Solid State Interactions Between Ketoprofen and Excipients in Solid Dosage Forms

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This study assesses the solid-solid interactions between the commercial form of Ketoprofen (KET), a non-steroidal anti-inflammatory drug of the propionic acid class, and several widely used pharmaceutical excipients. The work was carried out on drug-excipient mixtures, in 1:1 (w:w) ratio, blended in an agate mortar at room temperature. The compatibility/incompatibility of KET with the proposed excipients was highlighted by the most commonly used analytic methods: differential scanning calorimetry (DSC), Fourier transformed infrared spectroscopy (FT-IR) and powder X-ray diffraction (PXRD). The interactions between KET and three of the excipients, namely Macrogol 6000, magnesium stearate dehydrate and lactose monohydrate were evidenced by DSC and further confirmed by FT-IR and PXRD analysis.

Keywords: Ketoprofen, excipients, thermal analysis, FT-IR spectroscopy, X-ray diffraction

The aim of a pharmaceutical formulation development is to provide drugs in the required amount to the patient, constantly in a batch or from batch to batch, in order to ensure the drug bioavailability, dosage form and the manufacturability.

The preformulation stage, associated with fast and precise test methods, is essential in the active pharmaceutical ingredients (API) formulation in order to identify the undesirable interactions between drug-excipient or excipient-excipient [1]. For optimal formulation of stable and efficient solid dosage form the excipient selection is of great importance [2, 3]. Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug, included in the manufacturing process in a drug delivery system for protect, support or enhance stability, bioavailability or patient acceptability [4]. Drug-excipient incompatibility may alter the drug quality, such as physical, chemical or other properties, likewise the possible interactions of physical or chemical nature may lead to changes of APIs polymorphic form in the new formulation [5]. On the other hand, a suitable formulation can improve the bioavailability, solubility and dissolution rate of the drug, resulting in a more rapid absorption of API [6]. The excipients selection for a new formulation is based on the physical chemical compatibility or interaction with the drug. The drug-excipient compatibility can be predicted theoretically by computational methods, and studied experimentally, most often, in binary mixtures where drug and excipient are blended in 1:1 or customized rate (w:w), with or without water addition [3]. Also, the drug-excipient compatibility can be influenced by the polymorphic form of the APIs used in the formulation process [7]. In order to highlight the interactions and to determine the compatibility/incompatibility between the drug and excipients the well known analytic methods are used, such as: thermal analysis (differential scanning calorimetry - DSC, thermogravimetry - TG/DTG), powder X-ray diffraction (PXRD), Fourier transformed infrared spectroscopy (FT-IR) and high performance liquid chromatography (HPLC).

Ketoprofen (KET, fig. 1) ($C_{16}H_{14}O_3$) ((*RS*)-2-(3-benzoylphenyl)propanoic acid) is a non steroidal anti-inflammatory drug (NSAID) from the group of substituted 2-phenylpropionic acids with analgesic and antipyretic effects, introduced in 1973 in France and United Kingdom for anti-inflammatory use. Today is available in about 80 countries and has been approved for treatment of rheumatoid arthritis and osteoarthritis [8].

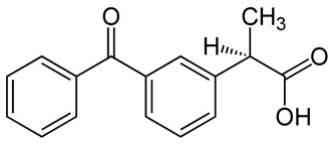

Fig. 1. Structural formula of Ketoprofen (KET)

In the literature there are some reports concerning the interactions of KET with the most used pharmaceutical excipients in solid dosage forms, revealed by different techniques, such as DSC, TG/DTG, Raman and FT-IR spectroscopy, inelastic neutron scattering (INS) or PXRD [9]. The studies showed some incompatibilities with polyvinylpyrrolidone and magnesium stearate [3, 10-13], PEG 6000 [3, 11], lactose [3, 10, 13], glyceryl palmitostearate, dicalcium phosphate dihydrate [10] or with palmitic acid, stearic acid and stearyl alcohol [11] and Mg-Al hydrotalcites [14]. Interactions that affect mainly the hydration/dehydration processes were found with cellulose ether derivatives [15].

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The objective of the present study consist in evaluation of compatibility between KET and some commonly employed pharmaceutical excipients: microcrystalline cellulose, Macrogol 6000 (M6000), corn starch, starch sodium glycolate, magnesium stearate dihydrate (MgSt), lactose monohydrate (Lact), titanium dioxide and talcum, using differential scanning calorimetry with the support of Fourier transformed infrared spectroscopy and powder X-ray diffraction.

The solid form of KET used in this study corresponds to that reported by Briard and Rossi in 1990 in the Cambridge Structural Database (ref. code KEMRUP) and PDF-4 (ref. code 00-065-2207) [16], being different from the form used in compatibility studies by Tita et al. [12, 17-19].

Experimental part

Materials

Ketoprofen (ShaSun Chemicals and Drugs LTD, India) and the pharmaceutical excipients: microcrystalline cellulose, Macrogol 6000 (PEG 6000), corn starch, starch sodium glycolate, magnesium stearate dihydrate, lactose monohydrate, titanium dioxide and talcum were supplied royalty free by the Faculty of Medicine and Pharmacy, Oradea University, Romania. All the chemicals were used as received without further purification.

Binary mixtures preparation

The excipients were blended and sieved on a 200 μm sieve, the granulometric fraction of 200μm being retained. For compatibility testing, the pure components, KET and excipients, were accurately weighted and physically mixed by grinding in an agate mortar, without water addition, in 1:1 (w:w) ratio, approximately for 5 min at room temperature.

Equipments

The DSC thermograms were obtained with a DSC-60 Shimadzu differential scanning calorimeter. The heating of the samples was done with a rate of 10°C/min in the 20-350°C temperature range using sealed aluminium cells under nitrogen atmosphere. A crimped cell containing alumina was taken as reference. FT-IR measurements were performed with a JASCO 6100 FT-IR spectrometer in the 4000-400 cm^{-1} spectral domain and 4 cm^{-1} resolution, using the KBr pellet technique. Powder X-ray patterns were obtained with a Bruker D8 Advance diffractometer in the 2θ (°) = 3-43 angular domain using Cu $K\alpha_1$ radiation. In order to increase the resolution a monochromator was used to eliminate the $K\alpha_2$ radiation.

Results and discussions

Differential Scanning Calorimetry

DSC is a commonly used method to identify the drug-excipient interactions and to determine the thermal stability of drug or drug-excipint mixtures. The obtained informations are useful to establish the suitable drug formulation technology and the storage conditions. The incompatibilities between drug and excipient are reflected in shifting or disappearance of characteristic melting signals and/or ΔH enthalpy variations [2, 20-24].

DSC analysis of the mixtures of KET with micro-crystalline cellulose, corn starch, sodium starch glycolate, titanium dioxide and talcum, in 1:1(w:w) ratio, shows no interaction between drug and excipient. The characteristic temperatures of the thermal events for these mixtures remained practically unchanged, like for the pure components, which suggest no interactions between KET and these excipients. In the case of mixtures with M6000, MgSt and Lact the DSC traces show differences in the thermal behavior compared with pure KET or excipient (figs. 2 - 4).

DSC trace of KET, recorded at controlled heating, presents a sharp endothermic melting peak at T_{onset} = 93.0°C with ΔH_{fus} = -142.4 J . g^{-1}, the decomposition occurs above 230°C.

On the DSC curve of M6000 a single sharp endothermic peak, corresponding to the melting point with T_{opset} = 55.8°C and ΔH_{fus} = -238 J . g^{-1} appears. The physical mixture KET-M6000 presents a single sharp endothermic peak at T_{onset} = 45.8°C with ΔH_{fus} = -151.7 J . g^{-1}, the melting temperature of the mixture being lower than of the pure components (fig. 2).

MgSt presents on the DSC curve a broad endothermic peak between 50 and 80°C with T_{onset} = 52.9°C and ΔH_{fus} = -98.9 J. g^{-1}, corresponding to dehydration of the sample. On the other hand, KET-MgSt mixture shows a sharper endothermic signal at a slightly lower temperature than the singular components with T_{onset} = 59.7°C and ΔH_{fus} = -192.0 J . g^{-1}, while the melting peaks of KET and MgSt does not appear (fig. 3).

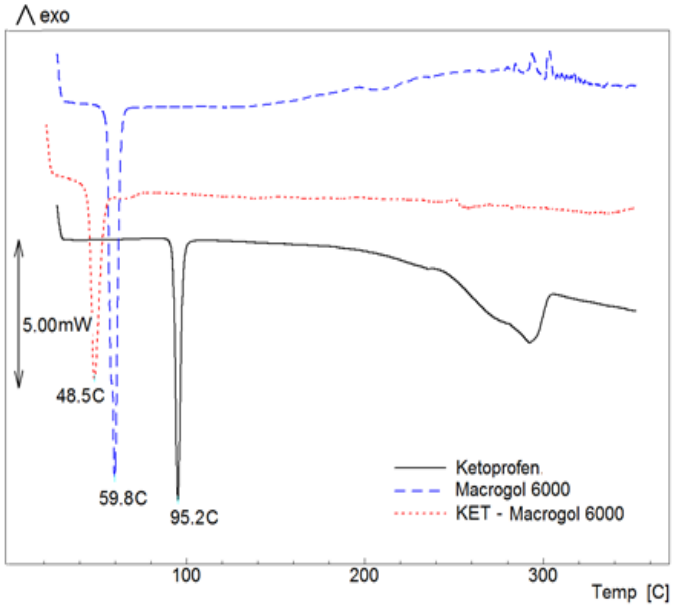


Fig. 2. DSC curves of KET, M6000 and KET-M6000 mixture.

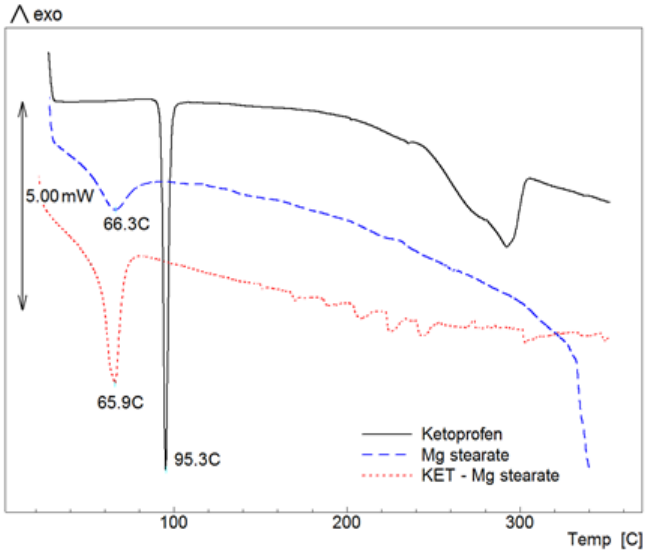


Fig. 3. DSC curves of KET, MgSt and KET-MgSt mixture.

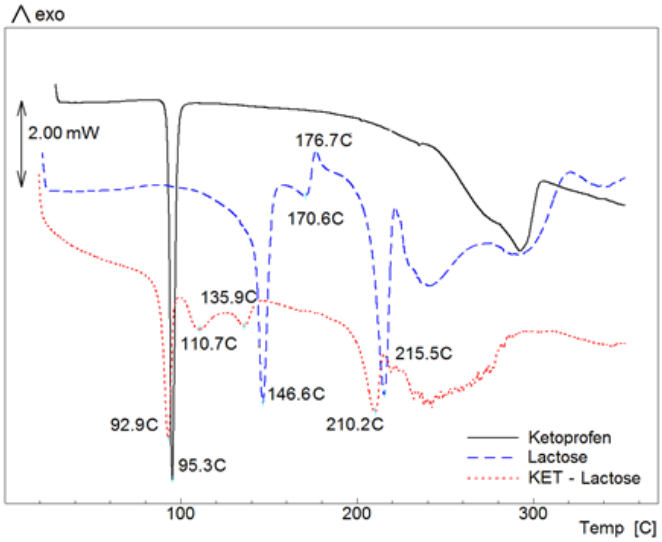


Fig. 4. DSC curves of KET, Lact and KET-Lact mixture

On the Lact DSC curve one can observe four thermal events: a sharp endothermic peak with T_{onset} = 142.9°C and ΔH_{fus} = -192.9 J . g^{-1} corresponding of the water elimination, a broad endothermic peak with T_{onset} = 164.8°C and ΔH_{fus} = -22.1 J . g^{-1} due to anomerization of Lact followed by an exothermic peak with T_{onset} = 174.6°C and ΔH_{fus} = 7.9 . g^{-1}, and a fourth endothermic peak with T_{onset} = 207.5°C and ΔH_{fus} = -157.9 J . g^{-1} corresponding to melting and decomposition [25]. The KET-Lact mixture is characterized by four endothermic peaks. The first sharp peak with T_{onset} = 89.6°C and ΔH_{fus} = -67.2 J . g^{-1} is probably due to the water elimination, the second and the third small broad peaks appear at T_{onset} = 102.7°C with ΔH_{fus} = -28.0 J . g^{-1} and at T_{onset} = 130.7°C with ΔH_{fus} = -14.0 J . g^{-1}, respectively, and the last peak at T_{onset} = 201.5°C, ΔH_{fus} = -49.5 J . g^{-1}, probably corresponds to melting followed by decomposition of the mixture (fig. 4).

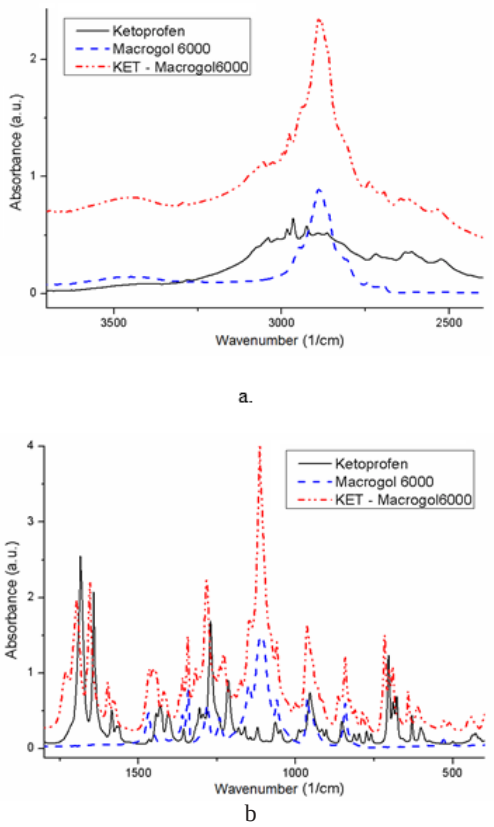
In the case of KET-M6000 and KET-MgSt one can observe the disappearance of KET and excipients melting peaks and a decrease of melting temperature of each mixture than the pure components, indicating some interactions between them in the 50-70°C temperature range. The interaction of KET with Lact is highlighted on the DSC trace by appearance of additional peaks and the corresponding melting peaks of the components are shifted at lower temperature values.

Fourier Transform Infrared Spectroscopy

FT-IR spectroscopy represents a complementary technique able to identify atoms/groups that are involved in drug-excipient interactions and to sustain the results obtained by thermal analysis [26]. The broadening or intensity changes of absorption band(s) or appearances of new ones are the main characteristics that evidence the interactions between the components [27, 28].

FT-IR spectra of the mixtures of KET with M6000, MgSt and Lact indicate possible interactions. In the case of the other KET-excipient mixtures the spectra remain practically unchanged, representing the sum of the vibration bands of pure components.

The spectrum of pure KET in the 3200-2400 cm^{-1} spectral region shows the characteristic vibration bands at 2995-2930 cm^{-1} corresponding to the stretching vibrations of aromatic C-H and OH of the carboxylic acid. The stretching vibrations of C-H and deformation of OH group appears at 2878 cm^{-1}. In the 1800-1000 cm^{-1} spectral domain the intense bands at 1700-1650 cm^{-1} represents the stretching vibration of the carboxylic C=O group and the carboxylic



Fig, 5. FT-IR spectra of KET, M6000 and KET-M6000: a - 3700-2400 cm^{-1} spectral domain, b - 1800-400 cm^{-1} spectral domain

O-H out of plane deformation, respectively. The C=C stretching vibrations of the aromatic ring appear at 1599 cm^{-1}. The 1450-1300 cm^{-1} region shows the bands corresponding to the asymmetric and symmetric deformations of the $-CH_3$ group and the C-C stretching vibrations [29, 30].

The M6000 FT-IR spectrum presents the characteristic stretching vibrations bands for $-CH_2$ groups at 2888, 1468, 1341 and 1280 cm^{-1} and for C-O-C bond at 1108 cm^{-1}, respectively [31]. In the KET-M6000 spectrum (fig. 5) a split of stretching vibration band of the $-CH_2$ groups (located at 2888 cm^{-1}) into two peaks at 2890 and 2882 cm^{-1}, respectively was observed. Also, a shift of the KET band from 2732 cm^{-1} to 2738 cm^{-1} was evidenced. In the 1800-1000 cm^{-1} spectral region a new vibration band appears at 1731 cm^{-1} and the shift of the M6000 bands from 1149 cm^{-1} and 1110 cm^{-1} to 1146 cm^{-1} and 1114 cm^{-1}, respectively was observed.

MgSt presents strong C-H stretching vibrations in the 2950-2850 cm^{-1} region. In the 1600-1400 cm^{-1} spectral domain, the asymmetric and symmetric stretching vibrations corresponding to COO^- and the bending vibrations of the aliphatic C-H bonds, respectively are observed [32]. As concerning the KET-MgSt mixture (fig. 6), a shift of the C-H vibration band of the MgSt from 2919 cm^{-1} to 2916 cm^{-1}

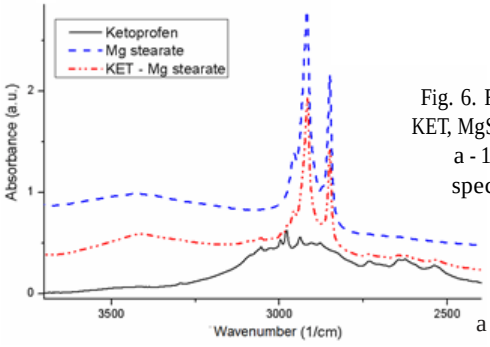


Fig. 6. FT-IR spectra of KET, MgSt and KET-MgSt: a - 1800-400 cm^{-1} spectral domain

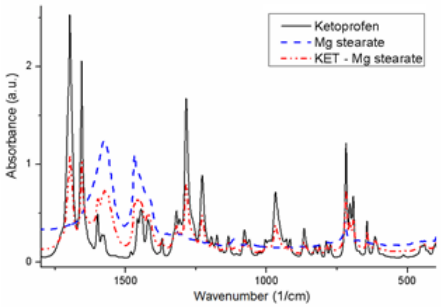
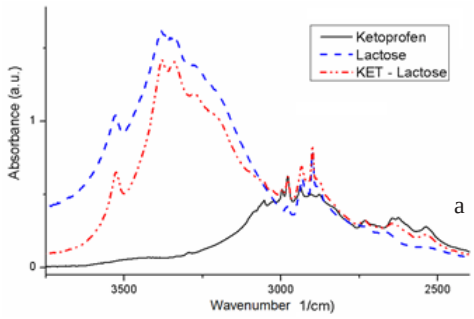


Fig. 6. FT-IR spectra of KET, MgSt and KET-MgSt: b - 3700-2400 cm^{-1} spectral domain



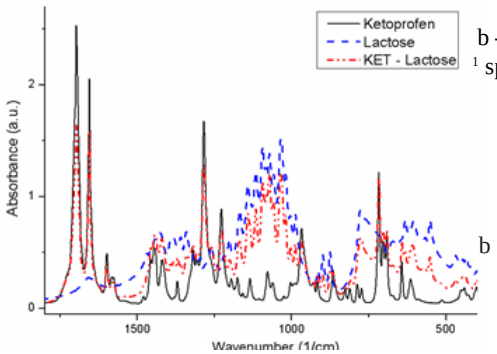


Fig. 7. FT-IR spectra of KET, Lact and KET-Lact: a - 1800-400 cm^{-1} spectral domain, b - 3750-2400 cm^{-1} spectral domain

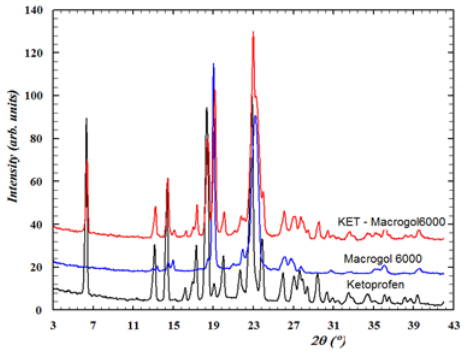


Fig. 8. X-ray diffraction patterns of KET, M6000 and KET-M6000

[1] was evidenced, while the C=O vibrational frequency of KET and the COO^- vibration of MgSt remain unmodified.

The Lact exhibits the following characteristic vibration bands: 3529 cm^{-1} (O-H stretching vibration), 2932, 2900, 1659, 1429, 1170-1033 cm^{-1} (aliphatic C-H, C=O, C-C, C-O, stretching vibrations), 1000-800 cm^{-1} (carbohydrate ring vibrations) 899, 778, 551 cm^{-1} [33]. In the spectrum of KET-Lact (fig. 7) a shift of the O-H stretching vibration from 3529 cm^{-1} to 3524 cm^{-1} was observed. On the other hand, in the 1700-1000 cm^{-1} spectral region no changes were observed.

Powder X-Ray Diffraction

PXRD can be used to establish the interactions that occur during the preformulation process between drug-excipient or excipient-excipient [9, 34]. In this regard, the powder patterns of the physical mixtures are compared with the patterns of the individual components. If the X-ray diffraction pattern of the mixture does not represent the sum of the individual components patterns, one can presume the existence of interactions between the components.

The interaction of KET with M6000, MgSt and Lact in the prepared physical mixtures, showed by the DSC measurements, was further investigated by PXRD. Regarding the other excipients used in this study, the PXRD

KET		M6000		KET-M6000	
2θ (°)	Intensity (a.u)	2θ (°)	Intensity (a.u)	2θ (°)	Intensity (a.u)
6.332	89.47			6.407	40.85
13.151	30.81			13.232	18.46
		13.410	5.35		
14.379	59.29	14.502	7.31	14.475	6.85
		14.989	8.37	15.132	7.40
16.196	10.55			16.279	7.05
16.915	13.34			16.998	8.81
17.299	30.48			17.375	19.29
18.361	94.65	18.500	9.41	18.448	50.24
19.092	12.41	19.033	99.88	19.157	72.94
20.018	25.50			20.097	15.94
		20.998	6.92	21.137	7.21
21.713	18.98			21.791	14.02
		21.950	13.56		
				22.118	12.91
22.857	100.14			22.988	99.61
		23.185	76.11	23.258	69.88
23.880	33.24			23.986	25.61
25.975	17.53	26.111	10.26	26.186	16.31
		26.761	9.24		
27.066	16.13			27.089	13.81
27.634	18.62	27.760	5.54	27.739	13.59
27.884	14.54			27.967	11.10
28.361	11.00			28.467	7.31
29.418	16.81			29.540	11.24
30.350	8.55			30.465	7.25
30.912	5.77			30.926	5.10

Table 1
PXRD DATA FOR KET, M6000 AND KET-M6000 (1:1 w/w)

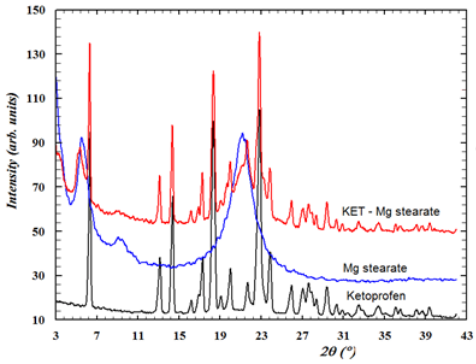


Fig. 9. X-ray diffraction patterns of KET, MgSt and KET-MgSt

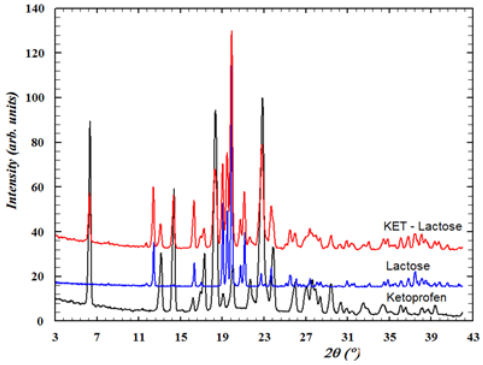


Fig. 10. X-ray diffraction patterns of KET, Lact and KET-Lact

Table 2
PXRD DATA FOR KET, MgSt AND KET-MgSt (1:1 w/w)

KET		MgSt		KET-MgSt	
2θ (°)	Intensity (a.u)	2θ (°)	Intensity (a.u)	2θ (°)	Intensity (a.u)
		5.518	72.44	5.365	45.63
6.332	89.47			6.310	95.06
		9.052	26.90	9.103	15.49
13.151	30.81			13.118	32.07
14.379	59.29			14.341	56.14
16.196	10.55			16.169	15.48
16.915	13.34			16.885	17.44
17.299	30.48			17.269	33.59
18.361	94.65			18.351	81.50
19.092	12.41			19.051	20.84
				19.677	28.78
20.018	25.50			19.982	39.17
		21.180	74.61	21.168	37.02
21.713	18.98			21.639	48.93
22.857	100.14			22.821	100.11
				23.287	30.49
23.880	33.24			23.855	35.94
25.975	17.53			25.955	20.39
27.066	16.13			27.056	16.61
27.634	18.62			27.634	18.62
27.884	14.54			27.884	14.54
28.361	11.00			28.357	13.40
29.418	16.81			29.407	19.57
30.350	8.55			30.320	11.32
30.912	5.77			30.898	9.14

Table 3
PXRD DATA FOR KET, Lact AND KET-Lact (1:1 w/w)

KET		Lact		KET-Lact	
2θ (°)	Intensity (a.u)	2θ (°)	Intensity (a.u)	2θ (°)	Intensity (a.u)
6.332	89.47			6.285	27.54
		12.450	20.38	12.409	30.07
13.151	30.81			13.099	13.74
14.379	59.29			14.334	26.54
16.196	10.55	16.331	11.30	16.292	24.05
16.915	13.34			16.915	8.27
17.299	30.48			11.243	11.64
18.361	94.65			18.303	38.22
19.092	12.41	19.070	38.20	19.036	41.17
		19.505	34.58	19.473	45.77
		19.922	100.11	19.898	100.21
20.018	25.50				
		20.768	10.29	20.730	15.49
		21.163	24.85	21.121	28.24
21.713	18.98			21.633	7.82
22.857	100.14	22.722	6.53	22.790	49.26
23.880	33.24	23.705	9.15	23.691	21.66
		25.514	5.65	25.486	10.48
25.975	17.53			25.964	9.43
		26.111	4.04		
27.066	16.13				
		27.418	4.17	27.395	27.10
27.634	18.62				
27.884	14.54			27.961	8.56
28.361	11.00			28.373	7.34
29.418	16.81			29.408	8.43
30.350	8.55			30.239	4.54
30.912	5.77			30.912	6.10

analysis has revealed no interactions with the drug, the diffraction patterns of the physical mixtures being the sum of the components patterns. The powder diffraction patterns of the binary mixtures formed by KET with M6000 (fig. 8) and Lact (fig. 9) show a good crystallinity compared with that of MgSt (fig. 10). Thus, KET-MgSt presents a distorted crystalline network, due to the influence of the amorphous excipient.

Comparing the diffraction pattern of KET with those of binary mixtures with the three excipients one can observe the appearance of new peaks, also the disappearance or slight shifting of some peaks. The more intense peaks of KET appear at the following 2θ (°) values: 6.332, 13.151, 14.379, 18.361, 22.857 and 23.880. PXRD data for KET, M6000, MgSt, Lact and their physical mixtures are illustrated in tables 1-3.

All this data obtained from PXRD indicates interactions of physical or chemical nature between KET and these three excipients, supporting the results of DSC analysis.

Conclusions

The compatibility between the non-steroidal anti-inflammatory drug Ketoprofen and some commonly used excipients (microcrystalline cellulose, Macrogol 6000, corn starch, starch sodium glycolate, magnesium stearate dihydrate, lactose monohydrate, titanium dioxide and talcum) in 1:1 (w/w) ratio for pharmaceutical formulations was studied with the following analytical methods: DSC, FT-IR and powder X-ray diffraction. The differential scanning calorimetry revealed a different thermal behavior of three of the eight studied physical mixtures, namely KET-M6000, KET-MgSt and KET-Lact. The melting process of the mixtures occurred at lower temperatures than of the pure compounds, which resulted in the existence of some physical or chemical interactions between the components. The other two analytical methods, FT-IR spectroscopy and PXRD, supported the thermoanalytical data, offering complementary information about the functional moieties involved in this drug-excipient interactions and the crystalline nature of the binary mixtures.

One can presume the existence of weak intermolecular hydrogen-bonding type interaction between KET and these three excipients. The present results are of great significance and provide useful information on understanding the solid-solid interactions that can occur between drug and excipients in the pharmaceutical formulation process.

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