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# STUDY ON COMPATIBILITY OF IMATINIB MESYLATE WITH PHARMACEUTICAL EXCIPIENTS

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Differential scanning calorimetry and thermogravimetric analysis with the support of X-ray powder diffraction and infrared spectroscopy were used as screening techniques for the compatibility testing of imatinib mesylate, with following excipients: magnesium stearate, polyvinylpyrrolidone, microcrystalline cellulose. In order to maximize the probability of interactions 1:1 (by mass) drug: excipient binary mixtures were analysed and compared to individual components. Additionally an influence of storage at temperatures of 25 and 40°C on physico-chemical stability on drug – excipient binary mixtures was investigated.

The largest visible changes were observed in the DSC curves of imatinib mesylate – magnesium stearate mixtures.

***Keywords:*** *compatibility, drug-excipient interactions, DSC, infrared spectroscopy, TG, X-ray powder diffraction*

## Introduction

In a solid dosage form 'inactive' ingredients – excipients should stabilize an active component – a drug substance but it is known that they can interact with a drug changing its stability, dissolution rate, solubility and bioavailability [1, 2]. Studies of an active drug substance – excipients interactions in preformulation mixtures are essential to design proper solid dosage forms [3].

Many factors have crucial influence on phase transformations in formulation and its shelf-life. The degree of crystallinity of an excipient, its polymorphic form and ability to inhibit hydrate formation of an active substance should be taken into account. Under enhanced moisture conditions a hygroscopic amorphous ingredient absorbs water more than a crystalline one. For this reason it is advisable to apply a hygroscopic excipient, which hinders the water sorption by the drug [4].

Differential scanning calorimetry has been used as a screening tool in prediction of interactions between components in preformulation studies. Shifts, a disappearance or an appearance of additional peaks, changes in enthalpy values can suggest about incompatibility. But it should be taken into consideration that interactions observed at higher temperatures do not have to be present or/and observed at room temperature. Solid–solid interactions are very slow at room temperature. When a reaction temperature increases the kinetics of physicochemical processes in a preformulation mixture is faster. In order to explain or exclude some ambiguity additional techniques e.g. X-ray powder diffraction or infrared spectroscopy should be used [5, 6].

Imatinib mesylate (Fig. 1) (4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-{[4-(3-pyridinyl)-2-pyrimidinyl]amino} phenylbenzamide monomethanesulfonate) (Gleevec® or Glivec®, the manufacturer – Novartis Pharmaceuticals [7]) is a novel therapy for the treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumors (GISTs). In CML, the Philadelphia chromosome leads to a fusion protein of abl with bcr. Imatinib mesylate is a 2-phenylaminopyrimidine derivative that decreases tyrosine kinase bcr–abl. Gastro-

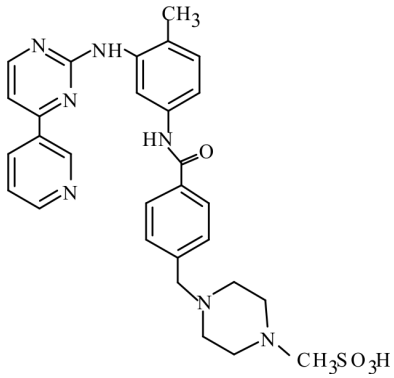


**Fig. 1** The structural formula of imatinib mesylate

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intestinal stromal tumors characterize resistance to chemotherapy. The first step of GIST development is probably the c-kit gene mutation. Imatinib mesylate has been also found to be useful as the c-kit tyrosine kinase inhibitor [8, 9].

Imatinib mesylate exists in two polymorphic forms: α and β. Both forms belong to the triclinic crystal system with the P-1 space group but have different cell parameters. The unit cell parameters are following for form α: $a$=9.467(1) Å, $b$=9.8820(1) Å, $c$=18.076(2) Å, α=99.11(3)°, β=89.45(4)°, γ=117.28(5)° and for form β: $a$=9.094(1) Å, $b$=10.527(2) Å, $c$=15.280(3) Å, α=93.37(4)°, β=93.90(5)°, γ=90.86(8)° [10]. In this investigation thermal behaviours of individual components as well as binary mixtures of form α are studied.

## Experimental

Form α of imatinib mesylate (IM) was manufactured at the Pharmaceutical Research Institute in Warsaw [11]. The active substance was characterised by low solvents content (below 0.5%). Residual solvents were determined by GC method. Gas chromatograph Schimadzu GC-2010 with flame-ionization detector, DB-624 column and headspace autosampler injector (PerkinElmer TurboMatrix 40) was used. Long-term tests proved polymorphic and chemical stability of form α.

As excipients, following commercial substances were used: magnesium stearate – Merck, polyvinylpyrrolidone (Kollidon CL) – BASF, microcrystalline cellulose (Vivapur 102Si) – IRS. The measurements were performed for individual ingredients as well as 1:1 (by mass) physical mixtures of imatinib ratio of imatinib mesylate and selected excipients.

Additionally, mixtures stored three months at temperatures of 25 (60% RH) and 40°C (75% RH) were investigated.

Thermal analyses were carried out by means of the DSC 822 with IntraCooler and the TG/SDTA 851 cells (Mettler Toledo) in the nitrogen atmosphere. Accurately weighed samples (4–7 mg) were packed in aluminium pans with pierced lids. In both experiments, samples were heated from 25 to 300°C, with the scanning rate of 10°C min$^{-1}$. The two-minute isothermal step at the temperature of 25°C preceded the dynamic temperature regime for DSC measurements. The DSC instrument was calibrated using indium and zinc as standards. For the calibration of the TG instrument measurements with indium and aluminium were performed. TG measurements were blank curve corrected.

XRPD studies were carried out by means of the MiniFlex diffractometer (Rigaku Corporation, Tokyo Japan) using $CuK_{\alpha 1}$ radiation. Samples were gently pressed on a glass plate and the instrument was operated in the continuous scan mode in the range from 3 to 40°.

Fourier transform infrared (FTIR) spectra (ν in cm$^{-1}$) were recorded from 4000 to 400 cm$^{-1}$ with a resolution of 4 cm$^{-1}$ using the PerkinElmer Spectrum BX spectrometer. The spectra were scanned by averaging 8 scans for each transmission spectrum. Before performing the FTIR spectrum of the substance in the KBr pellet, a background spectrum with the atmosphere as reference was recorded. Thus the spectral features of the air ingredient do not interfere with spectra of the substance. Samples for IR studies were prepared by mixing 2 mg of the analyzed substance with about 150 mg of spectral grade potassium bromide and compressing in a hand-held minipress at 10 tons for 10 s.

## Results and discussion

DSC curves and thermograms of individual substances, initial binary mixtures and stored three months are shown in Figs 2–4. Thermal data are collected in Table 1.

The DSC trace of IM substance demonstrates the single melting endotherm ($T_{onset}$=225.41°C, $\Delta H$=101.74 J g$^{-1}$). The TG measurement confirmed that the substance decomposes at its melting point. Kollidon and Vivapur show a very broad endothermic effect characteristic of the polymer dehydratation and the moisture evaporation respectively (Figs 2a and 3a). TG analysis proved a considerable mass loss

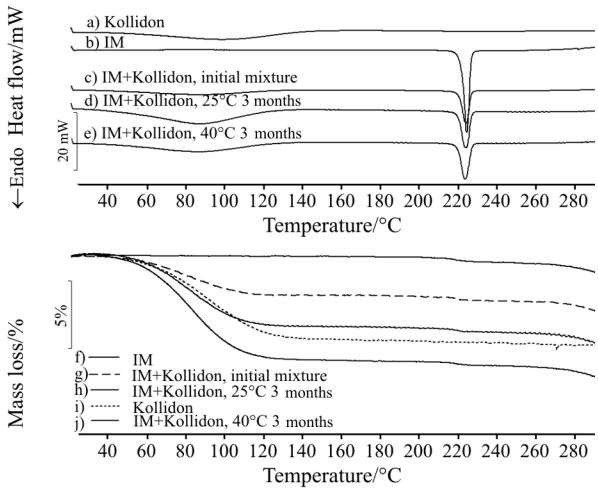


**Fig. 2** DSC and TG curves of individual components: Kollidon and IM as well as 1:1 *m*/*m* mixtures of IM and Kollidon before and after storage at 25°C (60% RH) and 40°C (75% RH)

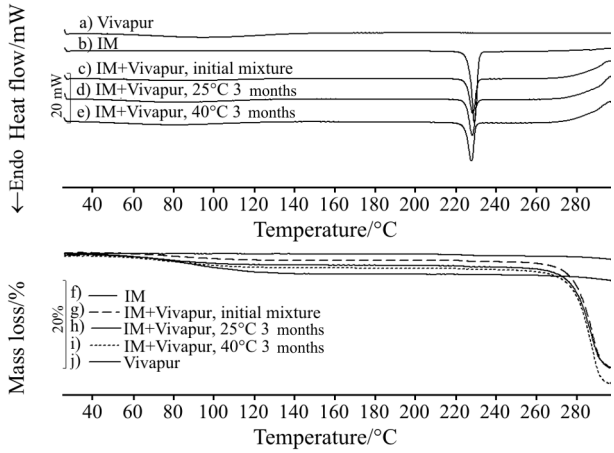


**Fig. 3** DSC and TG curves of individual components: Vivapur and IM as well as 1:1 *m*/*m* mixtures of IM and Vivapur before and after storage at 25°C (60% RH) and 40°C (75% RH)

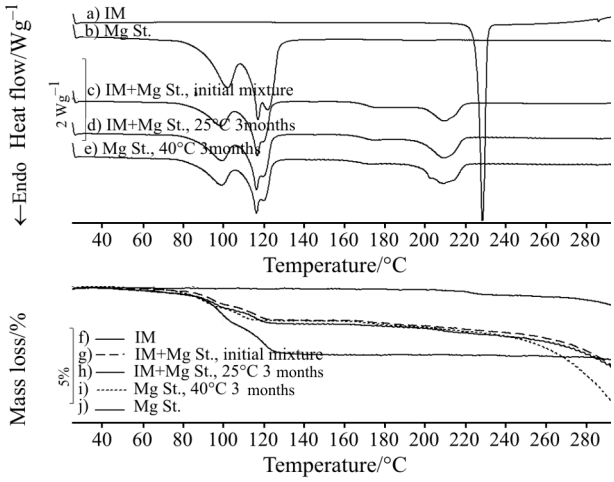


**Fig. 4** DSC and TG curves of individual components: magnesium stearate and IM as well as 1:1 *m*/*m* mixtures of IM and magnesium stearate before and after storage at 25°C (60% RH) and 40°C (75% RH)

for Kollidon (6.2%) and Vivapur (4.4%) (Figs 2i, 3j). A two-step dehydration process, with a total mass loss of 4.5%, revealed magnesium stearate (Fig. 4j).

DSC curves of the initial and the stored mixtures of IM and Kollidon are similar (Figs 2c–e). The onset temperature shift of the active substance by approx. 1°C towards lower temperatures, decrease in enthalpy and the peak height to width ratio were observed in comparison with the IM sample. TG analysis confirmed the tendency of Kollidon to water sorption. Double and triple rise in the water content was observed after storage at 25 and at 40°C respectively (Figs 2h and j), in comparison with the initial mixture (Fig. 2g). Powder diffractograms of the studied mixtures show only the presence of the IM

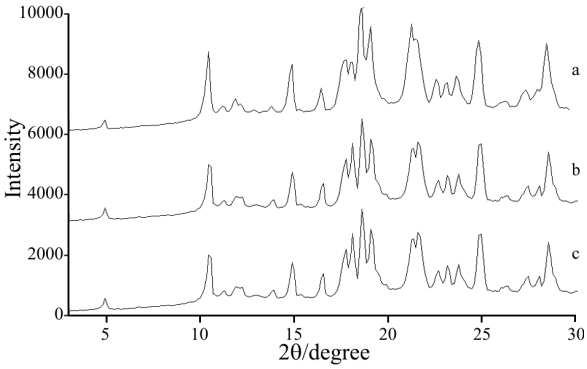


**Fig. 5** X-ray diffractograms of IM and Kollidon binary mixtures; a – initial mixture, b – mixture after storage at 25°C (60% RH), c – mixture after storage at 40°C (75% RH)

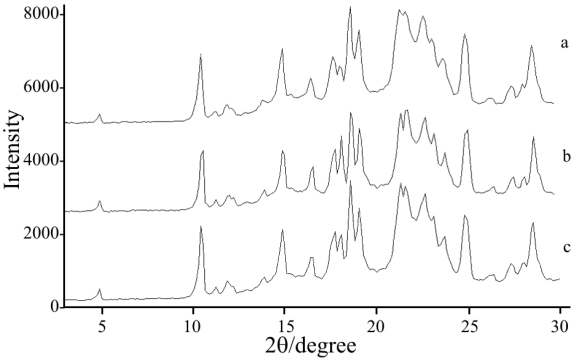


**Fig. 6** X-ray diffractograms of IM and Vivapur binary mixtures; a – initial mixture, b – mixture after storage at 25°C (60% RH), c – mixture after storage at 40°C (75% RH)

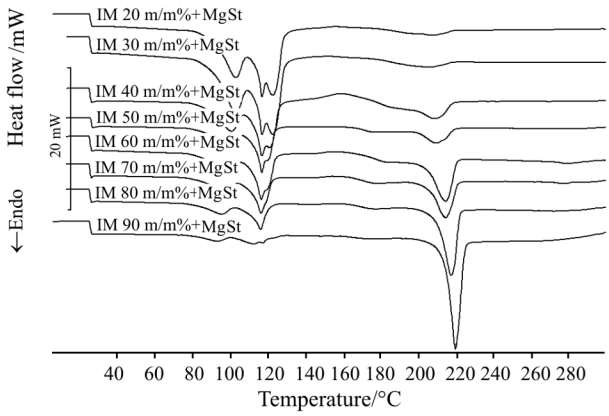


**Fig. 7** DSC curves of IM and magnesium stearate mixtures with a various composition of components

reflections with the amorphous background of Kollidon (Fig. 5).

For the initial and the stored mixtures of IM and Vivapur the endotherm of the IM substance was apparent from DSC curves (Figs 3c–e). Thermal

**Table 1** Thermal data of individual components as well as binary mixtures of imatinib mesylate

| Sample | $T_{onset}$/°C | $\Delta H$/J g$^{-1}$ | Peak height to width ratio | Mass loss/% |
|---|---|---|---|---|
| IM | 225.41 | 101.74 | 9.57 | 0.5* |
| Kollidon | – | – | – | 6.2 |
| IM+Kollidon initial mixture | 224.44 | 54.12 | 2.99 | 2.9 |
| IM +Kollidon 3 months, 25°C | 223.84 | 56.85 | 2.79 | 5.4 |
| IM +Kollidon 3 months, 40°C | 224.00 | 55.84 | 2.92 | 7.8 |
| Vivapur | | | | 4.4 |
| IM+Vivapur initial mixture | 224.38 | 53.50 | 4.16 | 1.7 |
| IM+Vivapur 3 months, 25°C | 224.18 | 50.99 | 4.49 | 2.4 |
| IM+Vivapur 3 months, 40°C | 223.71 | 53.76 | 5.08 | 2.7 |
| Mg St. | –** | – | – | 4.5 |
| IM+Mg St. initial mixture | – | – | – | 2.2 |
| IM+Mg St. 3 months, 25°C | – | – | – | 2.4 |
| IM+Mg St. 3 months, 40°C | – | – | – | 2.3 |

*The sum of residual solvents by the GC method and water, **In case of these mixtures, the interactions did not allow the clear identification of the active ingredient

parameters of the binary mixtures with Vivapur showed a similar tendency as Kollidon (Table 1). The water content increased by approx. 1%, in the mixtures after storage at 25 and 40°C, in comparison with the initial mixture (Figs 3g–j). The powder diffractograms of IM–Vivapur binary mixtures comprise of the amorphous background of Vivapur and the crystalline form α (Fig. 6).

Substantial changes are visible in DSC traces of the IM and magnesium stearate mixtures in comparison with IM (Figs 4a–e). Besides two peaks of water dehydration, an additional endothermic event in the temperature range from 160 to 220°C is observed. The interactions at high temperatures do not allow for the clear identification of the active ingredient melting. The mass losses of the initial and the stored mixtures at 25 and 40°C are comparable (Figs 4g–j) (Table 1). Additional mixtures with various compositions were prepared to verify facts about the formation of the eutectic mixture. The lack

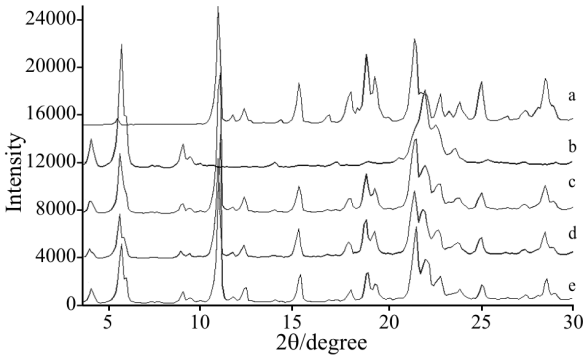


**Fig. 8** X-ray diffractograms of individual components as well as binary mixtures of IM and magnesium stearate; a – IM, b – magnesium stearate, c – initial mixture, d – mixture after storage at 25°C (60% RH), e – mixture after storage at 40°C (75% RH)

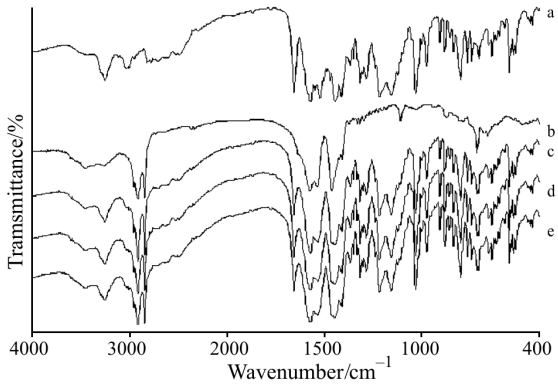


**Fig. 9** IR transmittance spectra (in KBr pellets): a – IM, b – magnesium stearate, c – initial mixture, d – mixture after storage at 25°C (60% RH), e – mixture after storage at 40°C (75% RH)

**Table 2** The identification of imatinib mesylate and magnesium stearate characteristic bonds by the IR method to determination of chemical identity in the studied mixtures

| Imatinib mesylate | Magnesium stearate (Mg St.) | Initial mixture | Mixture after storage at 25°C (60% RH) | Mixture after storage at 40°C (75% RH) |
|---|---|---|---|---|
| | | Band/$cm^{-1}$ | | |
| 3258(m)<br>N–H stretching vib. | | 3259(m) | 3258(m) | 3258(m) |
| 3057–2491(m)<br>C–H arom. stretching vib.<br>+C–H aliph. with broad structured band of $N–H^+$ stretching vib. in background | 2957–2860(s)<br>C–H aliph. stretching vib. | 3057–2850(m–w) | 3057–2850(m–w) | 3057–2850(m–w) |
| 1660(s)<br>C=O | | 1660(s) | 1660(s) | 1660(s) |
| 1572–1527(s)<br>C=N stretching vib.<br>+N–H deformation vib.<br>+C=C stretching vib. | 1578(s)<br>C=O asymmetric stretching vib. ($COO^-$) | 1573–1538(s) | 1572–1538(s) | 1572–1538(s) |
| 1474–1418(s)<br>C=N stretching vib.<br>+C=C arom. stretching vib. | 1465–1416(s)<br>C–H deformations vib. of $CH_2$ and $CH_3$ groups in aliphatic<br>+C=O symmetric stretching vib. ($COO^-$) | 1473–1416(s) | 1472–1416(s) | 1472–1416(s) |
| 1321–1290(s)<br>C–N stretching vib.<br>+N–H deformations vib.<br>+C–H arom. deformations vib. | | 1321–1290(s) | 1321–1290(s) | 1321–1290(s) |
| 1221–1161(s)<br>C–N stretching vib.<br>+N–H deformations vib.<br>+C–H arom. deformations vib. | | 1222–1162(s) | 1222–1162(s) | 1222–1162(s) |
| 1129(m)<br>C–O stretching vib. | | 1128(m) | 1128(m) | 1128(m) |
| 807(s)<br>C–H arom. deformations out of plane | | 807(s) | 807(s) | 807(s) |
| | 723(m)<br>C–H deformations vib. of $CH_2$ groups in aliphatic | 723(m) | 723(m) | 723(m) |

(s – strong, m – medium, w – weak, vib. – vibration, arom. – aromatic, aliph. – aliphatic)

of the eutectic endotherm in DSC scans excludes such a mixture formation (Fig. 7). However, it can be easily observed that powder diffractograms of the initial mixture, as well as these stored, consist of both the crystalline magnesium stearate and form α reflections (Fig. 8). The IR analysis also confirmed that there were not any visible changes between individual components in the initial and the mixtures stored under various conditions (Fig. 9) (Table 2).

The origin of similar behaviour in (1:1 *m*/*m*%) binary mixture with magnesium stearate was investigated e. g. by Oliveira *et al.* [12] and Balestrieri *et al.* [13]. In the first example incompatibility was proved by isothermal studies of an active substance decomposition with and without the presence of magnesium stearate. The excipient promoted a drug decomposition. In the second one, DSC scans could indicate interactions in a mixture but spectroscopic (UV, IR) and chromatographic (HPLC) analyses excluded it.

## Conclusions

The study demonstrated that except for the binary mixture of magnesium stearate and imatinib mesylate,

melting characteristics of remaining mixtures are the same as individual components. It means that, apart from the broad endotherm of water and the active substance melting peak, any additional events were not observed. In all the cases, the onset temperature of the drug active substance showed a slight shift towards lower temperatures. Changes concerned also enthalpy values and peak height to width ratios. Enthalpy values changed proportionally to the active substance content in the mixture. Such behaviour is characteristic of an active substance in a physical mixture rather than its incompatibility with an excipient. XRPD and IR studies of the initial and stored mixtures of Kollidon, Vivapur and IM additionally confirmed the absence of chemical interactions between components.

Profound changes, in DSC curves, in the case of the initial and stored mixtures of magnesium stearate and imatinib mesylate can indicate some interactions between components. Nevertheless, on the basis of XRPD and IR measurements we suppose that these interactions are very weak at room and storage conditions.

TG studies proved that the Kollidon mixtures were the most sensitive to accelerated storage conditions (40°C, 75% RH). For the Kollidon mixtures the water content increased approx. three times, in comparison with the initial mixture.

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