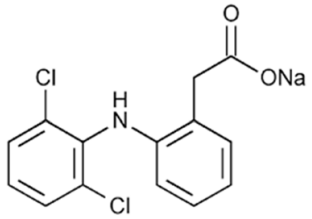
Compatibility Studies on Diclofenac Sodium – Fast and Easy with Thermal Analysis

Claire Strasser



1 Structure of diclofenac sodium ($C_{14}H_{10}Cl_2NO_2Na$) [4]

Introduction

A pharmaceutical formulation contains not only the active substance, but also excipients to ensure desired properties. Disintegrants allow tablets and capsules to break down into smaller fragments so that the drug can be released for absorption [1]. Other components act as anti-caking agents or as glidants, so that the pharmaceutical powder can flow during processing, while lubricants prevent the ingredients from adhering to pharmaceutical equipment [2].

During drug formulation, one must ensure that the efficacy of the main component is not affected by the excipients. In fact, interaction between a drug and the excipients could alter the stability of the drug and affect its safety and/or its efficacy [3].

DSC and TGA are fast and easy methods for obtaining initial information about the compatibility between a drug substance and the applied excipients.

In the following, the compatibility of the anti-inflammation drug substance diclofenac sodium (figure 1) with the following four excipients was studied by means of DSC and TGA:

- Pregelatinized starch
- Microcrystalline cellulose
- Colloidal silicone dioxide
- Magnesium stearate

Pregelatinized starches are used in the pharmaceutical industry as tablet and capsule disintegrants, as glidants, or as binders. Another advantage of using starches as excipients in medicines is that they absorb water rapidly, allowing tablets to disintegrate appropriately [1].

Microcrystalline cellulose is chemically inert and is neither degraded during digestion nor undergoes appreciable absorption. It is used as an excipient in tablets due to its excellent compressibility properties [5].

In the pharmaceutical industry, colloidal silicon dioxide has many uses in tablet-making, including as an anti-caking agent, disintegrant, or glidant to allow powder to flow freely when tablets are processed [6].

Magnesium stearate is useful for its lubricating properties for capsules and tablets in the pharmaceutical industry [7].

Sample Preparation

Diclofenac sodium, pregelatinized starch, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate were measured separately by means of DSC and TGA.

After that, mixtures of diclofenac with each excipient were prepared in the ratio 1:1 (mass), and also measured by means of the DSC and TGA methods.

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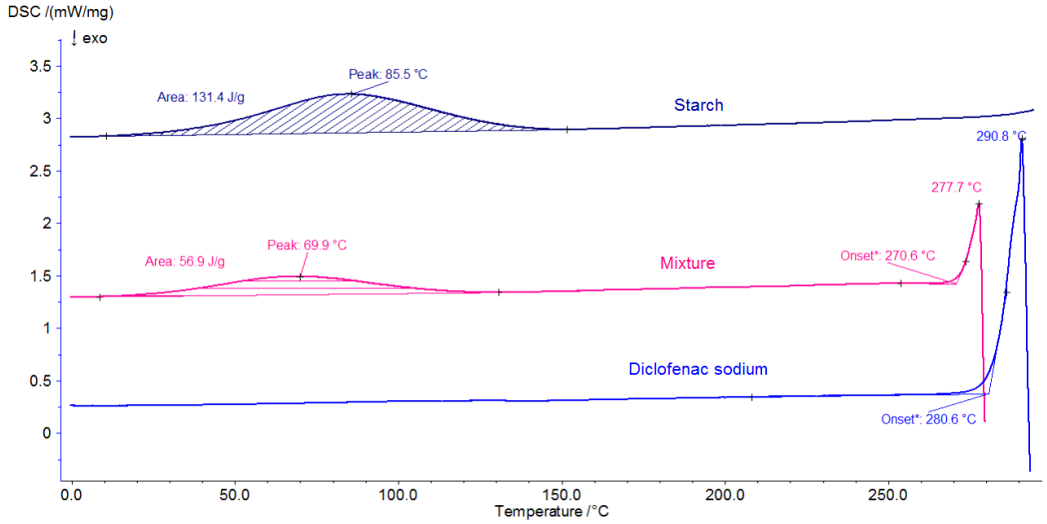
Measurement Conditions

The DSC measurements were carried out with a DSC 204 ***F1*** *Phoenix*® in a dynamic nitrogen atmosphere. Approximately 3 mg of each sample were placed in *Concavus*® aluminum pans with pierced lids. The samples were heated from -50°C to a maximum temperature of 300°C at a controlled heating rate of 10 K/min.

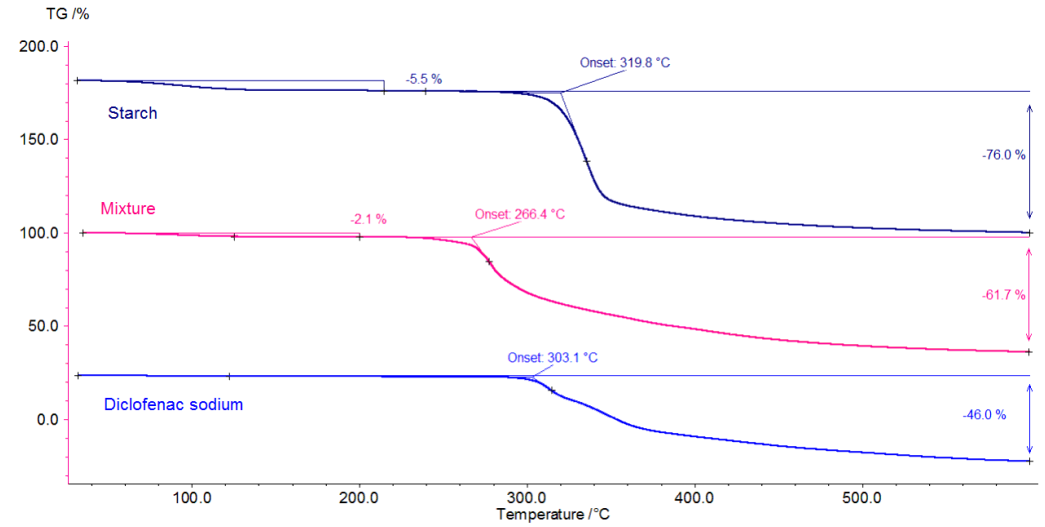
For the TGA measurements, the TG 209 ***F1*** *Libra*® was used. The samples were measured in a dynamic nitrogen atmosphere using sealed *Concavus*® aluminum crucibles that were automatically pierced just before the measurement. The mass changes were recorded during heating to 600°C at 10 K/min.

Measurement Results

Figures 2 and 3 depict the DSC and TGA curves for diclofenac, pregelatinized starch and the mixture of the two.



2 Comparison of the DSC curves of pure diclofenac (bottom), pure starch (top) and the mixture of diclofenac/starch (1:1) (middle)



3 Comparison of the TGA curves of pure diclofenac (bottom), pure starch (top) and the mixture of diclofenac/starch (1:1) (middle)

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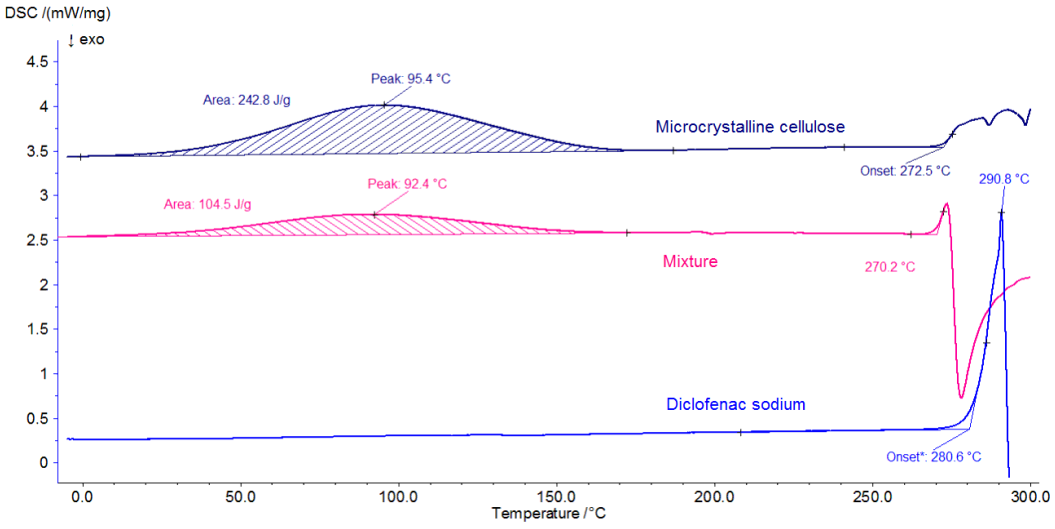
Diclofenac sodium (curve below) shows an endothermal peak at 291°C, corresponding to its melting. An exothermic process immediately following the melting is associated with a mass loss of 46% and results from the decomposition of diclofenac.

For pure starch (blue curve, on top) only an endothermal peak between room temperature and 150°C was detected in the temperature range studied. Its shape and its position are typical for the release of water. The gelatinization peak of starch would be situated in the same temperature range. However, as the measured starch is already pregelatinized, this effect can only come from the evaporation of water contained in the sample. According to the TGA curve, the initial sample contained 5.5% water (figure 3, blue curve). At the end of the DSC measurement, the increase in the baseline may indicate the beginning of degradation. This is confirmed by the mass loss at 320°C (onset temperature) amounting to 76% in the TGA plot.

It seems that the mixture (figure 3, pink curve) behaves the same way as pure diclofenac sodium: The sample melts just before it starts to decompose. However, this process occurs at a lower temperature than for the single component: The melting peak temperature is at 278°C (DSC curve) and degradation begins at 266°C (onset temperature of the TGA curve).

Figures 4 and 5 show the DSC and TGA curves of diclofenac, microcrystalline cellulose and of the mixture of the two. The endothermal peak between room temperature and 150°C (figure 4), associated with a mass loss of 5.8% (figure 5), indicates the evaporation of water during the heating of microcrystalline cellulose. As expected, the typical peak for the release of water is also detected in the DSC curve of the mixture as well as in the TGA curve as a mass loss. A further endothermal effect begins at 273°C in the DSC curve of microcrystalline cellulose, before this excipient begins to decompose at 297°C (TGA curve).



4 Comparison of the DSC curves of pure diclofenac (bottom), microcrystalline cellulose (top) and the mixture of diclofenac/microcrystalline cellulose (1:1) (middle)

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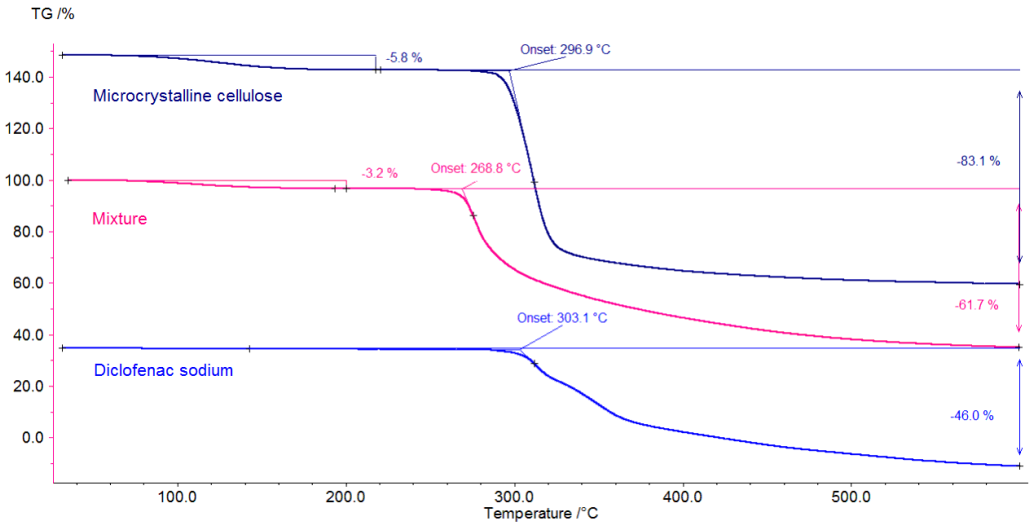

5 Comparison of the TGA curves of pure diclofenac (bottom), microcrystalline cellulose (top) and the mixture of diclofenac/microcrystalline cellulose (1:1) (middle)

Mixing the two substances influences melting as well as degradation. It is not possible to clearly determine whether the endothermal peak beginning at 270°C in the DSC curve of the mixture corresponds to the melting peak of diclofenac shifted to lower temperatures, or to the endothermal effect that was detected in the DSC curve of microcrystalline cellulose. However, the fact that this endothermal peak is immediately followed by an exothermal peak, exactly like the DSC curve of pure diclofenac, indicates that it is probably at least partly attributable to diclofenac. Furthermore, decomposition occurs for the mixture at a lower temperature than for either the pure drug substance or the excipient.

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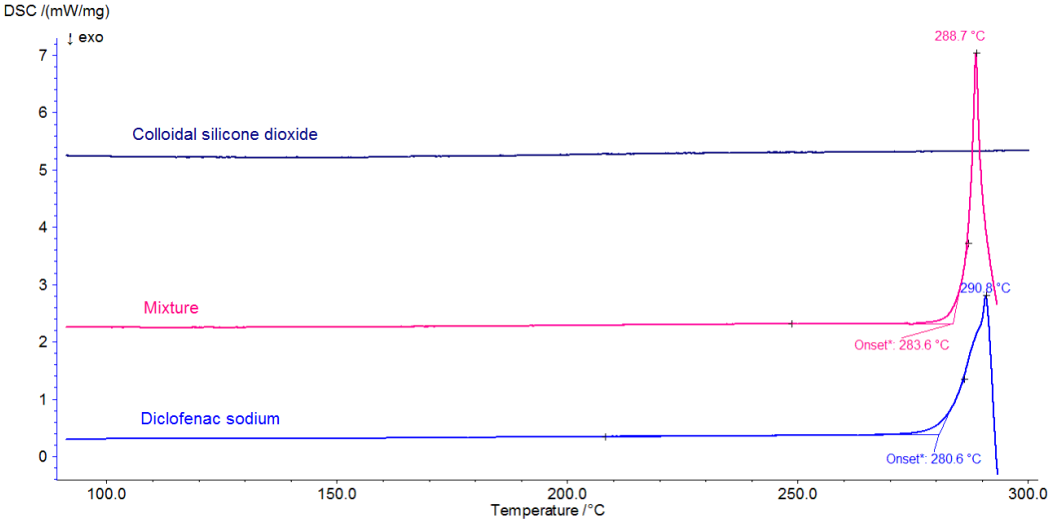
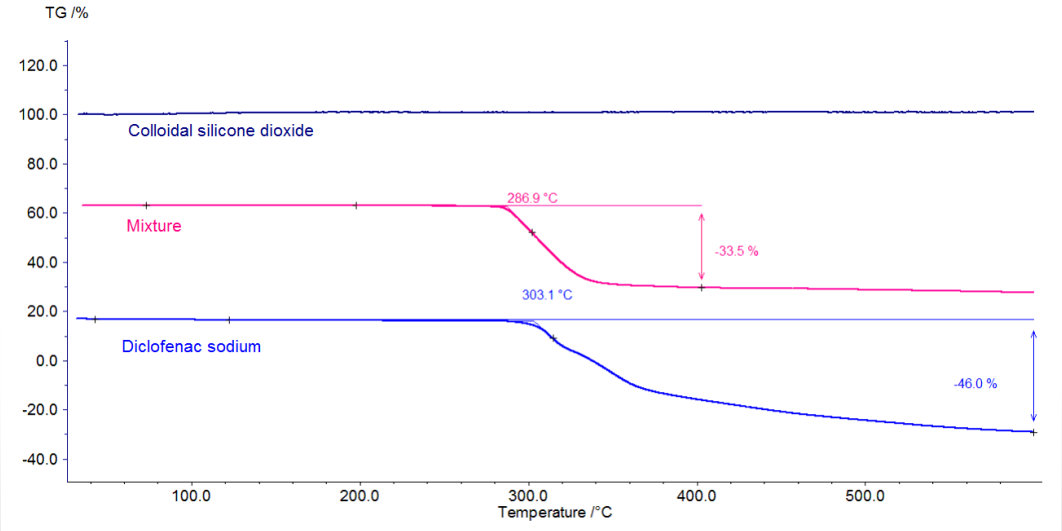
Figures 6 and 7 depict the DSC and TGA curves of diclofenac sodium, colloidal silicon dioxide and the mixture of the two.

The DSC and TGA curves of colloidal silicon dioxide show no effect in the temperature range to 300°C and to 600°C, respectively. Melting of the mixture was observed at a temperature similar to that for pure diclofenac. However, degradation begins earlier for the mixture than for pure diclofenac.



6 Comparison of the DSC curves of pure diclofenac (bottom), colloidal silicon dioxide (top) and the mixture of diclofenac/colloidal silicon dioxide (1:1) (middle)



7 Comparison of the TGA curves of pure diclofenac (bottom), colloidal silicon dioxide (top) and the mixture of diclofenac/colloidal silicon dioxide (1:1) (middle)

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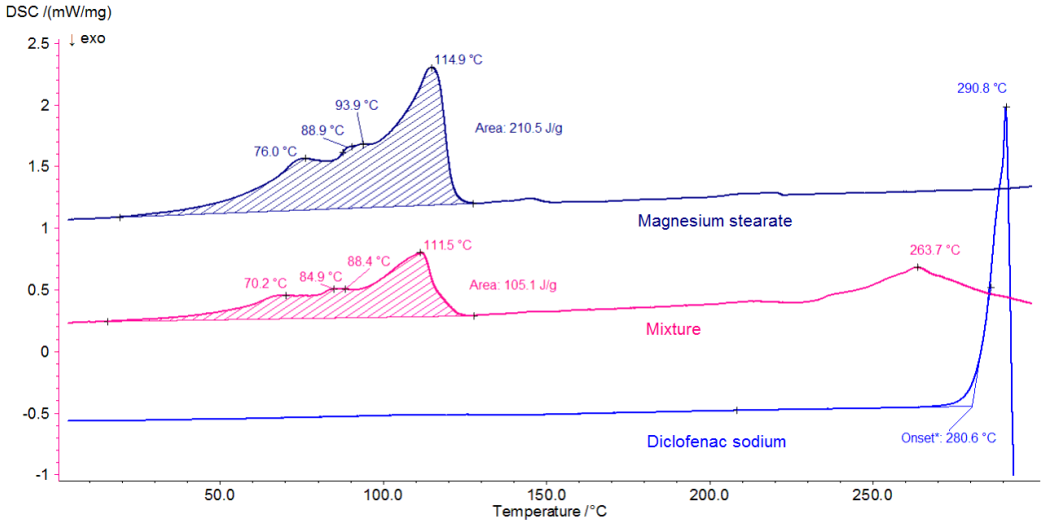
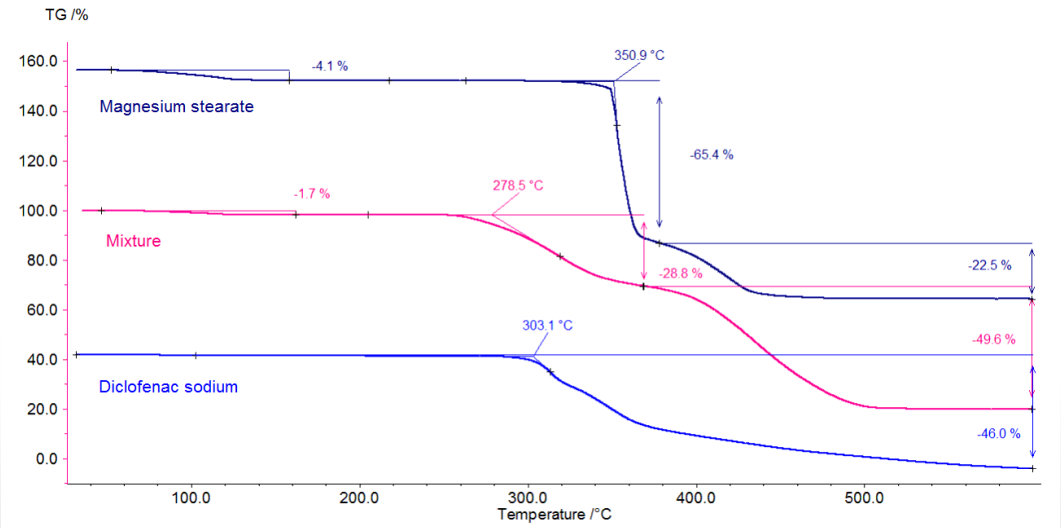
Figures 8 and 9 display the DSC and TGA curves of diclofenac, magnesium stearate and a mixture of the two substances. The endothermal peak between room temperature and 130°C detected in the DSC curve of magnesium stearate (blue curve, at the top) as well as in the mixture (pink curve, middle) is due in part to the evaporation of water. It corresponds to a mass loss in the TGA curve for this temperature range. The water release peak (4.1%) is overlapped by the melting of magnesium stearate [8].

Decomposition of the mixture (figure 9) begins at 278°C, i.e., at a lower temperature than for the excipient alone. The melting peak typical for diclofenac is no longer exhibited in the mixture. Instead, a broad endothermal peak with a peak temperature of 264°C is detected.



8 Comparison of the DSC curves of pure diclofenac (bottom), magnesium stearate (top) and the mixture of diclofenac/magnesium stearate (1:1) (middle)



9 Comparison of the TGA curves of pure diclofenac (bottom), magnesium stearate (top) and the mixture of diclofenac/magnesium stearate (1:1) (middle)

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Conclusion

The DSC and TGA measurements of the drug substance, the individual excipients, and the mixtures show that starch, microcrystalline cellulose and magnesium stearate all influence the melting and decomposition temperatures of diclofenac. Either the melting peak and decomposition step are both shifted to lower temperatures, or the melting peak of diclofenac disappears in the DSC curve of the mixture (magnesium stearate). This is often due to structural changes and indicates interaction and incompatibilities between the compounds [3].

DSC and TGA give an initial indication of the compatibility of diclofenac sodium with selected excipients.

Literature

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