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INFLUENCE OF SELECTED AUXILIARY SUBSTANCES ON SOME PHYSICOCHEMICAL PROPERTIES OF SOLID DISPERSIONS CONTAINING MAGNESIUM SALTS

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Abstract: In this survey magnesium salts in the form of solid dispersions were studied to examine the interaction of the drug and lecithin or Tego^R Betain L–7. The results of thermal analysis of solid dispersions containing magnesium adipate Mg[Adip] and compounds of this salt with glycine substituent, and the partition coefficient (logP) of this salts applied for solid dispersion, have been presented in this paper. Lecithin (45% phosphatidylcholine) or Tego^R Betain L–7 (30% solution of amide betaine) have been added to magnesium salts to obtain a solid dispersion. The influence of auxiliary substances: Tego^R Betain L–7 and lecithin on physicochemical properties of the examined preparations has been assessed. The results of thermal analysis (DTA, DSC, TG) of magnesium complexes indicated their good thermal resistance up to the temperature of 375 K.

Keywords: solid dispersion; magnesium organic salts; lecithin; Tego^R Betain L–7; coefficient

Magnesium ion belongs to the basic cations conditioning proper functions of the human organism (1–3). Magnesium preparations are applied not only to supplementary therapy of numerous illnesses related to magnesium deficit but also in prophylaxis. This invaluable element is commonly used in pharmaceutical preparations both as inorganic: (oxide, chloride, sulphide) and organic compounds such as: aspartate, gluconate, citrate. For oral formulations organic magnesium compounds seem to be the best because of their best absorption and the least side effects (4–6). Searching for new magnesium compounds of better therapeutic properties inspired the research into new magnesium preparations (7,8). In this report, lecithin (45% phosphatidylocholine) or Tego^R Betain L–7 (30% solution of amide betaine) were added to a magnesium salt in order to obtain solid dispersions. Both phosphatidylcholine and amide betaines have hydrophilic and hydrophobic parts (9).

These substances are good carriers of drugs. The research carried out on bioavailability of Mg ions from the solid dispersion containing magnesium salts – phospatidylcholine or magnesium salts–Tego ^{R}Betain L–7 showed a positive influence of the above mentioned auxiliary substances. While continuing research on optimalization of drug form with Mg salts it seems purposeful to make analysis of thermal properties of the systems.

In the process of drug permeability through the membrane, the biologically significant parameter is logP, partition coefficient which determines lipophilicity. This parameter indicates the degree of drug distribution in the organism.

Therefore, the properties of solid dispersions would be effected by these two factors. The first is the drug affinity to the hydrophilic and hydrophobic parts of phosphatidylcholine, while the second is that phosphatidylcholine and drugs interacting through a hydrogen bond (10,11).

This paper describes an interesting topic from the pharmaceutical point of view because bioavailability of magnesium is very important for the human health. The numerous studies were undertaken in order to elucidate the properties of organic and inorganic magnesium compounds. This paper is a continuation of them. This work reports about solid dispersions of magnesium salts – lecithin or of magnesium salts–Tego^R Betain L–7 and their effect on the physicochemical properties.

The thermal decomposition of magnesium complexes has been studied by M. Neantu et al. (12). The practical application of thermoanalytical methods in the composition control of solid and soft drug formulations have been studied by Wesołowski (13) and Izutsu (14). The thermal resistance of solid medicines is very important for the optimisation of technological production process and can be characterised by parameters of DTA, DSC, TG

curves. M.Fujii et al. (15) examined the dispersion system containing benzodiazepins with phosphatidylcholine.

There is still no data available concerning the influence of application of Tego^R Betain L–7 (30% solution amide betaine) and lecithin (45%–phosphatidylcholine) on thermal properties of dispersional systems with magnesium salts. Evaluation of possibilites for introducing the auxiliary substances under examination of the process of final forming of the drug was presented in this paper.

EXPERIMENTAL

Materials

The solid dispersions contained: adipate magnesium Mg[Adip] (288.8 mgMg^{2+}/23.7 mEq/100 g product), adipate–glycinate magnesium Mg[Adip–Gly] (199.8 mg Mg^{2+}/16.4 mEq/100g product) with 1% and 1.5% Tego^{R}BetainL–7(30% solution of amide betaine–Goldschmidt AG), adipate–glycinate magnesium Mg[Adip–Gly] (199.8 mgMg^{2+}/16.4 mEq/100 g product) with 1% lecithin (45% phosphatidylcholine–Mayer Hamburg). They were prepared by a simple granulation of micronized magnesium salts mixed with lactose, sucrose (2:1:1w.w.) and with ethanol, added later. The solvent was evaporated *in vacuo*. The components lecithin or Tego^R Betain L–7 were added at a concentration of 1% or 1.5% of the solid dispersion.

Methods

Thermogravimetry was carried out in air using a Paulik–Paulik–Erdey (MOM, Budapest) Derivatograph. The samples of powder weighing 80–326 mg were analysed. Decomposition was carried out in platinum crucibles at a rate of 2.5 deg/min up to 500 K using α–Al_2O_3 as standard material. Differential scanning calorimetry (DSC) was used for analysis. Measurements were performed using a Perkin Elmer DSC–7. Samples weight was 0.5–10 mg. They were heated at a rate of 20 deg/min in a dynamic nitrogen atmosphere, according to the Pyris Elmer program. All experiments were done in triplicate.

Partition coefficient: The partition coefficient was determined according to the Hansch theory (16).

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 determined by ultraviolet (UV) absorption. Data were shown as the mean of three experiments.

RESULTS AND DISCUSSION

Results are shown in Tables 1–2 and in Figures 1–3. The analysis of DTA curve provided information about the character of reactions proceeding in the process of thermal decomposition of the examined compounds. The reactions of dehydration and destruction gave endothermic peaks. The process of sample decomposition was registered up to the temperature of 500 K. The DTA curves (1,2) analyses in Figure 1 showed that modification of the Mg[Adip] particle structure by introducinig aminoacid of glycine influences the change of stability of this compound. At a temperature of about 380K of the modified compound an endothermic peak can be observed while in the case of the basic structure of Mg[Adip], the endothermic phase occurs at a temperature of above 420 K. The temperatures of the beginning and the extreme point are slightly shifted to lower values. The analysis of DTA curves (3,3') in Figure 1 showed that powdered substance of solid dispersion has no influence on the thermodynamic phase characteristics.

The presented results of derivatographic measurements show that adding of the auxiliary sub-

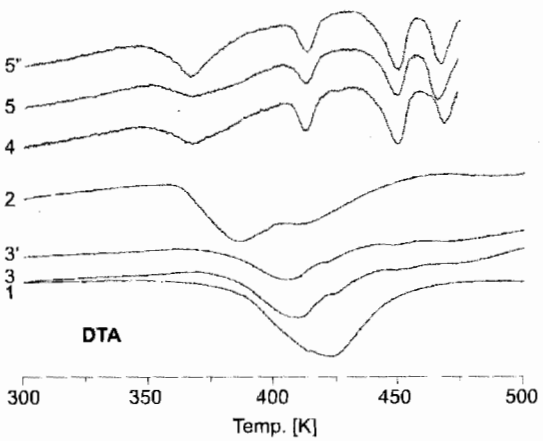

Figure 1. DTA curves of the thermal decomposition:
1. of Mg [Adip] substance
2. of Mg[Adip–Gly] substance
3. of solid dispersion with Mg[Adip–Gly]
3'. of solid dispersion with Mg[Adip–Gly] (powdered substance)
4 of solid dispersion with Mg[Adip–Gly] + 1% lecithin
5. of solid dispersion with Mg[Adip–Gly] + 1% Tego^R Betain L–7
5'. of solid dispersion with Mg[Adip–Gly] + 1.5% Tego^R Betain L–7

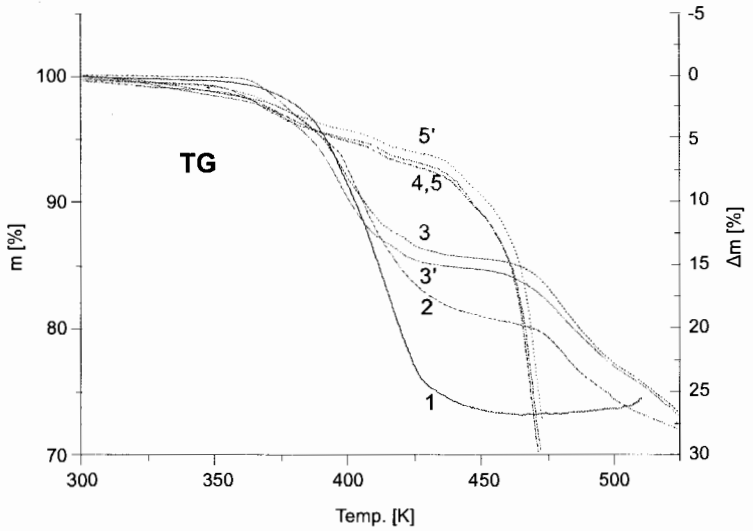

Figure 2. TG curves of thermal decomposition:
1. of Mg[Adip] substance
2. of Mg[Adip–Gly] substance
3. of solid dispersion with Mg [Adip–Gly]
3'. of solid dispersion with Mg[Adip–Gly] (powdered substance)
4. of solid dispersion with Mg[Adip–Gly]+ 1% lecithin
5. of solid dispersion with Mg[Adip–Gly] + 1% Tego^R Betain L–7
5'. of solid dispersion with Mg[Adip–Gly] + 1.5% Tego^R Betain L–7

stances in the applied concentration has no influence upon the character of thermodynamic phases. Accordingly, it seems that in this case the decomposition was practically the result of the same partial reactions and their mechanisms between the courses were also similar. It can, therefore be concluded that these two substances may be used together in drug formulations.

Comparing the curves (4,5,5') in Figure 1, it is seen that in the case of application of the surface acting substance Tego^R Betain L–7 at a 1.5% concentration the endothermic peak at a temperature of 367 K is deeper. In the case of addition of the Tego^R Betain L–7 at a 1% concentration, the endopeak at the same temperature is shallow. The peak area of the effect is proportional to the concentration of the auxiliary substance.

The results of TG analysis are in agreement with the DTA curves (Figures 1 and 2).

The analysis of TG curves (1,2) in Figure 2 showed that in the temperature range of 367 K to 460 K the dehydration process takes place for Mg[Adip], then the loss of mass weight of 25 % (3 water mole) was observed. However in the case of Mg[Adip–Gly] in the temperature range 358 K – 458 K the loss of mass weight was equal to 20% (3.8 water mol). Comparing TG curves (3,3') in Figure 2, a great similarity is shown. In the temperature range between 360 K – 457 K, the dehydration process for solid dispersion with Mg[Adip–Gly], the loss in weight of 15% (2.4 water mol) and in the case of the solid dispersion (powdered substance) with the modified salt of 16.5% (2.7 water mole) were observed.

Table 1. Results of the thermal analysis DSC of solid dispersions containing magnesium salts

Solid dispersion	DSC peak T [K]	ΔH[kJ/mole]
Mg[Adip]	400 424 461	39.62 2.76 2.44
Mg[Adip–Gly]	377 397 426 474	24.37 41.84 2.89 1.94
Mg[Adip–Gly] + lecithin.	424 461	1.83 10.33
Mg[Adip–Gly] + Tego^R Betain L7	406 423 460	1.91 4.21 8.37

Table 2. Results of the partition coefficients of magnesium salts for solid dispersions and substance

	Mg[Adip] substance	Mg[Adip–Gly] substance	Mg[Adip–Gly] solid dispersion	Mg[Adip–Gly] + Tego^R Betaine L–7 solid dispersion	Mg[Adip–Gly] + lecithin solid dispersion
log P	0.487	0.810	0.642	0.562	0.346

TG analysis reflects the influence of the applied substances Tego^R Betain L–7 and lecithin on the characteristics of these curves and on the process of thermal decomposition of solid dispersion.

To assess thermal resistance of samples, the TG curves were taken into consideration. The percentage of mass decrease was also determined (Figure 2).

The processes of sample decomposition up to the temperature of 500 K (Figure 2, curves–1,2,3,3') of solid dispersion with Mg[Adip–Gly] and substance: Mg[Adip] and Mg[Adip–Gly] but to 475 K (Figure 2, curves–4,5,5') for the solid dispersion containing Mg[Adip–Gly] with the auxiliary substances were conducted. DTA analysis of the examined systems showed that on increasing concentration of the auxiliary substance and application of mechanical stress (powdering) no significant influence upon their thermal properties was observed. That is why the systems were not examined in DSC analysis.

Differential Scanning Calorimetry (DSC) enabled us to estimate the enthalpy of the process. DSC curve analysis showed a significant influence of selected auxiliary substance on the transformation value. This is shown in the data compiled in Table 1 and Figure 3. The enthalpy values are corresponding to the characteristic peaks of each compound. However, their shape is very similar to the curves of the decomposition of solid dispersions. This is due to similar properties of the components of the matrix of solid dispersion. The DSC analysis curves showed that at a temperature of 400 K the endothermic peak is connected with dehydration of Mg[Adip], while the heat value of

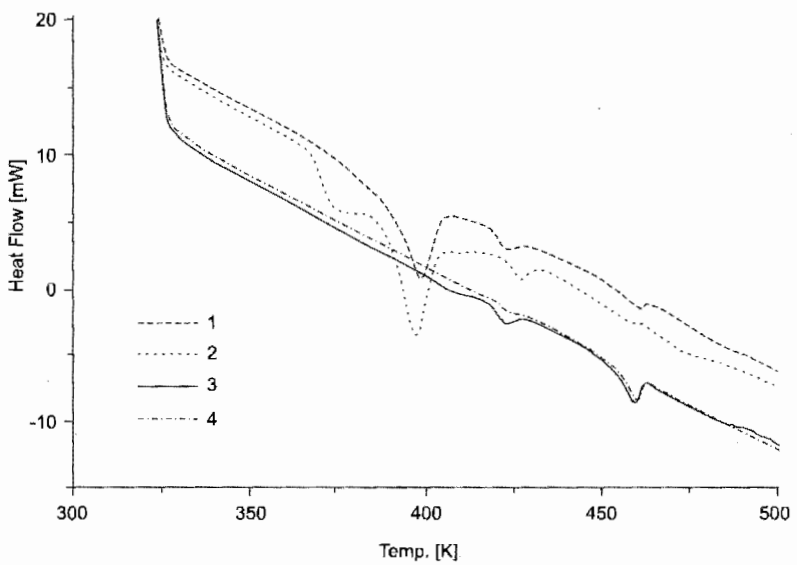

Figure 3. DSC curves of the thermal decomposition:
1. of solid dispersion with Mg[Adip]
2. of solid dispersion with Mg[Adip–Gly]
3. of solid dispersion with Mg[Adip–Gly] + 1% Tego^R Betain L–7
4. of solid dispersion with Mg[Adip–Gly] + 1% lecithin.

such transformation is equal to ΔH=39.62 kJ/mole. At a temperature of 461 K a small endothermic peak is observed which is connected with the compound decomposition value of ΔH=2.44 kJ/mol. In the case of a salt modified with glycine Mg[Adip–Gly], the first endothermic effect at 377 K shows dehydration process of the salt on the surface of which water was absorbed. At 397 K another endothermic peak is observed which is connected with the dehydration process value of ΔH=41.84 kJ/mole. Introduction of the aminoacid anion into the Mg[Adip] molecule slightly influences thermal properties of the magnesium salt.

Analysis of DSC thermogram shows that the auxiliary substances used do not cause additional thermal effects (Figure 3). Comparison of DSC curves shows that addition of the substances Tego^{R}Betain L–7 and lecithin influences the change of the first thermodynamic phase and decreases the enthalpy connected with them.

As a result of this research, it was found that adding lecithin to magnesium salts slightly lowered the temperature of transformation. Results of the analysis of DSC curves, shown in Figure 3, indicate that auxiliary substances can be used for their further application. At a temperature of 424 K the solid dispersion of lecithin and magnesium salts of thermal decomposition were observed.

Comparison of the results of these two methods, DTA and DSC, has shown the move of the endothermic peak to the higher values, which is caused by the difference in heating speed. DTA and DSC are very useful analytical tools during the prediction of physicochemical incompatibility (13).

Introducing of a ligand into the structure of the examined compounds induces a change of physicochemical properties. In Table 2 the results are shown of the measurements of the partition coefficient (logP) values for the examined magnesium salts contained in the solid dispersion. Logarithm of the partition coefficient between n–octanol and water phase was higher for a solid dispersion with Tego^R Betaine L–7 (1.5% concentration), (log P= 0.562) than for this same salt with lecithin (log P=0.346).

The obtained results would be compatible with the above considerations. So, it is considered that the chemical structure is an important factor of the formation of solid dispersion.

CONCLUSIONS

1. The modification of magnesium salt with aminoacid substituent influences its physicochemical properties.

2. The use of Tego^{R}Betain L–7 (30% solution amide betaine) and lecithin (45% phosphatidylcholine) in solid dispersions causes a decrease of transformation temperature, slightly influences the value ΔH.

3. The above auxiliary substances can be applied in the solid dispersions, they have an influence on logP.

4. The addition of Tego^R Betain L–7 (30% solution amide betaine) to the solid dispersion is more adventageous than the additation of lecithin (45% phospatidylcholine).

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