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Abstract

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Keywords (separated by '-')	Hydroxypropylcellulose - Klucel® LF - Klucel® MF - Xylitol - Glycerol - Lidocaine - Free films - DSC - TG–MS
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Tracking of the behaviour of lidocaine basis containing hydroxypropylcellulose free films with thermoanalytical method

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Keywords Hydroxypropylcellulose · Klucel® LF · Klucel® MF · Xylitol · Glycerol · Lidocaine · Free films · DSC · TG–MS

Introduction

Differential scanning calorimetry (DSC) is a widely used method to determine different properties of pharmaceuticals: glass transition in polymers (T_g) [1–5]; amorphicity and crystallinity [1, 6–9]; polymorphism [1, 10–14]; drug solubility in polymers [1, 15–18]; characterization of polymers and bio-polymers [1, 19–22]; and pharmaceutical dosage forms [23, 24]. Thermogravimetry (TG) is also used to characterize pharmaceuticals [18, 25–31].

Innovative pharmaceutical production has recently placed great emphasis on developing drug-containing bioadhesive films. In line with this, many of the increasing number of papers published in the literature report the investigation of thermal behaviour.

A novel organic–inorganic hybrid transdermal film-forming system was designed by a modified poly(vinyl alcohol) (PVA) gel plasticized with glycerol (GLY), using c-(glycidyloxypropyl)trimethoxysilane (GPTMS) as an inorganic-modifying agent, and poly(*N*-vinyl pyrrolidone) (PVP) as a tackifier. DSC was used to determinate the thermal behaviour of the samples. The system was first heated at a rate of 10 °C min^{-1} from 20 to 200 °C and kept there for 10 min then cooled down to 50 °C at a rate of 20 °C min^{-1}. The second heating scan from 50 to 200 °C at 10 °C min^{-1} was applied to determinate the glass transition temperature. It was found that all PVA–GPTMS–PVP–GLY samples exhibit the soft–hard segment microphase separation. The good skin adhesive properties of the films come from the flexible soft segments composed of

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uncross-linked PVA chain, PVP and GLY, which influenced the viscoelastic properties and low-temperature performance of the films. The hard segments (PVA–GPTMS and self-cross-linked GPTMS) give the mechanical strength and appropriate film-forming properties to the system [32].

For transdermal controlled drug delivery, a flurbiprofen (FB)–inorganic nanohybrid system was made. TG–DTA was used to investigate the samples; the temperature was increased from ambient to 800 °C at a heating rate of 2 °C min^{-1} under 100 ml min^{-1} airflow. The TG–DTA was used on the dry powder. Three mass losses were detected. The first mass loss of 6.51 % with a weak endothermic response at around 71.9 °C originated from the removal of absorbed water from the surface of the system. The second mass loss, approximately 8.03 % with an endothermic peak at around 166.26 °C, was connected to the dehydration of co-intercalated water in samples. The third mass loss around 47.06 % was associated with an exothermic reaction in the range from 225 to 520 °C [33].

Ibuprofen (IBU) mucoadhesive tablets containing chitosan and its half-acetylated derivative as excipients were compared. Polymer–IBU interactions and the degree of IBU crystallinity were investigated by DSC. Samples were heated under a nitrogen atmosphere at 5 °C min^{-1} from 25 to 90 °C. DSC was used to determine the effect of co-grinding and chitosan on IBU crystallinity. The onset of IBU melting was observed at 73.9 °C, and the enthalpy was 125.4 J g^{-1}. In the co-ground mixture with chitosan, IBU's onset melting point decreased by approximately 3 °C and the enthalpy was 121.6 J g^{-1} of IBU. Chitosan did not show any thermal changes over this temperature range. The decreased enthalpy on co-grinding equates to a 4 % loss in IBU crystallinity [34].

Matrix-type mucoadhesive tablet from a mixture of hard fat, ethylcellulose and polyethylene glycol, containing indomethacin, was developed. The thermal behaviour of matrix bases was investigated with DSC. Samples were heated at a rate of 10 °C min^{-1} from 20 to 170 °C in air. In the DSC curve, an endothermic peak was observed at approximately 150 °C [35].

Development of novel mucoadhesive pellets containing valsartan (VAL) was the goal of a study of *Caoa* et al. Two types of drug-loaded core pellets were prepared by different technology, namely extrusion/spheronization method. Pellets were dry-coated with a mixture of hydroxypropylmethylcellulose and carbomer at different ratios. The thermal properties of VAL, Povidone® K30, Poloxamer, Avicel® PH 101, NaOH and core pellet powders (F1 and F2) were determined with DSC. The samples were heated from 25 to 200 °C at a heating rate of 10 °C min^{-1} under nitrogen atmosphere. A broad single endothermic peak was found in case of pure VAL, while no melting peak was detected in the cases of both F1 and F2 pellets. This phenomenon confirmed that there was some impact between VAL and additives during extrusion process [36].

Pressure-sensitive IBU-containing adhesive was investigated by DSC. Samples were heated from 130 to 100 °C at a heating rate of 10 K min^{-1} under nitrogen atmosphere. The second heating runs were evaluated. It was found that IBU increasing in the formulation caused the decrease in the T_g, which phenomenon was connected to the plasticization effect of IBU on the product [37].

A hydrophobic mucoadhesive thiolated chitosan for pipirine (PIP) delivery was designed. The thermal degradation behaviour of the samples was determined with TG. The mass loss curves were recorded with a heating rate of 25 °C min^{-1} under nitrogen flow from 50 to 600 °C. For chitosan, the highest thermal decomposition stage occurred at 326 °C with a mass loss of 41.8 %. The TG curves of PIP revealed the highest thermal decomposition occurred at 363 °C. The chitosan–PIP microparticles curve showed a maximum decomposition rate at 293 °C, which was lower than the pure chitosan and may indicate a lower thermal stability of the PIP–chitosan microspheres than the chitosan ones [38].

Buccal poly(ethylene oxide) (PEO) film with (2-hydroxypropyl)-β-cyclodextrin (CD) was evaluated. Films were prepared at different PEO/CD ratios. The degree of crystallinity was determined by DSC. The degree of crystallinity was roughly constant for platform with a CD content ≤60 % w/w. On the other hand, PEO/CD75 and PEO/CD80 platforms showed a drastic decrease in the degree of crystallinity [39].

Novel sildenafil citrate (SC)-loaded PVA-polyethylene glycol (PEG) graft copolymer (Kollicoat1 IR)-based orally dissolving films (ODFs) were designed. The thermal properties and physicochemical behaviour of samples were evaluated using DSC. Kollicoat1 IR, sodium alginate (ALG-Na) and glycerol were combined. The films were heated at a rate of 10 °C min^{-1} from 10 to 250 °C under nitrogen flow. A sharp endothermic peak of SC was found at 198 °C, which was connected to the melting point of SC [40]. Melting SC peak was not detected in the curves of SC-loaded ODF. This indicated that interactions between SC and excipients had occurred in the preparation process of the film [40].

The goal of a study was to investigate the potential of isothermal calorimetry to monitor and characterize crystallization in indomethacin (IND)-loaded fast-dissolving PVP oral films. Subsequent analysis of the crystals with DSC was made. Samples were heated from 25 to 190 °C at 200 °C min^{-1} with nitrogen flow. It was found that isothermal calorimetry is able to monitor IND crystallization in polymer films [41].

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Lidocaine (LID)-loaded mucoadhesive buccal patches for controlled release in different formulations were studied. Films were loaded with LID–Compritol solid dispersion in the form of microspheres, and the effects of the composition were evaluated by DSC. Samples were heated at a rate of 10 °C min^{-1} between 30 and 300 °C. Melting points at 82 °C for lidocaine and at 75 °C for the main peak of Compritol were found. An irregularly shaped melting endotherm main peak at 73 °C was found for the microsphere samples. It suggested that the solid "microsphere" system was heterogeneous in nature [42].

Enrofloxacin (ENR)-loaded PVP thin films were formulated for enhanced drug delivery and were evaluated using DSC. Samples were heated from 25 to 300 °C with a heating rate of 10 °C min^{-1} in argon atmosphere. An endothermic peak of ENR was found at 222 °C corresponding to the melting point of the drug. A large endothermic peak of ENR–PVP at 94.57 °C was found. The absence/reduction in ENR peaks suggested that the drug is amorphous. The result indicated that there was good compatibility between ENR and PVP [43].

The excipients proved to exert strong effects on the physicochemical properties of the tested systems, and it is very important to study them intensively in preformulation studies in pharmaceutical technology. For this reason, in our earlier paper, we already reported our various physicochemical examinations with Klucel-containing films (tensile strength, surface properties and the measurement of the free volume with positron annihilation lifetime spectroscopy), which were performed to study and to describe the resulting film structure [44].

The aim of our present investigations was to study the thermal behaviour of the film-forming polymers with two different chain lengths, of the taste-enhancing and plasticizing excipients and also of the films prepared from them, as these data can provide useful information on the storage conditions and stability of drug-containing films.

Materials

HPC (Klucel MF and LF) (Aqualon; Hercules Inc., Wilmington, USA.) was used as a film-forming polymer. The main differences between the two Klucel products are in the molecular mass and the viscosity of the solution. MF has a higher viscosity in solution and a higher molecular mass. HPC is a non-ionic, water-soluble cellulose ether, and its films are appropriately flexible even without any plasticizer.

The local anaesthetic lidocaine basis (Lid) (Ph. Eur., Società Italiana Medicinali Scandicci, Firenze, Italy) was chosen as the active ingredient. Xylitol (Xyl) (Ph.Eur., Roquette, Lestrem, France) was used as the taste improver. Glycerol (Gly) (Ph. Eur., Molar Chemicals Kft., Budapest, Hungary) was used as a plasticizer, and in films it can act as a taste coverer.

Methods

Preparation of free films

The optimum polymer concentration was first established, 2 % w/w solutions were chosen for both types of Klucel as we wished to compare their physicochemical properties. Lidocaine (Lid) was grounded in a mill (Retsch RM 100, Retsch GmbH, Haan, Germany), and the 100–200-μm powder fraction was incorporated into the solution. Xylit (Xyl) dissolved readily, and glycerol (Gly) compounded well in the water–polymer mixture. Lid, Gly and Xyl were all used in the same concentration (5, 10 or 15 % w/w of the film-forming polymer). Samples were poured onto a non-stick surface. All the films were made by the same solvent-casting technology and stored at room temperature (25 °C/65 % RH) for a day and then placed into a climate chamber for 24 h (40 °C/50 % RH).

Thermoanalytical measurements

The thermoanalytical examinations of the materials were carried out with a Mettler Toledo TG/DSC1 instrument (Mettler Toledo, Switzerland). During the DSC measurements, the start temperature was −40 °C, the end temperature was 300 °C, and the applied heating rate was 10 °C min^{-1}. Argon atmosphere was used, and nitrogen was used as drying gas. 10 ± 1-mg sample was measured into an aluminium pan (40 μl). The curves were calculated from the average of three parallel measurements and were evaluated with STARe software.

For the TG and the DSC measurements, the start temperature was +25 °C, the end temperature was 400 °C, and the applied heating rate was 10 °C min^{-1}. Nitrogen atmosphere was used. 10 ± 1-mg sample was measured into an aluminium pan (100 μl). The curves were calculated from the average of three parallel measurements and were evaluated with STARe Software.

The thermal characteristics of the sample mass loss were determined with a thermal gravimetric analyzer (Mettler Toledo, model TG/DSC1) coupled with a quadrupole mass spectrometer (Pfeiffer Vacuum, model Thermostar™ GSD 320), operated under N_2 atmosphere (purity = 99.999 %, 70 ml min^{-1} flow rate). The connection between the TG and the mass spectrometer was made by means of a silica capillary, which was maintained at 120 °C.

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Results and discussion

The thermal studies were started by studying the film-forming polymers as well as the active ingredient and excipients to be used, and the changes were monitored between 25 and 400 °C at a constant heating rate. The changes in heat flow were followed with the help of DSC curves. The thermal behaviour of the two film-forming polymers, lidocaine used as an active ingredient and the two excipients (glycerol and xylitol) is shown in Fig. 1.

A slight endothermic baseline shift can be observed in the DSC curves of the Klucel® LF and MF polymers between 40 and 100 °C, which can be explained with the removal of the water content of the polymer. The heat flow curves show no difference until 340 °C, and then signs of decomposition appear in both curves.

The DSC curve of glycerol shows a definite endothermic peak between 50 and 150 °C due to the higher water content, while at about 200 °C signs of decomposition can be observed until 300 °C.

In the DSC curve of xylitol, an onset value of 92.2 °C is followed by a peak melting point at 95.6 °C. The enthalpy change of the process is 217.4 J g^{-1}. Xylitol has much greater thermal stability as the baseline change and the decomposition process start only at about 280 °C and end over 380 °C.

Lidocaine, which is used as an active ingredient, has a lower melting point than the excipients because the onset value is 67.2 °C and the peak of the melting point appears at 68.6 °C. The enthalpy change of the process is 59.1 J g^{-1}. The baseline change appears over 180 °C, and then the decomposition process is accelerated over 200 °C and finishes at about 330 °C.

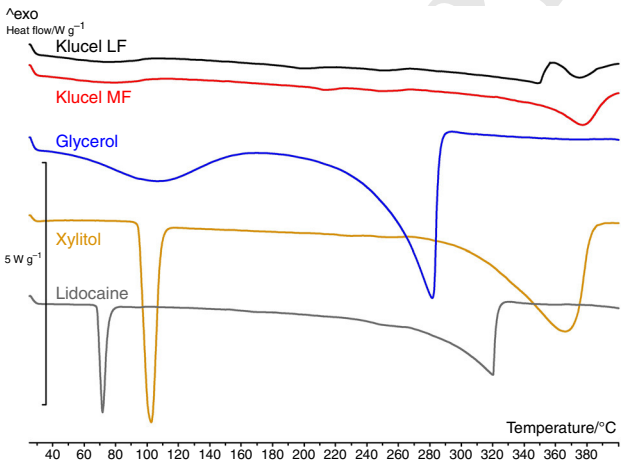

Fig. 1 Thermal properties of Klucel® film-forming materials, active ingredient and excipients as shown by the DSC curves

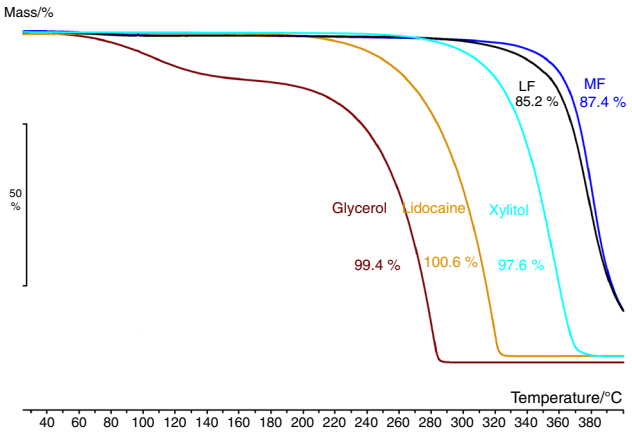

Fig. 2 Thermal properties of Klucel® film-forming materials, active ingredient and excipients as shown by the TG curves

The TG curves of the same materials in Fig. 2 show that the two different film-forming materials are thermally stable, a mass loss of only 1–1.5 % can be detected until 100 °C, the decomposition process starts over 300 °C, and mass loss is 85 % for Klucel LF and 87 % for Klucel MF until 400 °C. However, the rate of the decomposition process is different, and it is faster for the LF product and slower for the MF product, which is also shown clearly by the numerical data of the mass loss of the two polymers (see Table 1).

From the data, it can be stated that the mass loss of 1.0–1.5 % observed at the beginning of heating can be explained by the removal of water from the film, and then further mass loss starts only at about 300 °C. The thermal behaviour of the two polymers differs significantly between 340 and 400 °C, which can be explained by the different chain lengths of the two polymers. The Klucel® MF product with a longer chain has greater thermal stability, and probably the more stable structure is broken only at higher temperatures.

The thermal behaviour of the excipients as shown by their TG curves (see Fig. 2) can be described well, and it confirms the information obtained from the DSC curves. Although both excipients were entirely decomposed by the end of the examination, considerable differences can be observed in their behaviour. Xylitol proved to be the most stable as the decomposition process really starts only over 300 °C. Ensuing from its material properties, glycerol first loses its water content at the beginning of heating, and then its decomposition starts over 180 °C and finishes at 290 °C. The thermal behaviour of the active ingredient is somewhere between those of the two excipients, as in the case of lidocaine, the mass loss curve reveals that decomposition starts at about 180–200 °C (see Table 1.).

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Table 1 Mass change of various excipients and the active ingredient as a function of temperature

Sample	Mass loss/%								
	100 °C	180 °C	250 °C	300 °C	320 °C	340 °C	360 °C	380 °C	400 °C
Klucel LF	1.13 ± 0.01	1.13 ± 0.01	1.47 ± 0.01	2.72 ± 0.01	4.55 ± 0.03	8.43 ± 0.13	18.42 ± 0.59	55.64 ± 0.81	85.2 ± 1.430
Klucel MF	1.51 ± 0.32	1.81 ± 0.43	2.42 ± 0.2653	3.28 ± 0.26	4.10 ± 0.88	6.42 ± 1.19	14.1 ± 1.70	50.5 ± 2.12	87.4 ± 1.2653
Glycerol	4.99 ± 1.98	15.7 ± 5.04	31.4 ± 9.90	98.9 ± 4.30	99.3 ± 3.66	99.4 ± 3.67	99.4 ± 3.67	99.4 ± 3.67	99.4 ± 3.67
Xylitol	0.13 ± 0.02	0.39 ± 0.18	1.22 ± 0.47	6.26 ± 0.27	14.38 ± 0.16	35.3 ± 0.05	78.7 ± 0.35	100.9 ± 1.34	101.4 ± 1.49
Lidocaine	0.21 ± 0.01	0.04 ± 0.01	7.39 ± 0.76	45.4 ± 4.21	97.6 ± 5.69	100.6 ± 1.52	100.6 ± 1.54	100.6 ± 1.54	100.6 ± 1.55

After studying and learning about the thermal behaviour of the film-forming polymer and the excipients to be used, we wished to study the behaviour of the free films which were prepared from them and contained both excipient and active ingredient. As regards Klucel LF and MF products, differences in thermal stability were observed only over 300 °C, so they behaved in the same way when applied under the conditions of the oral mucosa. Klucel LF products were chosen for the formulation of bioadhesive films and the examination of their thermal stability, and these results are presented in this paper.

The thermal behaviour of Klucel® LF films containing both xylitol and glycerol is illustrated in Fig. 3.

Glycerol and xylitol were present in the films in the same concentrations (at 0–5–10–15 % w/w of the polymer). The shape of the TG curves shows that although the

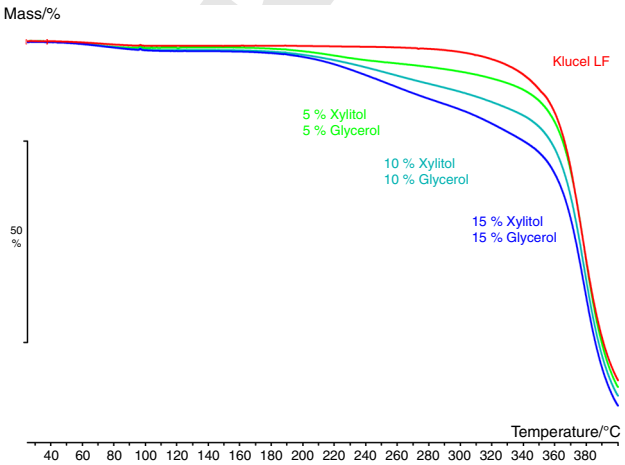

Fig. 3 Thermal properties of films made from Klucel® LF film-forming material containing xylitol and glycerol as shown by the TG curves

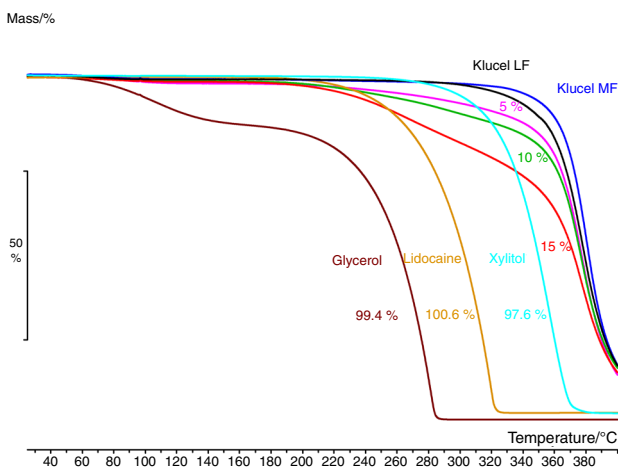

Fig. 4 Thermal properties of films made from Klucel® LF film-forming material containing lidocaine as well as xylitol and glycerol as shown by the TG curves

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decomposition process changes with the increase in the concentration of the excipients, when heated up to 400 °C, mass loss does not differ significantly compared to Klucel® LF films without excipients. At the beginning of heat treatment, mass loss can be explained by the removal of the water content in every case and it is proportional to the concentration of glycerol. However, over 180–200 °C, the decomposition processes start, and the TG curves open up more, which is probably due to the fact that the molecules built-in among the polymer chains loosen the structure, which in turn is decomposed more easily.

Then, we studied the thermal behaviour of drug-containing films. In Fig. 4, the thermal behaviour of Klucel® LF films containing lidocaine as well xylitol and glycerol is presented. The effect of the ratio (quantity) of the components on the shape of the TG curves as well as on the quantity and disproportion of the arising mass loss can be seen clearly. It is remarkable that while a smaller mass loss was observed for the 5 and 10 % films, the mass loss of the 15 % film was greater, which can be explained by the loosening effect of glycerol and lidocaine on the polymer structure.

The concentrations of the active ingredient and the excipients in the films were always the same (0–5–10–15 % w/w of the film-forming polymer). The shape of the TG curves is similar to the one shown by films without lidocaine, but they can be compared really well if the TG curves of films with lidocaine (continuous line) and without lidocaine (broken line) are plotted together (see Fig. 5). The temperature range (200–400 °C) of the greatest importance with respect to the phenomenon is focussed on here. The shape of the curves shows that in the case of the 5 and 10 % systems, the presence of lidocaine practically did not result in a significant difference in thermal stability, while in the concentration of 15 %, the films which contained lidocaine were decomposed more easily, which is due to the greater quantity of the materials used and to the ensuing looser structure.

This can probably be explained by the fact that the plasticizer, when used in a lower concentration, can be incorporated into the film structure, which we have already confirmed in the case of Metolose free films [45–47]. However, when it is applied in higher concentrations, the

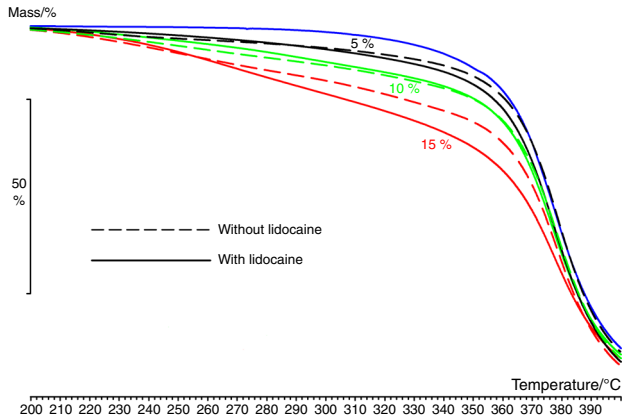

Fig. 5 Comparison of the thermal properties of xylitol and glycerol containing Klucel® LF films with and without lidocaine between 200 and 400 °C as shown by the TG curves

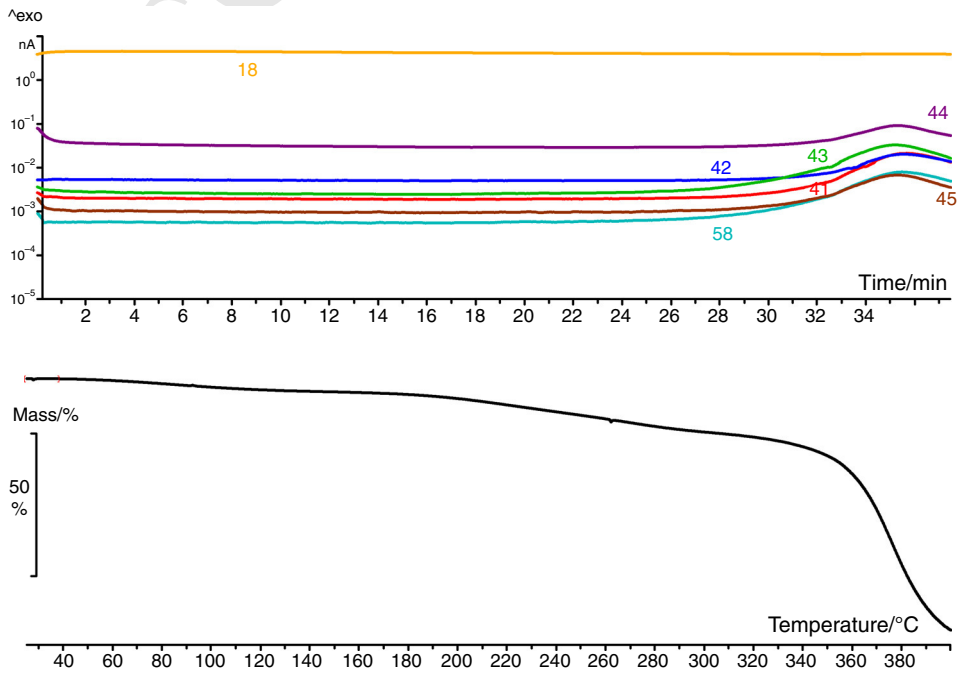

Fig. 6 Thermal properties of films made from Klucel® LF film-forming material containing 15 % glycerol as shown by the TG–MS curves

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stability of the film structure deteriorates, which is illustrated well by the presented curves, when 15 % of other components were used besides the polymer.

We also performed the TG–MS examination of all the films, we analysed the evolved gases with a mass spectrograph coupled with the TG in order to obtain information about the stability of the film structure. Among the several measurements, the data obtained with films containing 15 % glycerol are presented in Fig. 6. Although no change can be observed for the $m/z = 18$ fragment on axis "Y" with a logarithmic scale, in the case of an absolute scale water removal can be seen between both 40–150 and 350–400 °C, and with the start of decomposition, a concentration increase was experienced for further fragments ($m/z = 41, 42, 43, 44$, 45 and 58), starting practically at the same time. The peak intensity of the fragments depicted decreased in the following order: $m/z = 44$–43–42–41–58–45. All these indicate that carbon dioxide is formed in the greatest concentration, which is confirmed by the increase of $m/z = 44$. $m/z = 43$, 45 may indicate the development of acetic acid and/or isopropyl alcohol, while $m/z = 43$, 58 may be indicative of the formation of acetone.

Conclusions

In the course of our experiments, free films were prepared from Klucel film-forming materials with various chain lengths for buccal administration, with glycerol and/or xylitol taste enhancer excipient and lidocaine active ingredient incorporated in various concentrations. During the study of the bioadhesive films, it was found that the thermal behaviour of Klucel LF and Klucel MF film-forming polymers was different from each other only in the temperature range of 340–400 °C, which is due to the difference in the chain length of the polymer molecule.

Among the active ingredients and excipients used, glycerol proved to be the least stable thermally, while xylitol was the most stable. The shape of the TG curves shows that the decomposition process changes with the increase in the concentration of the excipients. In the case of glycerol, the decomposition processes start over 180–200 °C, and the TG curves open up more, which is probably due to the fact that the molecules built-in among the polymer chains loosen the structure, which in turn is decomposed more easily.

The role of the active ingredient lidocaine in thermal stability was also examined, and it was found that the shape of the curves shows that in the case of the 5 and 10 % systems, the presence of lidocaine did not result in a significant difference in thermal stability, while in the concentration of 15 %, the films which contained lidocaine were decomposed more easily, which is due to the greater quantity of the materials used and to the ensuing looser structure.

The TG–MS examinations revealed that with the start of decomposition, a concentration increase was seen in the case of $m/z = 41$, 42, 43, 44, 45 and 58 fragments, starting practically at the same time. The peak intensity of the fragments in the highest concentration may indicate the formation of carbon dioxide and also the development of acetic acid, isopropyl alcohol and acetone.

As a summary, it can be stated that the thermal stability of free films prepared from Klucel LF polymer is appropriate, and in the case of the 5 and 10 % systems, the presence of lidocaine did not result in a significant difference in thermal stability. The results not only help to choose the formulation conditions but also provide useful information concerning the packaging and storage conditions as well as the stability of the final product.

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