Predicting the suitability of microwave formulation using microwave differential thermal analysis (MWDTA)

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Abstract

Microwave-assisted formulation is becoming an established method of formulation in industry, providing a fast, economic and environmentally more favourable way to create products, such as those manufactured in the pharmaceutical industry. However, the effect of microwave-induced heating on a compound, or mixture of compounds, is yet to be fully explored, possibly indicating that this method of formulation may not be suitable in all cases. In this study, the effect of microwave heating was investigated through the application of microwave thermal analysis to six model pharmaceutical compounds and a set of four model excipients. Benzocaine, haloperidol, ibuprofen, indomethacin, ketoprofen and phenylbutazone were analysed, along with four excipients, namely β-cyclodextrin, D-mannitol, stearic acid and Syloid® XDP 3050 silica using microwave thermal analysis. Samples were heated by microwave irradiation at 5 °C min^{-1} to a minimum of 160 °C, held isothermally and then slowly cooled to room temperature. Thermal profiles were analysed and compared with data obtained using differential scanning calorimetry (DSC) and hot-stage microscopy (HSM). Overall, it was found that the process of microwave heating produced different thermal profiles to those seen using traditional, conductive heating. Investigating differences in thermal profiles can be a useful way to consider the effect of microwave-induced heating on formulations which can, in turn, help guide formulation choices.

Introduction

Almost 20 years ago, a new analytical technique was described for the first time, namely microwave differential thermal analysis (MWDTA), that combined the advantages of microwave heating with the benefits of differential temperature measurement to probe the thermal properties of materials [1]. The limited thermal response using conventional heating is avoided using microwave heating as there is a direct interaction of the material with the microwave energy. However, more importantly, microwave heating provides a unique means of investigating

thermal transitions based on the associated changes in the dielectric properties of the sample. These thermally induced changes, such as melting or decomposition, are then analysed based on the microwave power profiles obtained. When a material is subjected to microwave radiation, there are two important parameters that dictate the nature of the interaction, namely the dielectric constant and the dielectric loss factor. The former considers the way a material is polarised by the electric field and the latter the conversion from radiation to heat. This form of analysis has been successfully applied to a range of materials including decompositions, dehydrations and phase changes [2] and can provide qualitative and quantitative information of solid-state processes [3]. Furthermore, MWDTA can make a valuable contribution to the investigation of the so-called microwave effect, and these are anomalies that occur when certain materials are heated in a microwave field [4] as well as reveal fine details through the use of derivative plots of either the applied power or temperature [5]. In recent years, a variety of studies have investigated the application of

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MWDTA to both a range of materials, such as ceramics [6], and a range of more complex analytical systems [7].

In contrast to the use of microwave radiation as an analytical tool, a comparatively large volume of research has been undertaken to investigate the effects (and potential benefits) of using microwaves in a formulation capacity. For example, it has been shown that microwave radiation can affect the viscosity and gelatinisation of industrially utilised starch [8], be applied to synthesise novel maize protein-based functional materials [9], curing composites [10], enhancing rates of reaction [11] and considered for biodiesel production [12]. Possibly the most researched area of microwave-based formulation is regarding pharmaceutical applications where the limited physicochemical properties of compounds can be a significant barrier in the development of new medicines, thus requiring intervention, such as through alternative formulation methods including microwave heating, to enhance their properties. One fundamental property to ensuring the success of a drug is its solubility as this will ultimately dictate drug absorption within the body and therefore efficacy. Microwave treatment has been shown to enhance both the physicochemical and pharmacokinetic properties of pharmaceutical preparations, such as the solubility of efonidipine hydrochloride ethanolate [13], the formation of cocrystals [14], the solubility of nanocomposites [15], the dissolution of gemfibrozil [16], through modifying drug release characteristics [17], increasing yields [18] and controlling drug delivery profiles [19]. Research within our group has highlighted the benefits of using microwave processing for pharmaceutical compounds with the presence of excipients to create unique products including combinations of ibuprofen with stearic acid and polyvinylpyrrolidone, along with fenofibrate and mesoporous silicas [20, 21]. An interesting, and very recent, application of microwave irradiation is the concept of amorphisation within the tablet, i.e. creating the amorphous form of the drug in its final dosage form directly before administration [22].

In summary, microwave radiation has been previously employed for the analysis of compounds through the use of MWDTA, and separately, to formulate products that possess unique physicochemical properties that can be advantageous, especially in the pharmaceutical industry. However, as yet there has been no consideration for the use of MWDTA to investigate pharmaceutical compounds that are to be subjected to microwave irradiation during formulation to fully comprehend if such a process will be suitable and to fully understand the interactions that will occur. This paper considers the use of MWDTA on model pharmaceutical compounds to investigate the potential application of this form of thermal analysis on such compounds as an indicator of the suitability of microwave-based formulation methods.

Experimental

Materials

β-Cyclodextrin (β-CD), benzocaine (BZ), D-mannitol (D-Man), haloperidol, ibuprofen, indomethacin, ketoprofen, phenylbutazone and stearic acid (SA) were purchased from Sigma-Aldrich (Dorset, UK) with a minimum purity of $\geq 97\%$ and stored appropriately to avoid degradation. All the materials were of analytical grade, selected based on their diverse dielectric properties, and utilised as received. Syloid® XDP 3050 silica was received as a gift from Grace GmbH & Co. KG, Germany, and utilised as received.

Preparation of benzocaine binary mixtures

Following on from an investigation into the six model pharmaceutical compounds, one was selected for further analysis, namely benzocaine, prepared along with the four distinct excipients. Initially, a total mass of 500 mg benzocaine (BZ) and 500 mg Syloid® XDP 3050 silica was transferred into a 25-mL glass jar, i.e. to create a 1:1 (BZ:XDP) mixture. The sample was placed in a Turbula mixer (Turbula T10B) for 10 min at 72 rpm to achieve a homogeneous mixture and then removed and allowed to settle for 2 min. The procedure was repeated for the same mass of drug with a further three excipients: β-CD, D-Man and SA, at the same ratio of 1:1 (BZ:β-CD, BZ:D-Man and BZ:SA) drug to excipient mass ratio. This ratio was selected to maximise observable changes in the behaviour of the resultant products compared with the components.

Microwave differential thermal analysis (MWDTA)

Microwave thermal analysis of benzocaine (BZ), haloperidol, ibuprofen, indomethacin, ketoprofen and phenylbutazone, together with binary mixtures of benzocaine (BZ) with four excipients, β-cyclodextrin, D-mannitol, Syloid XDP (3050) and stearic acid, was performed using a known amount of each sample (30–90 mg) using a system previously published [5]. A known mass of each sample was placed into a quartz cell and heated at 5 °C min^{-1} from 25 to 160 °C or from 25 to 200 °C, depending upon the sample under analysis. The sample was held isothermally for 5 min and then cooled over a period of 70–90 min. All experiments were carried out under an air atmosphere utilising a microwave power of 30 W.

Differential scanning calorimetry (DSC)

DSC analysis was conducted using a DSC 1 apparatus (Mettler Toledo) containing 5–8 mg samples in sealed aluminium pans. Samples were heated at a scanning rate of 10 °C min^{-1} under a nitrogen flow of 80 mL min^{-1} from 25 to 160 °C or from 25 to 200 °C, depending upon the sample, and then cooled to 30 °C. The six model pharmaceutical compounds were analysed individually, as well as the binary mixtures of BZ with the four excipients (BZ:XDP, BZ:β-CD, BZ:D-Man and BZ:SA), with the resultant curves analysed and data compared with that obtained with MWDTA.

Hot-stage microscopy (HSM)

Particle morphology and visible changes (as a consequence of heating samples) were examined using hot-stage microscopy (HSM). An Olympus (SZ-CTV, Japan) polarising light microscope equipped with in-house constructed hot stage and software was used. A small amount of each sample was transferred into a quartz crucible, placed on the hot stage and heated at 5 °C min^{-1} from 25 to 160 °C or from 25 to 200 °C, depending upon the sample, and then cooled to 30 °C. Photomicrographs of the samples were collected at temperatures corresponding to any changes noticed in the sample as a function of temperature under a magnification of 4.5.

Results and discussion

MWDTA of pharmaceutical compounds

Six model pharmaceutical compounds were analysed using MWDTA, namely benzocaine, haloperidol, ibuprofen, indomethacin, ketoprofen and phenylbutazone. These compounds were selected for their range of physicochemical properties, thus covering the variety of types of compounds often encountered in the pharmaceutical industry. Firstly, benzocaine was investigated, as shown by the power-profile data in Fig. 1.

Apart from an onset variation at 13.6 W (1.6 min) at the start of the experiment, it can be seen that temperature control was smooth and featureless with a slow rise in MW power to maintain the set heating rate. However, at around 92.8 °C the power rose to 21.0 W from 20.0 W, i.e. a 1-W difference required to maintain the heating rate as a result of the occurrence of fusion, and thus, more energy was required to drive the endothermic process. At 97.1 °C, the fusion of benzocaine was complete and the temperature rose sharply to attain an equilibrium at 160 °C. The
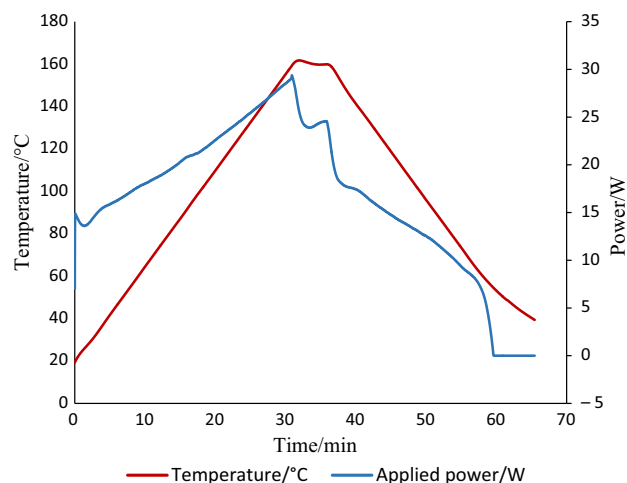

Fig. 1 Temperature and associated power profile for benzocaine heated at 5 °C min^{-1} to 160 °C and then cooled to 40 °C

equilibrium was maintained for a further 5 min at which point the temperature decreased from 160 to 40 °C. There was a rapid decrease in power at the equilibrium stage from 29.3 to 25.3 W, the stage was maintained for 5 min and then dropped again to 18.2 W with the overall change in power of 11.1 W. Initially, the applied MW power fell by 4.0 W and then decreased again by 7.1 W until the sample temperature returned to its set cooling rate where the power dropped back to 0 W without any change during the process. The dielectric change from solid to liquid revealed that less power was required to maintain the heating rate after the drug had become liquid, compared with before the transition. Results obtained for MWDTA of benzocaine (first and second cycles) are displayed in Fig. 2 in the form
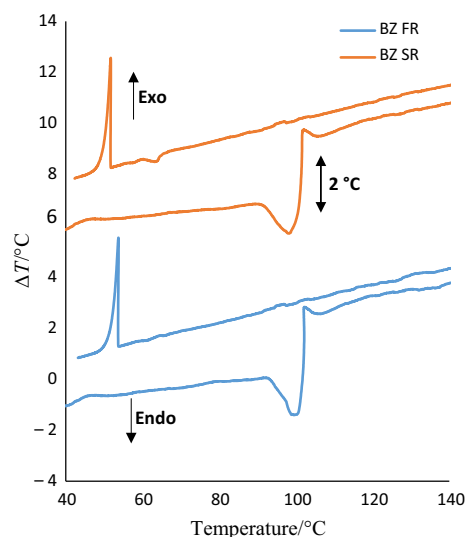

Fig. 2 Microwave differential thermal analysis (MWDTA) of benzocaine heating at 5 °C min^{-1} to 160 °C for the first and second run (FR and SR) and cooling at − 5 °C min^{-1} to 40 °C in both cases

of calculated ΔT ($T_{sample} - T_{reference}$) plotted as a function of sample temperature.

From Fig. 2, it can be seen that there was an onset variation at the start of the experiment and a broad event at 93.0 °C corresponding to the melting point of the drug which was slightly above that expected based on DSC data presented later in this study. The phase change of the drug due to the effect of temperature has been previously reported [23]. Many drugs decompose as a result of the effect of heat, oxygen, light and moisture; therefore, based on these factors, the second cycle was carried out to an increased temperature of 200 °C in an attempt to encourage decomposition of the compound. The second experimental cycle of the drug was characterised by a transition at 91.6 °C with recrystallisation occurring at 51.6 °C, i.e. only a slight shift was evident of the aforementioned transitions due to heating–cooling–reheating and re-cooling effects.

Changes observed in the profile of the drug obtained included a change in dielectric properties after the transition as the sample became molten which indicates that the sample was heating more efficiently than before the transition. This is also apparent in Fig. 1 whereby the power increased and decreased as the sample coupled variably with the microwave energy. The resultant profile provided the expected behaviour of a fusion process accompanied by a large dielectric change. These changes were not observed during DSC (results discussed later) as a consequence of heat capacity. These changes demonstrate the sensitivity of this technique to materials that undergo thermal transitions.

Secondly, haloperidol was analysed using MWDTA, as displayed in Fig. 3.

The MWDTA profiles of haloperidol (first and second run) shown in Fig. 3 revealed a sharp transition at 151.8 °C corresponding to the melting point of the drug [24]. A dielectric change can be seen after the transition as the sample couples more strongly with the microwave energy, which again suggests that the sample was heating more effectively than before the transition. When the temperature was changed from increasing to decreasing, a defined recrystallisation temperature was evident. In the second run, similar events were observed with a broadened, reduced intensity and shifted to a lower temperature for the fusion of the drug, namely a 12.6 °C difference in comparison with the first run which further confirms the nature of crystallinity of the drug. Again, minor events observed were not thought to be 'real' transitions but merely artefacts of the method employed.

Thirdly, indomethacin was analysed using MWDTA, as displayed in Fig. 4.

Figure 4 displays a sharp transition with an extrapolated onset at 159.3 °C in the first run indicating fusion occurred: further evidenced at 165.2 °C, corresponding to the known
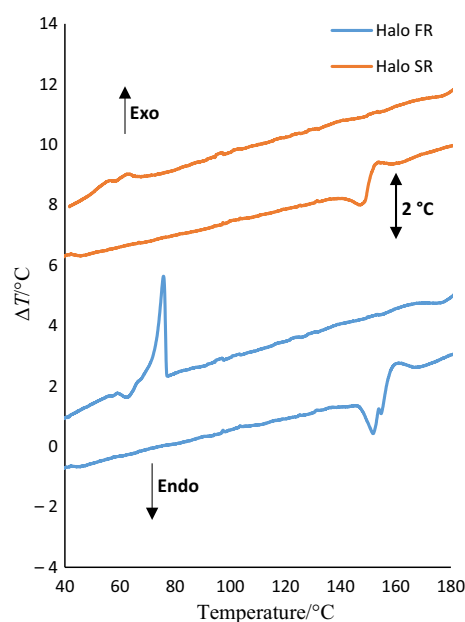

Fig. 3 Microwave differential thermal analysis (MWDTA) of haloperidol heating at 5 °C min^{-1} to 200 °C for the first (FR) and second (SR) run and then cooling at 5 °C min^{-1} to 40 °C in both cases
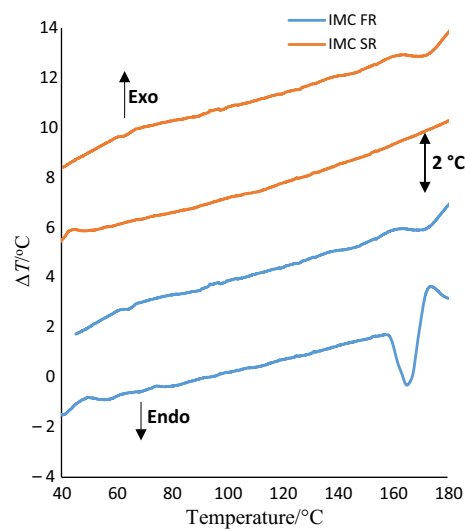

Fig. 4 Microwave differential thermal analysis (MWDTA) of indomethacin heating at 5 °C min^{-1} to 200 °C for the first (FR) and second (SR) run and then cooled at 5 °C min^{-1} to 40 °C in both cases

melting point of this drug [25]. The transition was accompanied by a significant dielectric change, and this change did not return to the baseline (as expected for this drug) as a consequence of the differing dielectric properties. Upon subsequent cooling, no significant phase transition was observed, implying that the drug did not recrystallise. No significant phase changes were observed in the second run (other than instrument recovery) further

justifying the theory that the sample remained in a glassy form.

Fourthly, ketoprofen was analysed using MWDTA, as displayed in Fig. 5.

In Fig. 5, apart from an initial variation at the onset of the experiment, the differential temperature in the first run was smooth and featureless until a transition occurred at 94.7 °C, corresponding to the melting point of the drug [26]. The temperature was increased further which brought about a change in baseline as a consequence of the increased coupling of the sample with microwave energy. Upon cooling, no significant transition event was observed, implying the sample remained in liquid form, i.e. no recrystallisation. In the second run, there was no event observed other than a decrease in tangent in the region of 124.8–140.0 °C, which was brought about by a dielectric change. The tangent gave a good indication of how effectively the sample converted the applied microwaves into thermal energy, i.e. the greater the heating via polarisation, the greater the thermal loss from the drug.

The fifth pharmaceutical compound to be analysed using MWDTA was phenylbutazone, as shown in Fig. 6.

The first run displayed in Fig. 6 does not reveal a significant change in baseline following the transition corresponding to the known melting point of the drug at 109.8 °C [27]. This finding indicates that there was no change in the dielectric properties of the sample after the transition—in contrast to the previously analysed compounds. No observable event corresponding to recrystallisation was evident during the first cooling. The second cycle of phenylbutazone was characterised by a transition at 93.4 °C, particularly surprising based upon data from the first run. Again, upon the second cooling no significant
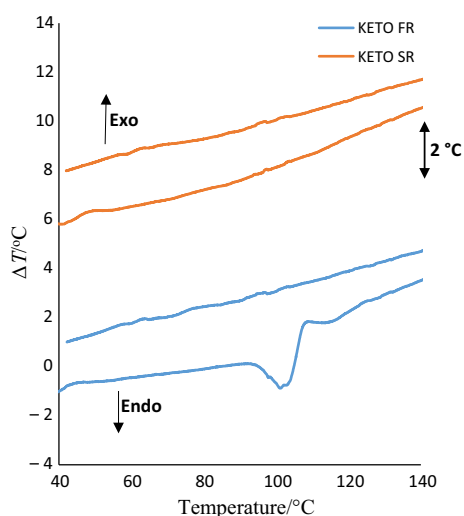

Fig. 6 Microwave differential thermal analysis (MWDTA) of phenylbutazone heated at 5 °C min^{-1} to 160 °C and then cooled to 40 °C for the first (FR) and second run (SR)

event occurred implying a lack of recrystallisation, as was the case with the first run. However, the presence of a small peak at 105.0 °C indicates that there was a small amount of semi-crystalline compound present.

The sixth compound of pharmaceutical interest analysed using MWDTA was ibuprofen, as shown in Fig. 7.

MWDTA (Fig. 7) of ibuprofen indicated one transition occurring at 76.2 °C. The transition corresponds to the expected fusion of the drug in the first cycle [28], and no increased coupling was observed after the transition. Furthermore, no recrystallisation event was apparent upon cooling. In the second cycle, a transition at 83.1 °C was

Fig. 5 Microwave differential thermal analysis (MWDTA) of ketoprofen heated at 5 °C min^{-1} to 160 °C and then cooled to 40 °C for the first (FR) and second (SR) run
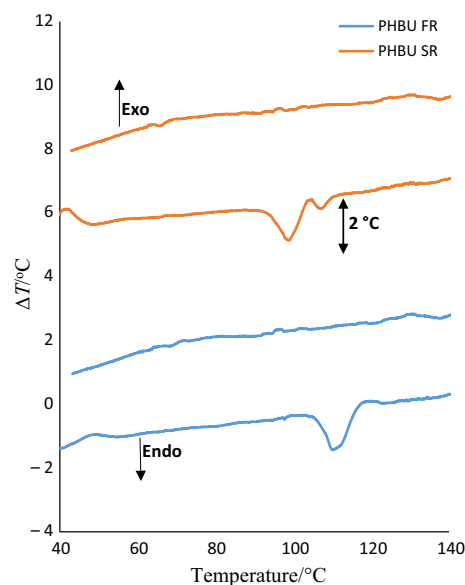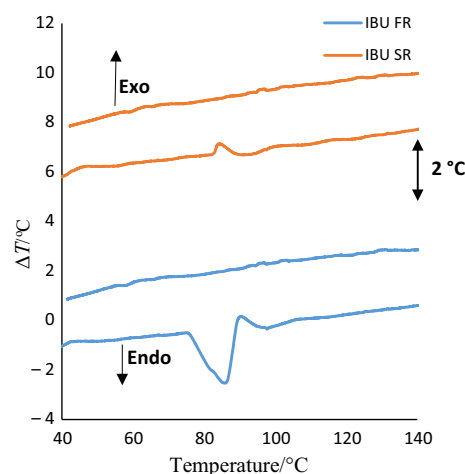

Fig. 7 Microwave differential thermal analysis (MWDTA) of ibuprofen heated at 5 °C min^{-1} to 160 °C and then cooled to 40 °C for the first (FR) and second (SR) run

unexpectedly observed, implying that some recrystallisation had occurred during the previous cooling cycle and the sample was able to undergo a melting transition.

Differential scanning calorimetry (DSC) of pharmaceutical compounds

DSC analysis was undertaken for the six model pharmaceutical compounds, and a summary of the values obtained can be seen in Table 1.

Benzocaine is a crystalline drug having a fusion temperature of 90.7 °C, as reported in the literature [23]. Pure benzocaine (FR) displayed an endothermic peak at 90.7 °C followed by a sharp peak with high intensity appearing during cooling at 48.5 °C, corresponding to the exothermic recrystallisation event. The appearance of the fusion peak confirms the crystallinity of the drug during the first cycle. The second cycle exhibited a broader melting peak with a small shift to 91.9 °C, in comparison with the first cycle. This result suggests that the drug molecules returned to a crystalline form after the first heating and cooling cycle, and again after the second cooling as a peak appeared at 50.3 °C. Upon the first heating cycle for haloperidol, an endothermic peak was observed at 152.1 °C, corresponding to the published melting point for the compound [24]. Subsequent cooling highlighted an exothermic event occurring at 92.3 °C corresponding to recrystallisation of the compound. In the second heating and cooling cycle, the initial peak temperature and subsequent exothermic event were observed at similar, but slightly lower, temperatures with an endothermic transition at 151.9 °C and recrystallisation at 88.9 °C. The thermal profile for indomethacin was characterised by a well-defined sharp endothermic peak corresponding to the expected fusion process at 160.5 °C, in agreement with published data [25]. The drug

Table 1 Physicochemical data and DSC peak values for the melting (T_m) and recrystallisation (T_m) of six compounds and four excipients

Material	M_w/g mol^{-1}[a]	Crystalline/amorphous	T_m/°C	T_r/°C
BZ	165.19	Crystalline	90.7	48.5
Halo	375.86	Crystalline	152.1	92.3
IBU	206.28	Crystalline	77.7	–
IMC	357.79	Crystalline	160.5	–
KETO	254.28	Crystalline	96.2	–
PHBU	308.37	Crystalline	107.5	–
β-CD	1134.98	Amorphous	–	–
D-Man	184.16	Crystalline	166.5	119.9
SA	284.48	Crystalline	70.1	61.2
XDP	–	Amorphous	–	–

[a]Average molecular weight (M_w) according to the supplier

did not appear to recrystallise upon cooling. Upon a second heating and cooling cycle, melting and recrystallisation peaks were not observed, most likely to be a consequence of the drug remaining in liquid form after fusion in the first heating cycle.

For the initial heating cycle of phenylbutazone, a single sharp endothermic peak was observed at 107.5 °C implying melting of the compound, and this value corresponded well with published data [27]. Upon cooling, no exothermic transition was observed, suggesting that there was no recrystallisation as the sample cooled. Upon the second heating and cooling cycle, a small and broad melting peak was observed at a slightly lower temperature than that seen in the first cycle, namely 97.3 °C. This small event suggests that the compound may have partially recrystallised although this was not observed in the first cooling cycle. For ketoprofen only one transition was observed at 96.2 °C, in the first heating cycle, corresponding to the published fusion temperature for the compound [26]. No significant events were observed in the second cycle, suggesting that the compound stayed in liquid form after the initial melt transition. In the case of ibuprofen, the DSC profiles are similar to those of ketoprofen. The only observable thermal event for ibuprofen was an endothermic peak at 77.7 °C indicating melting of the compound, only seen in the first cycle and closely related to that reported in the literature [28]. Once again, no significant event was observed in the second cycle, implying that the sample remained in liquid form after the initial transition.

Hot-stage microscopy (HSM) of pharmaceutical compounds

HSM was utilised to follow the transformation of the six compounds as a function of temperature to visibly observe changes. Photographic images were recorded and are presented in Supplementary Information at selected temperatures as Figures S1–S6. Firstly, benzocaine (Figure S1) initially appeared as a white crystalline solid and, upon heating, a visible melting event occurred at an appropriate temperature to correspond with that previously seen using MWDTA and DSC. Observations during the analysis revealed a colourless liquid material suggestive of fusion of the drug at ~ 93.7 °C followed by recrystallisation during the cooling.

For haloperidol, HSM analysis (Figure S2) revealed a white powder at 120.8 °C, transforming to a liquid at 139.4 °C followed by recrystallisation at 90 °C during cooling, as expected based on MWDTA and DSC data.

Figure S3 displays the images of solid indomethacin before the melt at 140.3 °C and then the transformation at 159.1 °C, indicating melting of the compound. Upon subsequent cooling to 30 °C, no transformation occurred, in

agreement with the previously presented MWDTA and DSC data.

Images for phenylbutazone were recorded at 91.3 °C and 109.7 °C (Figure S4) and demonstrate that the compound undergoes a solid-state transformation that started to occur at 91.3 °C, and was complete at ∼ 109.7 °C. Upon cooling, the sample returned to a glassy form at 30 °C. These findings are in agreement with those found using MWDTA and DSC analysis. Figure S5 displays the images of solid ketoprofen at 78.3 °C, upon melting at 96.7 °C and upon cooling to 30 °C. No observable transformation occurred after the initial melting, in agreement with the findings previously presented using MWDTA and DSC. Finally, Figure S6 displays the images of the white-powdered ibuprofen before the melt at 65.4 °C and upon melting at 78.5 °C. On cooling to 30 °C, no visible transformation occurred, in agreement with data evidenced from MWDTA and DSC analysis.

MWDTA of benzocaine and pharmaceutical excipients

Benzocaine was selected from the six model compounds for further analysis in the presence of a selection of four pharmaceutical excipients, namely β-cyclodextrin, D-mannitol, stearic acid and Syloid® XDP 3050 silica. Firstly, microwave thermal analysis of benzocaine with Syloid® silica, formulated at 1:1 ratio, was considered, and the resultant profile is shown in Fig. 8.

Figure 8 reveals a change in the baseline as the sample coupled more strongly with the microwave energy after the
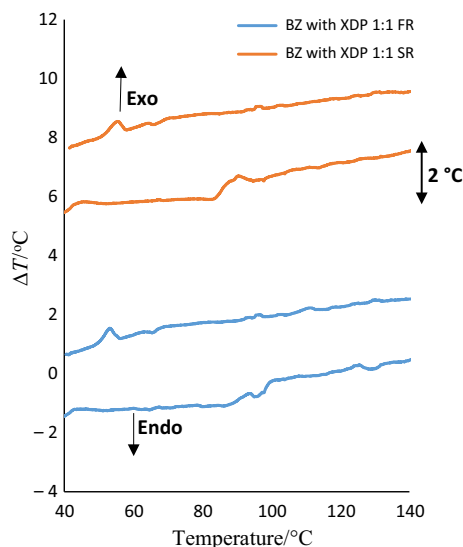
thermal transition of benzocaine at 88.3 °C, indicating a change in dielectric coupling. Compared with pure benzocaine (Fig. 2), a small reduction in the melting peak was observed, possibly indicating some loss of crystalline structure resulting from microwave energy interaction with the sample. Furthermore, this finding was interpreted as proof of the formation of a true inclusion complex with recrystallisation observed upon cooling at 54.0 °C within the first heating–cooling cycle. In the second cycle, there was a slight shift to lower temperature with a change in dielectric occurring from 82.7 to 91.6 °C and recrystallisation occurring at 56.3 °C. Secondly, MWDTA was undertaken for benzocaine formulated with β-cyclodextrin (β-CD), as presented in Fig. 9.

Fusion of benzocaine in β-cyclodextrin for the first heating cycle occurred at 91.2 °C with a large dielectric change after the transition, suggesting that the sample then coupled more strongly. Dehydration of the β-CD occurred in the region of 125.2–145.9 °C. This is consistent with the previous research where loss of solvation water from the β-CD cavity occurred at 140 °C [23]. This event appeared 40 °C higher than the standard boiling point of water, which indicated that water molecules are tightly held within the crystal lattice structure as a result of intermolecular forces such as hydrogen bonding, and therefore, additional energy was required to overcome these forces [29]. Upon cooling, recrystallisation occurred at 74.5 °C. Data for the second cycle displayed an increase in tangent after the transition with the melting peak occurring at 92.3 °C, recrystallisation at 74.3 °C and no dehydration peak. Observations of the samples post-analysis revealed a
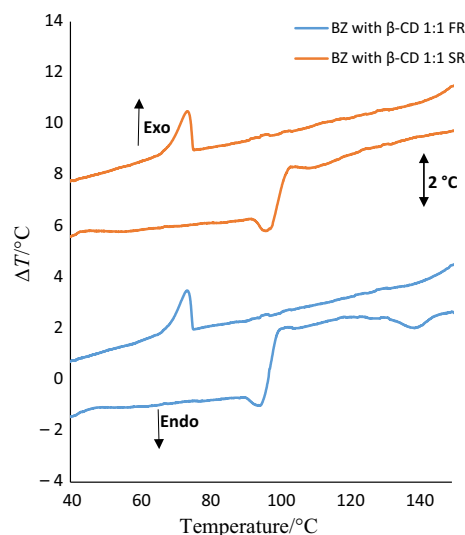

Fig. 8 Microwave differential thermal analysis (MWDTA) of benzocaine (BZ) with Syloid® silica (XDP) heated at 5 °C min⁻¹ to 160 °C for both the first (FR) and second (SR) run, cooled in both cases to 40 °C

Fig. 9 Microwave differential thermal analysis (MWDTA) of benzocaine (BZ) with β-cyclodextrin (β-CD) heated at 5 °C min⁻¹ to 160 °C for both the first (FR) and second (SR) run, cooled in both cases to 40 °C

white coloured material suggestive of the absence of decomposition after both cycles.

Thirdly, MWDTA was undertaken for benzocaine formulated with stearic acid (SA), as presented in Fig. 10.

MWDTA (Fig. 10) of benzocaine formulated with stearic acid was somewhat complex with two transitions occurring during the first heating cycle at 79.0 °C and 90.4 °C. It was assumed that the first transition corresponds to the melting of the stearic acid and the latter for benzocaine with two corresponding recrystallisation events upon cooling at 60.8 °C and 53.2 °C. There was a dielectric change after the transition, yet little (or no) interaction between the two compounds had occurred. In the second heating and cooling cycle, a sharp endothermic peak was observed at 79.1 °C and another at 87.8 °C and then upon cooling at 60.6 °C and 53.0 °C, i.e. somewhat similar to those temperatures observed during the first cycle.

Finally, benzocaine was analysed after formulation with D-mannitol, as shown in Fig. 11.

MWDTA of benzocaine displayed a transition peak at 92.7 °C with a dielectric change occurring after the transition, suggesting that the sample was heating more effectively after the transition. The event observed at 169.2 °C was deemed to be fusion of D-mannitol. Recrystallisation appeared to occur at 121.9 °C, with a high-intensity peak and another with reduced intensity at 64.7 °C, corresponding to that of benzocaine. The second cycle displayed an endothermic transition at 95.6 °C followed by a dielectric change and a second transition at 166.0 °C, i.e. similar to values observed within the first heating and
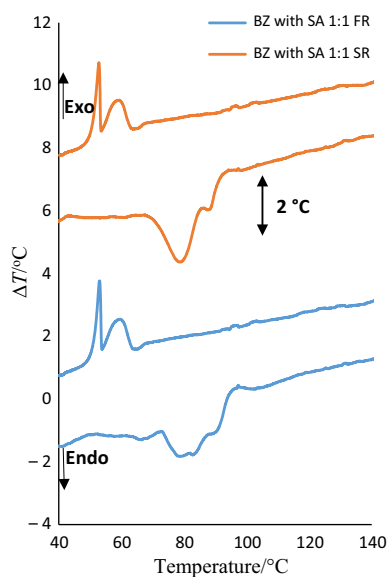

Fig. 11 Microwave differential thermal analysis (MWDTA) of benzocaine (BZ) with D-mannitol (D-Man) heated at 5 °C min^{-1} to 200 °C for both the first (FR) and second (SR) run then cooled in both cases to 40 °C

cooling cycle. Upon a second cooling, recrystallisation was evident at slightly different temperatures compared with the first cycle, namely at 116.6 °C and at 71.5 °C.

DSC of benzocaine and pharmaceutical excipients

Formulations of benzocaine with the four excipients under investigation were analysed using DSC for comparison with MWDTA data with peak values displayed in Table 2.

Benzocaine is a crystalline drug undergoing fusion at 90.71 °C as reported in the literature [23]. When benzocaine was formulated with Syloid® XDP 3050 silica, two transitions were observed at 83.8 °C and 92.0 °C, potentially a reflection that some benzocaine was 'bound' and some 'unbound' within the formulation. Upon cooling, recrystallisation was observed at 46.5 °C with reduced intensity and a broadened peak, i.e. at a temperature lower than that seen for pure benzocaine. This phenomenon was attributed to the transition from crystalline to semi-

Fig. 10 Microwave differential thermal analysis (MWDTA) of benzocaine (BZ) with stearic acid (SA) heated at 5 °C min^{-1} to 160 °C for both the first (FR) and second (SR) run, cooled in both cases to 40 °C
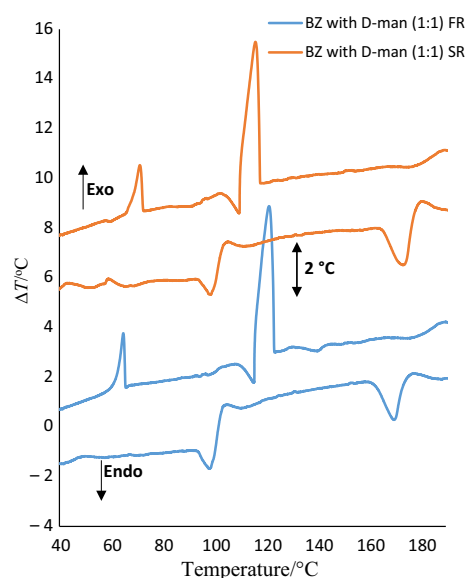
Table 2 DSC peak values for the melting (T_m) and recrystallisation (T_m) of benzocaine with four excipients

Material (1:1)	T_m/°C		T_r/°C	
BZ with XDP	83.8 and 92.0	–	46.5	–
BZ with β-CD	91.5	–	63.1	–
BZ with D-man	92.4	166.4	74.1	109.5
BZ with SA	84.6	69.9	57.9	54.9

crystalline state of benzocaine or that the drug was partially incorporated within the pores of the silica [16]. From a second heating cycle, a peak at 77.6 °C was observed at a lower melting point than for pure benzocaine. Furthermore, the compound appeared to recrystallise at 45.8 °C, significantly lower than that observed for pure benzocaine. In the presence of β-cyclodextrin, a small, broad endothermic peak was observed at 91.5 °C corresponding to fusion and almost a flat event in the region of 120–140 °C that was barely visible suggesting dehydration of β-CD with recrystallisation occurring at 63.1 °C. It should be noted that the dehydration event was significantly more apparent using MWDTA which further demonstrates the sensitivity of the microwave-based technique. These events were also observed in the second heating and cooling cycle (with the exception of dehydration event). These reversible events suggested that there was a little interaction between benzocaine and β-cyclodextrin when compared with the melting temperature of the pure compound [30].

For benzocaine formulated with stearic acid during the first heating cycle, a sharp endothermic peak was observed with an onset temperature of 69.9 °C and another at 84.6 °C, the former attributed to melting of the excipient and the latter to benzocaine. The reduction in the melting temperature of benzocaine, compared with pure drug, implies that some fractions of the molecules were dispersed in the excipient. Upon cooling, two events occurred at 57.9 °C and 54.9 °C implying some lack of homogeneity in the mixture after heating. The second heating and cooling cycle displayed peak temperatures of 68.6 °C and 83.6 °C indicating the existence of some benzocaine–stearic acid interactions. Recrystallisations at 57.8 °C and at 40.1 °C suggest that both benzocaine and stearic acid recrystallised at lower temperatures during the second cooling. DSC profiles for D-mannitol display endothermic peaks at 92.4 °C and at 166.4 °C. Upon cooling, two peaks were observed at 109.5 °C and 74.1 °C, corresponding to recrystallisation of the excipient and benzocaine in the first cycle. In summary, all of the benzocaine–excipient formulations displayed no thermal transitions other than the fusion endotherm and exotherm of benzocaine, similar events for the excipients and, in one case, possibly dehydration of the β-CD, thus confirming thermal stability and absence of any polymorphic transitions.

HSM of benzocaine–excipient formulations

HSM was utilised to follow the transformation of benzocaine with the four excipients as a function of temperature to visibly observe changes. Photographic images were recorded and are presented in Supplementary Information at selected temperatures as Figures S7–S10. Firstly, Syloid® XDP 3050 silica was analysed (Fig. S7) and,

although hard to distinguish, did appear to show partially melted benzocaine at 93.2 °C, followed by recrystallisation when cooled to 30 °C. For benzocaine with β-cyclodextrin, HSM (Fig. S8) enabled the observation of the fusion process of benzocaine at around 92.8 °C within β-cyclodextrin, confirming that benzocaine became molten, as evidenced during MWDTA and DSC profiles with dehydration occurring in the region of 120–140 °C. Furthermore, HSM confirmed that the drug recrystallised during the cooling process as expected based on the previous analytical data.

HSM images for benzocaine formulated with stearic acid are shown in Fig. S9. In conjunction with MWDTA and DSC data (shown earlier), it can be concluded that stearic acid loses its crystalline structure and undergoes a solid-state transformation near 71.2 °C, which corresponds to the melting point of the excipient. A second transformation at 89.4 °C was attributed to the fusion of benzocaine, followed by recrystallisation upon cooling.

For benzocaine formulated with D-mannitol (Fig. S10), HSM revealed a white powder at 75.0 °C with some melting at ~ 93.2 °C and complete transformation at 167.8 °C. These findings match those seen in the previously presented MWDTA and DSC data with recrystallisation upon cooling at 30 °C.

Conclusions

In conclusion, the effect of microwave heating was investigated through the application of microwave thermal analysis to six model pharmaceutical compounds and a set of four model excipients. Thermal profiles were analysed and compared with data obtained using differential scanning calorimetry (DSC) and hot-stage microscopy (HSM). Overall, it was found that the process of microwave heating produced different thermal profiles to those seen using traditional, conductive heating and more importantly indicated transitions and subtle phenomena that were not observed using DSC. Investigating differences in thermal profiles can be a useful way to consider the effect of microwave-induced heating on formulations which can, in turn, help guide formulation choices.

References

1. Parkes GMB, Barnes PA, Charsley EL, Bond G. Microwave differential thermal analysis in the investigation of thermal transitions in materials. Anal Chem. 1999;71(22):5026–32. https://doi.org/10.1021/ac990760w.
2. Parkes GMB, Barnes PA, Charsley EL, Bond G. Microwave thermal analysis—a new approach to the study of the thermal and dielectric properties of materials. J Therm Anal Calorim. 1999;56(2):723–31.
3. Parkes GMB, Barnes PA, Bond G, Charsley EL. Qualitative and quantitative aspects of microwave thermal analysis. Thermochim Acta. 2000;356(1–2):85–96. https://doi.org/10.1016/s0040-6031(00)00458-5.
4. Nair BKS, Parkes GMB, Barnes PA, Sibley MJN, Bond G. Development of a novel instrument for microwave dielectric thermal analysis. Rev Sci Instrum. 2006;77(4):045108. https://doi.org/10.1063/1.2179412.
5. Parkes GMB, Bond G, Barnes PA, Charsley EL. Development of a new instrument for performing microwave thermal analysis. Rev Sci Instrum. 2000;71(1):168–75. https://doi.org/10.1063/1.1150179.
6. Savu SV. Microwave differential thermal analysis technique of the $Fe_2O_3 + BaCo_3$ homogeneous mixture. Adv Mater Res. 2014;1036:24–9.
7. Nesbitt A, Navabpour P, Degamber B, Nightingale C, Mann T, Fernando G, et al. Development of a microwave calorimeter for simultaneous thermal analysis, infrared spectroscopy and dielectric measurements. Meas Sci Technol. 2004;15(11):2313–24. https://doi.org/10.1088/0957-0233/15/11/018.
8. Colman TAD, Demiate IM, Schnitzler E. The effect of microwave radiation on some thermal, rheological and structural properties of cassava starch. J Therm Anal Calorim. 2014;115(3):2245–52. https://doi.org/10.1007/s10973-012-2866-5.
9. Singh S, Gaikwad KK, Lee M, Lee YS. Microwave-assisted micro-encapsulation of phase change material using zein for smart food packaging applications. J Therm Anal Calorim. 2017. https://doi.org/10.1007/s10973-017-6768-4.
10. Kersting DF, Wiebeck H, Esper FJ. Processing and characterization of composites curing by microwave irradiation. Macromol Symp. 2016;367(1):49–54. https://doi.org/10.1002/masy.201500132.
11. Lewis DA, Summers JD, Ward TC, McGrath JE. Accelerated imidization reactions using microwave radiation. J Polym Sci, Part A: Polym Chem. 1992;30(8):1647–53. https://doi.org/10.1002/pola.1992.080300817.
12. Wu L, Zhu H, Huang K. Thermal analysis on the process of microwave-assisted biodiesel production. Biores Technol. 2013;133:279–84. https://doi.org/10.1016/j.biortech.2013.01.009.
13. Otsuka M, Maeno Y, Fukami T, Inoue M, Tagami T, Ozeki T. Solid dispersions of efonidipine hydrochloride ethanolate with improved physicochemical and pharmacokinetic properties prepared with microwave treatment. Eur J Pharm Biopharm. 2016;108:25–31. https://doi.org/10.1016/j.ejpb.2016.08.008.
14. Fuliaş A, Vlase G, Vlase T, Şuta LM, Şoica C, Ledeţi I. Screening and characterization of cocrystal formation between carbamazepine and succinic acid. J Therm Anal Calorim. 2015;121(3):1081–6. https://doi.org/10.1007/s10973-015-4473-8.
15. Bergese P, Colombo I, Gervasoni D, Depero LE. Microwave generated nanocomposites for making insoluble drugs soluble. Mater Sci Eng, C. 2003;23(6–8):791–5. https://doi.org/10.1016/j.msec.2003.09.137.
16. Hussain T, Waters LJ, Parkes GMB, Shahzad Y. Microwave processed solid dispersions for enhanced dissolution of gemfibrozil using non-ordered mesoporous silica. Colloids Surf A. 2017;520:428–35. https://doi.org/10.1016/j.colsurfa.2017.02.007.
17. Wong TW. Use of microwave in processing of drug delivery systems. Curr Drug Deliv. 2008;5(2):77–84. https://doi.org/10.2174/156720108783954842.
18. Solanki HK, Prajapati VD, Jani GK. Microwave technology—a potential tool in pharmaceutical science. Int J PharmTech Res. 2010;2(3):1754–61.
19. Bonde MN, Sohani AC, Daud AS, Sapkal NP. Microwave: an emerging trend in pharmaceutical processes and formulations. Int J Pharm Technol. 2011;3(4):3499–520.
20. Waters LJ, Bedford S, Parkes GMB. Controlled microwave processing applied to the pharmaceutical formulation of ibuprofen. AAPS PharmSciTech. 2011;12(4):1038–43. https://doi.org/10.1208/s12249-011-9671-5.
21. Waters LJ, Hussain T, Parkes G, Hanrahan JP, Tobin JM. Inclusion of fenofibrate in a series of mesoporous silicas using microwave irradiation. Eur J Pharm Biopharm. 2013;85(3 PART B):936–41. https://doi.org/10.1016/j.ejpb.2013.08.002.
22. Doreth M, Hussein MA, Priemel PA, Grohganz H, Holm R, Lopez de Diego H, et al. Amorphization within the tablet: using microwave irradiation to form a glass solution in situ. Int J Pharm. 2017;519(1-2):343–51. https://doi.org/10.1016/j.ijpharm.2017.01.035.
23. Pinto LMA, Fraceto LF, Santana MHA, Pertinhez TA, Oyama S Jr, De Paula E. Physico-chemical characterization of benzocaine-β-cyclodextrin inclusion complexes. J Pharm Biomed Anal. 2005;39(5):956–63. https://doi.org/10.1016/j.jpba.2005.06.010.
24. Avula SGC, Alexander K, Riga A. Thermal analytical characterization of mixtures of antipsychotic drugs with various excipients for improved drug delivery. J Therm Anal Calorim. 2016;123(3):1981–92. https://doi.org/10.1007/s10973-015-4763-1.
25. Lin HL, Zhang GC, Lin SY. Real-time co-crystal screening and formation between indomethacin and saccharin via DSC analytical technique or DSC-FTIR microspectroscopy. J Therm Anal Calorim. 2015;120(1):679–87. https://doi.org/10.1007/s10973-014-3787-2.
26. Oliveira LJ, Stofella NCF, Veiga A, Féderle S, da Graça TTM, Bernardi LS, et al. Physical–chemical characterization studies of ketoprofen for orodispersible tablets. J Therm Anal Calorim. 2018;133(3):1521–33. https://doi.org/10.1007/s10973-018-7195-x.
27. Forni F, Coppi G, Iannuccelli V, Cameroni R. Thermal behaviour of melt crystallized phenylbutazone. J Therm Anal. 1990;36(1):35–44. https://doi.org/10.1007/bf01912065.
28. Maswadeh HM. Incompatibility study of ibuprofen in ternary interactive mixture by using differential scanning calorimetry. J Therm Anal Calorim. 2016;123(3):1963–71. https://doi.org/10.1007/s10973-015-4773-z.
29. Rabel Riley SR. An integrated approach to thermal analysis of pharmaceutical solids. J Chem Educ. 2015;92(5):932–5. https://doi.org/10.1021/ed500640d.
30. Mura P. Analytical techniques for characterization of cyclodextrin complexes in the solid state: a review. J Pharm Biomed Anal. 2015;113:226–38. https://doi.org/10.1016/j.jpba.2015.01.058.