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Compatibility study between ketoprofen and pharmaceutical excipients used in solid dosage forms

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ABSTRACT

Thermogravimetry/derivative thermogravimetry (TG/DTG) and differential scanning calorimetry (DSC) techniques were used for assessing the compatibility between ketoprofen (KT) and several excipients as: corn starch, microcrystalline cellulose (PH 101 and PH 102), colloidal silicon dioxide, lactose (monohydrate and anhydre), polyvinylpyrrolidone K30, magnesium stearate and talc, commonly used in the pharmaceutical form.

In order to investigate the possible interactions between the components, the thermal curves of KT and each selected excipients were compared with those of their 1:1 (w/w) physical mixtures.

For KT, the DSC curves have shown a sharp endothermic peak at 96.8 °C which corresponds to the melting process (literature value: 94–97 °C), respectively the TG curves demonstrated a simple stage of mass loss in the temperature range of 235–400 °C.

FT-IR spectroscopy and X-ray powder diffraction (XRPD) were used as complementary techniques to adequately implement and assist in interpretation of the DSC results.

On the basis of thermal results, a possible interaction was found between the KT with polyvinylpyrrolidone K30 and magnesium stearate, which could influence the stability of the KT in the binary mixtures. These possible incompatibilities were confirmed by FT-IR and X-ray analysis.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs in the world, primarily for symptoms associated with osteoarthritis and other chronic musculoskeletal conditions. Also, NSAIDs reduce the risk of mortality from colon cancer by about half and constitute prototypical colon cancer chemo preventive agents.

Ketoprofen, [2-(3-benzoylphenyl)propionic] acid, a member of the NSAIDs, is an inhibitor of prostaglandin synthetase. It is effective in the long-term management of rheumatoid arthritis, ankylosing of rheumatoid arthritis, ankylosing spondylistis, osteoarthritis and acute out, as well as mild to moderate pain and dysmenorrhea, and has been used as model drug for such investigations [1].

However, the use of ketoprofen is limited because of its significant adverse effects, which include gastrointestinal side effects (such as dyspepsia, gastrointestinal bleeding, and even perforation), renal side effects and some additional side effects (such as hypersensitivity reactions and distinct salicylate intoxication) [2].

The study of drug–excipient's compatibility represents an important phase in the preformulation stage for the development of all dosage forms. In fact, potential physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drugs and, consequently, their therapeutic efficacy and safety [3–6].

Throughout, the different methods reported on drug–excipient's compatibility studies, DSC has been shown to be an important tool at the outset of any solid dosage form preformulation study to quickly obtain information about possible interactions among the formulation components, according to appearance, shift or disappearance of endothermic or exothermic peaks and/or variations in the corresponding enthalpy values in thermal curves of drug–excipient mixtures [7–9].

However, the interpretation of the thermal data is not always easy and, to avoid misinterpretations and misleading of thermal analysis' results, it must be emphasized that the interactions observed at high temperatures may not always be relevant under ambient conditions. Moreover, the presence of a solid–solid interaction does not necessarily indicate pharmaceutical incompatibility, but it might instead be advantageous, e.g. as a more

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desirable form of drug delivery system. Therefore, the use of other analytical techniques, such as FT-IR spectroscopy, X-ray powder diffractometry and scanning electron microscopy (SEM) as complementary tools to assist in the interpretation of TA findings is greatly advisable [10,11].

In the present study, the compatibility of KT with 9 different pharmaceutical excipients of common use in the development of solid dosage forms was evaluated. For this purpose, simultaneous TG/DSC measurements were carried out on each of the components, both in the pure form and the corresponding 1:1 (w/w) physical mixtures. The absolute value of the difference between the melting endothermic peak temperature of pure drug and that in each analyzed mixture and the absolute value of the difference between the enthalpy of the pure KT melting peak and that of its melting peak in the different analyzed mixtures were chosen as indexes of the drug–excipient interaction degree. FT-IR spectroscopy and X-ray powder diffraction were used as complementary techniques to adequately implement and assist in interpretation of the DSC results.

2. Experimental

2.1. Materials and samples

The KT drug was supplied by S.I.M.S, Italy (lot: 138315).

The excipients were as follows: corn starch hydrated (Roquette Freres, France, lot: E1209); microcrystalline cellulose PH 101 (MC-101) and PH 102 (MC-102) from J. Rettenmaier & Sohne GmbH, Germany (lot: 6610173917 and 5610273320); colloidal silicon dioxide (CSD – Aerosil 200) from Degussa AG, Germany (lot: 3157040314); lactose monohydrate (α-lactose) and lactose anhydre (β-lactose) from Friesland Foods Domo, Holland (lot: 620831 and 620214); polyvinylpyrrolidone K30 (PVP K30 or PVP) from BASF Aktiengesellschaft, Germany (lot: 95658675LO); magnesium stearate (MS) from Undesa, Spain (lot: 484931) and talc (Luzenac Val Chisone, Italy, lot: S1094/06).

Physical mixtures of KT with each selected excipient were prepared in the 1:1 (w:w) ratio by simple mixture of the components in an agate mortar with pestle for approximately 5 min. The 1:1 (w/w) ration was chosen in order to maximise the probability of observing any interaction.

2.2. Methods

2.2.1. Thermal analysis

The TG/DTA instrument was calibrated by the Netzsch supplier using indium, zinc, aluminium, silver and gold, under the same conditions as for the samples, those temperatures and enthalpies of melting are well known.

The TG/DTG curves were recorded using a Netzsch-STA 449 TG/DTA instrument in the temperature range of 20–500 °C, under a dynamic atmosphere of nitrogen (20 mL min^{-1}) and at a heating rate (β) of 10 °C min^{-1} in the 20–500 °C temperature range, using platinum crucibles and weighed samples of approximately 20 mg.

The DSC apparatus was calibrated with indium (156.6 ± 0.2 °C) and zinc (419.5 ± 0.3 °C) standards melting point. The heat flow and enthalpy were calibrated by indium heat of fusion (28.58 ± 0.3 J g^{-1}) using the same conditions of the drug samples.

DSC experiments were carried out with a Netzsch differential scanning calorimeter, model DSC-204, using aluminium crucibles with samples of approximately 3 mg, under dynamic nitrogen atmosphere (50 mL min^{-1}) and a heating rate of 10 °C min^{-1}, up to a temperature of 500 °C.

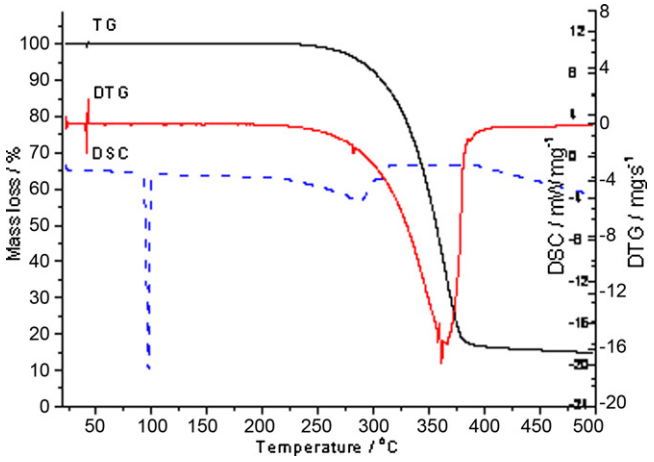

Fig. 1. TG/DTG and DSC curves of pure KT.

2.2.2. Fourier transformed infrared spectroscopy (FT-IR) and X-ray diffraction

FT-IR spectra of drug, excipients and grinding mixtures were recorded on a Perkin-Elmer Model 1600 apparatus using KBr stressed discs in the range of 4000–400 cm^{-1}.

X-ray diffraction patterns (XRPD), for the same category of substances, were obtained with a Bruker D8 Advance X-ray diffractometer using MoKα radiation (Zr filter on the diffracted beam, 50 kV and 40 mA) in a Bragg–Brentano θ:2θ configuration, with Soller and fixed slits and a NaI (Tl) scintillation detector. The measurements of 2θ ranged between 0° and 30°. Data analysis and acquisition were performed using DIFFRACT^{plus} software from Bruker AXS.

3. Results and discussion

3.1. Thermal behaviour of KT

The TG/DTG and DSC curves obtained for KT are presented in Fig. 1.

Thermal decomposition of KT in a nitrogen atmosphere occurs in one event and starts at 235 °C, as presented in Fig. 1. The temperature range of decomposition is included between 235 and 400 °C, with the mass loss of 86% and $T_{peak\ DTG}$ = 361.4 °C.

Over 400 °C, the TG/DTG curves indicate a slow and continuous mass loss caused by elementary carbon formation from decomposition step, as consequence of the rupture of the aromatic ring.

The DSC curve of KT (for β = 10 °C min^{-1}) presents a sharp endothermic event at 96.8 °C (T_{onset} = 91.2 °C; ΔH_{fus} = 343.1 J g^{-1}) indicating the melting and which corresponds to the values indicated in literature (94–97 °C). In this temperature range, the TG/DTG curves did not show mass loss.

3.1.1. Compatibility study with excipients

In fact, DSC has been proposed to be a rapid method for evaluating physico-chemical interactions between components of the formulation through the comparison of thermal curves of pure substances with the curve obtained from a 1:1 physical mixture and therefore select adequate excipients with suitable compatibility.

The thermoanalytical data of KT and tested excipients, obtained from the thermal curves, are collected in Table 1, and for the PVP and MS which are susceptible to presents some interactions, the characterisation is made detailed. Because of the fact that the DSC curves were compared with those of their 1:1 (w:w) physical mixtures, these are presented in Fig. 2.

Table 1
Thermoanalytical data of KT and excipients.

Substance	TG/DTG curves		DSC curves		Nature of the process
	T_{onset} (°C)	$T_{peak\ DTG}$ (°C)	T_{onset} (°C)	$T_{peak\ DSC}$ (°C)	
KT	235	361	90	96.8	Decomposition
Starch	32; 284	65; 325	66	93.8	Dehydratation; decomposition
MC-102	30; 311	60; 354	52; 316	73; 350	Dehydratation; decomposition
MC-101	314	352	50; 315	72; 361	Dehydratation; decomposition
CSD	–	–	–	–	–
α-Lactose	95; 219; 266	158; 239; 315	140; 203	145; 215	Dehydratation; melting; decomposition
β-Lactose	100; 232; 275	140; 252; 310	126; 219	140; 235	Dehydratation; melting; decomposition
PVP	36; 390	62; 441	51	82	Dehydratation; decomposition
MS	50; 320	78; 362	50	75	Dehydratation; decomposition
Talc	–	–	–	–	–

The TG/DSC curves of PVP, below 150 °C display on initial mass loss of ≈9%. This mass loss is accompanied by a broad endothermic phenomena 53.2–113.5 °C (DSC_{peak} = 81.6 °C) over an ill-defined baseline which makes evaluation of the dehydration enthalpy quite uncertain. The sample readily dehydrates and its initial mass depends upon the moisture content of the atmosphere. Apparently, dehydration is completed at 113.5 °C (DTG_{peak} = 64 °C) in N_2. However, a second loss stage (≈2%) begins past 150 °C and completes around 250 °C. Thermal analysis, SEM and XRPD all show that the compound is in a vitreous phase with glass transition near 200 °C. Decomposition begins around 384 °C (DTG_{peak} = 442 °C, Δm = 86%) up to 485 °C [12,13].

Simultaneous TG/DSC curves of MS show several dehydration stages below 110 °C. The first endothermic effect is due to release of a small amount of surface water. Around 50 °C begins the first dehydration stage of structural water, which partially overlaps with a second stage at higher temperature. The overall mass loss due to surface water and to the first stage is ≈3%, while the amplitude of the second stage is ≈1.5% of the initial mass. DSC curve of MS initially show wide endothermic effect (T_{peak} = 75 °C), representing dehydration. Melting begin at ≈110 °C and produce an endothermic peak with a shoulder in the high temperature side which is caused by melting of magnesium palmitate or high-melting polymorphs. The decomposition of the sample begin around 311 °C (DTG_{peak} = 362 °C) and to 480 °C, 92.5% of sample mass is lost. Corresponding to the decomposition process, the DSC curve presents a sharp endothermic with T_{max} = 372 °C [14,15].

The possible interactions between components are derived or deduced from DSC curves by appearance, shift, or disappearance of DSC peaks, especially the melting peak, and/or variations in expected enthalpy (ΔH) values. An interaction was assumed to result in a decrease, respectively increase of the ΔH in the case of overlapping a more complex process.

Modifications in the peak shape, peak onset or peak maximum temperature may indicate an interaction, but it is necessary to bear in mind that some broadening of peaks is a result of the missing process, which lowers the purity of each component in the mixture.

The DSC curves of KT–excipient mixtures are shown in Fig. 3.

In the 1:1 physical mixtures when there is no any interaction between KT and excipient, the T_{peak} value of melting event (DSC curve), respectively the T_{onset} and $T_{peak\ DTG}$ values of the decomposition of KT (TG/DTG curves) remain practically unchanged, similarly when the drug is alone. In this case the thermal profiles of the mixture can be considered as a superposition of the curves of KT and adequate excipients.

According to the thermal curves, especially DSC curves that provide the most complete information, majority of the 1:1 (w/w) physical mixtures of KT with each of these excipients, reflecting substantially the characteristic features of the respective individual components. Practically, the thermal curves of binary mixtures can be considered as a superposition of the adequate curves of KT and excipients, evidencing the absence of the incompatibility between KT and starch, MC, CSD, α and β-lactose and talc.

Meaningful differences were found out only for the binary mixtures of KT with PVP, respectively MS, which were discussed further on.

The DSC curve of the physical mixture of KT with PVP presents a broad and weak peak which corresponds to the dehydration, between 44.7 and 94.7 °C with DSC_{peak} = 70.1 °C (Fig. 4). The main finding of the DSC curve is the disappearance of the characteristic KT fusion peak, showing it was a chemical interaction between these substances due to heating. The reason for this behaviour could be because of shifting of KT peak to lower temperature, which could

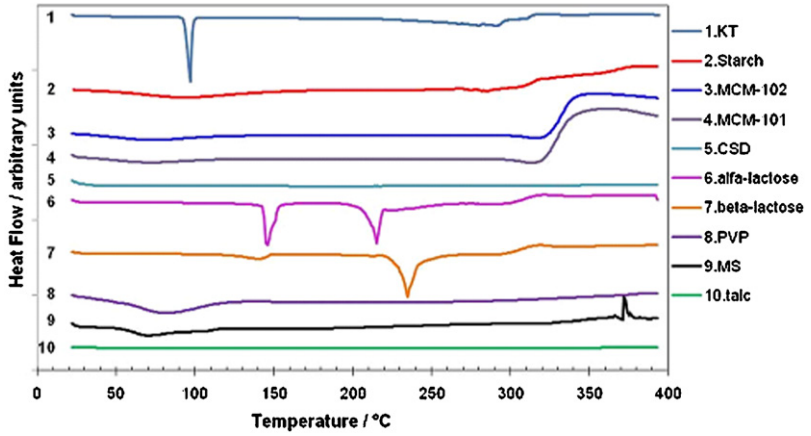

Fig. 2. DSC curves of all substances used in compatibility study.

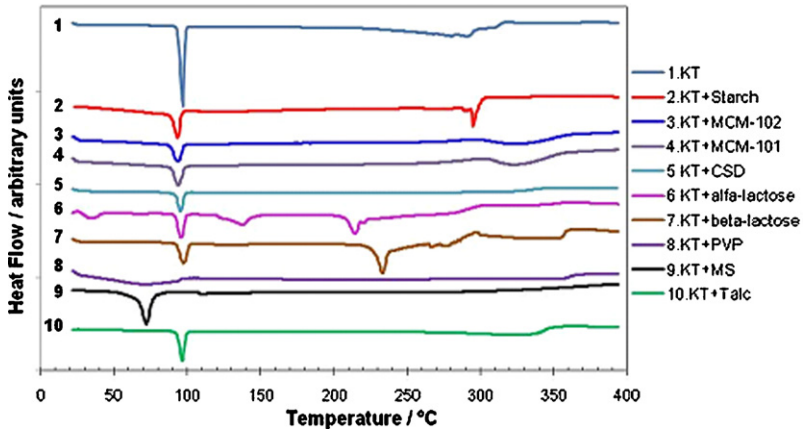

Fig. 3. DSC curves of KT and its 1:1 physical mixtures.

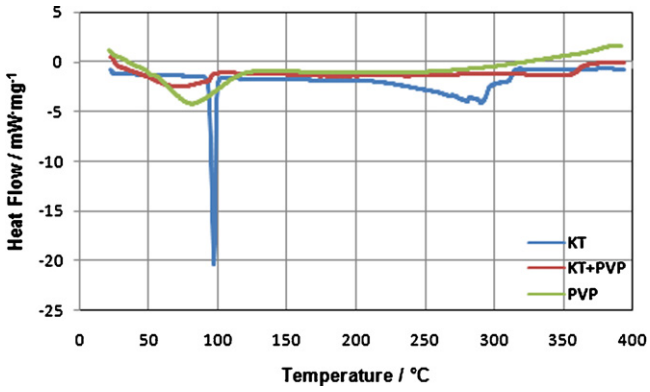

Fig. 4. DSC curves of KT, PVP, and its 1:1 physical mixture.

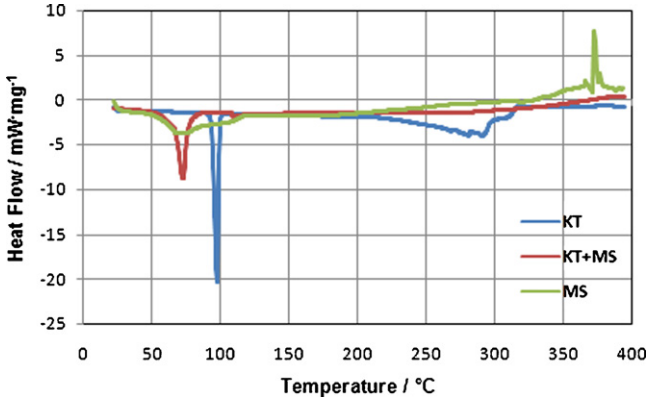

Fig. 5. DSC curves of KT, MS, and its 1:1 physical mixture.

have merged with the water's loss peak of PVP. Another possibility including that the water, which emerged from PVP (in the temperature range of 53.2–113.5 °C) resulted in dissolution of KT (high water solubility of drug coupled with the increasing of the temperature during DSC experiment), because of which KT's peak disappears.

The same behaviour was described in the literature for the mixtures of PVP with other drugs such as naproxen, cetoprofen, ibuprofen, captopril, indicating the occurrence of a solid–solid interaction with heating [13,16,17]. One considers that this way of interaction takes place by so-called dissolution of the drug in the presence of humidity and at heating.

The TG/DTG curves of this binary mixture showed that the beginning of the decomposition step of KT was shifted towards a lower temperature. The value observed to this temperature is T_{onset} = 218 °C lower than the value obtained to the corresponding event in TG/DTG curves from KT alone (Table 1). Also, $T_{peak\ DTG}$ is with 15 °C lower (Table 1). These modifications of the temperature's values showed a reduction of thermal stability for KT in the presence of PVP, due to the mentioned interaction.

By the comparison of the DSC curves (Fig. 5) of pure KT and MS with their 1:1 physical mixture, the differences are well visible and these can be attributed to any incompatibility (interaction) between the two components. The endothermic peak of the melting point of KT ($T_{peak\ fusion}$ = 96.8 °C) disappeared and the signal of MS was changed. A new one appears below 25.6 °C (49.5–86.5 °C) which is superposed on the dehydration peak of MS. The DSC curve of the binary mixture KT–MS indicates a chemical interaction between substances due to heating.

For further explanation regarding the mentioned interaction, it must be underlined that used MS is a mixture of magnesium salts of different fatty acids (mainly stearic acid and palmitic acid, respectively a minor proportions of other fatty acids). Both stearic and palmitic acids give one endothermic peak at their melting points: 70.6 °C for stearic acid and 61.4 °C for palmitic acid. Since the new endothermic peak for the KT–MS mixture (72.2 °C) corresponds practically to the melting temperature of stearic acid, we assumed the appearance of this acid, magnesium salt of KT and a very small quantity of palmitic acid.

In the literature, other interactions between MS and drugs, such as glibencamide, atenolol, captopril, olanzapine are detailed [18–20].

Due to the comparison of the TG/DTG curves of KT, MS and the binary mixtures of these compounds, it was concluded that the thermal stability of KT in these mixtures changed. Thus, it was established that the MS accelerated the thermal decomposition of KT ($\Delta T_{peak\ DTG}$ = 315 °C), in same time, the beginning of the mentioned process has also decreased (ΔT_{onset} = 215 °C). Due to these modifications, the thermal stability of KT in the presence of MS was lower, due to the mentioned interaction.

The results obtained from the TG/DTG and DSC curves for the binary mixtures are collected in Table 2.

Generally, the melting peak of KT was preserved and the enthalpy's values are reduced to half, less for the two binary mixtures mentioned. The slight lowering and/or broadening of the melting temperature, respectively beginning and maximum temperature of decomposition may be attributed to the mixing process, which lower the purity of each component in the mixture.

Table 2
Thermoanalytical data of KT and drug:excipient physical mixtures.

Samples	DSC		ΔH_{fusion} (J g^{-1})	DTG		Δm (%)
	$T_{onset\ (fusion)}$ (°C)	$T_{peak\ (fusion)}$ (°C)		T_{onset} (°C)	$T_{peak\ DTG}$ (°C)	
Drug						
KT	91.2	96.8	343.1	235	361	86
Drug/excipient						
Starch	86.2	93.3	154.5	225	288	75
MC-102	85.5	93.5	139	215	332	80
MC-101	87.1	93.7	150.8	210	335	78
CSD	88.0	95.8	108	200	329	45
α-Lactose	89.4	95.7	160.2	200	285	77
β-Lactose	89.2	97.6	156.5	200	287	80
PVP*	*	*	*	218	346	45
MS**	59.0	72.2	324.8**	215	315	47
Talc	89.4	96.6	164.2	215	345	47

* The value not calculated due to absence of drug's melting event or undefined peak.
** The value represents the sum of two or more processes not only drug's melting event.

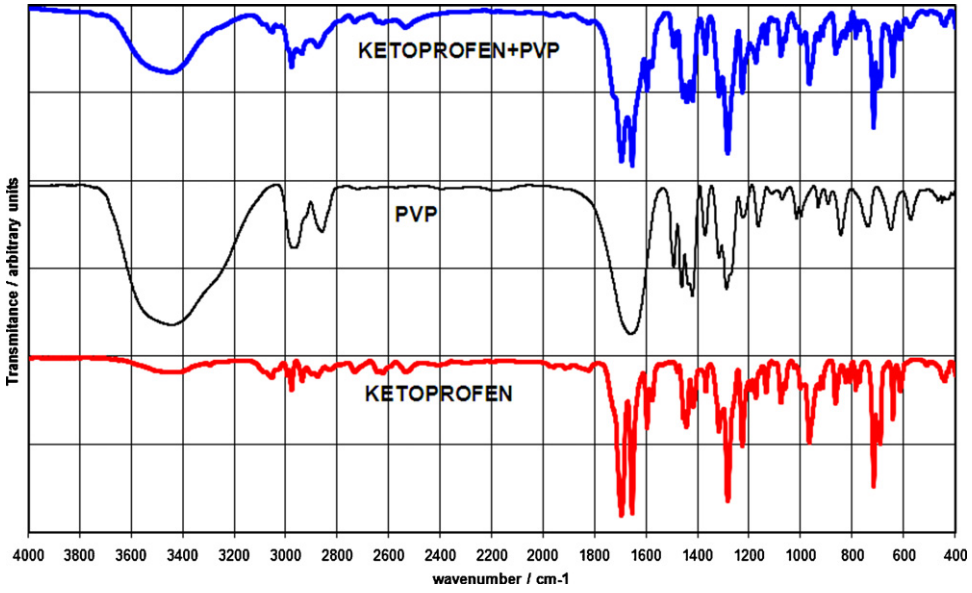

Fig. 6. IR spectra of PVP, KT and 1:1 blend as simple mixture of KT and PVP.

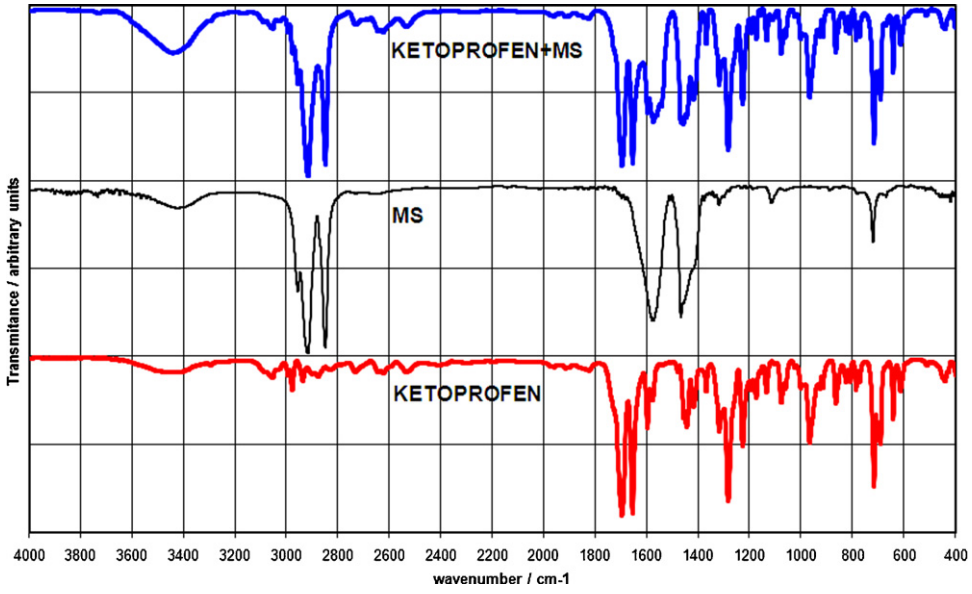

Fig. 7. IR spectra of MS, KT and 1:1 blend as simple mixture of KT and MS.

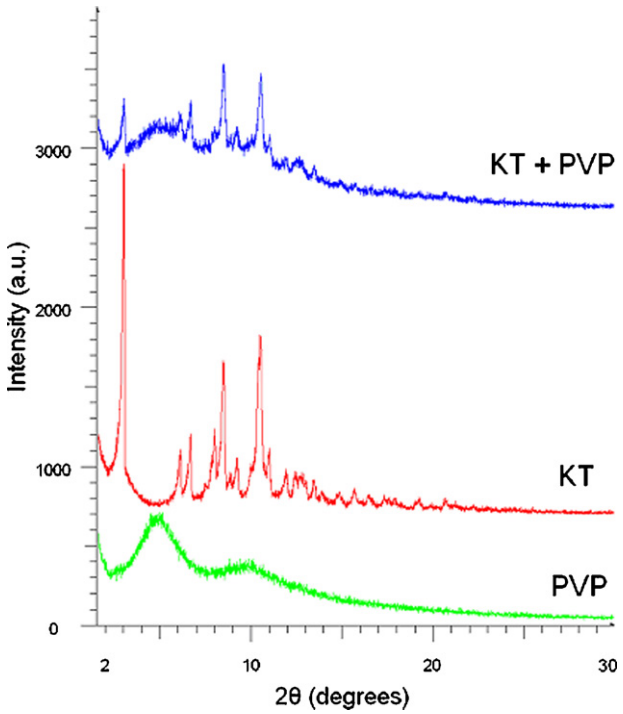

Fig. 8. X-ray diffractogram of PVP, KT and 1:1 blend as simple mixture of KT and PVP.

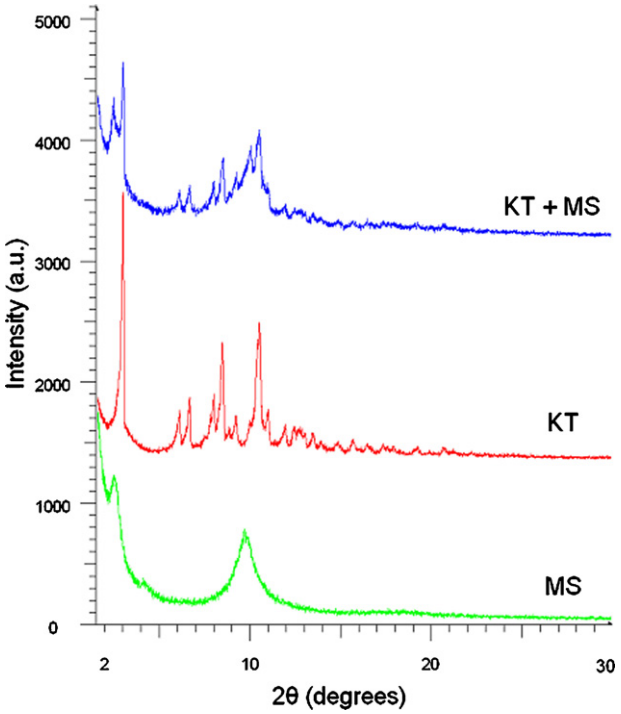

Fig. 9. X-ray diffractogram of MS, KT and 1:1 blend as simple mixture of KT and MS.

Appreciably decreasing or the absence of the melting temperature, respectively values of ΔH_{fusion}, suggests a process which takes place with low intensity or even disappears (the case of binary mixture KT–PVP).

A higher value of ΔH_{fusion} shows an overlapping of two processes (the case of binary mixture KT–MS, with melting and dehydration).

The small variations in the enthalpy's values for the binary mixtures can be attributed to some heterogeneity in the small samples used for the DSC experiments (3–4 mg).

The difference of enthalpy for the binary mixture KT–CSD can suggest a physical interaction which not determines an incompatibility.

The FT-IR spectroscopy was used as a supplementary technique in order to investigate the possible chemical interaction between drug–excipient and to confirm the results obtained by the thermal analysis. It is the most suitable technique of the non-destructive spectroscopic methods and has become an attractive method in the analysis of pharmaceutical solids, since the materials are not subject to thermal or mechanical energy during sample's preparation, therefore preventing solid-state transformations. The appearances of new absorption band(s), broadening of band(s), and alteration in intensity are the main characteristics to evidence interactions between drug and excipients [19,21,22].

The FT-IR spectra were drawn for KT, excipients, respectively for the corresponding mixtures.

For the binary mixtures which present compatibility according the DSC results, the FT-IR spectra can be considered as the superposition of the individual ones without absence, shift or broadening in the vibration bands of KT. So, it confirms the absence of physical or chemical interactions between KT and the corresponding excipients.

Further, it will be presented only the spectra for the cases where the thermal analysis indicates a possible interaction, namely: KT, PVP and the mixture KT:PVP (Fig. 6), respectively KT, MS and the corresponding mixture (Fig. 7).

The main differences resulting from comparing the spectra are presented below.

For the binary mixture KT–PVP:

- the significant decrease (≈20%) of the band attributed to the OH group (3450 cm^{-1}), with the movement of the absorption's maximum at 3480 cm^{-1};
- the bands in the 3000–2800 cm^{-1} region appear as a broad band with a maximum of absorption increased (≈20%) at 2979 cm^{-1} accompanied by two shoulders in the right;
- the intensity of the main absorption bands (1698, 1669, 1655, 1598, 1291, 1284, 1228, 968, 717 cm^{-1}) is maintained or increased until 45% (band from 717 cm^{-1}). The first four bands turn into a wider band, of two maximums of absorption and a shoulder in the right side, more intense than the maximum of 1598 cm^{-1};
- the bands in the 1495–1421 cm^{-1} region become a single narrow band, practically with a triple maximum of absorption (1460, 1450, 1424 cm^{-1}) and the intensity increases until 20%.

Based on the submitted aspects one can sustain chemical interactions between KT and PVP.The mains differences observed in the FT-IR spectrum of binary mixture of KT:MS were:

- a significant increase (≈30%) of the band attributed to the OH group (3450 cm^{-1}), respectively for the bands from 2732 to 2543 cm^{-1} region (≈45%);
- the intensity of the absorption bands from 1700, 1655, 1575, 1455, 1285, 970, 720 cm^{-1} is maintained or increased (≈15%).

On the basis of mentioned differences it may be considered that the KT interacts with MS and the appearance of the new bands is not possible because of the obtained products from the chemical interaction (the magnesium salt of KT and free stearic acid).

The X-ray powder diffraction has been used for qualitative and quantitative identification of crystallinity in order to investigate the possible interaction of KT with PVP and MS, besides the FT-IR

spectroscopy which is a qualitative analysis technique [12,17,22]. The X-ray diffraction patterns of the KT, PVP and KT–PVP mixture, respectively KT, MS and KT–MS mixture are shown in Figs. 8 and 9.

The additional prominent DSC peaks in the mixtures of the drugs and excipients are a positive indication of chemical interaction of the drugs with excipients. Such interaction should result in the partial or complete disappearance of the reactant phases and appearance of new phases, which can be inferred from X-ray diffraction patterns. X-ray diffraction patterns of the mixture, prepared at room temperature, when compared with those of its individual components showed appearance of new lines and disappearance of some of the lines present in the individual components.

The X-ray patterns of KT–PVP mixture prepared at room temperature did not show the lines in addition to those present in patterns of the individual components (Fig. 8). However, the number of lines present in the XRD patterns of the individual components was found missing in the similar pattern recorded for the mixture. The significant difference in the X-ray patterns of the drug–excipient mixtures compared to those of individual drugs and excipient indicates possible incompatibility of the drugs with the excipient, even at room temperature. The presence of majority of the lines of the parent substances in the thoroughly ground mixture prepared at room temperature, corresponding to the significant increase of the peak's intensities indicates the interaction of KT with PVP at room temperature, which could increase with the increased temperature.

The diffractogram of the binary mixtures KT–MS (Fig. 9) does not show the appearance of new lines. The same diffractogram indicates disappearance of some of the diffraction lines of higher, moderate and lower intensities in the mixture which are originally present in the X-ray diffraction patterns of the individual components. In the same time, the intensities of the majority peaks are appreciably increased. These differences indicate the interaction of KT with MS at room temperature, which could increase with the increased temperature.

4. Conclusions

The compatibility and stability of KT with different excipients was studied by the thermal methods of analysis, the FT-IR spectroscopy and X-ray diffraction patterns.

The results confirmed that thermal analysis is an effective and reliable technique in the compatibility studies of drug–excipient mixtures. Moreover, the DSC technique offers significant advantages, so that it is considered as a fast screening tool for drug–excipient interaction in a preformulation process.

The changes in the profile of thermoanalytical curves (TG/DTG and DSC) in the case of some binary mixtures indicate the production of some interactions as a function of heating.

According to the thermal curves, especially DSC curves, one can say that all tested excipients, less PVP and MS, present compatibility with KT. This fact is supported by the differences between the values of T_{fusion} and of the enthalpies of melting (ΔH_{fusion}).

Considering that the enthalpies of melting are quantitative data since they may be expressed as a fractional change, it could be said that PVP and MS certainly interact chemical with KT. In the same context, the small variations of ΔH_{fusion} for the other binary mixtures can be attributed to some heterogeneity in the small samples. For the binary mixture KT–CSD, it can consider that a physical interaction takes place, an interaction which is not supposed to the corresponding compatibility.

Because, the presence of solid–solid interaction does not necessarily indicate pharmaceutical incompatibility, other analytical techniques were also used, such as FT-IR and XRPD, which can help in the interpretation of thermal results generally, respectively of DSC results particularly, in order to confirm the changes observed in drug–excipients curves.

The interaction of PVP, respectively MS with KT was confirmed by FT-IR spectroscopy and by X-ray diffraction patterns. For the other excipients, the two mentioned techniques do not indicate an incompatibility with KT because the absorption bands, respectively the diffraction peaks of KT remained unchanged in the physical mixtures.

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