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SCREENING OF POTENTIAL NEW SOLID FORMS OF VITAMIN B1 WITH VITAMIN B3

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ABSTRACT. The present study aimed to obtain new solid forms between Vitamin B1 (thiamine hydrochloride) and Vitamin B3 (nicotinamide) following the mechanochemistry route. The samples prepared by grinding in different solvents, of thiamine hydrochloride with nicotinamide in 1:1 and 1:2 molar ratios were investigated by X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR). The XRD and FTIR results point out that for the chosen ratios of components and for the aqueous ethanol solution and for ethyl acetate used as solvents, none solid forms were obtained, but only physical mixtures. For the sample with1:2 molar ratio of B1:B3, the FTIR analysis reveals very small changes of few absorption bands consisting in a weak shift towards higher wavenumbers, due to grinding process.

Keywords: *thiamine hydrocloride; nicotinamide; mechanochemistry; XRD; FTIR.*

INTRODUCTION

Mechanochemistry is a method that uses mechanical force to initiate chemical reactions. A popular tool choice amongst mechanochemical researchers is the ball mill (BM), which also is used for forcing bulky molecules to react [1]. Solvent-drop grinding is an effective screening tool, that requires small amount of solvent, and gives often the possibility of create new co-crystals, which are not traditionally obtainable [2].

Solubility of pharmaceutical compounds is an important step in the development of the final product, and co-crystallization is one of the most common operations used to obtain new solid forms with improved properties.

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Thiamine hydrochloride belongs to a class of water-soluble vitamins essential for the body and is also called Vitamin B1. It has the chemical structure $C_{12}H_{18}Cl_2N_4OS$ (Fig. 1a) and has the molar mass 337.3 g/mol. Thiamine hydrochloride is a hygroscopic salt. This compound plays an important role in the digestive system, nervous system and normal activity of the heart [3-5], and is mainly used in animal feed as nutritional supplements, as well as in the feed industry, in medicines, but also in cosmetic products [6,7]. Various new solid forms of thiamine hydrochloride have been reported in the literature [8,9]. It has been shown that hemihydrate form of thiamine hydrochloride is the most stable in contact with water up to 120ºC, when dehydration of the substance begins [8,10].

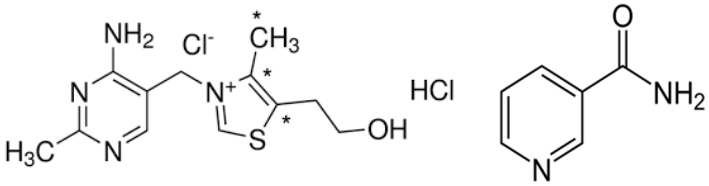

Fig. 1 Chemical structure of thiamine hydrochloride (a) and nicotinamide (b).

In the field of pharmaceutics, the new solid forms (solvates, hydrates, co-crystals and salts) play an important role in the design of new solid forms [11]. Differences in solid forms often lead to differences in thermodynamic parameters and physico-chemical properties (solubility, dissolution rate, stability and mechanical properties) [12].

The co-crystal formation involves the co-crystallization of an agent active pharmaceutical ingredient and another agent named coformer. Thus, the purpose of this study was to obtain new solid forms of thiamine hydrochloride, using nicotinamide as a coformer.

Nicotinamide ($C_6H_6N_2O$, Fig. 1b) is part of the class of vitamins B too, and is named vitamin B3. It is used as a dietary supplement and as neuroprotective agent [13]. The molar mass of nicotinamide is 122.1 g/mol, about three times larger than that of nicotinamide. This was one of the reasons to consider nicotinamide as a possible conformer in obtaining new solid forms with thiamine hydrochloride, because in this case the forming of a complex seems to have a relative high probability. On the other hand, the nicotinamide molecule has donor sites, as pyridine ring nitrogen

(N+) and amino-nitrogen, while thiamine hydrochloride has 4 hydrogen bond acceptors, and 2 hydrogen bond donors. Therefore, the two molecules are expected to form new bonds.

In the present study were investigated two samples prepared by solvent assisted ball milling of vitamins B1 and B3, which were aimed to form by mechanochemistry solid forms of thiamine hydrochloride with nicotinamide as coformer. The samples were analyzed using X-ray diffraction and infrared spectroscopy.

EXPERIMENTAL

Thiamine hydrochloride (THC) and nicotinamide (NICA) provided by Alfa Aesar and Sigma Aldrich, respectively, were used without any further purification. Two samples with thiamine hydrochloride and nicotinamide were prepared as follows:

1. THCNICA-BM1: 25 mg THC (0.074 mmol), 9.14 mg NICA (0.074 mmol), were ground together for 60 minutes using a Retsch MM200 ball mill, with 40µl aqueous ethanol solution (EtOH / water, 1: 1 v / v)
2. THCNICA-BM2: 25 mg THC (0.074 mmol), 2x9.14 mg NICA (2x0.074 mmol), were ground together for 60 minutes using a Retsch MM200 ball mill, with 40µl ethylacetate.

After milling, the samples were dried at 37ºC before analysis by powder X-ray diffraction and infrared spectroscopy.

The structural analysis was made by X-ray powder diffraction using a Shimatzu XRD-6000 diffractometer with graphite monochromator. The measurements were performed at room temperature, in 2θ range between 3–40°, with Cu K_α radiation (λ = 1.5406 Å, operating conditions 40 kV and 30 mA).

For the analysis by Fourier-transform infrared spectroscopy (FTIR) 1.6 mg of each sample were well mixed with 150 mg KBr of spectroscopic grade purity, and pressed into 13 mm diameter disks under a pressure of 12 tons. The measurements were carried out with a JASCO 6200 FTIR spectrometer (256 scans; resolution 4 cm^{-1}; spectral range 4000-400 cm^{-1}) and the recorded spectra were analysed using Spectra Analysis software.

RESULTS AND DISCUSSION

The X-ray powder diffraction patterns obtained for solvent assisted ball milled THCNICA-BM1 and THCNICA-BM2 samples was compared with that of the starting thiamine hydrochloride (THC) and nicotinamide (NICA). From X-ray diffractograms (Fig. 2)

one observes that in both cases, after milling, all diffraction lines represent a superposition of the diffraction lines corresponding to the ball milled components. There are no new lines to signalize the achievement of a new structure and no lines from thiamine hydrochloride and nicotinamide patterns are missing.

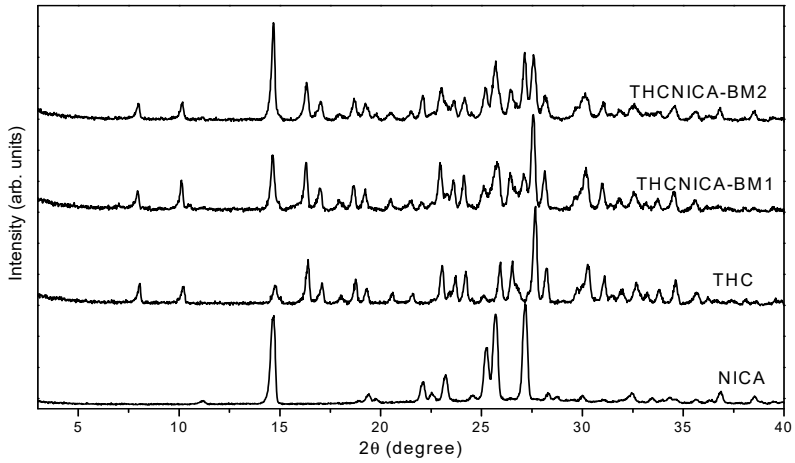

Fig. 2 X-ray powder diffraction patterns of thiamine hydrochloride and nicotinamide along with the powder diffraction patterns of the samples obtained by their solvent assisted ball milling.

Concerning the difference observed in the intensities of the diffraction lines recorded from the ball milled samples, this clearly reflects the double amount of nicotinamide used for BM-2 sample, wherein the ratio vitamin B1/vitamin B3 is half of the same ratio in BM-1 sample. According to these XRD results, no new solid forms of thiamine hydrochloride were developed, and only two physical mixtures were formed under the mentioned synthesis conditions.

Further analysis of the samples was carried out by Fourier transform infrared spectroscopy. The infrared spectra of starting materials THC and NICA (Fig**.** 3) were compared in the spectral range of interest with the spectra obtained for the solvent assisted ball milled samples THCNICA-BM1, THCNICA-BM2 (Fig. 4).

The FTIR spectrum of vitamin B1/ THC (Fig. 3a) contains characteristic bands of C-H stretching vibrations located at 3491 cm^{-1} and N-H stretch band at 3423 cm^{-1}; the N-H stretching vibrations at 3289 cm^{-1}, and C-N vibration at 3042 cm^{-1}; the N-H stretching vibration of primary amine is identified at 2909 cm^{-1}. The C-OH stretching vibration was observed at 1045 cm^{-1} and C-Cl at 766 cm^{-1} and 640 cm^{-1}.

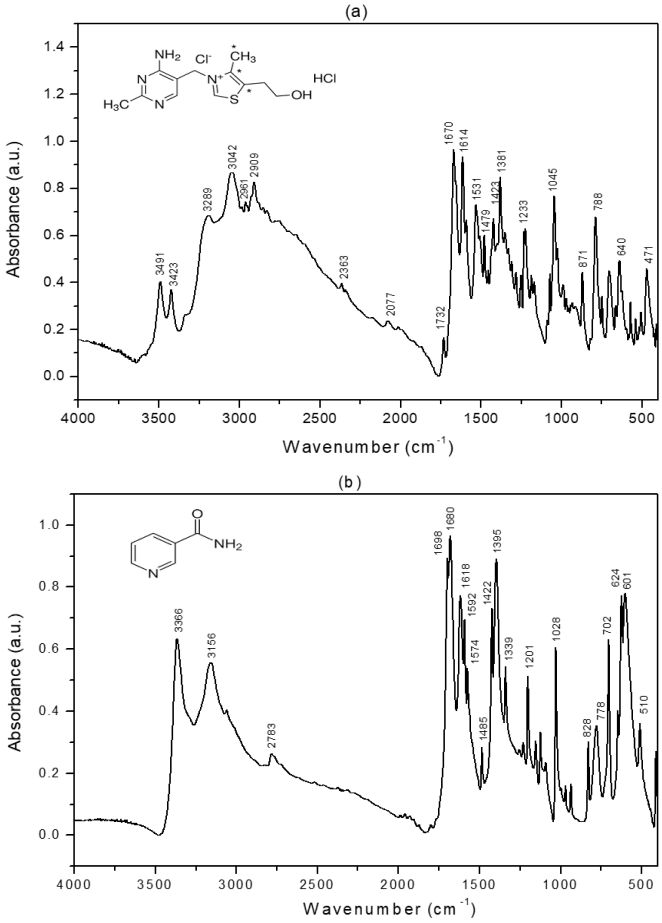

Fig. 3 FTIR spectra of thiamine hydrochloride (a) and nicotinamide (b).

In the FT-IR spectrum of Vitamin B3/NICA (Fig.3b) two strong characteristic bands appear at 3366 and 3156 cm^{-1}, attributed to asymmetric and symmetric stretching vibrations of the NH_2 group. Strong bands assigned to C=O bond vibrations are observed for nicotinamide at 1698 and 1680 cm^{-1} [14, 15]. The bands at 1614 cm^{-1} and 1618 cm^{-1} were attributed to NH_2 scissoring vibration [16].

By comparing the FTIR spectra of the obtained samples with the FTIR spectra of the starting materials (Fig. 4), it can observe that the characteristic bands of the starting materials are found in both prepared sample, without any major differences.

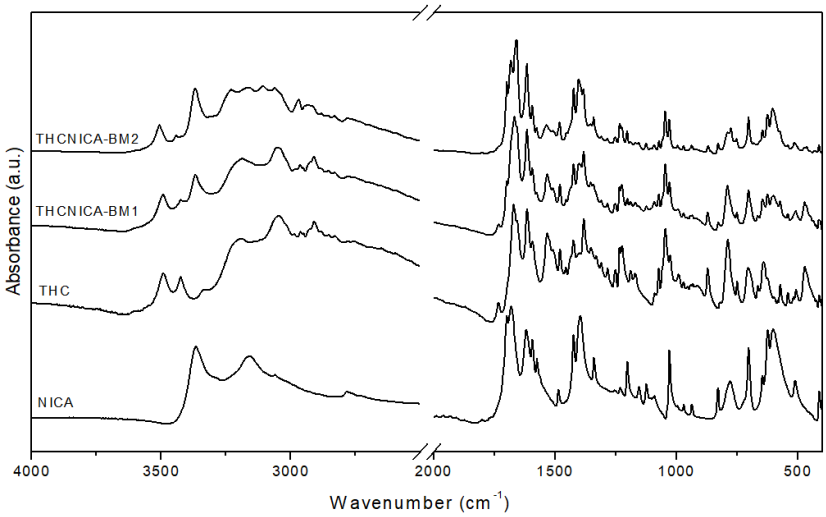

Fig. 4 FTIR spectra of nicotinamide (NICA) and thiamine hydrochloride (THC) along with the patterns of the samples obtained by their solvent assisted ball milling BM1 and BM2.

Further, if we compare the sum of the FTIR spectra for the starting materials (THC + NICA) with the FTIR spectra of the obtained samples, in the case of the THCNICA_BM1 sample, only a physical mixture between THC and NICA is highlighted (Fig. 5).

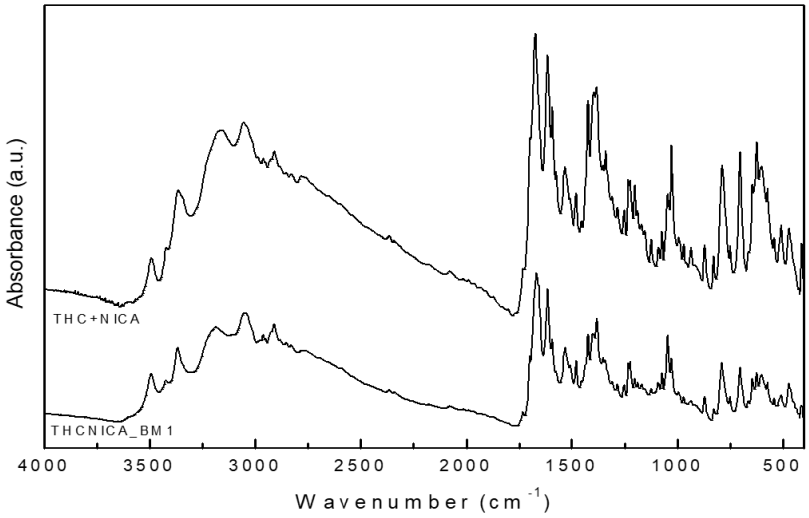

Fig. 5 Sum of FTIR spectra of thiamine hydrochloride and nicotinamide (THC+NICA) compared with the FTIR spectrum of the THCNICA_BM1 sample.

For the THCNICA_BM2 sample, it can be observed that a few absorption bands appear slightly shifted to higher wavenumbers, like the vibration from 3491 cm^{-1} who appears at 3506 cm^{-1}, and the one from 3423 cm^{-1} which appears at 3440 cm^{-1} (Fig. 6). It can be observed that these shifts are very small and cannot be attributed to the formation of new solid form of thiamine hydrochloride with nicotinamide as a coformer. Also, in the 3000 cm^{-1} ÷ 3300 cm^{-1} spectral region of FTIR spectrum of THCNICA_BM2 an overlapping bands can be observed, compared with the same region in the THC+NICA spectrum, where the same spectral lines are better resolved. This overlapping and the shifts too, are most likely due to the grinding process and the presence of water in the analyzed samples.

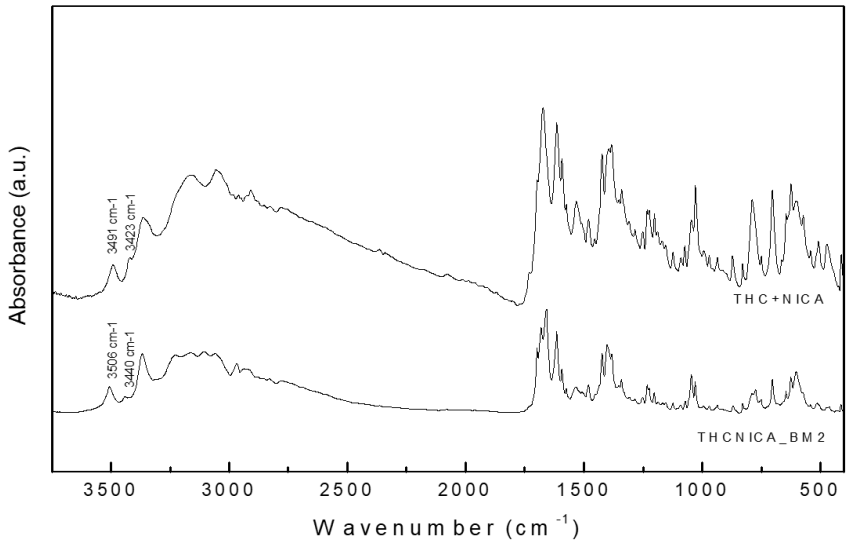

Fig. 6 Sum of FTIR spectra of thiamine hydrochloride and nicotinamide (THC+NICA) compared with the FTIR spectrum of the THCNICA_BM2 sample.

CONCLUSIONS

The present study aimed to obtain potential new solid forms by combining Vitamin B1 (thiamine hydrochloride) with Vitamin B3 (nicotinamide), in different molar ratios and using different solvents, by mechanochemistry method. Two physical mixtures were obtained using solvent drop grinding of thiamine with nicotinamide as coformer. For the THCNICA_BM2 sample the FTIR analysis reveals very small changes of few absorption bands, consisting in a weak shift towards higher wavenumbers and overlapping bands, due most likely to grinding process.

The results indicate that other molar ratios and/or other solvents should be investigated with regard to the use of Vitamin B3 as a conformer, or to consider other co-formers, in order to obtain new solid forms of Vitamin B1 with improved properties.

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