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Solid-state interaction of ibuprofen and Neusilin US2

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ABSTRACT

The aim of the present study was to evaluate the influence of magnesium aluminometasilicate (Neusilin US2) on ibuprofen stability at higher temperatures. Seven binary mixtures of the drug and the silicate were prepared. They were examined by thermogravimetry (TGA), quadrupole mass spectrometry (QMS) and differential scanning calorimetry (DSC). The results confirmed that in the presence of the magnesium aluminometasilicate ibuprofen free acid reacted to form a higher melting, less volatile salt. The presence of the salt was additionally confirmed by FT-IR and H NMR spectra. It leaded to the conclusion that Neusilin US2 had a beneficial effect on the drug stability. The drug to silicate ratio to protect the highest amount of the drug from evaporation by using the lowest amount of the excipient was found to be 40:60 and 50:50 weight percent.

1. Introduction

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) widely used in the therapy as an analgesic and antipyretic agent. Its chemical formula can be described as (RS)-2-(4-isobutylphenyl)propionic acid. Ibuprofen is colourless, crystalline powder of molecular weight 206 g/mol and melting point 75–77 °C [1]. From an open container ibuprofen evaporates and exhausts the material before it reaches the boiling point at 157 °C [2]. The evaporation process is zero order and limited to the surface area [3,4]. The activation energy is from 81.8 to 87.0 kJ mol^{-1} [3]. The enthalpy of vaporization is in the range 42.7–46.1 kJ mol^{-1}, suggesting that ibuprofen molecules are existing as dimers in the liquid state and dissociate to monomers in the vapor state [2,3]. In spite of the fact that ibuprofen is sensitive to thermal, oxidative and photolytic degradation, which yield a number of products some showing toxic effects, it is considered as the one of the safest NSAID drugs and several liquid, or solid formulations are still developed [5,6].

During the formulation development, efforts have been made either to predict possible interactions between the formulation components or to assure the stability of the drug, especially if the heating process was involved in the technology. Many interactions in the solid state between ibuprofen and excipients have been described [7–10].

Devay et al. [7] focused on the incompatibility between ibuprofen and povidone in their physical mixtures that resulted in the formation of a glass-like phase at the ambient temperature. The presence of eutectic mixtures after blending ibuprofen with stearic acid was stated using differential scanning calorimetry (DSC) by Lerdkanchanaporn et al. [8]. The same authors investigated also the influence of a starch on the stability of ibuprofen in binary mixtures [2,9]. Based on the TGA results, they showed that the increase in the ibuprofen content involved the increase in the temperature of the drug evaporation [9].

As a weak acid ibuprofen forms salts with basic oxides, hydroxides, and with other salts. Solid-state interaction between magnesium oxide and ibuprofen, resulting in a salt formation, has been reported by Kararli et al. [10]. The authors observed that to initiate this kind of reaction in the solid state, the presence of water was required. The role of water was to facilitate the diffusion of the acidic and basic compounds in the system. Tablets containing ibuprofen and magnesium oxide in the molar ratio 1:1 became softer and sticker during storage, under the influence of the arising amount of water, which was, beside the magnesium ibuprofenate, the product of the reaction.

In the recent years, the growing attention has also been paid to synthetic silicates as multipotential excipients for solid dosage forms manufacturing [10–17]. Because of high specific surface area and high porosity, silicates can be used as adsorbents, especially with regard to small drug molecules [11,13–15]. They have been used for loading as well as for controlled releasing of drugs [14].

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Spray-dried synthetic magnesium aluminometasilicate (Neusilin) is the excipient which currently attract scientific attention. There are more than 10 grades of Neusilin which differ in physical appearance, bulk density, pH of the slurry, specific surface area, or adsorbing capacity. Neusilin US2 (NEU) consists of amorphous microporous granules of magnesium aluminometasilicate with high surface area (300 m^2/g) [18,19]. Neusilin is amorphous and contains either tetrahedron or octahedron of Al, octahedron of Mg and tetrahedron of Si which are randomly attached to form a complex three dimensional structure [19]. Like many complex silicates, the surface of Neusilin has different types of silanol groups, which make it a potential proton donor as well as an acceptor. The hydrogen bonding potential of silanols in the local environment on silica surfaces is well documented [20,21]. Neusilin is practically insoluble in water. The pH of the 4% (w/v) slurry of NEU in water is 7.4, indicating its neutral nature [18]. However, titration curves of NEU are more characteristic of a universal buffer. It may be that OH groups associated with Si, Mg and Al have different acidic and basic strengths [18].

The application of a synthetic magnesium aluminometasilicate was the subject of several studies [16–23]. It has been used mainly as a carrier for solid dispersion to improve drug dissolution, or to granulate oily formulations as well as to increase the formulation stability. Kukita et al. [24] reported that the incorporation of magnesium aluminum silicate into the tablet matrix containing bromhexine hydrochloride prevented the desorption of the drug from tablets to the package material upon storage [24]. Due to the high specific surface area of the silicate, bromhexine hydrochloride adsorbed to the silicate rather than to the polyethylene film of the blisters that resulted in improved stability of the tablets. Bahl and Bogner [25] studied the effect of NEU on the amorphization of indomethacin during co-grinding. They described interactions occurring between indomethacin and the surface of NEU, which led to the physical stabilization of the drug. It was found that the process of co-grinding might be a potential strategy to manufacture physically stable indomethacin in the amorphous form. Similar results obtained Gupta et al. [18] who investigated the formation of physically stable amorphous drugs such as ketoprofen, indomethacin, naproxen and progesterone by milling with Neusilin.

In the present study the effect of the magnesium aluminometasilicate (NEU) on the stability of ibuprofen is investigated. Taking into account the chemical composition of NEU as well as its adsorbing properties, it is interesting to identify: (i) if any solid-state interaction between the drug and the excipient occurs, (ii) to see if the presence of the silicate influences the temperature properties of ibuprofen, (iii) to find the binary mixture composition which assure the protection of the highest amount of the drug from evaporation using the lowest quantity of the excipient. To our best knowledge this topic has not been reported in the literature.

2. Materials

Racemic ibuprofen (IB 100, Shasun Chemicals and Drugs Ltd., India) was used as a model drug for the present study. Synthetic, spray-dried magnesium aluminometasilicate—Neusilin grade US2 (NEU, Fuji Chemical Industry Ltd., Japan) was used as an excipient. On the base of TGA results the molecular formula of NEU used in the present study was described as $Al_2O_3{\cdot}MgO{\cdot}1.7SiO_2{\cdot}5.5H_2O$ with the molar mass for theoretical calculations of 343 g/mol.

3. Preparation of binary mixtures

The binary mixtures of ibuprofen and magnesium aluminometasilicate were prepared by blending both substances in a mortar at room temperature for 5 min. Seven physical mixtures were prepared in different ibuprofen to Neusilin mass ratios as listed in Table 1. The results from micro-Raman spectrometry confirmed the uniformity of the samples [26].

4. Methods

The properties of the mixtures were examined using thermogravimetry (TGA), quadrupole mass spectrometry (QMS), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR) and nuclear magnetic resonance spectroscopy (^{1}H NMR). All the analyses were carried out 24 h after the binary mixtures preparation. The same measurements were made for the pure ibuprofen (IB 100) and Neusilin (NEU) as the references.

5. Thermogravimetric analysis (TGA–QMS)

The TG curves were obtained using TGA/SDTA 851^e Mettler Toledo instrument connected to ThermoStar GSD300T Balzers quadrupole mass spectrometer (QMS). The instrument was calibrated with indium, zinc and aluminum. Its accuracy is equal to 10^{-6} g. The sample mass varied from 9.87 to 11.54 mg. Measurements were made in Ar (80 cm^3/min) from 25 to 300 °C with the heating rate $\beta = 5$ °C/min, or from 25 to 800 °C with $\beta = 10$ °C/min. The mass spectrometer was operated in electron impact (EI) mode using channeltron as a detector. Screening analyses were performed in the selected-ion monitoring (SIM) mode. The ions characteristic of each compound such as 16, 17, 18 for water and 27, 43, 77, 91, 119, 163 for ibuprofen were monitored.

Table 1
Parameters derived from TG/DTG and DSC experiments for pure components and their binary mixtures.

Sample	Composition [%]		TG			DTG				DSC [a]	
	IB	NEU	Mass loss [%]			T_{peak} [°C]	Mass loss [%]			ΔH [J/g]	IB involved in salt [%]
			Cal.[b]	Exp.[c]	Δ[d]		Cal.[b]	Exp.[c]	Δ[d]		
NEU	0	100	17	17	0	197	2	2	0	–	–
IB10	10	90	25	17	8	197	12	2	10	–	10
IB25	25	75	38	20	18	190	26	3	23	2	24
IB40	40	60	50	28	22	175	41	7	34	11	31
IB50	50	50	59	37	24	186	51	17	34	30	26
IB60	60	40	67	47	20	189	60	28	32	43	25
IB75	75	25	79	65	14	202	75	51	24	73	17
IB90	90	10	92	83	9	214	89	76	13	102	9
IB100	100	9	100	100	0	221	99	99	0	126	–

[a] Melting of ibuprofen.
[b] Mass loss calculated for mixtures on the assumption that there is no interaction between ibuprofen and Neusilin.
[c] Results of the experiment.
[d] Difference between calculated and measured values.

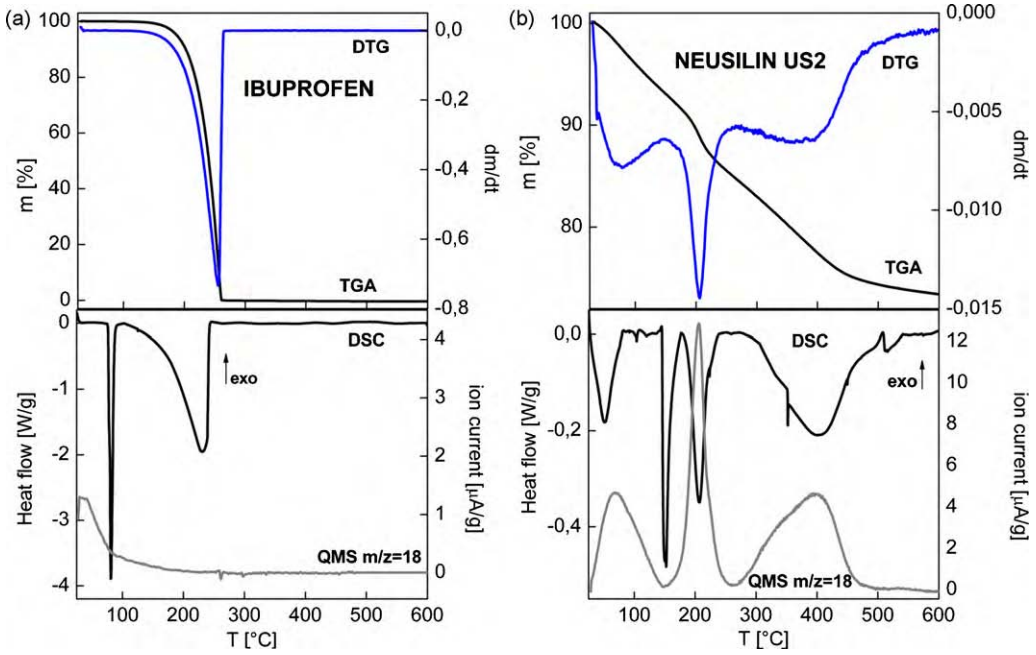

Fig. 1. TG, DTG, QMS and DSC profiles of ibuprofen (a) and Neusilin (b).

6. Differential scanning calorimetry analysis (DSC)

The DSC plots were obtained using DSC 821^e Mettler Toledo apparatus in the Ar atmosphere (80 cm^3/min). The instrument, which accuracy is equal to 10^{-6} W was calibrated with indium and zinc. All samples were heated from 25 to 300 °C with scanning rate 5 °C/min. The sample mass varied from 8.71 to 13.92 mg. All measurements were performed with an aluminum open pan. The empty pan was used as the reference sample.

7. Fourier transform infrared spectroscopic analysis (FT-IR)

FT-IR spectra of ibuprofen, Neusilin and their binary mixtures were prepared. Samples of approximately 1 mg were blended with 400 mg of KBr and compacted to form a tablet. The spectra were recorded in the absorbance scale by using the Bio-Rad spectrometer type FTS 60 MV. The average of 256 scans for each sample was collected within the MIR spectra region from 4000 to 400 cm^{-1}. The resolution was set at 2 cm^{-1}.

8. Nuclear magnetic resonance analysis (^{1}H NMR)

The ^{1}H NMR spectra were obtained using a Mercury-VX 300 MHz spectrometer. DMSO was used as a solvent. The ^{1}H NMR spectra of the pure substances as well as the binary mixtures were studied and recorded in 5 mm tubes at room temperature. The following conditions were adopted: frequency 300 MHz, 45° pulse, relaxation delay 1 s, acquisition time 1.998 s, spectral width 4.20 kHz. Sixteen repetitions were performed.

9. Results and discussion

The TG–QMS and DSC curves of ibuprofen alone (IB 100) and Neusilin were plotted in Fig. 1a and b, respectively. The TGA of ibuprofen shows the total mass loss up to 270 °C due to the evaporation of the sample. DTG plot shows clearly a zero order process which is consistent with the process of evaporation [3]. The thermal instability of ibuprofen do not allow to record QMS signal from the pure drug. There was only a very small amount of water detected by mass spectrometer during the simultaneous measurement. DSC curves of ibuprofen show two endothermic peaks: the first with onset at 75 °C corresponds with the drug melting; the second with the onset at 150 °C originates from evaporation [2,3]. The process of ibuprofen evaporation is completed at about 270 °C.

In case of pure Neusilin, the weight loss was about 30%. The only volatile component was water that evaporated from the sample up to 500 °C. From the QMS profiles of Neusilin three peaks originating from water can be seen. The water might have been adsorbed on the surface, included between powder granules or crystallized in the lattice. DTG curve confirmed three-step mass loss and the minimum of the peaks were in agreement with the positions of peaks in the QMS signal. DSC curve for Neusilin exhibited four endothermic peaks. Three of them overlapped with DTG and QMS peaks showing thermal effects of a dehydration process. The peak with minimum at about 150 °C had different origin, but describing its nature was not the aim present study.

TGA and DTG plots for seven binary mixtures of ibuprofen and Neusilin in different ratios are shown in Fig. 2.

The samples were heated with $\beta = 5$ °C/min from 25 to 300 °C. After the experiments all samples remained white. As can be seen from Fig. 2, the heating of the sample up to 300 °C causes the total evaporation of ibuprofen from the samples. However, the weight loss observed on the TG profiles is lower than it has been expected taking into account the mixtures composition. It indicates the interaction between ibuprofen and Neusilin in the solid state.

FT-IR and ^{1}H NMR methods were chosen to study the character of the interaction between the drug and excipient. The FT-IR and ^{1}H NMR spectra of ibuprofen (IB 100), Neusilin (NEU) and their binary mixture IB 50 are shown in Fig. 3a and b, respectively. In the FT-IR spectrum of ibuprofen a band of high intensity corresponding to the stretching vibration from carbonyl group ($\nu_{C=O}$) can be seen at 1722 cm^{-1} [27]. Its intensity in the spectrum of the mixture IB 50 decreases seven times, and a new band characteristic of the carboxylate ion appears at 1597 cm^{-1}. It leads to the conclusion that during blending ibuprofen with Neusilin at room temperature a salt is formed. Similar conclusions have already been reported on the base of FT-IR spectra for ibuprofen salts formed with other silica materials [10,14,16].

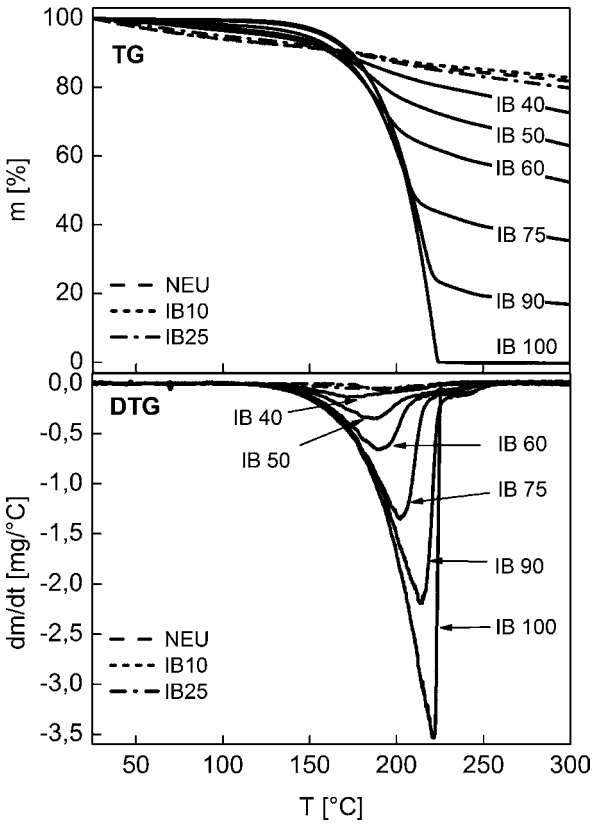

Fig. 2. TG and DTG profiles for pure components and studied binary mixtures.

^{1}H NMR analysis of the pure ibuprofen and its binary mixtures confirms the hypothesis that ibuprofen interact with Neusilin to form a salt. As it can be seen from ^{1}H NMR spectra, in case of the pure drug the signal characteristic of the proton from the carboxylic group is detected at 12.20 ppm (Fig. 3b). The height of the peak is 3.97 but its intensity decreases to 2.51 for the mixture IB 90, to completely disappear for IB 50. It confirms that there is no free carboxylic group in IB 50. These findings are in good agreement with the data shown in Table 1.

Kukulska-Zajac et al. [27] studied the reaction of the acetic acid with surface sites such as Mg–OH, Si–OH and Al–OH in porous silicates. They concluded that acetate ions were the product of the reaction between the acetic acid and OH groups of MgO and Al_2O_3 even at room temperature. They reported also that SiO_2 does not take part in the reaction. Thus the interaction of a similar mechanism may occur when ibuprofen is blended with Neusilin.

To determine the amount of ibuprofen, which reacted with Neusilin and then remained in the mixtures in the form of a salt, the differences between a theoretical weight loss and experimental data obtained from TG experiments were calculated (Table 1). The theoretical calculations were performed assuming that there was no interaction between ibuprofen and Neusilin and all the amount of ibuprofen present in the mixture evaporated. However, the results taken from TG curves might be encumbered with errors, which are difficult to estimate because the amount of water that was formed in the reaction and then evaporated, may influence calculated parameters.

The values derived from the same experiments but based on DTG plots seem to give more reliable results. DTG curve for pure ibuprofen (Fig. 2) shows a single peak with the onset at 150 °C originated from the drug evaporation [2]. There are no such peaks in case of pure Neusilin and IB 10, or IB 25. The peak from the samples containing the amount of the drug in the range 50–90% exhibits a complex character. It seems to be the result of overlapping two peaks: one with the onset at 150 °C (evaporation of ibuprofen) and the second with the onset at about 210 °C. The area under the main peak describes the weight loss in the temperature range from 130 to 220 °C, illustrating mainly the evaporation of the unreacted ibuprofen from the mixture.

The thermogravimetrical experiments show that only for the mixtures with the lowest ibuprofen content (i.e. IB 10 and IB 25)

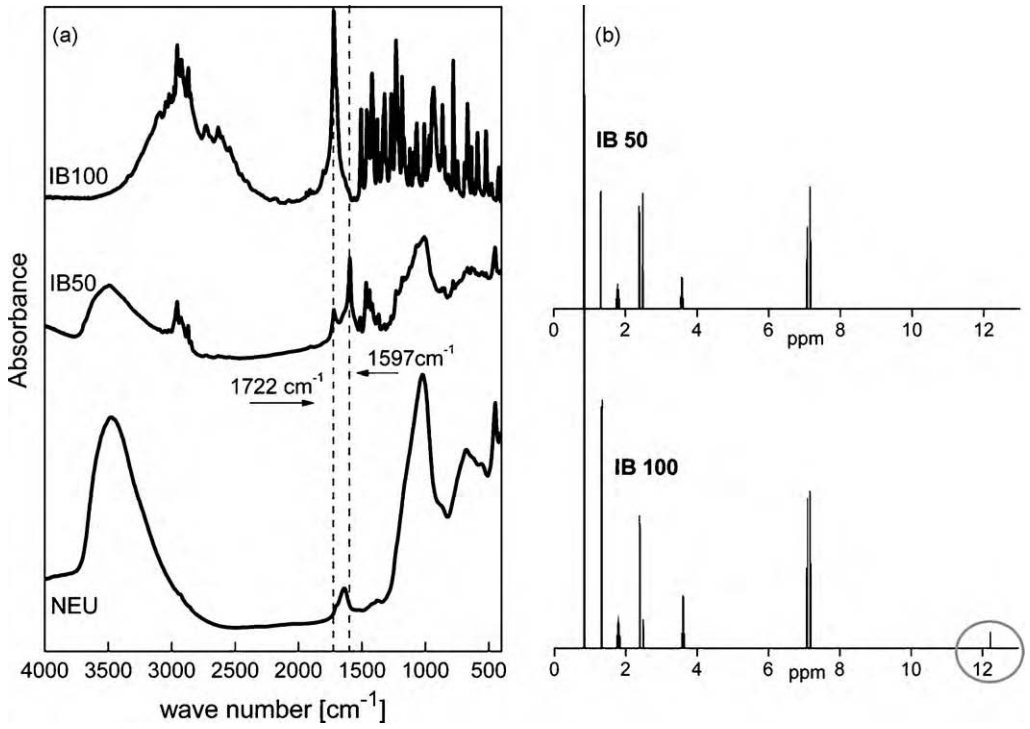

Fig. 3. (a) FT-IR spectra of pure ibuprofen, Neusilin and the binary mixture IB 50 and (b) ^{1}H NMR spectra of pure ibuprofen and binary mixture IB 50.

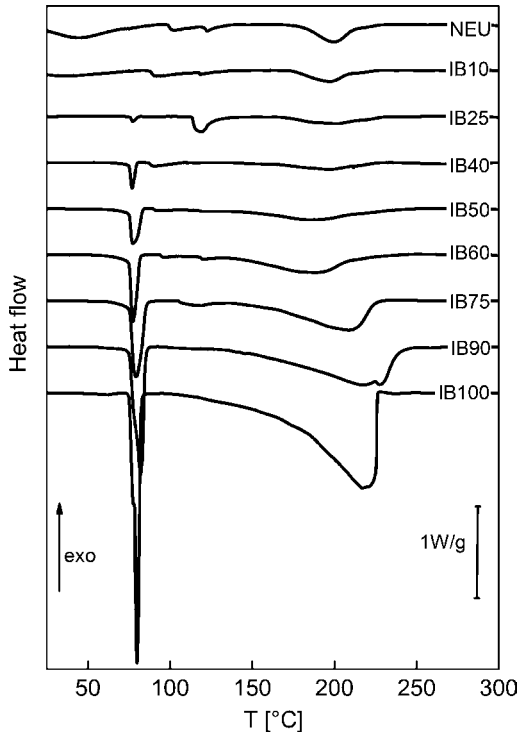

Fig. 4. DSC profiles for IB 100, NEU and their binary mixtures.

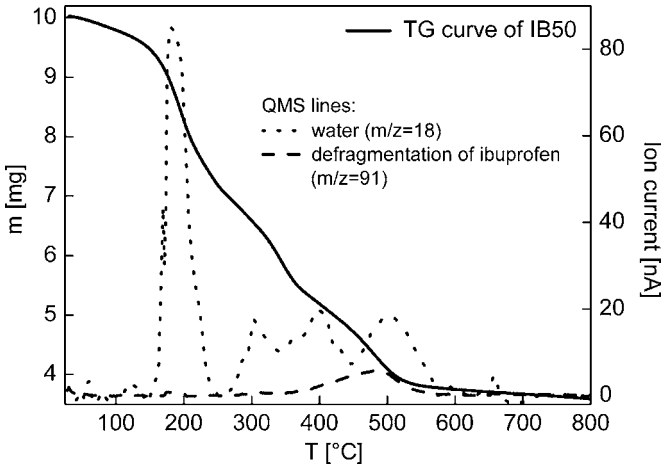

Fig. 5. TG/QMS curves of the IB 50 mixture.

all drug remains in these samples in the temperature range from 25 to 300 °C. For other mixtures only a part of ibuprofen reacts with Neusilin and the weight loss resulted from the evaporation of the unreacted drug and water. For the mixtures with the highest ibuprofen concentration, a part of ibuprofen remains unreacted because the amount of Neusilin is insufficient. The values calculated from DTG curves as a difference between theoretical and experimental data for all studied samples can be considered, with good approximation, as the amount of ibuprofen, which remains in the binary mixtures in the form of the salt.

In the DSC plots, the melting endotherm (onset at 75 °C) characteristic to pure ibuprofen, can be seen (Fig. 4). Its intensity decreases gradually with increasing the content of Neusilin in the mixture. In case of IB 25 the peak is very small, but another peak with the onset at 115 °C appears. Its origin needs further studies. Finally, the peak characteristic to pure ibuprofen disappears completely for the mixture IB 10.

In studies on the solid-state interaction between ibuprofen and magnesium oxide, Kararli et al. [10] described the appearance of a new endothermic peak at 161 °C and attributed it to the IB–Mg salt formation. In our investigation such peak was not observed. This is in agreement with the hypothesis that the salt formed when ibuprofen is blended with Neusilin does not precipitate as $Mg(IB)_2$ but stays in the mixture in ionic or complex form.

The quantitative data obtained from DSC experiments are listed in Table 1. Due to the fact that the peaks originated from the drug evaporation overlap with these from water evaporation, only the peaks illustrating the melting of ibuprofen are taken into consideration. The values of the enthalpy calculated from DSC profiles confirm that not total amount of the drug presented in the mixture undergoes melting during the heating process. A part of ibuprofen reacts with Neusilin and forms of a new compound of different thermal properties. Moreover, the peak illustrating the evaporation of ibuprofen from the samples (onset at 150 °C) actually disappears when the amount of the drug in the mixture is less than 50%. It confirms that the interaction between ibuprofen and Neusilin starts when the substances are blended together at room temperature and becomes more effective after the melting of the drug.

Although samples were subjected to the heat treatment under the same conditions twice, reporting the statistical data are not advisable [2,28]. The purpose of performing a few runs was only to ensure repeatability of the TGA and DSC experiments. There are two main reasons why the data were reported without their precision to allow the statistical calculation. Firstly, the results were taken directly from the measurements performed on the instruments of such a high accuracy that gives very small statistical error (c.a. 1%). However, they might be additionally encumbered with other errors, more difficult to estimate. These errors might originate from the data analyzing process (e.g. assumption of the integration limits), weighting the samples for DSC experiments, influence of water produced during a salt formation, etc. Therefore it would be a simplification to consider the statistical error as the main one. Secondly, the data in Table 1 were listed with the aim of showing the tendency rather than to give the quantitative information about the mixtures. It leads to the conclusion that the amount of the salt created at high temperatures is the highest in case of the mixtures IB 40 and IB 50. To protect the highest amount of the drug from evaporation by using the lowest amount of the excipient, it was necessary to prepare the binary mixtures using the following drug to silicate ratio 40:60 and 50:50 weight percent.

To complete the thermal characteristics of the binary mixtures, additional TG–QMS experiments were carried out. The samples were heated from 25 to 800 °C with the heating rate $\beta = 10$ °C/min. As an example, thermal decomposition of the binary mixture IB 50 is shown in Fig. 5. The total weight loss at the studied temperature was 64%. The main products were water, unreacted drug and its salt. A small peak originated from ibuprofenate ions is found between 400 and 550 °C in the QMS profile. The fact that it was possible to observe the QMS signal from ibuprofen proves also that at high temperature the drug was in less volatile form [10].

The remainders collected after the experiment, were black while pure Neusilin heated to 800 °C remained white. The effect was observed for all studied samples except for IB 10 which was grey. It suggests that at high temperature salt form of ibuprofen undergoes decomposition and a carbon deposit is formed. The samples changed the colour again from black to white after further heating

to 1400 °C in the air atmosphere, and according to expectations, carbon dioxide evolved.

10. Conclusions

The results obtained confirm that in the presence of the magnesium aluminometasilicate (Neusilin) the stability of ibuprofen at high temperatures is improved. TGA analysis shows that at the temperature range from 25 to 300 °C ibuprofen is still present in the sample, in form of salt, whereas the pure ibuprofen evaporates completely up to 250 °C. Nevertheless, it is revealed that the composition of the binary mixture determines the amount of ibuprofen remaining in the sample. No ibuprofen evaporation is found in case of the mixtures containing from 10 to 25 weight percent of the drug.

The mechanism of the phenomenon can be explained by the formation of a salt in the reaction between the carboxyl group of ibuprofen and OH groups from the surface of Neusilin. It is also found that the reaction is initiated during blending the drug and the excipient at room temperature.

The drug to silicate ratio to protect the highest amount of the drug from evaporation by using the lowest amount of the excipient was found to be 40:60 and 50:50 weight percent. Furthermore, ibuprofen remains in the binary mixture containing 50% of the drug even at higher temperature.

Finally, the obtained results show that the interaction between ibuprofen and Neusilin can be used to prevent the evaporation of ibuprofen at high temperatures. These findings may allow the application of the drug in technologies that involve the heating process.

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