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# Properties of solid dispersions of selected magnesium salts and the absorption process of $Mg^{2+}$ ions in vitro

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The paper presents an application of phosphatidylcholine 45% (PC 45) and polyvinylpyrrolidone (PVP) in formulations of magnesium salts such as $Mg(VitB_6)$ and $Mg(VitB_6Arg)$ prepared by solid dispersion (SD) techniques. The evaluation of influence of the selected carriers on some physicochemical properties of solid dispersions and on the absorption process of $Mg^{+2}$ ions in vitro were made. An infrared (IR) spectra study suggested creation of a hydrogen bond between the carriers and the examined magnesium salts. The results of the following thermal analysis: differential thermal analysis (DTA), thermogravimetry (TG), and differential scanning calorimetry (DSC) showed that application of PVP into SD lower the temperature of the decomposition process. However, in the case of PC 45 into SD the characteristic thermal effects of higher temperatures were observed. Moreover, values of the enthalpy SD of decomposition process were decreased. The results of these studies on absorption process of $Mg^{2+}$ ions in vitro showed the positive influence of the applied carriers on the partition coefficient values (log P) in the examined formulation.

**Key Words**: Vitamin B6, Arginine, Polyvinylopirrolidone, Phosphatidylcholine, Small intestine.

## Introduction

Numerous studies dealing with magnesium and with its physiological significance showed that in the case of lack of this element there is a dependence between its content in tissues and its

absorption by the organism. Magnesium belongs to those elements which are difficult to absorb. It is absorbed from the digestive tract mainly in small intestine within the range of 30 to 50 percent [12, 17]. In order to complete deficiency of Mg various magnesium preparations are most often supplemented. In result of the studies carried out so far it has been shown that vitamin $B_6$ ($VitB_6$) positively influences the course of absorption of magnesium.

Bara [1,2] et De Souza [4] conducted comparative experimental study of Mg lactate, vitamin $B_6$ and their associations which influence the permeability of a human membrane and also their effect on cellular and paracellular ionic transfer through the isolated amniotic membrane. Kozielec studied influence of oral magnesium supplementation of the preparation Slow-Mag$B_6$ on serum lipids in patients with dislipidemia. As the results of these experiments, a significant increase of magnesium and HDL fraction concentration in blood correlating with a decrease of TG and LDL concentration was found in the examined patients [13].

Activity of the drugs presented in the paper should be considered in two aspects: supplementation of bioelement (magnesium) and of a ligand amino acids which are known as convenient factors modifying functioning of pharmacologically active compounds. Preparations with arginine (Arg) have been used in treatment of cordial ischaemia and obliterative atherosclerosis of lower limbs. Arginine cationic groups and anionic ones have considerable influence on electric load of protein, stimulating its synthesis [21]. Arginine as amino acid was selected as a modifying factor for a molecule of Mg ($VitB_6$). The main purpose of modern pharmaceutical technology is to obtain the form of a drug with desirable pace of releasing of the substance which can have therapeutic effect. Its effect depends on physicochemical properties of the drug substance as well as on the form of the drug and the auxiliary applied substances. In technology of oral forms of the drug with modified release of the drug substance carriers dissolving in water, the so called hydrophilic substances are being used [14, 19].

Solid dispersion is a method for improving the dissolution rate of poorly water soluble drugs by dispersing the drug in a carrier [3]. The goal of modern technology was obtained in the aspect of preparation methods for solid dispersions (SD) where their interesting carriers are PC and PVP, respectively [7, 8, 9, 20]. The interest in surface − active and emulsifying carriers for solid dispersion (SD) of poorly water-soluble drugs increased greatly in recent years [6]. PC has both hydrophilic and hydrophobic parts so the properties of solid dispersion would be affected by the two of the above factors. Fujii and Sudha reported that a hydrogen bond between the NH of phenobarbital and the phosphate of PC was formed [7, 20]. Torre explained the result as the dispersion effect of the hydrophilic carrier and by possible lowering of the surface tension of the use PVP [22]. According to Trapani, valproic acid and

polyvinylpyrrolidone (PVP) interacted with the formation of a hydrogen bond in solid dispersion [23]. In recent years, a ratio of drug to carriers become the controlling factor for dissolution and bioavailability improvement, what was reported [5, 10, 18]. In our study we estimated the influence of arginate anion on the absorption process of magnesium ions obtained from the magnesium salts. The results of influence of PC or PVP carriers on variations of some physicochemical properties and of the partition coefficient values (log P) used for solid dispersion (SD) containing Mg($VitB_6$), Mg($VitB_6$Arg) were presented in this paper.

## Experimental

### Materials

The examined magnesium salts were synthesized according to the previously described procedure [15].

- magnesium pyridoxinate –Mg($VitB_6$ ), Mg($C_8$ $H_{11}$ $NO_3$), mol. wt =192.5,
- magnesium-arginine-pyridoxinate-Mg(VitB6Arg),-Mg(C14H11NO3C6H14N4O2),-mol.wt=365.7
- 1 mol Mg(VitB6) contains equimolar amounts of pyridoxine and Mg; on weight basis, the complex contains 89.5% VitB6, 10.5% Mg, 1mol Mg(VitB6Arg) contains 50.8% VitB6, 43.1% Arg, 6% Mg.
- lecithin, (phosphatidylcholine 45%)-PC 45 (Lucas Mayer Ltd.),
- polyvinylpyrrolidone-PVP (Severa),
- lactose, sucrose, ethanol (Sigma).

Other chemicals were of reagent grade.

### Preparation of SD

The solid dispersions were prepared in a granule form. Micronized magnesium salts were mixed with the selected carriers (PC 45 or PVP) in molar ratio (1: 9) and were dissolved in ethanol. The ethanol was then evaporated *in vacuo* sometimes warmed to 313 K. Next, these dispersions were mixed with lactose, sucrose (2:1:1) and with ethanol, added later. The solvent which evaporated *in vacuo* resulted with a residue, while being dried under vacuum for 3h. The obtained granules were made unified by means of a sieve (1.0). IR spectra of the SD

examination were obtained on a Fourier Transform Infrared Spectrometer Nicolet Magna IR type 560 at room temperature using the KBr pellet technique.

## Physicochemical properties of SD

Thermal decomposition was studied by means of a Derivatograph (MOM, Budapest).

Thermogravimetry (TG) and differential thermal analysis (DTA) was carried out in platinum crucibles at the rate of 2.5 deg/min up to 500 K, using $AL_2O_3$ as standard material in air atmosphere. The samples of powder had a weight of 80- 200 mg.

Differential scanning calorimetry (DSC) was used for the analysis (Perkin Elmer DSC-7). Weight of the samples ranged within 0.5-10 mg and they were heated at the rate of 20 deg/min in atmosphere of nitrogen, according to the Perkin Elmer program. All studies were made in triplicate.

## Partition coefficient ( logP)

The partition coefficient log P for SD for the system of n-octanol / water was determined according to the Hansch theory [21]. A pH=7.4 buffer solution containing c.a. 0.2 mg/ml of the magnesium salt was vigorously shaken with the same volume of n-octanol at 298 K for 2 h. The partition coefficient was determined by measuring the drug concentration in the water phase before and after shaking. Drug concentrations were measured by ultraviolet (UV) absorption on a Jasco model V – 550 UV-Vis spectrophotometer, in the cases of $Mg(VitB_6)$ (219 nm) and $Mg(VitB_6Arg)$ (214 nm). Data were shown in Table 2 as the mean of three experiments.

## Absorption process of $Mg^{2+}$ ions in vitro for the Mg salts

Investigation of the absorption process of $Mg^{2+}$ ions in vitro for magnesium salts was carried out on the *in vitro* model, according to the method described in our earlier paper [16]. Measurements of the absorption process of $Mg^{2+}$ were carried out with the use of the flow-through apparatus with a segment of the small intestine (ileum) of a rat. The essential part of this apparatus was thermostated at $37^{+}$ $1^{o}C$ glass chamber with volume of 30 $cm^3$, filled with the 4 mM solution of the analysed magnesium salt. The aqueous 0.9% NaCl solution was pumped with a peristaltic pump through the intestine segment at a constant rate of 1.2 ml/min.

Samples were collected every 15 min and the magnesium content was measured by atomic absorption spectrophotometer Carl Zeiss Jena model AAF 3 at the wavelength of 285.2 nm. Absorption of $Mg^{2+}$ ions in the segment of the small intestine was in agreement with the first-order kinetics. On the basis of the obtained results, the absorption rates constant (k) and the absorption half – time ($t_{50\%}$) were calculated.

### Statistical analysis

Results are presented as mean values obtained by the four experiments. Standard deviation (SD) and variance (W) were determined. The statistical significance of the obtained data was calculated by using the Student's test. The level of significance was $p < 0.05$.

## Results and discussion

### Solid state studies

The analysis of the IR spectra of SD, of SD +PC 45 and of SD+PVP, presented in Fig.1, shows the differences between them, especially within the range of 1700 to 1630 $cm^{-1}$. It is interesting to observe the characteristic absorption band of the pure substance at 1639$cm^{-1}$ connected with vibrations of the carbonyl group and the intensity of changes which occur in lower frequencies (1672 $cm^{-1}$) for the Mg($VitB_6$Arg) + PC 45 system and also for the Mg($VitB_6$Arg) + PVP (1660 $cm^{-1}$) one. Comparing to the infrared spectra for the pure substance with the examined solid dispersions granules, the changes were observed in the range of 3600-2900 $cm^{-1}$. For Mg($VitB_6$Arg)/SD and Mg($VitB_6$)/SD with carriers (PC 45, PVP), the IR spectra in the range of 1400-950 $cm^{-1}$ were similar. This may indicate that an interaction between Mg ($VitB_6$Arg) and PC 45, PVP takes place and most probably it results in hydrogen bondings.

Both quantitative and qualitative evaluation of solid dispersions with magnesium salts with PC 45 and PVP, were made by thermal analysis method. The results of the study were presented in Fig. 2 and 3 and also in Table 1. Results from DTA analysis application of PVP for formulation of solid dispersions showed lowering of temperatures as characteristic effects in the process of decomposition.

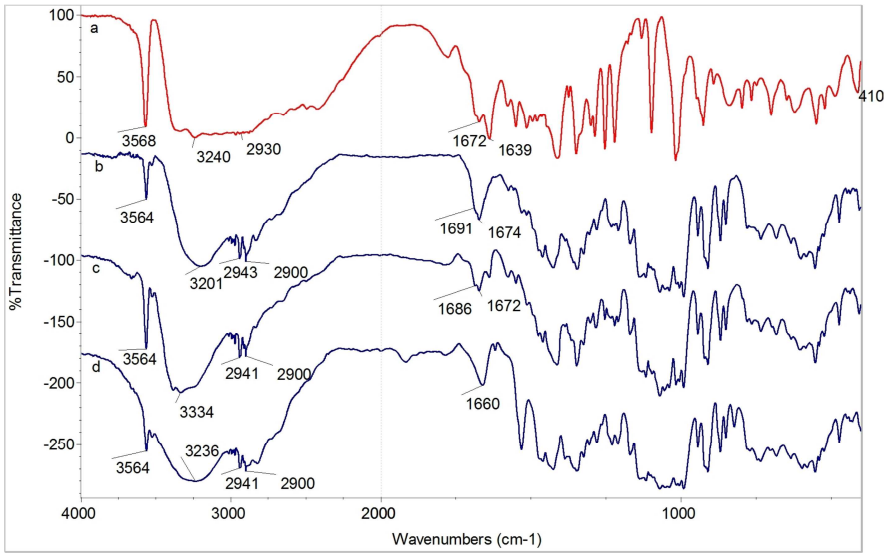


**Figure 1.** IR spectra of a) Mg(VitB$_6$Arg) – pure substance, b) Mg(VitB$_6$ Arg / SD, c) Mg(VitB$_6$ Arg) / SD + PC 45, d) Mg(Vit B$_6$Arg) / SD + PVP.

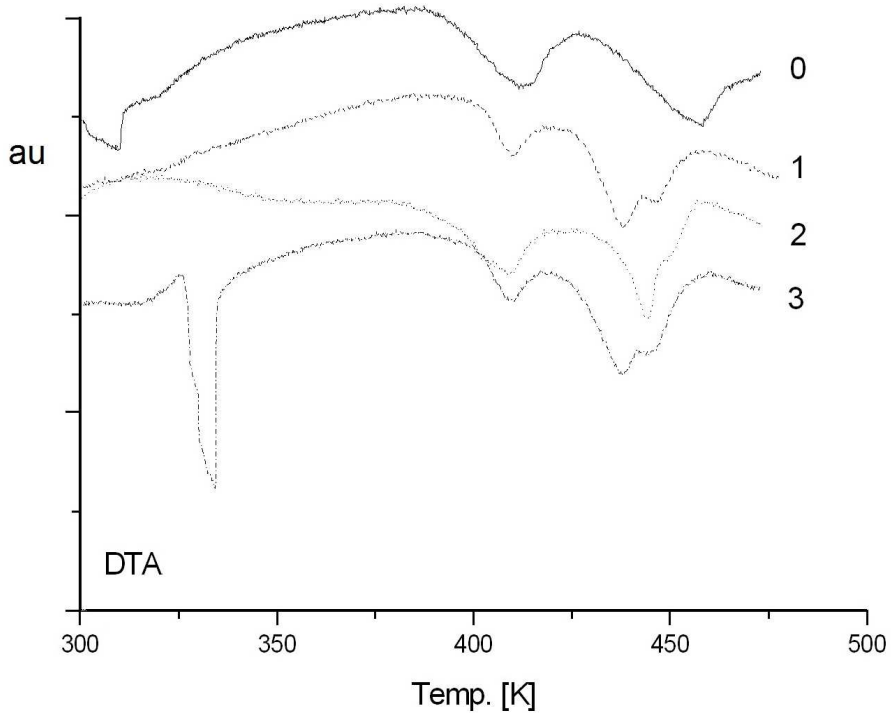


**Figure 2.** DTA thermal profiles of: 0 – Mg(VitB$_6$Arg) – pure substance, 1 – Mg(VitB$_6$Arg)/SD, 2 – Mg(VitB$_6$Arg) /SD + PC 45, 3 – Mg(VitB$_6$Arg) SD / + PVP

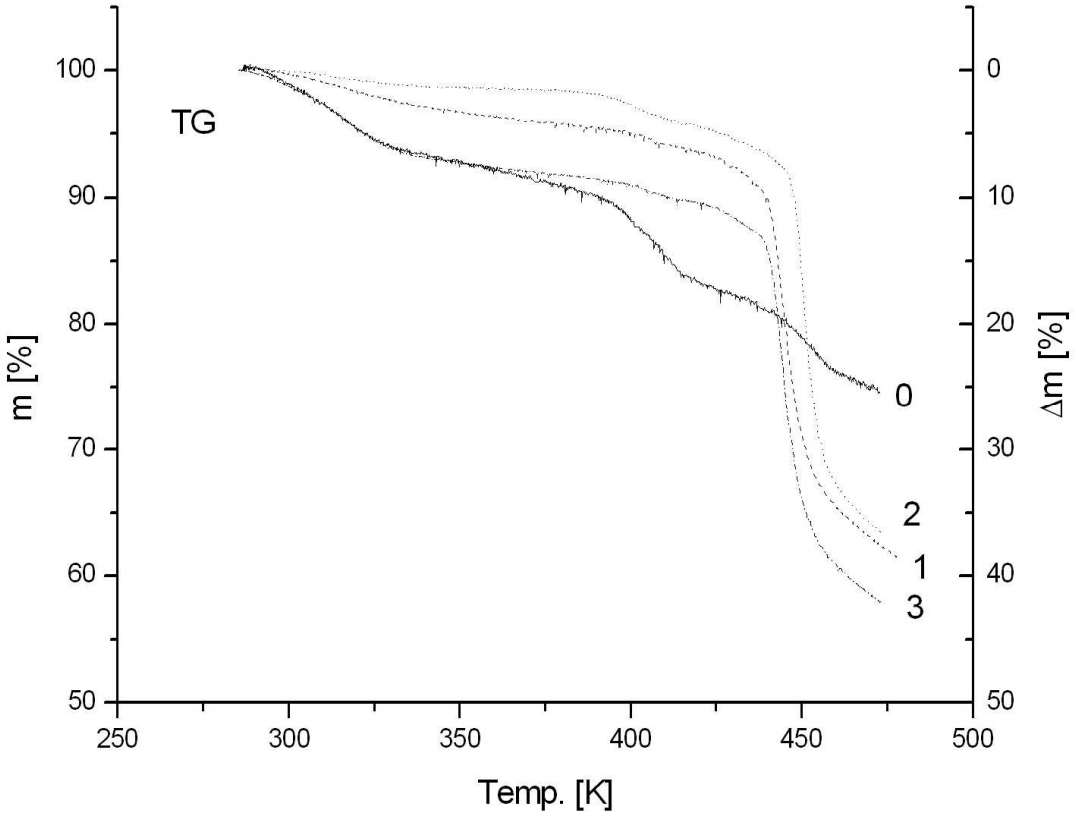


**Figure 3.** TG thermal profiles of: 0 – Mg(Vit$B_6$Arg)-pure substance, 1 – Mg(Vit$B_6$Arg)/SD, 2 – Mg(Vit$B_6$Arg) / SD + PC 45, 3 – Mg(Vit$B_6$Arg) / SD + PVP.

**Table 1.** Results of DSC analysis for solid dispersions in containing magnesium salts

| Formulation | T [K] | ΔH [kJ/mol] |
|---|---|---|
| Mg(Vit$B_6$Arg) Pure substance | 428<br>468 | 106.3<br>108.1 |
| Mg(Vit$B_6$Arg)/SD | 428<br>457<br>464 | 15.7<br>49.6<br>26.3 |
| Mg(Vit$B_6$Arg)/SD+PC 45 | 450<br>462<br>475 | 15.7<br>6.4<br>61.9 |
| Mg(Vit$B_6$Arg)/SD+PVP | 420<br>456 | 26.3<br>93.5 |

Comparison of the course of DTA profiles, for SD containing PVP or PC 45, with the DTA profile, for SD without a carrier, indicates that PC 45 additive slightly changes DTA profile.

In Fig. 2., for SD with PVP, the first endoeffect connected with dehydration of SD appears in the temperature of 334 K. The second endothermic peak is connected with dehydration process in the temperature of 410 K. In temperatures of 430 K and 446 K a wide peak can be observed indicating decomposition of SD. DTA profile for SD with PC 45 shows that endoeffect appears in the temperature of 406 K, connected with the dehydration process. The second endoeffect was observed in the temperature of 445 K, a small endoeffect is seen also in temperature 450 K and it is connected with SD decomposition. The course of DTA in the temperature between 360 K and 470 K for the examined SD is similar. The results show that adding of the PC 45 and PVP in the applied concentration has no influence upon the character of thermodynamic phases.

Thermogravimetry (TG) of the examined solid dispersions shows that during the heating of the samples up to the temperature of 500 K, some loss of mass, connected with decomposition, can be observed (Fig 3). The analysis of TG curves (Fig. 3 profiles of 0) showed that in the temperature range between 300 and 382 K the dehydration process took place for the examined pure substance and dispersion; then the loss of mass weight of 5% - 8% (1.1 –1.7 water mol. on the surface absorbed) was observed. In the temperature range of 430 K to 460 K, the dehydration process for solid dispersion containing $Mg(VitB_6)$ with added PC 45 showed the loss in weight of 25% (6.7 water mol.) and in the case of the solid dispersion with PVP in the temperature range of 425 K to 450 K it was 27.6% (7.7 water mol), respectively.

Addition of PC 45 carrier to SD causes smaller loss of mass which indicates its influence on greater thermal stability of SD. In the case of applying PC 45 we observe greater loss of mass connected with SD dehydration compared with SD with PC 45 and also without additional auxiliary substance.

DSC analysis enabled us to estimate the enthalpy of the process. DSC analysis shows the influence of auxiliary carriers of SD on enthalpy of decomposition process of SD during heating up to the temperature of 500 K (Table 1). In the case of SD with PC 45, the transformation process is connected with the enthalpy value $\Delta H$= 61.9 kJ/mol in the temperature of 475 K,

Meanwhile, for SD with PVP in the temperature of 456 K, the enthalpy value is $\Delta H$= 93.5 kJ/mol. Enthalpy value in thermodynamic transformation process for SD without any additional auxiliary substances is considerably lower in the temperature of 457 K, $\Delta H$= 49.6 kJ/mol and in 464 K, $\Delta H$ = 26.3 kJ/mol.

Comparison of the results of these two methods, DTA and DSC, has shown transition of the endothermic peak to higher values caused by difference in heating speed.

## Partition coefficient

Lipophilic properties of Mg salts were determined by means of partition coefficient of log P. The partition coefficient (log P) for the system of n-octanol/water was determined according to Hansch theory [11]. The calculated values of log P for the examined salts and solid dispersions containing these salts with PC 45 or PVP were presented in Table 2.

**Table 2.** Partition coefficients of magnesium salts for solid dispersions

| | $Mg(VitB_6)$ SD | $Mg(VitB_6Arg)$ SD | $Mg(VitB_6Arg)$ SD+PC45 | $Mg(VitB_6Arg)$ SD+PVP |
|---|---|---|---|---|
| *Log P* | 0.356 | 0.657 | 0.672 | 0.752 |

Analysis of the results showed that introduction of arginine into the molecule of Mg salt influences increase of log P value in comparison with the initial salt. Application of auxiliary substances like PC 45, PVP into SD causes increase of partition coefficient compared with SD without the above substances. As results from the above data addition of PC 45 into SD causes increase by one of 2.28% of log P value and eventually improvement of lipophilic properties of the examined SD. PC 45 is amphothenside which influences hydrophilic-hydrophobic balance and makes permeability of drugs substances by the lipid barrier easier. The obtained results confirm the fact, that some selected auxiliary substances are of great importance for the magnesium salts because they enable permeability of a drug through intestine. PVP activity, similarly to PC 45, influences the increase by one of 14.46 % of the log P values and consequently both of them may affect the salt absorption, due to molecular chemical properties, and formation of hydrogen bonding between the drug substance and those of PVP and PC 45. The correlation between absorption and values of logarithm of the coefficient was observed (r=0.90).

## Absorption process of $Mg^{2+}$ ions in vitro

Mean values of pharmacokinetic parameters obtained for the Mg salts were presented in Table 3.

As it can be seen, the absorption rate constant of $Mg^{2+}$ ions was the highest for magnesium connected with ($VitB_6Arg$) anion ($k=3.701\ 10^{-3}$), contrary to one with $Mg(VitB_6)$ absorption rate constant of $Mg^{2+}$ion ($k=3.278\ 10^{-3}$). Based on the analysis of the study results connected with degree of Mg absorption from the studied salts in vitro model of the positive influence of amino acid ligand on transportation of $Mg^{2+}$ ions was shown. Increase in amount of the absorbed Mg after two hours continuation of the experiment was found both in the case of $Mg(VitB_6Arg)$ 38% and in the case of $Mg(VitB_6)$ 30%. It was proved that the arginine anion added into the structure of the molecule of $Mg(VitB_6)$ had an effect on increase of lipophilicity of the compound and on permeability through the cell membrane. It may also indicate various intramolecular reactions like donor-acceptor reaction and hydrogen bonding.

**Table 3.** Parameters describing $Mg^{2+}$ ions absorption from magnesium salts, for solid dispersions.

| Compounds | K ($min^{-1}$) | $t_{50\%}$ (min) | Total Mg (%) | SD | W (%) |
|---|---|---|---|---|---|
| $Mg(VitB_6)$ | $3.278\ 10^{-3}$ | 211.44 | 30.45 | 0.20 | 0.65 |
| $Mg(VitB_6Arg)$ | $3.701\ 10^{-3}$ | 187.25 | 38.77 | 0.01 | 0.025 |

## Statistic analysis

Statistic analysis of parameters of the constant speed of absorption and partial time of $t_{50\%}$ showed that introduction of the additional ligand into the structure of the initial compound had some influence on fast diffusion of the salts through intestine. These differences were of significant statistic value ($p< 0.05$).

## Conclusions

IR spectra suggested that a weak interaction between PC 45, PVP and Mg(Vit$B_6$Arg), probably created the hydrogen bond. Auxiliary substances, like PC 45 and PVP, introduced into solid dispersion in the form of SD granules containing the examined magnesium salts proved to be good carriers of $Mg^{2+}$ ions.

It is the most probable that the increased water dissolution of magnesium compound is dispersed in hydrophilic PVP and PC 45 matrix.

The enhancement of absorption process of $Mg^{2+}$ ions, by using the solid dispersions examined in this study, was thought to be due to the different factors including the drug solubilization effect and the increase of drug permeability through the intestine. The authors of the paper found that the absorption process of $Mg^{2+}$ ions in solid dispersions depended upon the physicochemical properties of magnesium salts and log P. Therefore, this system might be applied to formulate solid dosage forms of these salts. The choice of the selected carriers to produce solid dispersions was an essential factor which significantly influenced pharmaceutical availability of the drug substance.

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