

ORIGINAL ARTICLE

Investigation of thioctic acid, magnesium stearate and pyridoxine hydrochloride compatibility

Výzkum kompatibility kyseliny thioktové, magnesium-stearátu a pyridoxin-hydrochloridu

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Received October 7, 2019 / Accepted Januar 15, 2020

Summary

To identify possible interactions of components in dosage forms, studies are usually carried out at the stage of pharmaceutical development. Such studies can predict compatibility of active pharmaceutical ingredients and excipients in order to optimize drug formulation and certain parameters of technological process. Compatibility of some components of a newly developed neuroprotective medicinal product ‘Neuronucleos’, namely, thioctic acid, pyridoxine hydrochloride, magnesium stearate and magnesium lactate, was studied by means of differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR). No interactions were observed between thioctic acid and pyridoxine hydrochloride. Formation of an intermolecular complex between thioctic acid and magnesium stearate was established, in which this acid substitutes the crystalline water of magnesium stearate. No significant interactions were found for magnesium lactate with thioctic acid or magnesium stearate. Thus, pharmaceutical compatibility of the most of the tested ‘Neuronucleos’ components was studied and established, with the only exception (thioctic acid with magnesium stearate). Moreover, the present study provides valuable information about thermal effects in a certain temperature range, which is important for setting the technological process parameters.

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Key words: pharmaceutical compatibility • thioctic acid • pyridoxine hydrochloride • magnesium stearate • differential scanning calorimetry • IR-spectroscopy

Souhrn

Pro identifikaci možných interakcí složek v lékových formách se studie obvykle provádějí ve stadiu farmaceutického vývoje. Takové studie mohou předpovídat kompatibilitu aktivních farmaceutických látek a pomocných látek za účelem optimalizace složení přípravku a vhodného nastavení parametrů technologického postupu. Vzájemná kompatibilita některých složek nově vyvinutého neuroprotektivního léčivého přípravku „Neuronukleos“, konkrétně kyseliny thioktové, pyridoxin-hydrochloridu, magnesium-stearátu a magnesium-laktátu, byla studována pomocí diferenciatní skenovací kalorimetrie (DSC) a infračervené spektroskopie s Fourierovou transformací (FTIR). Žádné interakce mezi kyselinou thioktovou a pyridoxin-hydrochloridem nebyly pozorovány. Byl vytvořen intermolekulární komplex kyseliny thioktové a magnesium-stearátu, ve které kyselina thioktová nahrazuje krystalickou vodu magnesium-stearátu. Pro magnesium-laktát nebyly nalezeny žádné významné interakce ani s kyselinou thioktovou ani magnesium-stearátem. V rámci této studie byla prokázána farmaceutická kompatibilita většiny testovaných složek přípravku „Neuronukleos“ s jedinou výjimkou (kyselina thioktová a magnesium-stearát). Předkládaná studie navíc poskytuje hodnotné informace o tepelných jevech v určitém teplotním rozmezí, což je důležité pro nastavení parametrů technologického procesu.

Klíčová slova: farmaceutická kompatibilita • kyselina thioktová • hydrochlorid pyridoxinu • stearát hořečnatý • diferenciatní skenovací kalorimetrie • IR-spektroskopie

Introduction

Studies of components compatibility in combined dosage forms are an important stage in pharmaceutical

development because physico-chemical interactions are possible between some components. As a result of incompatibility, changes in a medicinal product appearance and increase of impurities level may take place. Therefore, the compatibility study at the stage of pharmaceutical development can reveal significant interactions between the components of a dosage form that could adversely affect stability and efficacy of this dosage form.

Calorimetric techniques are considered to be among the basic in the field of pharmaceutical compatibility investigations¹. Deformations or disappearance of characteristic calorimetric peaks in a mechanical mixture of substances serves as incompatibility markers. Molar ratios of components in such mixtures are generally chosen as 1 : 1 or as the corresponding mass ratio in the dosage form^{1,2}.

The compatibility studies were carried out during pharmaceutical development of a new combined medicinal product in capsules, which was notionally named 'Neuronucleos'. The medicinal product formulation was developed on the basis of literature data and our own experimental experience. The developed medicinal product is recommended for treatment of disorders of the peripheral nervous system that are symptoms of osteoarticular, metabolic and infectious diseases. The medicinal product formulation includes uridine-5-monophosphate disodium salt and cytidine-5-monophosphate disodium salt, as well as other active pharmaceutical ingredients, *viz* pyridoxine hydrochloride, thioctic acid and magnesium lactate dihydrate, which enhance the effect of the former ones. Silica and magnesium stearate were chosen as excipients. It should be noted that a medicinal product with a similar performance under the name Nucleo CMP forte (Ferrer International S.A., Spain) is widely administered in Europe.

In order to obtain a medicinal product of appropriate quality containing thioctic acid, compatibility data were required for this acid as the most sensitive active substance of the dosage form. In the present work the experimental data are collected concerning the compatibility of thioctic acid (TA), pyridoxine hydrochloride (PH), magnesium stearate (MgSt) and magnesium lactate dihydrate (MgLac).

Materials and methods

Several components of the capsules 'Neuronucleos' were examined. Among these components were thioctic acid (TA) (Shanghai Modern Pharmaceuticals, China, batch 1104001 A); pyridoxine hydrochloride (PH) (DSM Nutritional Products GmbH, Germany, batch UQ 11113337); magnesium lactate dihydrate (MgLac) (Moec Cantabria, Spain, batch 2327), and magnesium stearate (MgSt) (Calmags GmbH, Germany, batch 02021011). MgSt (Magnesia, Germany, batch 15000959/0) was additionally used to obtain the binary phase diagram of MgSt : TA. All the components were of pharmacopeia grade.

The compatibility studies were performed by means of differential scanning calorimetry (DSC) using a Mettler DSC 1 microcalorimeter (Mettler Toledo). To obtain DSC thermograms, 4 to 7 mg of a sample were placed into a standard 40 μ l aluminum crucible with a perforated lid (additionally, a 0.3 mg sample of MgSt was used, which corresponds to the MgSt amount in the sample of TA : MgSt mixture). Thermal scanning was carried out in the air atmosphere within the temperature range of 0 to 150 $^{\circ}$ C at the scanning rate of 5 $^{\circ}$ C/min. Original DSC thermograms were plotted as heat flow (mW) *vs.* sample temperature ($^{\circ}$ C). Normalized DSC thermograms are also used, where the original values of heat flow are normalized by the TA mass (W/g). The processing of the obtained DSC thermograms (determination of DSC peaks maxima, peak normalization, etc.) was performed using the original STARE SW 11.00 software of the microcalorimeter. Experimental error of the determination of peak temperatures was 0.3 $^{\circ}$ C.

Thermal stability studies of TA were performed by thermogravimetric analysis (TGA) using the TG 10 A block of the Mettler TA 3000 thermoanalytical system. For TGA studies, about 7 mg of the sample were placed into a 70 μ l aluminum oxide crucible without a lid. Thermal scanning was carried out in the air atmosphere within the temperature range of 30 to 250 $^{\circ}$ C at the scanning rate of 5 $^{\circ}$ C/min. TGA curves were plotted as sample mass (percents of the initial value) *vs.* sample temperature. Experimental error of sample mass determination was 0.1 mg.

Fourier-transform infrared (FTIR) spectra were obtained using a Spectrum One spectrophotometer (Perkin-Elmer). The samples were placed between ZnSe plates by 'crushed drop' technique and examined in the range of 4000 to 400 cm^{-1} at room temperature. The original FTIR spectra were obtained in the values of optical transmission and then they were recalculated

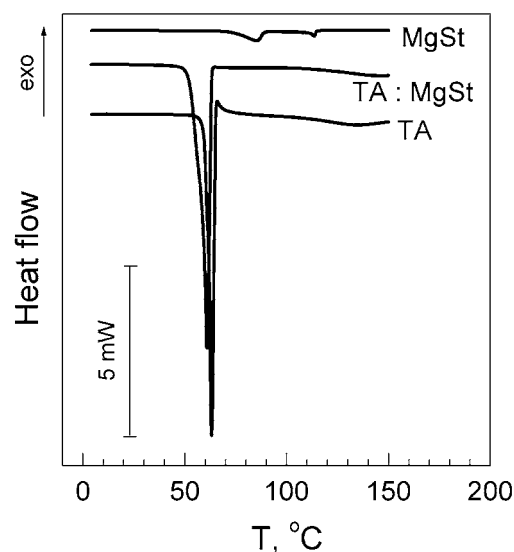


Fig. 1. Original DSC thermograms of individual TA, MgSt and mixture TA : MgSt 20 : 1 by mass

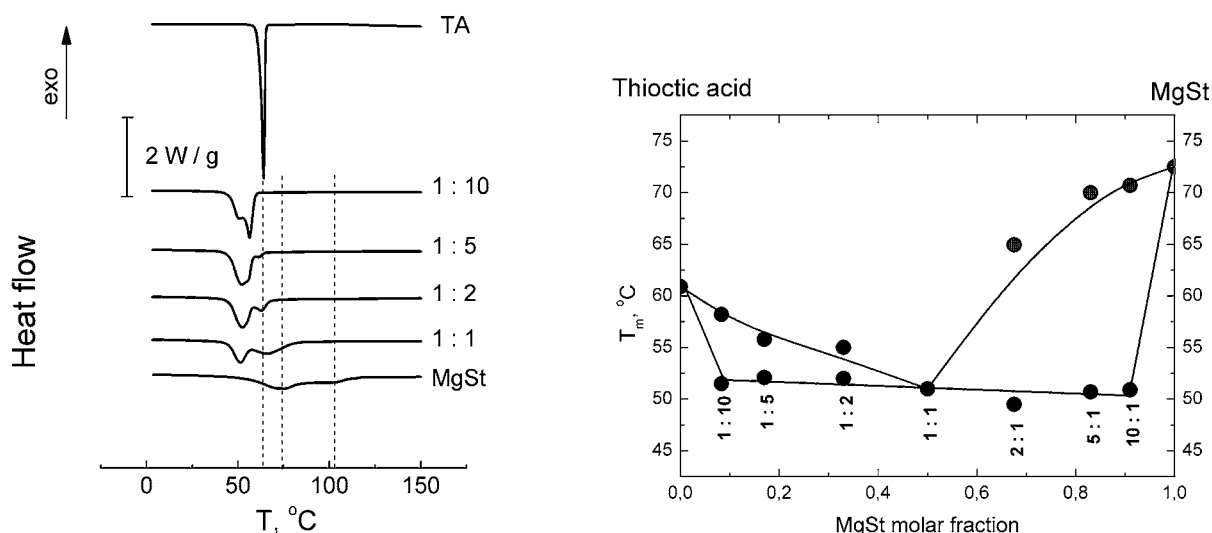


Fig. 2. a) Normalized DSC thermograms of TA-MgSt mixtures (vertical lines are plotted to trace the characteristic peaks of TA and MgSt); b) binary phase diagram of TA-MgSt melting. MgSt : TA molar ratios are indicated beneath the experimental points

into the values of absorbance with subtraction of the baseline (absorption of the ZnSe plates). Experimental error of wavelength values was 1 cm^{-1} .

Results and discussion

The results of the TA and MgSt compatibility studies are shown in Figure 1. As it can be seen, the DSC thermogram of TA contains a single endothermic peak with the maximum about $60.9 \text{ }^\circ\text{C}$, which originates from TA melting³. The DSC thermogram of MgSt contains two characteristic endothermic peaks. The first one ($98.0 \text{ }^\circ\text{C}$) corresponds to elimination of crystallization water, and the second one ($112.7 \text{ }^\circ\text{C}$) is related to MgSt melting⁴. It should be underlined that both peaks are clearly distinguished in DSC thermograms of MgSt samples of 0.3 mg weight, which corresponds to MgSt amount in the sample of TA : MgSt mixture (Fig. 1, upper curve). The weight loss of the MgSt samples after heating was about $6 \text{ } \%$ w/w. Basing on this value, crystallization water content was estimated as 2.0 mol/mol . This indicates that the tested substance is MgSt dihydrate, which is considered to be the optimal for the use as an excipient⁵.

In the mixture TA : MgSt (Fig. 1, middle curve) the peak of TA melting decreases by $2.2 \text{ }^\circ\text{C}$ and becomes smeared, whereas both characteristic MgSt peaks are absent. It could indicate incompatibility of TA and MgSt¹. A possible reason of such incompatibility is the formation of a complex between these components, which involves both the polar and non-polar parts of the MgSt molecule.

The disappearance of MgSt peaks in TA : MgSt mixtures with various MgSt content is shown in Figure 2a. The whole binary phase diagram of TA : MgSt melting is presented in Figure 2b. The shape of the diagram clearly suggests the formation of eutectic TA : MgSt mixture with $1 : 1$ stoichiometry.

The absence of the DSC peak of MgSt dehydration in TA : MgSt mixture (Fig. 1) may result from two possible mechanisms: (1) substitution of crystalline water in MgSt by TA; (2) formation of water bridges between TA and MgSt. In order to clarify this matter, FTIR spectra were obtained for the individual substances and for their mixture (Fig. 3). The absorption band at $\sim 3400 \text{ cm}^{-1}$ corresponding to valence vibrations of OH groups in water molecules served as a characteristic marker of water content. This band is inherent to the MgSt spectrum and evidently corresponds to the crystalline water. The band disappears in the mixture, so it can be assumed that dehydration of MgSt occurs in the presence of TA. This hypothesis is supported by comparing the MgSt spectra in the initial state and after drying ($70 \text{ }^\circ\text{C}$, 30 min). After MgSt drying, the sample mass was

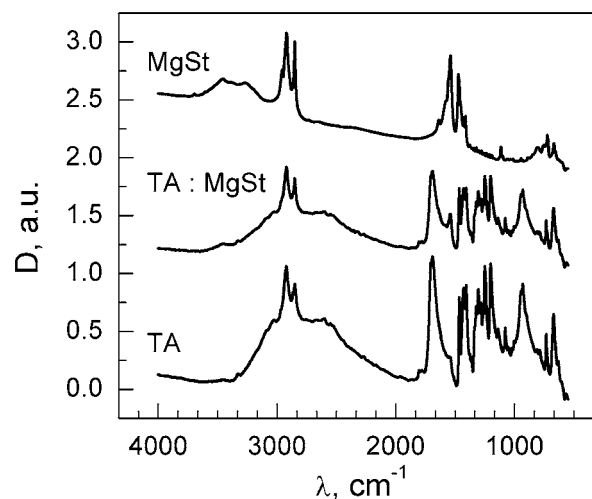


Fig. 3. FTIR spectra of MgSt, TA and their mixtures $20 : 1$ (w/w)

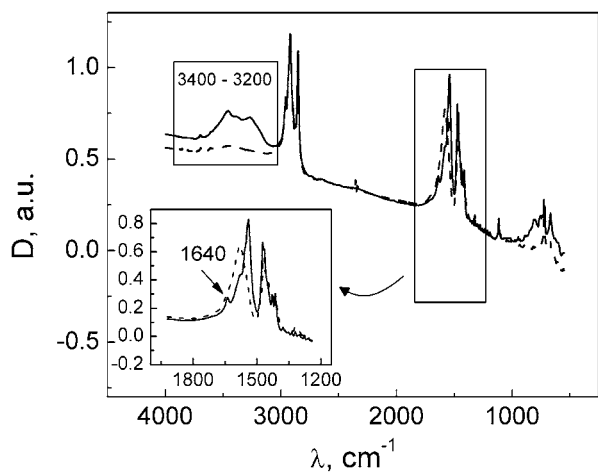


Fig. 4. FTIR spectra of MgSt in the initial state (solid line) and after drying (dashed line)

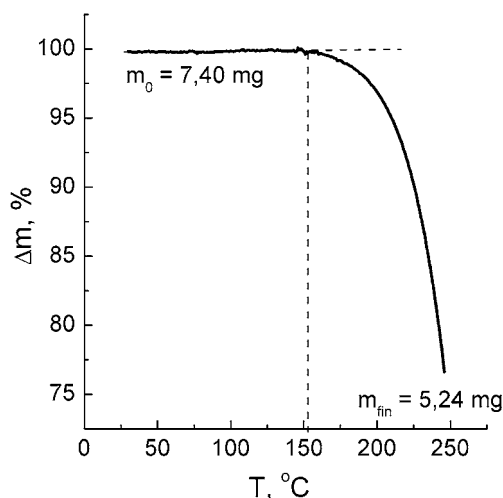


Fig. 5. TGA curve of TA sample. The dotted lines are plotted to show the limit of thermal stability of the TA. The values of initial and final sample mass (m_0 and m_{fin} , respectively) are indicated.

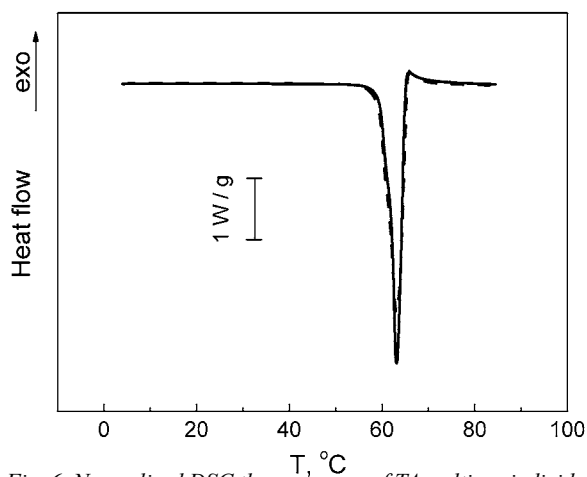


Fig. 6. Normalized DSC thermograms of TA melting: individual TA (solid line); mixture TA : PH 2 : 1 (w/w) (dashed line)

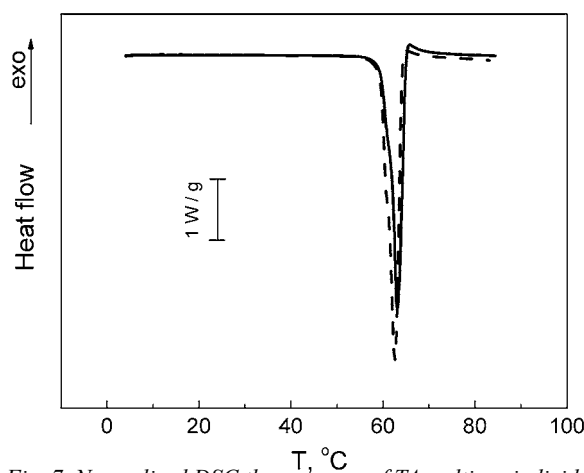


Fig. 7. Normalized DSC thermogram of TA melting: individual TA (solid line); mixture TA : MgLac 1 : 4 (w/w) (dashed line)

decreased by 4% w/w, and the characteristic band at $\sim 3400\text{ cm}^{-1}$ almost disappeared (Fig. 4). Similar changes were observed for another characteristic water absorption band, about 1640 cm^{-1} , which corresponds to the librational vibrations of OH groups. Thus, FTIR data prove the complex formation of TA with MgSt, where TA substitutes the MgSt crystalline water. It should be noted that MgSt is generally characterized by high ability for complex formation with a number of active pharmaceutical ingredients, but this fact is usually neglected considering a low MgSt content in dosage forms^{1, 6-8}).

The investigation of TA and PH compatibility requested a preliminary examination of TA thermal stability because the melting point of PH is 207 °C . As it was established by the TGA technique, TA is stable up to 150 °C under the given thermal regime (Fig. 5). Above 150 °C , a rapid weight loss of the sample takes place indicating thermal destruction of TA. Therefore,

heating of the TA : PH mixture to the temperature of PH melting point seems inappropriate.

Taking into account the above finding, the investigation of TA : PH mixture was carried out in the temperature range of 0 to 90 °C , which only contained the melting peak of TA. DSC thermograms for TA and TA : PH mixture coincides within the experimental error (Fig. 6), thereby the absence of TA and PH interaction in the studied mixture could be asserted.

No notable interactions could be observed for other combinations of the compounds studied. As can be seen from Figure 7, the melting peak of TA is decreased by 0.5 °C in the TA : MgLac mixture. In the mixture of MgSt : MgLac, the dehydration peak of MgSt decreases by 1.5 °C , while the melting MgSt peak remains unchanged (Fig. 8). To our mind, it rather reflects minor restructuring of hydrogen bonds of MgSt crystallization water than significant intermolecular interactions between the components. The temperatures

Table 1. The maxima of calorimetric peaks of the individual components and their mixtures : melting temperatures (T_m) and dehydration temperature (T_{dh}) of the corresponding substances

| Components | T_m (TA), °C | T_m (MgSt), °C | T_{dh} (MgSt), °C |
|------------------------------|----------------|------------------|---------------------|
| TA | 63.1 | | |
| TA : PH 2 : 1 (w/w) | 63.1 | | |
| TA : MgSt 20 : 1 (w/w) | 60.9 | no peak | no peak |
| TA : MgLac 1 : 4 (w/w) | 62.6 | | |
| MgSt | | 112.5 | 98.0 |
| MgSt : MgLac 1 : 1 (mol/mol) | | 112.5 | 96.4 |

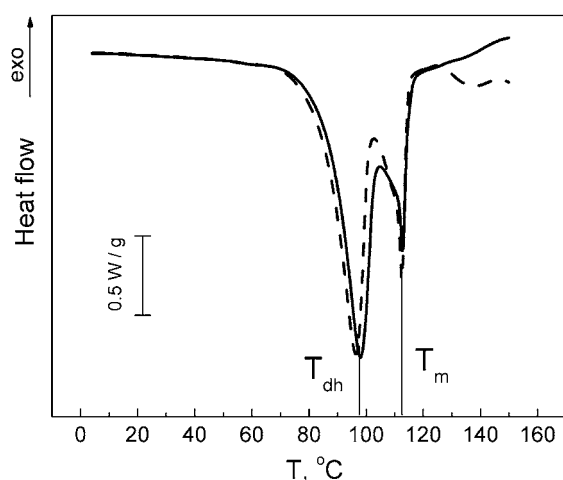


Fig. 8. Normalized DSC thermograms of MgSt (solid line) and MgSt : MgLac (dashed line). The vertical lines indicate the dehydration temperature (T_{dh}) and the melting temperature (T_m) of MgSt.

of the calorimetric peaks observed in all the tested systems are presented in Table 1.

Conclusions

The pharmaceutical compatibility between some components of the capsules ‘Neuronucleos’ (thioctic acid, pyridoxine hydrochloride, magnesium stearate dihydrate and magnesium lactate dihydrate) was studied using differential scanning calorimetry, thermogravimetry, and Fourier-IR spectroscopy techniques. No interactions were found between thioctic acid and pyridoxine hydrochloride. A complex formation between thioctic acid and magnesium stearate was established, in which thioctic acid substitutes the crystalline water of magnesium stearate. No significant interactions were found for magnesium lactate with thioctic acid and magnesium stearate. Thus, pharmaceutical compatibility of the tested ‘Neuronucleos’ components was established, with exception of thioctic acid interaction with magnesium stearate. The obtained results were used in the technology

development of the combined medicinal product in the capsules ‘Neuronucleos’.

Conflict of interest: none.

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