

EVALUATION OF SOLID DISPERSIONS CONTAINING MAGNESIUM LEVULINATE SALTS WITH SELECTED CARRIERS

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Abstract

Among the methods applied to ensure optimal pharmaceutical availability of a drug is the incorporation of solid dispersions, i.e. combinations containing a therapeutic substance and a carrier deprived of its pharmacological activity. While manufacturing solid dispersions, special attention must be paid to carriers with a polymeric structure and hydrophilic properties, e.g. polyvinylpyrrolidone (PVP) and also phosphatidylcholine (PC).

The aim of this study has been to evaluate the influence of the carriers PVP and PC 45 on pharmacokinetic parameters of Mg^{2+} absorption from $Mg(Lev)_2$, $Mg(LevGly)$, $Mg(LevArg)$ as well as from solid dispersions containing these salts.

The o/w partition coefficient was determined and the log P value calculated for pure salts and for solid dispersions containing the salts during this study.

The process of Mg^{2+} absorption was examined *in vitro* on a model of the rat's small intestine. Our analysis of the results indicates that addition of PVP or PC 45 to solid dispersions (containing magnesium levulinate salts) significantly improves the degree of Mg^{2+} ion absorption. It has been found that addition of PVP and PC 45 to solid dispersions with magnesium levulinate salts significantly influences the rate of Mg^{2+} absorption from the formulations. Moreover, the results indicate that additional ligand (glycine or arginine) in the structure of magnesium levulinate triggers the effect consisting in depressed lipophilicity for these compounds.

Using the PVP or PC 45 carriers for making solid dispersions containing magnesium levulinate and derivatives with glycine or arginine ligands is quite a promising solution for attaining improved pharmaceutical availability of drugs.

Keywords: magnesium levulinate, solid dispersion, log P, absorption, amino acids: glycine, arginine.

OCENA STAŁYCH ROZPROSZEŃ ZAWIERAJĄCYCH SOLE LEWULINIANU MAGNEZOWEGO Z WYBRANYMI NOŚNIKAMI

Abstrakt

Jedną z metod osiągnięcia optymalnej dostępności farmaceutycznej leku jest zastosowanie stałych rozproszeń, układów zawierających substancję leczniczą i nośnik, który jest pozbawiony własnego działania farmakologicznego. Przy wytwarzaniu stałych rozproszeń na szczególną uwagę zasługują nośniki o budowie polimerowej i właściwościach hydrofilowych. Należą do nich m.in. poliwinylpirolidon (PVP), a także fosfatydylocholina.

Celem badań była ocena wpływu wybranych nośników: poliwinylpirolidonu (PVP) i roztworu fosfatydylocholino (PC 45) na poprawę parametrów farmakokinetycznych procesu wchłaniania jonów Mg^{2+} z soli lewulinianu magnezowego $Mg(Lev)_2$, $Mg(LevGly)$, $Mg(LevArg)$ oraz ze stałych rozproszeń zawierających te sole.

W badaniach wyznaczono współczynnik podziału o/w i wyliczono wartość $\log P$ dla czystych soli oraz dla stałych rozproszeń zawierających te sole.

Badania procesu wchłaniania jonów Mg^{2+} przeprowadzono metodą *in vitro* na modelu jelita cienkiego szczura. Wykazano, że dodatek PVP lub PC 45 do stałych rozproszeń zawierających sole lewulinianu magnezowego znacząco wpływa na poprawę stopnia wchłaniania. Na podstawie tych badań stwierdzono, że dodatek PVP lub PC 45 do stałych rozproszeń z solami lewulinianu magnezowego istotnie ($p=0.01$) wpływa na szybkość procesu wchłaniania jonów Mg^{2+} z otrzymanych formułacji. Ponadto wyniki badań wskazują, że dodatkowy ligand (glicyna, arginina) w strukturze cząsteczki lewulinianu magnezowego wywołuje efekt zmniejszenia lipofilowości dla tych związków.

Zastosowanie nośników PVP lub PC 45 do wytwarzania stałych rozproszeń zawierających lewulinian magnezowy i pochodne z ligandami glicyny lub argininy jest obiecujące w poprawie dostępności farmaceutycznej.

Słowa kluczowe: lewulinian magnezu, stałe rozproszenia, $\log P$, wchłanianie, aminokwasy: glicyna, arginina.

INTRODUCTION

Magnesium is one of the essential nutrients necessary for maintaining functions of the human organism. It is one of the macronutrients which determine the course of fundamental biological processes (RAYSSIGUIER et al. 2001). Magnesium is a stabilizer of cell membranes, which affects their fluidity and permeability (KONRAD et al. 2004). Magnesium is essential in human diet and its shortage can cause many diseases (FELLET-COUDRAY et al. 2005).

Studying inorganic and organic magnesium salts in compounds is interesting because of the high biological activity of magnesium and its supplements as well as their practical role in pharmacotherapy (SCHMITASCHEK, REMPIS 2001, VORMAN 2003, COUDRAY et al. 2005).

Magnesium creates complexes with amino acids, which are essential for the magnesium transport through membranes and blood vessel barriers into blood and tissues. A review of the current research on magnesium and ami-

no acid compounds shows that the number of papers dedicated to such systems is highly varied (RANDE, SOMBERG 2001). Amino acids, such as glycine or arginine are components of live cells. Amino acids are convenient factors modifying functioning of pharmacologically active compounds.

Owing to numerous studies we have learnt that magnesium compounds containing organic anions (FIROZ, GRABER 2001) are the best supplements; they facilitate magnesium transport through walls of the intestines and release metal ions into the serum. Pursuing our studies on the absorption process of Mg^{2+} from magnesium organic salts (in order to obtain a drug with improved Mg^{2+} absorption), we have synthesized magnesium levulinate. Modification of the structure of organic magnesium salts by ligand of glycine or arginine had positive influence on the kinetics parameters of Mg^{2+} absorption both *in vitro* and *in vivo* as described in the previous paper (MARCOIN, SZULC 2002, MARCOIN 2006, MARCOIN, SZULC-MUSIOŁ 2009).

By defining the pharmaceutical availability we can determine the amount and rate of release of a therapeutic substance in a given form of a drug. Absorption of a pharmaceutical substance from the gastrointestinal tract depends on the process and rate of releasing a biologically active substance, thus indicating its potential availability.

The concept of modern pharmaceutical technology is to obtain the form of a drug with a desirable rate of releasing the substance which can have a therapeutic effect. Its effect depends on physicochemical properties of the substance as well as on the form of the drug and the applied auxiliary substances (CORRIGAN et al. 2002).

Creation of molecular solid dispersions is one of the methods used to improve pharmaceutical availability of medications. There are numerous studies concerning the problems of enhancing the pharmaceutical availability of medicinal preparations. A large number of studies in this field imply (among other factors) an appropriate selection of the carriers of absorption. In order to increase the dissolution rate of therapeutic substances from solid dispersions, substances with solubilising and moisturising properties such as polyvinylpyrrolidone (PVP), polyethylene glycols, cellulose derivatives, alginate, phospholipids are tested. Solid dispersion can improve the dissolution rate of poorly water-soluble drugs by dispersing the drug in a carrier (KARAVAS et al. 2006, PATEL, PATEL 2007).

The subject of this paper has been to evaluate the absorption of Mg^{2+} by an *in vitro* method from magnesium levulinate $Mg(Lev)_2$, including a modifying factor such as glycine or arginine. Furthermore, evaluation of the process of Mg^{2+} absorption from solid dispersions containing the analysed compounds has been made. Finally, the influence of the absorption of Mg^{2+} from solid dispersions containing magnesium salts has been examined. The effects of the influence of the carriers, PVP and PC 45, on the pharmacokinetic parameters of magnesium salts and solid dispersions containing $Mg(Lev)_2$, $Mg(LevGly)$, $Mg(LevArg)$ are presented in this paper.

MATERIALS AND METHODS

The study was carried out on salts:

- magnesium levulinate: $\text{Mg}(\text{Lev})_2$, $\text{Mg}(\text{C}_5\text{H}_7\text{O}_6)_2$, mol. wt. 254.33;
- magnesium glycine-levulinate: $\text{Mg}(\text{LevGly})$, $\text{Mg}(\text{C}_7\text{H}_{11}\text{O}_5\text{N})$, mol. wt. 213.33;
- magnesium arginine-levulinate: $\text{Mg}(\text{LevArg})$, $\text{Mg}(\text{C}_{11}\text{H}_{20}\text{O}_5\text{N}_4)$, mol. wt. 312.37.

The auxiliary substances such as polyvinylpyrrolidone (PVP), (Serva) and phosphatidylcholine 45%, (PC 45), 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 levulinate was carried according to the procedure described previously (MARCOIN, RYSZKA 1991).

Modification of the magnesium levulinate structure with ligand of glycine or arginine was achieved in a reaction of magnesium levulinate and an appropriate amino acid in water solution of the molar ratio 1:1. The synthesis was carried out by stirring the mixture vigorously at 60-70°C for 3 hrs.

The products were isolated from the solution by water evaporation (a Unipam 350 evaporator), crystallized from acetone and dried at room temperature. The content of magnesium in the salts was measured by atomic absorption spectrophotometry (Carl Zeiss Jena model AAF 3) at the wavelength 258.2 nm.

Solid dispersions were prepared in the granulated form. After previous micronization, each magnesium salt was mixed with the selected carrier (PC 45 or PVP) in a molar ratio (1:10) and dissolved in ethanol. After complete evaporation of ethanol and drying under vacuum, the solid dispersions thus obtained were unified with a sieve (1.0 mm).

For the solid dispersions, the o/w partition coefficient for the system of *n*-octanol/phosphate buffer was determined using the traditional shake-flask method. Lipophilicity was characterized by the log P.

The absorption of Mg^{2+} from magnesium salts was carried out on an *in vitro* model according to the method described previously (MARCOIN, SZULC 2002), in which the absorption area was the small intestine (ileum) of a rat. The study had been approved by the Bioethics Committee of the Medical University of Silesia. The results consisting of the absorption rate constant (k) and absorption half time ($t_{50\%}$) were calculated. The measurements were repeated twelve times in order to minimize statistical errors. Standard deviation (SD) and variance (V) were determined. Statistical significance was tested by repeated measures using ANOVA followed by Kruskal-Wallis test or else Post Hoc multiple comparisons were done. $P < 0.05$ was considered significant.

RESULTS AND DISCUSSION

Lipophilic properties of $\text{Mg}(\text{Lev})_2$, $\text{Mg}(\text{LevGly})$ and $\text{Mg}(\text{LevArg})$ were determined by means of the partition coefficient of log P. The calculated values of log P for the examined pure salts and the solid dispersions containing these salts with PVP or PC 45 are presented in Figure 1.

The results of our analysis showed that introduction of additional ligands of amino acids such as glycine or arginine into the molecule of $\text{Mg}(\text{Lev})_2$ leads to a decrease in the log P value. In the case of $\text{Mg}(\text{LevGly})$, the value of log P decreases by about 2.6 times in comparison with the parent salt.

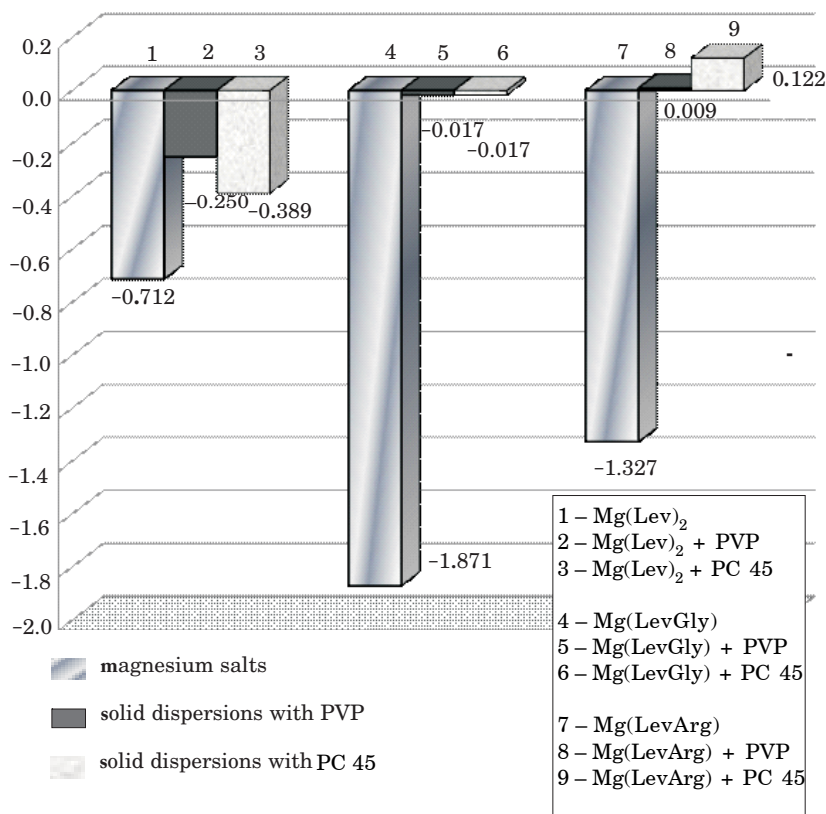


Fig. 1. The values of partition coefficient (logP) for pure magnesium salts and for solid dispersions containing these salts. Values are expressed as mean \pm SD ($n=12$).

2,3 bars: $*P \leq 0.01$ vs. 1 bar; 5,6 bars: $*P < 0.01$ vs. 4 bar; 8,9 bars: $*P < 0.01$ vs. 7 bar.

Magnesium salts: $\text{Mg}(\text{Lev})_2$, $\text{Mg}(\text{LevGly})$, $\text{Mg}(\text{LevArg})$. Solid dispersions: $\text{Mg}(\text{Lev})_2$ + PVP, $\text{Mg}(\text{Lev})_2$ + PC 45, $\text{Mg}(\text{LevGly})$ + PVP, $\text{Mg}(\text{LevGly})$ + PC 45, $\text{Mg}(\text{LevArg})$ + PVP, $\text{Mg}(\text{LevArg})$ + PC 45

Meanwhile, the modified structure of the parent salt with an additional ligand of arginine depresses log P values by about 1.8-fold. This value is statistically significant at $p=0.01$.

The influence of surface parameters, volume and molecule mass on the penetration parameters of a therapeutic substance through the lipid barrier became noticeable. Electrically charged compound particles were restrained inside the environment into which they had been introduced while electrically neutral complexes could easily penetrate the biological membranes. This phenomenon was described by BLAQUIERE, BERTHON (1987) and confirmed in this study.

The application of a PVP carrier to solid dispersions containing Mg(LevGly) and Mg(LevArg) salts causes increased lipophilicity, so that the calculated value of log P for Mg(LevGly) + PVP increased by 1.854 units and for Mg(LevArg) + PVP by 1.336 units compared with the log P values calculated for pure salts of Mg(LevGly) and Mg(LevArg). While using PC 45 for solid dispersions containing Mg(LevGly) and Mg(LevArg), the log P value increased by 1.854 and 1.449, respectively, compared with pure salts (Figure 1).

The mean values of pharmacokinetic parameters obtained for levulinate magnesium salts and solid dispersions containing these salts with PVP or PC 45 are presented in Table 1. It has been found that absorption of Mg^{2+} in the small intestine was in agreement with the first-order kinetics. As seen

Table 1

Kinetic parameters Mg^{2+} absorption from solid dispersions containing magnesium salts in the small intestine

Solid dispersions	$k \cdot 10^{-3}$ (min)	$t_{50\%}$ (h)	Total amount (%) of absorbed Mg^{2+} within 2 h of the experiment	W (%)	(\pm) SD
Mg (Lev) ₂	2.584	4.469	24.90	9.66	2.407
Mg (Lev-Arg)	0.924 ^a	12.497 ^a	11.80 ^a	11.66	1.376
Mg (Lev-Gly)	0.681 ^a	16.963 ^a	9.80 ^a	9.61	0.942
Mg (Lev) ₂ + PVP	2.565	4.503	28.42	8.23	2.340
Mg (Lev-Arg) + PVP	2.784 ^c	4.149 ^c	31.26 ^c	4.65	1.454
Mg (Lev-Gly) + PVP	2.638 ^b	4.381 ^b	29.30 ^b	4.41	1.295
Mg (Lev) ₂ + PC 45	2.616	4.415	25.32	5.91	1.497
Mg (Lev-Arg) + PC 45	3.727 ^c	3.099 ^c	34.96 ^c	11.04	2.797
Mg (Lev-Gly) + PC 45	2.792 ^b	4.137 ^b	28.56 ^b	4.08	1.167

k – absorption rate constant;

$t_{50\%}$ – absorption half – time;

W – variance;

SD – standard deviation ^a $P \leq 0.01$ vs. Mg(Lev)₂, ^b $P \leq 0.01$ vs. Mg(Lev-Gly), ^c $P \leq 0.01$ vs.

Mg(Lev-Arg).

from Table 1, the highest (k) value among the pure magnesium salts was found for $\text{Mg}(\text{Lev})_2$ ($k=2.584 \cdot 10^{-3}$ min), while the k value for $\text{Mg}(\text{LevGly})$ was $0.681 \cdot 10^{-3}$ min. For $\text{Mg}(\text{LevArg})$, (k) was equal to $0.924 \cdot 10^{-3}$ min. By analysing the research results on Mg^{2+} absorption from the salts in an *in vitro* model, the negative influence of an amino acid ligand (Gly or Arg) on transportation of Mg^{2+} has been shown.

The amount of absorbed Mg^{2+} after 2 hours of the experiment was significantly higher ($p=0.01$) for $\text{Mg}(\text{Lev})_2$ than for $\text{Mg}(\text{LevGly})$ and $\text{Mg}(\text{LevArg})$; these values were 24.90% for $\text{Mg}(\text{Lev})_2$, 11.80% for $\text{Mg}(\text{LevArg})$ and 9.80%, for $\text{Mg}(\text{LevGly})$. As demonstrated above, the glycine or arginine ligand added into the structure of a molecule of $\text{Mg}(\text{Lev})_2$ depressed the lipophilicity of the compound (Figure 2).

The results of our analysis (Table 1) showed that by adding an auxiliary substance such as PVP or PC 45 into solid dispersions containing the examined salts, the pharmacokinetic parameters are elevated. Application of PVP and PC 45 to manufacturing preparations of solid dispersions containing levulinate salts significantly influences ($p=0.01$) both the quantity and the rate of absorption of the tested medicinal preparations.

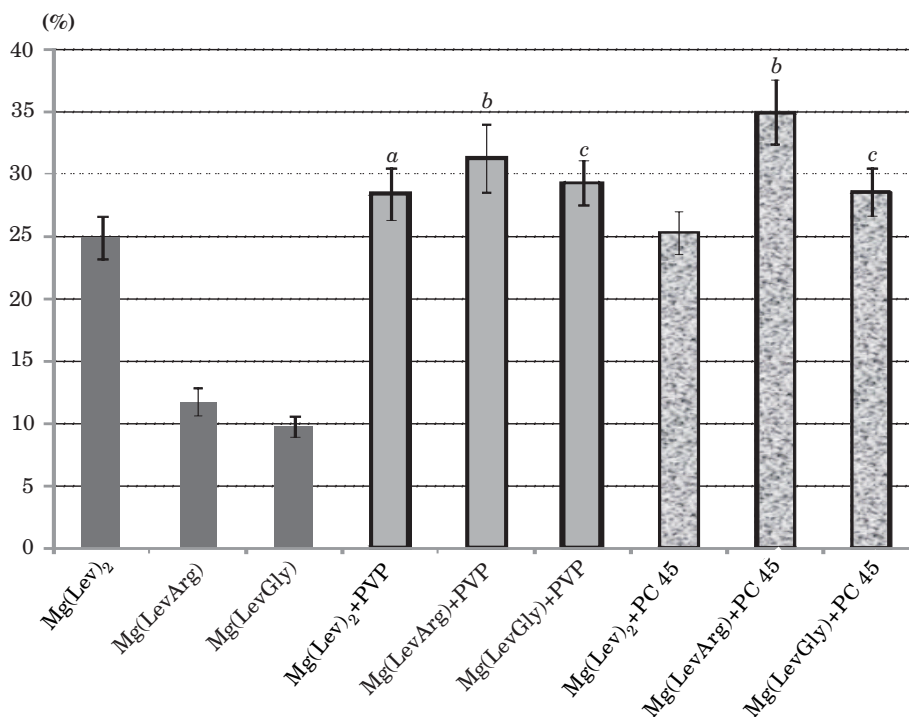


Fig. 2. Total amount (%) of absorbed Mg^{2+} through the rat's small intestine in 120 minutes of the experiment. Values are expressed as mean \pm SD ($n=12$)

^a $P \leq 0.05$ vs. $\text{Mg}(\text{Lev})_2$, ^b $P \leq 0.01$ vs. $\text{Mg}(\text{LevArg})$, ^c $P \leq 0.01$ vs. $\text{Mg}(\text{LevGly})$
at the same time point

Adding the PC 45 carrier into solid dispersions containing magnesium levulinate and its derivatives raised the rate of absorption. The highest values were obtained for Mg(LevArg) + PC 45 $k=3.727 \cdot 10^{-3}$ min.

In another study, JADHAY et al. (2009) aimed at developing microemulsion based on lecithin (PC) organogel formulations with fluconazol and investigating its suitability. The results showed that of the surfactant action of the EO-lecithin organogels was safe enough for the purpose in question. The influence of lecithin (PC) on solubility of aceclofenac organogels was also described by SHAIKH et al. (2009), whose results indicate positive influence of lecithin (PC) as a pharmaceutically acceptable surfactant.

Besides, the addition of PVP into solid dispersion with levulinate magnesium salts positively influences the transportation of Mg^{2+} from these preparations. Application of magnesium levulinate salts as a solid dispersion improved the pharmacokinetic parameters, absorption rate and constant (k) of Mg ions, which was as follows: $k=2.784 \cdot 10^{-3}$ min for Mg(LevArg)+PVP, $k=2.638 \cdot 10^3$ min for solid dispersions with Mg(LevGly) + PVP and $k=2.565 \cdot 10^{-3}$ min for solid dispersions with Mg(Lev)₂ + PVP.

During the present research, it has been found that by adding PVP and PC 45 to solid dispersions containing magnesium salts their solubility is altered. These carriers for solid dispersions improve their pharmaceutical availability and, consequently, bioavailability. The results confirm that these auxiliary substances are of great importance to using the examined salts. Addition of the carrier PC 45 to a solid dispersion releases 4.96% if it contains Mg(LevArg) Mg^{2+} , and 28.56% Mg^{2+} it has Mg(LevGly), compared to solid dispersion containing Mg(Lev)₂ – 25.32% Mg^{2+} . Similarly, the activity PC 45 significantly influences ($p=0.01$) dissolution and improves absorption of Mg^{2+} .

There was a correlation between the results of log P values as a factor characterizing lipophilicity and the total amount of absorbed Mg^{2+} ions during 2 hours of the experiment, confirmed by the results of a kinetic study of the absorption process. A higher value of the absorbed Mg^{2+} was found for the solid dispersion of Mg(LevArg) +PC 45, where the log P value was 0.122.

In order to improve the solubility of Tenoxicam or Flurinazine, PVP is used as a carrier of these substances in solid dispersion (EL-GAZAYERLY et al. 2000). Other researchers described the results of their studies (SILVA et al. 2010) in which they applied PVP K 15 to produce solid dispersions containing Simvastatin, which is practically insoluble in water. These inert carriers significantly improved the release profile of a drug from all solid dispersions. LATINEN et al. (2010) prepared a tablet readily dissolving in the mouth, which consists of a stable solid dispersion with PVP K 30, PEG 8000. Investigations have verified an improved dissolution profile of Valdecoxib when solid dispersion with PVP K 30 was used (MODI, TAYADE 2006). Dissolution of Valdecoxib improved significantly in solid dispersion products (< 85% in 5 minutes).

CONCLUSIONS

This study suggests that the analysed auxiliary substances (PVP, PC 45) are good carriers, which improve the lipophilic properties of the examined solid dispersions, thus facilitating the permeability of the medicinal substances through the lipid barrier. Moreover, the magnesium salts improve the permeability of pharmaceuticals through the intestine.

It has been noticed that there is some correlation between the total amount of the absorbed Mg^{2+} and the lipophilic properties of the examined magnesium salts and their solid dispersions.

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