THE ACHIEVEMENT OF A NEW COCRYSTAL BETWEEN KETOPROFEN AND NICOTINAMIDE

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Resumo

Uma pesquisa sobre cocristal de cetoprofeno com nicotinamida como conformador foi realizada utilizando a mecanoquímica e o método de contato de Kofler. Não foi possível obter cocristal nas condições experimentais investigadas entre cetoprofeno e nicotinamida por mecanoquímica. No entanto, as experiências conduzidas pelo método de Kofler confirmaram que, sob determinadas condições, o cetoprofeno interage com a nicotinamida dando origem a um novo co-crystal.

Palavras-chave: Cocristal, cetoprofeno, nicotinamida, mecanoquímica, método de Kofler.

Abstract

An investigation on ketoprofen cocrystal with nicotinamide as a conformer was performed using the Kofler contact method and mechanochemistry. It was not possible to obtain cocrystal under the experimental conditions investigated between ketoprofen and nicotinamide by mechanochemistry. However, experiments conducted by the Kofler method confirmed that ketoprofen interacted, under determined conditions, with nicotinamide giving rise to a new cocrystal.

Keywords: Cocrystal, ketoprofen, nicotinamide, mechanochemistry, Kofler method.

Introduction

There are several ways to improve the physicochemical properties of an API, such as salt formation, polymorphic forms and solvates or hydrates [1]. Recently, cocrystal screening has become an important and innovative approach to improve the physicochemical properties of an API by using suitable molecules such as cocrystal formers [1,2].

Ketoprofen (KET) belongs to Class II (high permeability, low solubility) of the biopharmaceutics classification system (BCS) [3,4]. It is a non-steroidal anti-inflammatory, which is derived from phenylpropionic acid and characterized pharmacologically by its anti-inflammatory, antipyretic and analgesic action. For those reasons it is widely used in the medical and veterinary fields. Its mechanism of action is through the inhibition of prostaglandin and the synthesis of leukotriene [5].

An essential factor considered in the selection of the cocrystal formers is the pKa difference (ΔpKa) between the API and the other molecules. According to Johnson and Rumon [6], an acid−“aromatic nitrogen hydrogen bond may be formed if the ΔpKa is less than 3.75. KET and nicotinamide (NA) fully satisfy this condition, since their pKa values are 4.53 [7] and 3.35 [8], respectively. Furthermore, the FDA regards nicotinamide as GRAS (generally recognized as safe) [9].

The Kofler contact method can provide a qualitative and rapid indication about the formation of cocrystals [10, 11]. Grinding experiment was also used to prepare possible cocrystals, which were studied using DSC, FTIR and XRPD.
Objective
The aim of this work was the achievement of a new cocrystal between ketoprofen and nicotinamide through the mechanochemistry and Kofler contact method.

Materials and methods
Ketoprofen 98% and nicotinamide 99% were purchased from Aldrich®. A Retsch MM400 ball mill was used to grind the KET with the NA. A total mass of about 50 mg was ground for 30 min at a frequency of 15 Hz.

Pure ketoprofen and the solids that were obtained were characterized by PLTM using a Linkam hot stage system, model DSC600, with a Leica DMRB microscope and a Sony CCD-IRIS/RGB video camera. The microscope slide was placed over a Linkam DSC 600 furnace and the heating run was carried out at 2 ºC/min to observe the mixed zone behavior.

The studies were performed on a PerkinElmer Pyris1. The samples, at a mass of ~2 mg, were hermetically sealed in 30 µL aluminum pans and an empty pan was used as reference. A 20 mL/min nitrogen purge was employed.

FTIR-ATR spectra of the solids were obtained on a Bruker Vertex 70 spectrometer with a scanning range between 400-4000 cm\(^{-1}\) (resolution 4 cm\(^{-1}\)) and a diamond crystal as support.

X-ray powder diffractograms were obtained on a Siemens DMAX 2000 X-ray diffractometer using Cu K\(\alpha\) radiation (\(\lambda = 1.5406\) Å) and settings of 20 kV and 2 mA. The samples were placed on a glass support and exposed to the radiation (3º ≤ 2θ ≤ 50º).

Results and discussions

Kofler contact method
This experiment was performed according to Berry et al. [11]. Figure 1 shows the images obtained during the heating of the KET from 25 to 140 ºC at a rate of 2 ºC/min in a nitrogen atmosphere. It is possible to see that the KET started melting at 80 ºC and ended between 88 and 90 ºC. At around 120 ºC the beginning of the melting of the NA should have been observed. However, instead of that, what was observed was the formation of a cocrystal of KET and NA from 120 ºC onwards; this cocrystal began to melt from 140 ºC. The sample was left to cool and in a second heating, this time up to 160 ºC, it was observed that the complete melting of the co-crystal occurred at about 153 ºC. Part of that sample was scraped off to a DSC capsule and the results showed that it had a completely cyclical thermal behavior. Furthermore, after crystallization, FTIR experiments pointed out the difference between the compounds. Among these spectra we would highlight the differences between the asymmetric stretches of the NH\(_2\) group of the NA, which arose at 3358 cm\(^{-1}\) in the KET+NA compound and at 3230 cm\(^{-1}\) in the cocrystal, indicating that the amide group was involved in a stronger hydrogen bond in the cocrystal than that in the crystalline nicotinamide network.
Sample prepared by mechanochemistry
Cocrystal synthesis was tried by solid-state grinding. The solid mixture (1:1) that was obtained was studied by DSC, XRPD and FTIR. The thermal behavior of this system shows that the NA melting occurred at 33.8 °C above the melting temperature of the KET. The DSC curves of the KET+NA (1:1) mixture showed a peak with a lower melting temperature than the KET and NA, suggesting a formation of a cocrystal or a eutectic compound. A typical diagram for the formation of a eutectic compound were obtained with a similar composition to that predicted by the Schroder-van Laar equation [12], since the theoretical eutectic composition was 0.64 mol KET, and composition determined experimentally was 0.61 mol KET. Thus, we can clearly verify that is not possible to obtain a cocrystal between KET and NA by grinding.

Conclusions
Although the phase diagrams, DSC and XPRD experiments indicated that it is not possible to obtain cocrystals between KET and NA, the Kofler contact method and FTIR spectra confirmed the possibility of the formation of cocrystal between these two compounds. The crystallization of KET (with cocrystal formation) can occur during the heating process. However, although it is thermodynamically favorable, it was found that the kinetic reactions were slow, since the KET crystallization took about 30 days.

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References

