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APPLICATION OF DSC AND NIRS TO STUDY THE COMPATIBILITY OF METRONIDAZOLE WITH DIFFERENT PHARMACEUTICAL EXCIPIENTS

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The purpose of the present work was to study the compatibility of metronidazole with different pharmaceutical excipients (hydroxypropyl methylcellulose, poly(ethylene oxide), microcrystalline cellulose, dicalcium phosphate dihydrate, and anhydrous dicalcium phosphate) using differential scanning calorimetry and diffuse reflectance spectroscopy. Dicalcium phosphate dihydrate was the only excipient that showed interaction with metronidazole even before storage. Changes referring to a possible transition to dihydrate form were observed in the thermal curves of anhydrous dicalcium phosphate after four weeks of storage. Although dicalcium phosphate dihydrate can be replaced by the anhydrous form in pharmaceutical formulations, the observed transition might negatively influence the stability of dosage forms.

Keywords: *anhydrous dicalcium phosphate, compatibility, dicalcium phosphate dihydrate, DSC, metronidazole, NIRS*

Introduction

Metronidazole is an antimicrobial agent with a daily dose of 500 to 2250 mg depending on the type and severity of the disease [1]. Sustained release formulations could reduce both the amount and frequency of drug intake, and thus the occurrence of side effects. Hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO) are gel-forming polymers, which can modify the release kinetics of the active ingredient; while microcrystalline cellulose (MC), dicalcium phosphate dihydrate (DPD) and anhydrous dicalcium phosphate (ADP) can be used as fillers [2].

The excellent flow properties, low hygroscopicity and cost of DPD make this excipient an appropriate choice for different formulations. However, its tendency to lose its water of crystallization can seriously affect the stability of the dosage form. This phenomenon is reported to be initiated by high humidity, which can occur both upon processing and storage. The released water of crystallization can alter the hardness of solid dosage forms or even initiate chemical reactions inside the system. Application of ADP seems to be a solution for this problem, as its flow properties, cost and hydrophobicity are similar to DPD. The differences in physical characteristics, which can be circumvented by the addition of other excipients, can be found in the literature [3–6].

To determine the compatibility of various excipients with a certain drug, differential scanning calorimetry can be a useful tool. DSC is in daily use in pharmaceutical industry to allow faster evaluation of possible incompatibilities between the formulation components, according to appearance, shift or disappearance of peaks and/or variations in the corresponding enthalpies [7–13] and compatibility studies based on isothermal microcalorimetric measurements have been reported in [14]. Since variation of temperature and relative humidity occur by processing and storage, changes of the solid state may have a considerable effect on activity, toxicity and stability of the compounds. Modelling of such conditions is therefore of high importance, and following the changes in the individual substances and mixtures can reveal some unexpected phenomena [15–18].

In order to find a possible explanation for the behaviour of ADP and DPD, the DSC measurements were completed with near-infrared spectroscopy studies. This method has been extensively used in the food and agricultural industries, but its potential force has been shown in the pharmaceutical field, as well. It is highly suitable for the non-invasive and rapid investigation of solid materials. NIR wavelength-range spreads from 800 to 2500 nm and contains overtones and combination bands which are mainly caused by the vibrations of OH, CH and NH groups. Due to the smaller molar absorptivities in this region, it is possible to use undiluted samples and obtain remarkable depth of penetration into solid samples [19].

The purpose of the present work was to compare the compatibility of metronidazole with different tableting excipients under stress conditions.

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Experimental

Materials

Metronidazole (MET; batch no. 0074A64) was purchased from Unichem Laboratories Ltd. (Maharashtra, India). The used excipients were hydroxypropyl methylcellulose (HPMC; Methocel K4M CR Premium; batch no. RC29012N11) from Colorcon Ltd. (Dartford Kent, UK), polyethylene oxide (PEO; Polyox WSR 303; batch no. RI2255S5R1) from The Dow Chemical Company (New Milford, USA), microcrystalline cellulose (MC; Avicel Ph-101; batch no. 6312C) from FMC Europe N.V. (Brussels, Belgium), dicalcium phosphate dihydrate (DPD; Emcompress; batch no. E10B) from JRS Pharma LP (Rosenberg, Germany) and anhydrous dicalcium phosphate (ADP; Di-Cafos AN; batch no. 0040A74) from Chemische Fabrik Budenheim KG (Budenheim, Germany).

Thermoanalytical experiments

1:1 physical mixtures of MET and the excipients were prepared by their mass and then mixed thoroughly for 5 min in a mortar.

Individual substances and mixtures were stored at 40±1°C, 75% relative humidity (achieved by oversaturated NaCl solution) for 4 weeks. Samples were taken before storage and after 1, 2 and 4 weeks. 5–6 mg was weighed from each sample into an open aluminium pan and was heated in dry nitrogen atmosphere at β=10 K min^{-1} using TA Instruments DSC 2920 unit (Newcastle, Delaware, USA). The DSC scans were performed from room temperature to 300°C.

Thermogravimetric experiments have been performed using TA Instruments 2050 thermobalance (Newcastle, Delaware, USA) applying β=10 K min^{-1} of heating rate and nitrogen purging. The initial sample masses were 9–10 mg.

Near-infrared spectroscopy

The near infrared spectra of MET, ADP, DPD, 1:1 MET-ADP and 1:1 MET-DPD mixtures were obtained using a Hitachi U-3501 Spectrophotometer in the 2600–200 nm wavelength range with a resolution of 8 cm^{-1}. Samples were not stored under stress conditions.

Results and discussion

Figures 1–5 illustrate the DSC curves of MET and different excipients before storage and their physical mixtures after 0, 1, 2 and 4 weeks of storing. Tables 1 and 2 show the characteristic temperature and enthalpy values for MET alone and in the presence of excipients. MET has a melting endotherm around 160°C and it evaporates completely between 180–260°C. This latter endotherm broadened and shifted to lower temperatures in the mixtures, as a result of the larger available surface for the evaporation of MET. The DSC curves of HPMC and MC show a broad endotherm effect (Figs 1 and 2, respectively), due to their dehydration in the 35–100°C temperature range [20]. The melting of PEO is indicated by an endotherm peak around 70°C (Fig. 3). According to their DSC curves no remarkable interaction could be observed in the MET–HPMC, –MC and –PEO mixtures. However, concluding from the decrease of the melting enthalpy values calculated for the MET–PEO mixture, degree of crystallinity of MET in this mixture decreased along the four weeks of storage (Table 1). Such observations can be found elsewhere in the literature and could be explained with the amorphizing effect of the polymer on the crystalline active ingredient [21–23].

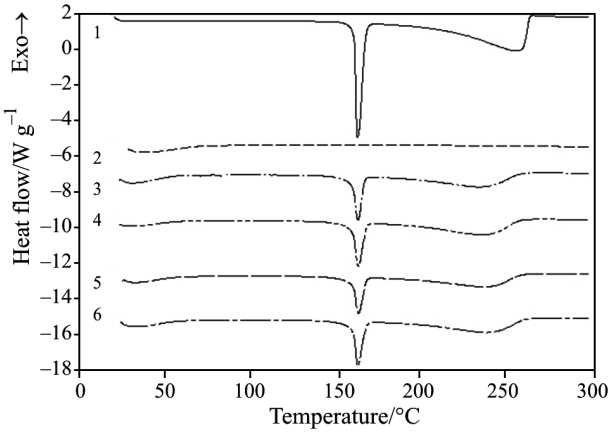

Fig. 1 DSC traces of MET, HPMC and their physical mixture. 1 – MET before storage, 2 – HPMC before storage, 3 – mixture before storage, 4 – mixture after 1 week, 5 – mixture after 2 weeks, 6 – mixture after 4 weeks

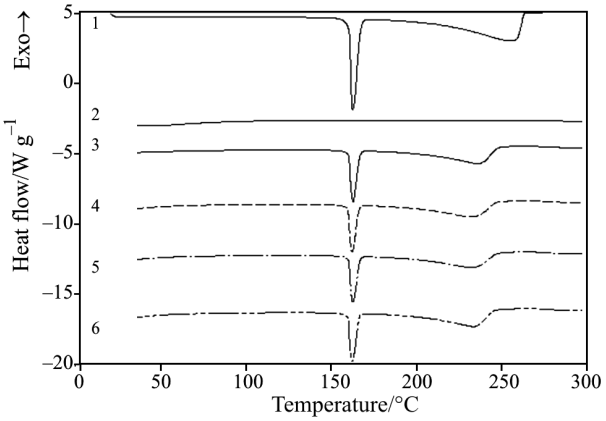

Fig. 2 DSC traces of MET, MC and their physical mixture. 1 – MET before storage, 2 – MC before storage, 3 – mixture before storage, 4 – mixture after 1 week, 5 – mixture after 2 weeks, 6 – mixture after 4 weeks

In the DSC curves of DPD (Fig. 4) three endotherms were observed in the scanned temperature range. Previous studies confirmed that between 85–100°C some adsorbed water is lost (first endotherm peak). Water of crystallization is released in two steps: 0.5 mole is between 120–160°C, while the remaining 1.5 mole evaporates up to 250–300°C [24, 25]. The mechanical mixture of MET and DPD showed interaction even before starting the storing experiments. On one hand the melting endotherm of MET somewhat broadened and its evaporation shifted to lower temperatures, while the endotherm peak referring to the loss of 1.5 mole crystalline water of DPD also shifted to lower temperatures. The melting peak of MET and the peak referring to the loss of the remaining 1.5 mole of water of crystallization of DPD appeared to fuse, but the obtained common enthalpy values were 7–13% higher than the expected sum of enthalpies characterizing the two processes separately (data for DPD not shown).

Similarly to MET-HPMC and MET-MC, no interaction was found between MET and ADP upon storing and heating (Fig. 5).

To follow the possible transformations from DPD to ADP and vice versa, thermogravimetric experiments have been performed. By the comparison of the TG curves of the starting ADP and DPD with

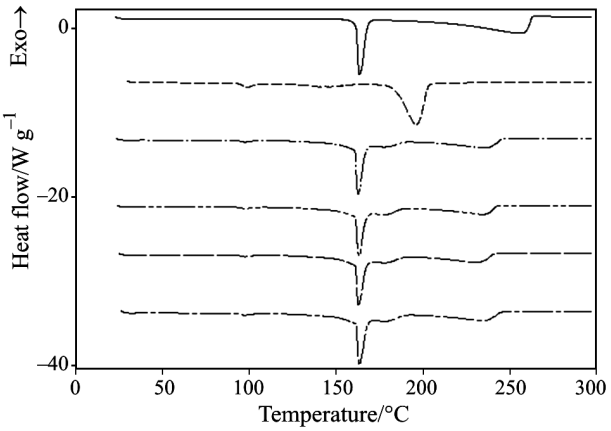

Fig. 4 DSC traces of MET, DPD and their physical mixture. 1 – MET before storage, 2 – DPD before storage, 3 – mixture before storage, 4 – mixture after 1 week, 5 – mixture after 2 weeks, 6 – mixture after 4 weeks

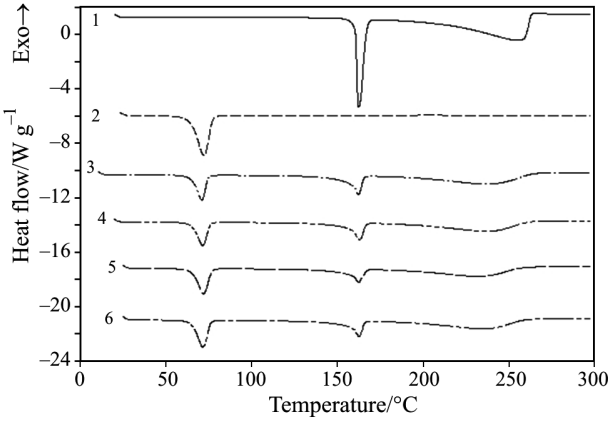

Fig. 3 DSC traces of MET, PEO and their physical mixture. 1 – MET before storage, 2 – PEO before storage, 3 – mixture before storage, 4 – mixture after 1 week, 5 – mixture after 2 weeks, 6 – mixture after 4 weeks

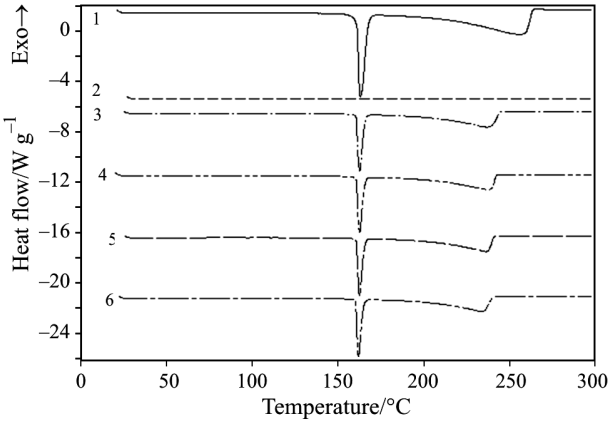

Fig. 5 DSC traces of MET, ADP and their physical mixture. 1 – MET before storage, 2 – ADP before storage, 3 – mixture before storage, 4 – mixture after 1 week, 5 – mixture after 2 weeks, 6 – mixture after 4 weeks

Table 1 Peak temperature and enthalpy values for melting of MET with and without excipients after 0, 1, 2 and 4 weeks of storage

Time/week	MET	+HPMC	+PEO	+MC	+DPD	+ADP
			T_{peak}/°C			
0	162.3	162.6	162.1	162.6	161.5	162.0
1	162.5	162.7	162.8	162.0	162.1	162.0
2	162.3	162.9	162.5	162.4	161.7	161.8
4	162.2	162.4	162.5	162.0	162.2	161.2
			enthalpy/J g^{-1}			
0	190.8	85.5	86.7	95.4	*296.1	91.8
1	187.6	93.7	79.8	89.5	*295.7	88.3
2	187.8	76.5	67.2	88.4	*296.9	86.3
4	188.6	89.9	72.4	94.2	*315.1	81.7

*endotherms of DPD involved

Table 2 Peak temperature and enthalpy values for evaporation of MET with and without excipients after 0, 1, 2 and 4 weeks of storage

Time/week	MET	+HPMC	+PEO	+MC	+DPD	+ADP
			T_{peak}/°C			
0	256.5	235.9	239.0	236.3	235.9	236.7
1	255.9	237.8	238.5	234.1	234.9	237.4
2	257.2	238.9	234.1	233.2	231.2	236.0
4	254.9	239.2	236.3	234.1	235.3	233.6
			enthalpy/J g^{-1}			
0	382.4	169.0	193.8	201.7	136.2	183.1
1	368.6	186.6	177.0	196.8	121.3	174.6
2	372.6	151.7	157.9	192.0	121.2	170.9
4	378.2	175.8	164.6	206.9	124.9	161.2

*endotherms of DPD involved

the ones recorded after 4 weeks of storage, DPD remained unchanged (the loss of water of crystallization could not yet be observed) – while a slight amount of ADP (about 1%) has transformed to DPD (curves here are not presented). As this transition could be observed even after a short period, long-term storage might lead to an extent of this alteration which would considerably affect the stability of dosage forms containing an active ingredient incompatible with DPD.

In order to find an explanation for the interaction between MET and DPD, NIR measurements were carried out. Samples were used without storing, because the observed interaction detected with DSC occurred even before applying stress conditions. Figure 6 represents the first derivatives of the NIR spectra of MET and its 1:1 physical mixtures with ADP and DPD. In the mixture with DPD, a red shift of the first derivative of the band of MET in the first O–H overtone region (1400–1500 nm) [26] can be observed. The reason of this phenomenon might be the formation of new H-bonds between the O–H group of MET and the water of crystallization of DPD, leading to an easier excitation of the former one. The increased enthalpy of the fused peaks compared to the ones corresponding to the separate processes (i.e. melting of MET and loss of water of crystallization of DPD) can be the result of the more ordered structure formed this way. This interaction could modify the process of losing the water of crystallization of DPD, leading to the alteration of the related endotherm on the DSC curve. This phenomenon could also give an explanation to the decreased enthalpy and temperature values of the evaporation of MET in the mixtures, as the evaporating water molecules might enhance the evaporation of the active ingredient. In contrast, in the case of the mixture with ADP, such a shift of the mentioned band cannot be seen, which refers to the lack of interaction. The non-invasive NIR examinations prove that the interaction between MET and DPD occurs not only under stress conditions, which could lead to disadvantageous changes in a dosage form.

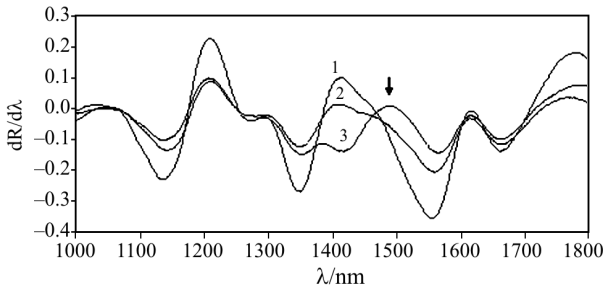

Fig. 6 First derivatives of the NIR spectra of 1 – MET and its 1:1 physical mixtures with 2 – ADP and 3 – DPD

Conclusions

The compatibility of metronidazole with various pharmaceutical excipients could be tracked by DSC and NIR measurements. No remarkable interaction was found between MET and HPMC, MC, PEO and ADP, while MET and DPD have interacted upon storage.

Due to the possible incompatibility between MET and DPD, depending on the time and circumstances (especially on the relative humidity) of storage, the extent of the anhydrous-dihydrate transition of ADP can be an impact in the aspect of formulation of MET.

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