

# INFLUENCE OF THE SELECTED ANTIBIOTIC ON ABSORPTION PROCESS OF $Mg^{2+}$ IONS FROM SOLID DISPERSIONS CONTAINING GLUTAMATE MAGNESIUM SALTS

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## Abstract

Numerous papers concerning the research on the role of magnesium in an organism and the effects of its deficiency indicate many causes and mechanisms leading to a negative balance of this macroelement. One of the causes of magnesium deficiency in systems may be its malabsorption from the digestive track resulting from taking compounds complexing magnesium ions or using drugs destructive to saprophytic flora.

The results of our experiments testing *in vitro* the influence of  $\beta$ -lactam of penicillin G on the process of  $Mg^{2+}$  ions absorption through the intestinal membrane from solid dispersions containing phosphatidylcholine (PC 45) and the salts of magnesium glutamate and its derivatives from glycine and arginine ligands are presented in this paper.

In order to make solid dispersions containing glutamate magnesium salts, auxiliary substances, polyvinylpyrrolidone (PVP) and phosphatidylcholine (PC45), were used. For the solid dispersions obtained by the Hansch method, partition coefficient in the system *n* - octanol/phosphate buffer was determined. Log P was calculated for the examined dispersions.

Research on the degree of absorption of  $Mg^{2+}$  ions solid dispersions, which was the subject of the experiment, was done by the *in vitro* method, making use of a model of the intestine (ileum) of a rat. The evaluation of penicillin G influence on the degree of absorption of  $Mg^{2+}$  ions from solid dispersions containing magnesium salts was carried out by the above method.

The results of experiments indicate that an additional ligand (glycine, arginine) in the structure of magnesium glutamate particle significantly influences the change of the value of of the kinetic absorption parameter of  $Mg^{2+}$  ions from solid dispersions containing magnesium salts. Introducing an additional ligand induces an accelerated rate of diffusion of the examined salts through the intestine.

It has been found that penicillin G hinders the degree of  $Mg^{2+}$  ions absorption of the examined solid dispersions in the small intestine.

**Key words:** magnesium glutamate, amino acids: glycine, arginine, penicillin G, solid dispersion, log P, absorption.

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## INTRODUCTION

An antibiotic therapy may weaken the immune system and induce magnesium deficiency. In such a situation, antibiotics are sometimes administered with magnesium supplements. Inorganic magnesium ions reduce the bioavailability of antibiotics (SATTERWHITE et al. 1992). The latest research results on interactions of antibiotics with minerals show that calcium, zinc, magnesium and iron compounds can interact with tetracycline, preventing absorption of an antibiotic. ARAYNE et al. (2005) described that magnesium forms insoluble complexes with tetracyclines. GUZ and BUGLA-PŁOSKOŃSKA (2007) explain that the inhibitory activity of tetracyclines is the effect of chelation of  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ . Medications from the antacida group diminish the absorption of antibiotics and limitate their efficacy. Simultaneous administration of both vitamin and mineral medications plus tetracycline causes undesirable reactions in and organism. Aminoglycoside antibiotics worsen Mg excretion in urine, causing or exacerbating its shortage (SANDSTROM 2001). Lactam antibiotics significantly affect the process of methylation of the carboxyl groups in the protein, lowering the ascorbic acid (vitamin C) content (RODRIGUEZ 1991, GUZ, BUGLA-PŁOSKOŃSKA 2007). SULIBURSKA (2010) showed that there is interaction between the drug and the diet, which influences the process of absorption and metabolism. Inhibited and delayed absorption of penicillin and amoxicillin has been noticed in the presence of ingested food. This negative effect on drug absorption is explained by creation of their insoluble forms.

Solid dispersions are systems which enable one to control release of a therapeutic substance. A choice of the suitable method for making solid dispersions, including the type and amount of the carrier, are decisive for the availability of a given pharmaceutical (DHIMAN et al. 2012, AHUJA et al. 2012). The up-to-date research on absorption shows that phosphatidylcholine (PC 45) and polyvinylpyrrolidone (PVP) are good carriers of  $\text{Mg}^{2+}$  ions from solid dispersions containing magnesium salts (MARCOIN 2006, MARCOIN, SZULC-MUSIOŁ 2009, 2011). Phosphatidylcholine (PC45) was a natural carrier which can be biodegradable and metabolized since it is a part of biological membranes. Polyvinylpyrrolidone (PVP) the hydrophilic synthetic polymer was the carrier which enhanced the solubility of drugs. DUA et al. 2010, prepared solid dispersions of aceclofenac with various hydrophilic carriers such as: PVP, ureamannitol, and PVP/VA-64. with an aim to improve their dissolution. Other researches (RAO et al. 2010) also the solid dispersion technique are methods proved to be improving the dissolution and bioavailability of simvastatin. According to patent (CURATOLO et al. 2012) solid dispersions containing sparingly soluble drug and PVP, HPMC (hydroxypropyl methylcellulose acetate succinate), HPC (hydroxypropyl cellulose) provide water solubility and availability in the used medium. TEBEREKIDIS et al. (2006), DHIMAN et al. (2012), showed that the improvement of the solubility

of felodipine is a result of the formation of hydrogen bonding between PVP and the drug.

The subject of this paper is to evaluate the absorption of  $Mg^{2+}$  by an *in vitro* method from solid dispersions containing magnesium salts such as:  $Mg(Glu)_2$ ,  $Mg(Glu-Gly)$  and  $Mg(Glu-Arg)$  and carriers PVP or PC45. Evaluation of penicillin G influence on degree absorption of  $Mg^{2+}$  from solid dispersions containing magnesium glutamate salts and phosphatidylcholine (PC 45) was made.

## MATERIALS AND METHODS

The following were the subject of the experiment:

- magnesium glutamate- $Mg(Glu)_2$ ,  $(C_5H_8O_4N)_2Mg$ ; mol.wt. – 316,33
- magnesium glycine-glutamate- $Mg(Glu-Gly)$ ,  $C_7H_{12}O_6N_2Mg$ ; mol.wt. – 244,32
- magnesium arginine-glutamate- $Mg(Glu-Arg)$ ,  $C_{11}H_{21}O_6N_5Mg$ ; mol.wt. – 343,36
- penicillin G benzatine salt - Sigma Chemical Co. (Lot 50H0450)

The auxiliary substances such as polyvinylpyrrolidone (PVP by Serva) and phosphatidylcholine 45% (PC 45 by Lucas Meyer, Ltd) were used in order to produce solid dispersions containing the above magnesium salts. All the chemicals were of the analytical reagent grade.

The synthesis of magnesium glutamate was carried out according to the procedure previously described by MARCOIN and RYSZKA 1991. The magnesium glutamate-glycine  $Mg(Glu-Gly)$  and magnesium glutamate-arginine  $Mg(Glu-Arg)$  were obtained through modification structure of the magnesium glutamate with the ligand of glycine or arginine (Figure 1). The synthesis of

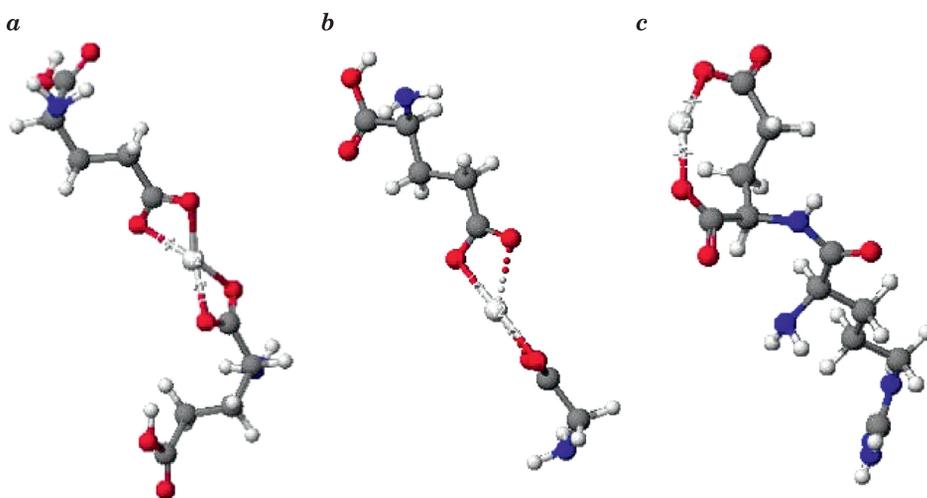


Fig. 1  $Mg(Glu)_2$  – a,  $Mg(Glu-Gly)$  – b,  $Mg(Glu-Arg)$  – c

these compounds was carried out similarly to the compounds described in previous research work (MARCOIN, SZULC-MUSIOŁ 2011). The content of magnesium 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 magnesium salts were prepared by FP VIII method. After previous micronization each magnesium salt was mixed with the selected carrier (PVP or PC 45) in a molar ratio (1:10) and dissolved in ethanol. The solid dispersions were isolated from the solution after evaporation of ethanol and drying under vacuum and which unified by a sieve (1,0 mm).

Partition coefficient o/w was determined for the solid dispersions, according to the Hansch theory and also the log P as alipophilicity parameter.

The absorption of  $Mg^{2+}$  from magnesium salts was carried out on an *in vitro* model (the method described previously (MARCOIN, SZULC-MUSIOŁ 2002) in which the absorption area was the small intestine (ileum) of rat. Similar procedure of the study of absorption of  $Mg^{2+}$  ions from solid dispersion containing magnesium salts with addition of PC45 carrier in the presence of penicillin G (50 mg) was carried out. The study was approved by the Bioethics Committee of the Medical University of Silesia. Constant ( $k$ ) rate of absorption and of absorption half time ( $t_{50\%}$ ) were also calculated. These results are considered significant statistically verified using the Anova followed by Kruskal-Wallis test or else Post Hoc multiple comparisons were made  $p \leq 0.05$ .

## RESULTS AND DISCUSSION

Lipophilic properties of magnesium salts were determined by means of the partition coefficient of log P for the *n*-octanol/phosphate buffer system. The calculated partition coefficient (log P) values for the solid dispersions containing the examined magnesium salts with PVP or PC 45 are presented in Table 1. Based on these results, the modification of the structure of the parent ligand of glycine or arginine affects the growth of the log P values. In the case of Mg(Glu-Gly), an increase in the log P value for the parent compound is 0.175, whereas for Mg(Glu-Arg), the difference is greater, up to 0.965. Analysis the results showed that introduction of an additional ligand, such as glycine or arginine, into a molecule of  $Mg(Glu)_2$  influences lipophilic properties of the examined salts. The chain lengthened with a (-CH<sub>2</sub>) group

Table 1

Values of log P of the partition coefficient for solid dispersions containing magnesium salts

Log P	Mg(Glu) <sub>2</sub>	Mg(Glu-Gly)	Mg(Glu-Arg)	Mg(Glu) <sub>2</sub>		Mg(Glu-Gly)		Mg(Glu-Arg)	
	-1.061	-0.886	-0.096	PVP	PC45	PVP	PC 45	PVP	PC45
				-0.768	0.148	-0.078	0.176	-0.026	0.250

as well as the presence of the nucleophilic group (-NH<sub>2</sub>) are the factors conditioning intercellular and intermolecular interactions.

The use of PVP or PC 45 as carriers in solid dispersions significantly contributed to the increase in the value of log P, thus raising the hydrophobicity of these systems.

It needs to be noted that the log P values for the solid dispersions with the addition of PC 45 were higher in each case. The impact of the interaction between the carriers and magnesium salts was noted. The calculated log P value for the solid dispersions containing Mg(Glu-Arg) with the addition of the PC 45 carrier (log P = 0.250) is higher than the log P value for solid dispersions containing Mg(Glu-Arg) and PVP (log P = -0.026). The calculated log P value for the solid dispersion, containing the Mg(Glu-Gly) PC45 carrier increased by 0.290 units compared with the log P values for the dispersion of Mg(Glu-Gly) without PC45. Use of PC 45 as a carrier in forming of solid dispersion containing Mg(Glu-Arg) causes an increase of the value of log P.

Phosphatidylcholine (PC 45) as a carrier significantly improves lipophilicity (increased log P values). To study the absorption of Mg<sup>2+</sup> ions from solid dispersion in the presence of the selected antibiotic, the PC 45 carrier was used. Other authors who carried out studies of solid dispersions of various drugs using other carriers also obtained positive results. The addition of phosphatidyl choline to solid dispersion containing active ingredients increases dissolution. Other authors (LAW 1992, MARSAC 2008) explained the presence of intermolecular hydrogen bonding as a factor creating an amorphous form of a crystal structure drug. BIKIARIS et al. (2005) as well as JAGADEESAN et al. (2013) used phosphatidylcholine for solid dispersions of poorly water-soluble drugs and determined parameters of physicochemical properties. They found that addition of phosphatidylcholine increased the dissolution rate and consequently improved bioavailability of the examined drugs. SINGH et al. (2011) were those who also reported that addition of the carrier may contribute to increasing dissolution rates and consequently better bioavailability of the drug.

Table 2 shows the mean value of pharmacokinetic parameters in the process of Mg<sup>2+</sup> ions absorption from solid dispersions containing magnesium glutamate salts with PC 45.

Table 2  
Kinetic parameters of Mg<sup>2+</sup> absorption in the small intestine from solid dispersions containing magnesium salts

Solid dispersions	$k \cdot 10^{-3}$ (min)	$t_{50\%}$ (h)	Total amount (%) of absorbed Mg <sup>2+</sup> within 2 h of the experiment	(±) SD	V (%)
Mg (Glu) <sub>2</sub>	1.569	7.361	12.70	0.67	5.27
Mg (Glu-Gly)	1.843	6.266	15.28	0.73	4.77
Mg(Glu-Arg)	1.742	5.842	16.28	0.66	4.05

$k$  – absorption rate constant,  $t_{50\%}$  – absorption half-time,  $V$  – variance, SD – standard deviation at  $p \leq 0.05$

In the course of our experiments, it was established that  $\text{Mg}^{2+}$  absorption can take place according to two independent transport mechanisms. The first one employs a passive diffusion process, while the other one occurs by facilitated diffusion from the intestinal lumen into epithelial cells, followed by the flow from cells into blood by means of a mechanism depending on the energy supply. The absorption of  $\text{Mg}^{2+}$  ions by the small intestine of a rat is in agreement with first order kinetics. When modified with glycine  $\text{Mg}(\text{Glu-Gly})$ , an increase of the constant rate of absorption was observed ( $k = 1.843 \cdot 10^{-3}$  min) in comparison with the matrix compound  $\text{Mg}(\text{Glu})_2$  ( $k = 1.569 \cdot 10^{-3}$ ), whereas the absorption half-time ( $t_{50\%}$ ) is shorter for  $\text{Mg}(\text{Glu-Gly})$  ( $t_{50\%} = 6.266$  h) than for solid dispersions containing  $\text{Mg}(\text{Glu})_2$  ( $t_{50\%} = 7.361$  h). The calculated values of absorption rate ( $k$ ) and absorption time 50% for solid dispersions containing  $\text{Mg}(\text{Glu-Arg})$  ( $k = 1.742 \cdot 10^{-3}$ ,  $t_{50\%} = 5.842$  h) are lower than the analogous values for solid dispersions containing  $\text{Mg}(\text{Glu-Gly})$ .

Modification with an arginine ligand also influences beneficially the profile of absorption parameters: the amount of absorbed  $\text{Mg}^{2+}$  ions during 2 h  $\text{Mg}(\text{Glu-Arg})$  was 16.28% versus 12.70% for the  $\text{Mg}(\text{Glu})_2$  matrix compound in the case of  $\text{Mg}(\text{Glu-Gly})$ , this value was 15.28%. Structural properties significantly influenced the effect of lipid phase (cellular membranes). Moreover, parameters of the surface, volume and molecular mass affect the ability of an active substance to penetrate through the lipid barrier.

The analysis of the research results on absorption of  $\text{Mg}^{2+}$  ions from solid dispersions containing the examined salts and in presence of penicillin G showed that pharmacokinetic profile changes significantly depended on the type of salt (cf. Table 3). The results of our analysis showed that the absorption rate constant ( $k$ ) for solid dispersions containing  $\text{Mg}(\text{Glu})_2$ ,  $\text{Mg}(\text{Glu-Gly})$  and  $\text{Mg}(\text{Glu-Arg})$  salts in the presence of penicillin G causes a decrease of  $k$  by 0.888, 0.287 and 0.028, respectively, compared with solid dispersions containing these salts without penicillin G. The calculated values of absorption half-time ( $t_{50\%}$ ) for the examined solid dispersions with  $\text{Mg}(\text{Glu})_2$ ,  $\text{Mg}(\text{Glu-Gly})$  and  $\text{Mg}(\text{Glu-Arg})$  increased by about 9.602 h, 1.145 h, 0.895 h, respectively, compared with the reference system. The amount of absorbed

Table 3

Kinetic parameters of  $\text{Mg}^{2+}$  absorption in the small intestine from solid dispersions containing magnesium salts in the presence penicillin G

Solid dispersions	$k \cdot 10^{-3}$ (min)	$t_{50\%}$ (h)	Total amount (%) of absorbed $\text{Mg}^{2+}$ within 2 h experiment	( $\pm$ ) SD	V (%)
$\text{Mg}(\text{Glu})_2$ + penicillin G	0.681	16.963	9.80	0.942	9.612
$\text{Mg}(\text{Glu-Gly})$ + penicillin G	1.556	7.411	12.31	0.54	4.38
$\text{Mg}(\text{Glu-Arg})$ + penicillin G	1.714	6.737	14.21	4.48	3.15

Explanations see Table 2

Mg<sup>2+</sup> after 2 hours of the experiment was significantly ( $p \leq 0.05$ ) increased for solid dispersions in the presence of penicillin G with Mg(Glu)<sub>2</sub> by 2.90%, with Mg(Glu-Gly) by 2.97% and with Mg(Glu-Arg) by about 2.07 % compared with the reference system. On the basis of the completed experiment, an interaction was found in the phase of the pharmacokinetic process of Mg<sup>2+</sup> ion absorption from the examined dispersions.

Values of kinetic parameters of Mg<sup>2+</sup> absorption from solid dispersions containing the examined glutamate magnesium salts were lower than the values of kinetic absorption parameters of Mg<sup>2+</sup> absorption from solid dispersions without penicillin G.

In brief, penicillin G hinders the process of Mg<sup>2+</sup> ion absorption from the examined dispersions.

## CONCLUSION

Modifying the structure of Mg(Glu)<sub>2</sub> with an additional ligand glycine or arginine significantly improves the kinetic profile of the absorption of Mg<sup>2+</sup> ions from solid dispersions containing magnesium salts of the carrier PC 45.

The presence of  $\beta$ -lactam antibiotic inhibits the Mg<sup>2+</sup> absorption process from solid dispersions, which was the subject of our research.

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