acceptor medium depending on time. The area was calculated with the trapezoidal method in time intervals from 0 to 120 min.

These results are considered significant statistically verified using the Anova followed by the Kruskal-Wallis test or else Post Hoc multiple comparisons were done. $P<0.05$ was considered significant.

RESULTS AND DISCUSSION

The calculated mean values of kinetic parameters of Mg^{2+} ion absorption from the nicotinate magnesium salts and their solid dispersions are shown in Table 1. Release profiles of Mg^{2+} ions from nicotinate magnesium salts and

Table 1

Kinetic parameters of the absorption Mg^{2+} ions from selected magnesium salts and their solid dispersions with PC 45, in the presence or absence of penicillin, obtained in in vitro studies

Drug	Amount penetration Mg^{2+} ions (%) ± SD	k ($\cdot 10^{-3}$ min^{-1}) ± SD	$t_{1/2}$(h) ± SD
$Mg(Nic)_2$	19.82 ±0.73	1.89 ±0.08	6.00 ±0.05
Mg(Nic-Arg)	22.51±0.66	2.63±0.05	4.39±0.06
Mg(Nic-Gly)	21.49±0.67	2.07±0.09	5.57±0.11
$Mg(Nic)_2$ + penicillin	15.98±0.67[a]	1.67±0.09[a]	6.92±0.07[a]
Mg(Nic-Arg) + penicillin	18.23±0.44[b]	1.98±0.05[b]	5.83±0.07[b]
Mg(Nic-Gly) + penicillin	17.05±0.73[c]	1.74±0.11[c]	6.64±0.09[c]
$Mg(Nic)_2$ +PC45+ penicillin	18.50±0.59[d]	2.09±0.06[d]	5.53±0.08[d]
Mg(Nic-Arg) +PC45+ penicillin	21.57±0.46[e]	2.20±0.07[e]	5.29±0.09[e]
Mg(Nic-Gly) +PC45+ penicillin	19.66±0.66[f]	2.16±0.08[f]	5.34±0.09[f]

k – absorption rate constant, $t_{1/2}$ – absorption haft-time, SD – standard deviation; AUC – the area under the curve of magnesium concentration changes in acceptor medium depending on time. Magnesium salts: $Mg(Nic)_2$, Mg(Nic-Arg), Mg(Nic-Gly). Solid dispersions: $Mg(Nic)_2$ + PC45, Mg(Nic-Arg) + PC45, Mg(Nic-Gly) + PC45. Statistical significance: [a,d] $p \leq 0.05$vs. $Mg(Nic)_2$, [b,e] $p \leq 0.05$vs. Mg(Nic-Arg), [c,f] $p \leq 0.05$vs. Mg(Nic-Gly)

their solid dispersions are presented in Figure1. The absorption of Mg^{2+} ions by the small intestine of a rat proceeded in agreement with the first order kinetics.

The results of the experiments showed that a modification of the particle $Mg(Nic)_2$ structure by introducing of amino acids such as glycine or arginine had positive influence on the pharmacokinetic parameters of Mg^{2+} ion absorption from the preparations obtained.

In the case of Mg(Nic-Gly), a significant ($p<0.05$) increase in the constant rate of absorption was observed ($k = 2.07 \cdot 10^{-3}$ min^{-1}) by 0.18 units compared to the parent compound $Mg(Nic)_2$ ($k = 1.89 \cdot 10^{-3}$ min^{-1}), whereas for Mg (Nic-Arg) ($k = 2.63 \cdot 10^{-3} min^{-1}$) the difference was by 0.74 units higher.

The calculated values of absorption half-time ($t_{1/2}$) for magnesium salts modified by glycine or arginine, i.e. Mg(Nic-Gly) and Mg(Nic-Arg), significantly decreased ($p<0.05$) by about 0.43 h, 1.61 h, respectively, compared with the parent compound $Mg(Nic)_2$ ($t_{1/2}$= 6.00 h).

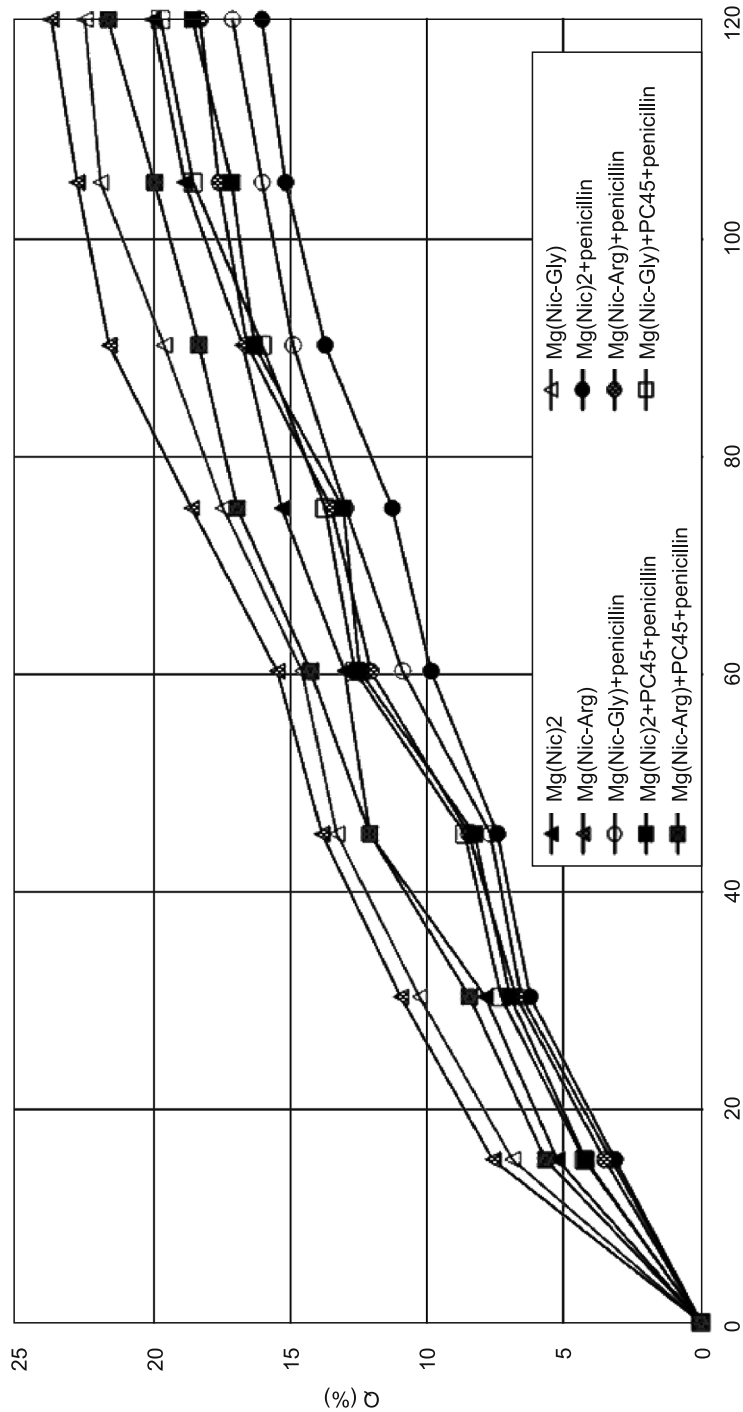

Fig.1. Mean absorption profiles of Mg^{2+} from selected magnesium salts and their solid dispersions with PC 45, in the presence or absence of penicillin. Significant at $p<0.05$: $Mg(Nic)_2$ + penicillin; $Mg(Nic)_2$ + PC45 + penicillin vs. $Mg(Nic)_2$, Mg(Nic-Arg) + penicillin; Mg(Nic-Arg) + PC45 + penicillin vs. Mg(Nic-Arg), Mg(Nic-Gly) + penicillin; Mg(Nic-Gly) + PC45 + penicillin vs. Mg(Nic-Gly)

The analysis of the research results on the absorption of Mg^{2+} ions from the examined salts in the presence of penicillin G showed that pharmacokinetic profile changes significantly depended on the type of salt. The results showed that the absorption rate constant (k) for $Mg(Nic)_2$, Mg(Nic-Gly) and Mg(Nic-Arg) salts in the presence penicillin G causes a decrease of k by 0.22, 0.33 and 0.65 respectively, compared with the reference system.

The amount of absorbed Mg^{2+} ions after 2 h of the experiment was significantly higher ($p<0.05$) for Mg(Nic-Gly) (21.49%) and for Mg(Nic-Arg) (22.51%) than for $Mg(Nic)_2$. As demonstrated above, the modification of the magnesium nicotinate structure with a ligand of glycine or arginine influenced the effect of a lipid phase (cellular membranes). Structural properties significantly influenced the ability of the active substance to penetrate through the lipid barrier.

The total amount of the drug absorbed in the organism in the time 0-t range is determined by the pharmacokinetic parameter AUC. The parameter AUC is a measure of drug absorption degree, and therefore its availability.

The calculated AUC values showed that the absorption of Mg^{2+} ions from the magnesium salt amounted to Mg (Nic-Arg), Mg (Nic-Gly) and Mg $(Nic)_2$: 68.151 mmol min^{-1} dm^{-3} and 72.801 mmol min^{-1} dm^{-3}, 59.016 mmol min^{-1} dm^{-3}, respectively. The value of this parameter for Mg(Nic-Gly) and Mg(Nic-Arg) was by 14.48% and 23.36% higher than for $Mg(Nic)_2$.

Modification with an additional ligand affects positively the profile of absorption parameters: the amount of absorbed Mg^{2+} ions during 2 hours was significantly higher ($p<0.05$), namely for Mg(Nic-Arg) it was 22.51%, and for $(MgNic)_2$ – 19.80%. In the case of Mg(Nic-Gly) the result was 21.49%.

In our study, the analysis of the calculated results (AUC) of the total amount of Mg ions absorbed from the salts studied confirmed that the modification of Mg structure $(MgNic)_2$ with an arginine or glycine ligand significantly affects the availability of Mg.

Studies on the influence of a β-lactam antibiotic on the availability of Mg^{2+} ions from solid dispersions containing magnesium salts showed that the values (AUC) of the amount of absorbed Mg^{2+} ions were significantly ($p<0.05$) reduced (Figure 2). It was observed that the AUC values of Mg^{2+} ions for these salts were: Mg $(Nic)_2$ (52.452 mmol min^{-1} dm^{-3}), Mg(Nic-Gly) (54.408 mmol min^{-1} dm^{-3}) and Mg (Nic-Arg) (63.687 mmol min^{-1} dm^{-3}). These values in the presence of penicillin G were significantly decreased ($p<0.05$): by 17.12%, 12.44% and 15.72%, respectively, in comparison with solid dispersions containing these salts.

Our analysis of the results showed that the presence of an additional ligand, such as glycine or arginine, may influence the physicochemical properties and biological activity of a magnesium compound. It was proved that an increased length of a magnesium nicotinate chain by the $(-CH_2)$ group positively influenced polarity. Also, the presence of a nucleophilic and an electron acceptor groups (e.g. NH_2, αCOOH) affected intramolecular reac-

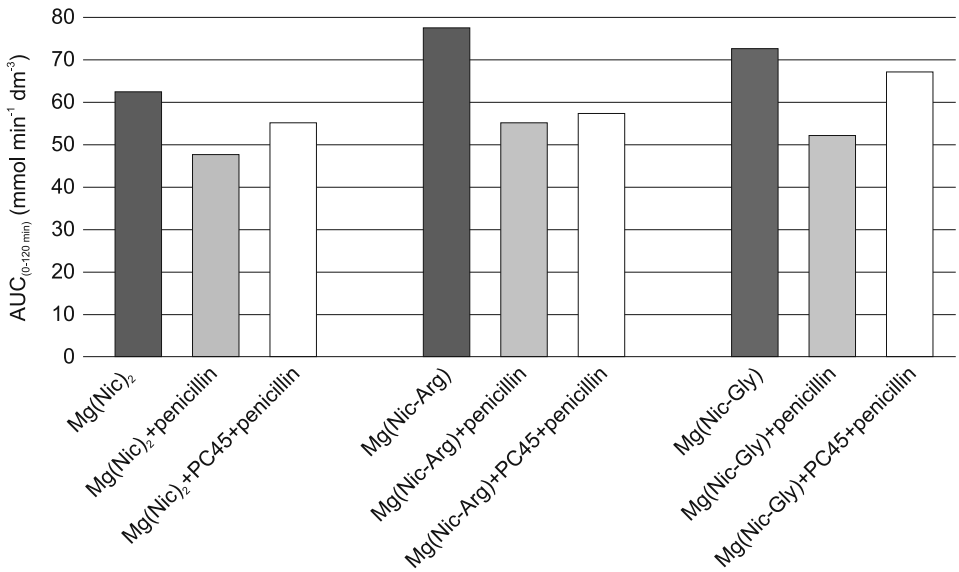

Fig. 2. Influence of penicillin on the availability of Mg^{2+} ions from selected magnesium salts and their solid dispersions.
Significant at $p<0.05$: $Mg(Nic)_2$ + penicillin; $Mg(Nic)_2$ + PC45+ penicillin vs. $Mg(Nic)_2$, Mg(Nic-Arg) + penicillin; Mg(Nic-Arg) + PC45 + penicillin vs. Mg(Nic-Arg), Mg(Nic-Gly) + penicillin; Mg(Nic-Gly) + PC45 + penicillin vs. Mg(Nic-Gly)

tions, e.g. the occurrence of donor-acceptor and hydrogen bonding. Structural properties had significant influence on the lipid phase (cellular membranes). Moreover, parameters of the structure volume and molecular mass affected the ability of the active substance to penetrate through the lipid barrier.

Formation of molecular solid dispersions is one of the methods used to improve pharmaceutical availability and, consequently, the bioavailability of therapeutic medications (Sareen et al. 2012, Shi et al. 2015, Rumondor et al. 2016). The beneficial effects of phosphatidylcholine (PC 45) as a carrier for solid dispersions of poorly soluble drugs have also been demonstrated by other authors (Hussain et al. 2012, Khadka et al. 2014, Shi et al 2015, Kawakami et al. 2017).

Phosphatidylcholine (PC 45) has hydrophilic and hydrophobic groups. In this study, the effect of the interaction between the carrier and a magnesium salts was noted. Phosphatidylcholine (PC 45) as a carrier significantly improves the absorption process of Mg^{2+} ions from solid dispersions containing the magnesium salts studied (Marcoin, Szulc-Musioł 2015).

Our analysis of the research results on the absorption of Mg^{2+} ions from solid dispersions containing the examined salts and in the presence of penicillin G showed that the profile of pharmacokinetic changes significantly depended on the type of a salt (Table 1).

The amount (%) of released Mg^{2+} ions for solid dispersions containing

$Mg(Nic)_2$ (18.50%), Mg(Nic-Gly) (19.66%) and Mg(Nic-Arg) (21.57%) salts in the presence of penicillin G causes an increase of Q to 11.57%, 15.30% and 18.32%, respectively, compared with the examined magnesium salts with penicillin G. The absorption half-time ($t_{1/2}$) for the solid dispersions containing these salts with penicillin G increased significantly ($p<0.05$) by about 1.39 h, 1.30 h and 0.54 h respectively, compared with the reference system.

It was seen that the absorption rate constant (k) in the case of solid dispersions containing $Mg(Nic)_2$, Mg(Nic-Gly) and Mg(Nic-Arg) salts in the presence of penicillin G causes an increase of k when compared with magnesium salts in the presence of penicillin G.

The experiments have demonstrated that magnesium creates complexes with penicillin G. Penicillin G in its structure has two potential coordination positions: oxygen atoms of the carboxyl group and a nitrogen atom of the amide group, which are protonation (Canzani, Aldeek 2017). Results of a study on a complex reaction in double systems containing Cu^{2+} and one ligand of penicillin G, D-glucuronic acid were described by Nowak and Jastrząb (2015).

The research presented herein shows that the modification of the structure of magnesium nicotinate by glycine or arginine positively affects the absorption of Mg^{2+} ions because it changes the values of the kinetic parameters of this process. Glycine and arginine are good carriers transporting Mg^{2+} ions. Moreover, an addition of the PC45 carrier to the solid dispersion with nicotinate magnesium salts significantly influences dissolution and improves the absorption of Mg^{2+} ions. Summarizing the results, penicillin G hinders the process of Mg^{2+} ion absorption from the solid dispersions.

CONCLUSION

Modification of the structure of $Mg(Nic)_2$ by additional ligand amino acids such as arginine or glycine markedly improved the intestinal absorption of Mg^{2+}ions from solid dispersions. The solid dispersions containing the examined magnesium salts with the selected carrier phosphatidylcholine (PC45) constitute an effective way of improving the dissolution and absorption of Mg^{2+} ions from the prepared formulations. The process of Mg^{2+} ion absorption through the membrane of the small intestine from the examined solid dispersions containing magnesium salts significantly decreased in the presence of a β-lactam antibiotic (penicillin G).

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