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Compatibility of the antitumoral β-lapachone with different solid dosage forms excipients

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Abstract

The objective of the present study was to evaluate the compatibility of the β-lapachone (βLAP), an antitumoral drug in clinical phase, with pharmaceutical excipients of common use including diluents, binders, disintegrants, lubricants and solubilising agents. Differential scanning calorimetry (DSC) was used for a first screening to find small variations in peak temperatures and/or their associated enthalpy for six drug/excipient combinations (magnesium stearate, sodium estearyl fumarate, dicalcium phosphate dihydrate, mannitol, randomized methyl-β-cyclodextrin and hydroxypropyl-β-cyclodextrin), which indicate some degree of interaction.

Additional studies using Fourier transformed infrared spectroscopy (FTIR), optical microscopy (OM) and heating–cooling DSC (HC-DSC) confirmed the incompatibility of βLAP with magnesium stearate and dicalcium phosphate dihydrate. Those excipients should be avoided in the development of solid dosage forms.

Keywords: β-Lapachone; Compatibility; Excipient; Differential scanning calorimetry

1. Introduction

The β-lapachone (βLAP) is an antitumoral drug in clinical phase that presents good perspectives for its incorporation in the therapies in the near future. βLAP is obtained on a small scale from South American trees of the families Bigoniaceae and Verbenaceae [1]. On a larger scale it can be produced following the method developed by Hooker and co-workers in 1892 through cyclization of lapachol in sulphuric acid [2].

Recent studies have demonstrated that βLAP possesses a potent antineoplasic activity. *In vitro* and *in vivo* studies have shown that βLAP inhibits conventional therapy-resistant tumors, particularly the malignant neoplasm of slow cell cycle like prostate, colon and some ovarian and breast cancer [3–5]. Despite its interesting potential applications, preformulation studies have not yet been performed.

The study of drug–excipient compatibility is an important stage in the development of a solid dosage form as their incompatibility can alter the stability and/or the biovailability of drugs, thereby, affecting its safety and/or efficacy. Two types of chemical incompatibilities have been described between excipients and drugs: those corresponding to intrinsic chemical drug degradation such hydrolysis or oxidation but without significant direct covalent chemical reactions, and those corresponding to covalent reaction between the drug and the excipient [6].

Throughout the different methods reported on drug–excipient compatibility studies, DSC has been shown to be a rapid, sensitive and simple technique used in routine experiments. Small variations in peak temperature or associated enthalpy are interpreted as an indication of interaction and possible incompatibility. Despite the advantages of DSC there are certain limitations. The extrapolation of findings obtained at high temperatures, are not always in agreement with the drug real situation in the formulation [7,8]. Therefore, the DSC results must be interpreted carefully and some complementary techniques, such as infrared spectroscopy, microscopy or X-ray diffractometry can be useful in avoiding misleading conclusions [9].

In the present study the compatibility of βLAP with 12 different pharmaceutical excipients of common use in the development of solid dosage forms was evaluated. Five cyclodextrins

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have also been included because βLAP has an extremely low hydrosolubility and, recently, cyclodextrins have been shown to be useful in overcoming this problem [10–12].

2. Experimental

2.1. Materials

βLAP was a gift from UFPE, Brazil (lot L503) with a purity of 99.9% by HPLC and DSC. Following excipients were purchased from commercial sources and used as such. Microcrystalline cellulose PH 101 (MCC, Guinama/Spain), pregelatinized maize starch (starch, Guinama/Spain), lactose monohydrated (lactose, Guinama/Spain), magnesium stearate (MGST, Guinama/Spain), sodium estearyl fumarate (PRUV, Juliá-Parrera/Spain), talc (talc, Guinama/Spain), hydroxypropylmethyl cellulose K100LV Premium (HPMC, Guinama/Spain), polyvinyl pyrrolidone (PVP, BASF/Germany), dicalcium phosphate dihydrate Emcompress (DCPD, United Mendell/UK), medium-viscosity carboxymethyl cellulose (CMC, Sigma/España), sodium croscarmellose (explocel, FMC/USA), mannitol (mannitol, AstraZeneca/Spain). The cyclodextrins β-cyclodextrin (βCD) and randomized methyl-β-cyclodextrin (RMβCD, molar substitution 0.5) were donated by Roquette/France; the hydroxypropyl-β-cyclodextrin (HPβCD, molar substitution 2.7) was facilitated by Janssen Pharmaceutica/Belgium; the α-cyclodextrin (αCD) was provided by Wacker/Germany and the sulfobutylether-β-cyclodextrin (SBβCD, molar substitution 1.0) was donate by Cydex/EUA.

2.2. Study protocol

The flow diagram (Fig. 1) presents the protocol used for the βLAP–excipient compatibility evaluation. Firstly, DSC measurements on binary βLAP–excipient mixtures were selected for rapid screening. Investigation on mixtures showing interactions or changes in the thermal profile of components were completed with Fourier transformed infrared spectroscopy (FTIR), optical microscopy (OM) and heating–cooling DSC studies (HC-DSC).

2.3. Sample preparation

βLAP–excipient physical mixtures in a ratio of 1:1 (w/w) were prepared by mixing in a Turbula WAB T2C (Switzerland) for 15 min. This proportion was chosen to maximize the probability of interactions between materials. Those samples have been denoted as PM.

PM samples were stored in an oven at 40 °C and 75% relative humidity in closed containers using sodium chloride saturated solutions for a month [13]. Those stressed samples have been denoted as SM.

Additionally, the drug, some excipients and its mixtures were subjected to thermal stress by heating up to 160 °C at a rate of 10 °C min^{-1}. This treatment was proven to be non-destructive for the isolated materials, which maintained their physical and chemical entity when cooling. Those samples have been denoted as TSM.

2.4. Differential scanning calorimetry (DSC)

Samples weighing 3–4 mg were placed in open aluminium pans and heated from 30 to 300 °C at a rate of 10 °C min^{-1} using a temperature modulated DSC Q100 calorimeter (TA Instruments, USA). Nitrogen was used as purge gas at a flux rate of 50 mL min^{-1}. The calibration of temperature and heat flow was performed with standard indium samples. Heating–cooling DSC (HC-DSC) studies were carried out at a rate of 10 °C min^{-1} following the sequence 30–170–30–300 °C.

2.5. Fourier transformation-infrared spectroscopy (FTIR)

Infrared spectra were obtained using a Bruker IFS-66V spectrometer (Bruker Daltonics Inc., Germany). Samples were ground, mixed thoroughly with potassium bromide, and compressed in a hydraulic press. Thirty-two scans were obtained at a resolution 4 cm^{-1}. Results were compared with reference excipient spectra in the literature [14].

2.6. Optical microscopy (OM)

The morphological characteristics of the samples were analysed using an Olympus SZ60 (Opelco, Japan) microscope connected to a video camera Olympus DP12 (Opelco, Japan). The images were processed using Analysis® version 3.2.

3. Results and discussion

3.1. Drug–excipient compatibility first DSC screening

DSC data of the βLAP and excipient thermal events in single or PM and SM binary systems are presented in Tables 1 and 2.

The βLAP DSC curve (Table 1) displays two events; a sharp endotherm at 157.3 °C, due to the drug melting with an associated enthalpy of 104.0 ± 1.5 J g^{-1} and the drug decomposition after 230 °C. This profile is characteristic of an anhydrous crystalline substance. The melting βLAP event is highly repeatable even when βLAP is blended with the different excipients (peak shifts higher than 0.5 °C are in bold type in Table 1). Variations in the enthalpy values for the binary mixtures can be attributed to some heterogeneity in the small samples used for the DSC experiments (3–4 mg) [7,9].

Some excipient endothermic events are melting (lactose, mannitol, MGST or PRUV) or dehydration phenomena (lactose, DCPD) but the most are broad peaks associated to their loss of adsorbed water (Table 2) with inherent important variations in their enthalpies, particularly for the SM samples which have been stored at 40 °C and 75% RH. A careful analysis of excipient thermal behaviour is required in order to avoid misinterpretations. Bold type indicates important changes in the excipient DSC profiles in Table 2.

Thermograms obtained by DSC analysis of individual components were compared with those of the mixtures, before (PM) and after its storage at 40 °C and 75% RH (SM). Of the 17 commonly used excipients tested only six showed interactions with βLAP. The profiles of the mixtures were an overlapping of

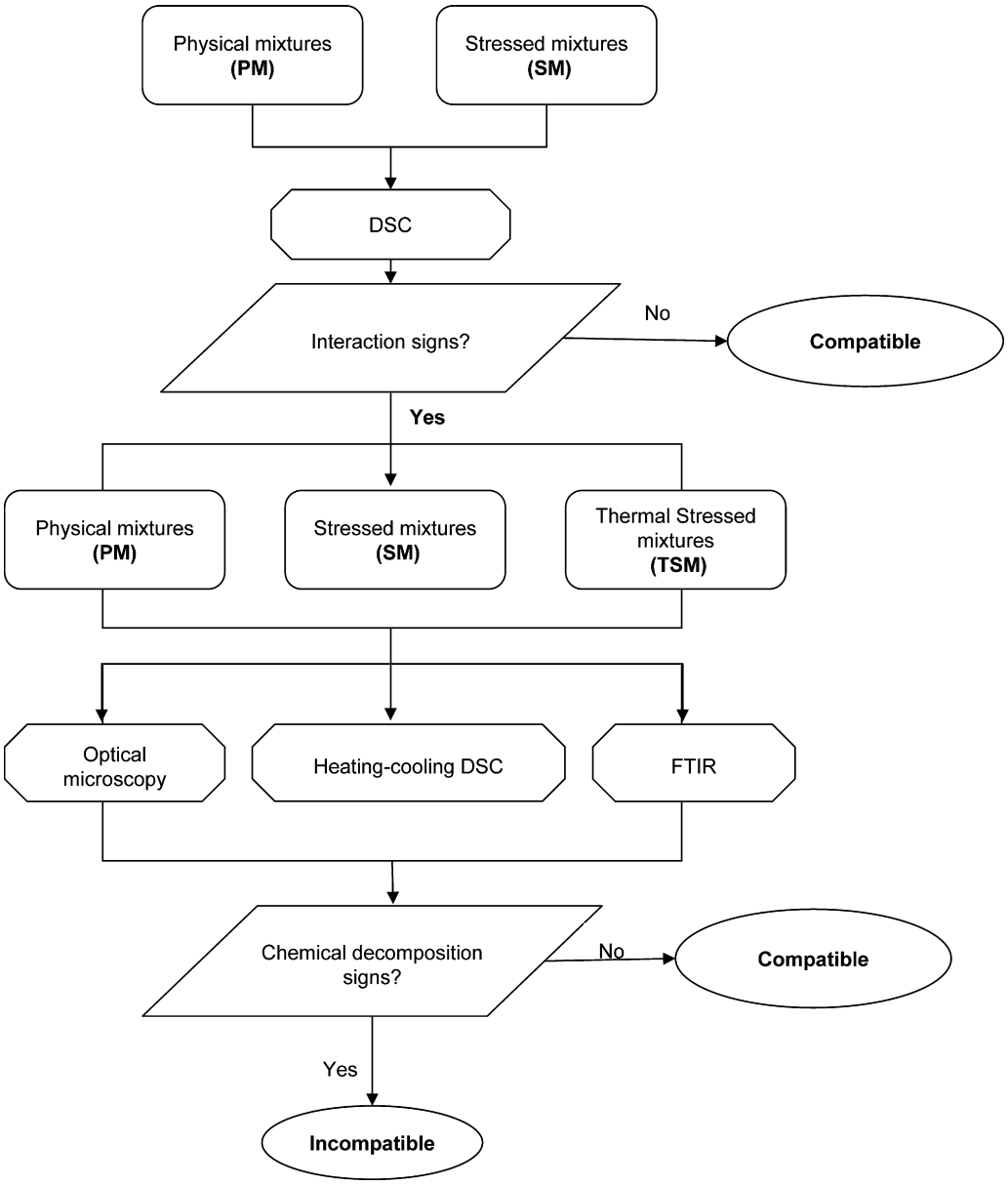


Fig. 1. Strategy for the βLAP–excipient compatibility study.

the thermograms of the single components for MCC, starch, lactose, talc, HPMC, PVP, CMC, explocel, αCD, βCD and SBβCD, which is accepted as compatibility evidence between materials [15]. Changes in βLAP events and/or excipient DSC profiles in the binary systems (PM) could be detected in two diluents, DCPD and mannitol; two lubricants, MGST and PRUV and two solubilising agents HPβCD and RMβCD. Those variations are slightly accentuated with ageing at 40 °C and 75% relative humidity (SM samples).

Mixtures of βLAP with mannitol and DCPD have shown changes, among diluents studied, in both drug and excipients DSC events (Figs. 2 and 3). Mannitol is an excipient with a well-defined thermal profile characterized by a melting peak at 168.9 °C indicative by its crystalline and anhydrous state (Fig. 2) [16]. Binary blending βLAP–mannitol (PM and SM) present shifts in melting peaks of drug and mannitol, as have been

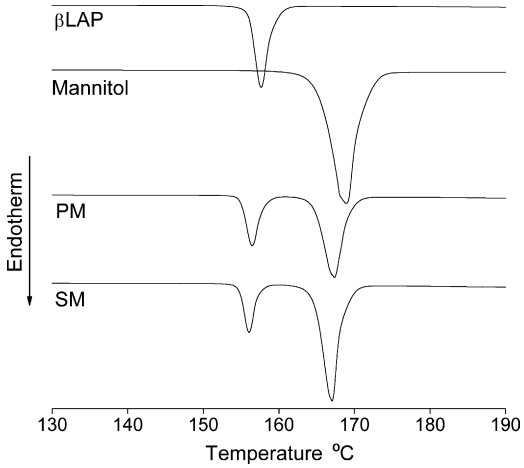


Fig. 2. DSC analysis of βLAP, mannitol and βLAP–mannitol combinations.

Table 1
Thermal data from DSC of βLAP melting event, in single and PM and SM binary systems studied

Raw Material	PM			SM		
	Range (°C)	T_{peak} [a] (°C)	ΔH (J g^{-1})	Range (°C)	T_{peak} [a] (°C)	ΔH (J g^{-1})
Single βLAP	152-162	157.3	104.0			
+ DCPD	**154-162**	**154.9**	**155.5**	**154-161**	**154.8**	**145.1**
+ lactose	153-162	157.6	55.1	153-162	157.1	62.4
+ mannitol	**152-160**	**156.5**	57.2	**152-160**	**156.0**	50.0
+ MCC	152-162	157.5	49.5	151-162	157.5	74.3
+ starch	153-162	157.4	58.7	153-162	157.0	68.9
+ CMC	153-162	157.3	65.3	152-162	157.3	65.6
+ HPMC	152-162	157.3	53.9	152-162	157.2	71.6
+ PVP	152-162	157.4	34.4	152-162	157.6	51.8
+ explocel	153-162	157.3	47.8	153-162	157.3	66.5
+ MGST	151-161	**156.8**	41.2	**151-160**	**156.7**	44.0
+ PRUV	**148-164**	**153.3** **155.1**	60.3	**147-162**	**153.0** **156.1**	87.6
+ talc	152-162	156.9	58.4	152-162	157.1	51.7
+ αCD	152-162	157.7	51.1	153-162	157.4	59.1
+ βCD	152-162	157.8	65.6	152-162	157.3	53.1
+ HPβCD	152-162	157.2	40.5	153-161	**156.8**	58.8
+ RMβCD	152-162	157.4	55.0	152-162	**156.8**	65.5
+ SBβCD	153-163	157.9	65.0	153-163	157.9	65.8

[a] Peak temperature

pointed out for other drugs such as amoxicillin, paracetamol or vitamin D [17–19].

The DCPD DSC profile is associated with the loss of water of hydration from this material and the formation of anhydrous dicalcium phosphate. The dehydration process occurs in two stages at 150.8 and 191.1 °C (associated enthalpies 100 and 310 J g^{-1}, respectively) in agreement with different authors (Table 2), the contribution of which depends on the DCPD variety and its particle size [20,21]. As it can be observed (Fig. 3), mixing βLAP with DCPD caused a shift in the melting peak of the drug and the disappearance of the DCPD characteristic events. Additionally, the enthalpy associated 155.5 J g^{-1} (Table 1), is lower than that corresponding to the addition of the thermal phenomena of components (about 250 J g^{-1}). These results suggest a robust interaction between components.

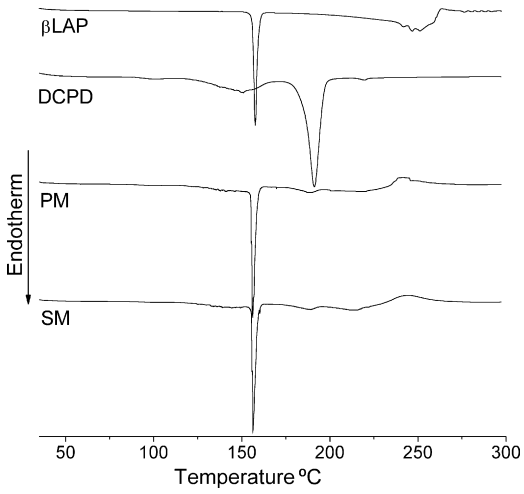


Fig. 3. DSC analysis of βLAP, DCPD and βLAP–DCPD combinations.

The MGST has been shown to be incompatible with an important number of drugs, such as glibenclamide or aspirin [22,23]. This excipient presents two molecules of water hydration (5.5% of weight approximately). The dehydration process occurs in several steps at over 70 °C. Additionally, it presents a melting peak at approximately 120 °C, which sometimes appears at lower temperatures or even superimposes the dehydration events as a consequence of the product being a mixture of magnesium palmitate and stearate [9,24,25]. Our DSC results agree with previous information (Fig. 4 and Table 2), MGST showing a wide endotherm with two events at 73.0 and 103.7 °C. The PM mixture thermogram presents a slight shift in the βLAP melting peak and a reduction in the associated enthalpy (Table 1). No changes can be denoted in the MGST events. However, the stressed sample (SM), exhibits important modifications regarding the MGST thermogram (Table 2). Those variations can be attributed to the modifications associated to the MGST ageing ($MGST_{aged}$) at the above conditions (40 °C and 75% RH) as it can be seen in the $MGST_{aged}$ DSC profile (Fig. 4). The hydration

Table 2
Thermal data from DSC of excipients studied and PM and SM binary systems

	Excipient events			PM			SM		
	range (°C)	T_{peak} [a] (°C)	ΔH (J g^{-1})	range (°C)	T_{peak} [a] (°C)	ΔH (J g^{-1})	range (°C)	T_{peak} [a] (°C)	ΔH (J g^{-1})
DCPD	117-170 172-204	150.8 191.1	101.4 310.0	-	-	-	-	-	-
lactose	110-156 195-223	143.6 217.7	146.4 153.1	110-150 195-223	143.7 217.6	55.6 54.1	110-150 195-221	144.0 217.2	53,5 35.3
mannitol	155-177	168.9	307.0	**161-173**	**167.4**	137.6	**161-172**	**167.1**	177.7
MCC	30-147	77.8	175.2	30-123	61.9	83.9	30-105	60.4	55.6
Starch	30-184	102.0	395.1	30-148	94.2	162.7	30-140	74.8	134.6
CMC	30-196	96.3	510.7	30-120	72.1	128.0	30-122	75.1	163.0
HPMC	30-122	75.8	177.9	30-98	58.5	78.2	30-95	60.8	82.5
PVP	30-151	92.9	428.0	30-123	74.7	227.9	30-127	76.7	221.8
explocel	30-183	87.6	407.9	30-140	78.3	177.8	30-127	70.5	129.5
MGST	30-132	73.0 103.7	205.5	30-122	73.7 103.4	112.2	**56-81** **90-122**	**72.5** **113.0**	**11.1** **73.6**
PRUV	72-117 117-147 197-205	110.2 135.2 200.4	131.9 80.2 30.8	72-113 **113-124** **124-144**	108.7 **117.9** **131.1**	60.4 **10.2** **38.8**	**75-110** **111-123** **124-139**	**103.3** **117.2** **129.9**	**21.3** **8.8** **21.5**
talc	-	-	-	-	-	-	-	-	-
αCD	30-155	75.5	411.8	30-143	73.5	200.5	30-140	72.0	204.5
βCD	30-145	107.8	339.4	30-125	97.8	178.4	30-125	105.7	200.1
HPβCD	30-150	88.0	260.9	30-135	79.6	166.6	30-120	70.2	116.5
RMβCD	30-145	91.6	277.5	30-130	79.7	149.6	30-127	78.6	177.2
SBβCD	30-196	88.8	383.9	30-140	73.1	87.9	30-147	63.5	127.3

[a]Peak temperature

of MGST seems to increase the interaction with βLAP, which could affect on the drug stability negatively.

Mixtures of βLAP and PRUV also exhibit diverse variations in the thermal behaviour of both products (Fig. 5 and Table 2). The PRUV DSC profile is characterized by three endothermic events at 110, 135 and 200 °C [26]. The PM mixtures show important variations in the positions of the three events. In this respect, peaking at 110 °C it seems to split into two; the peak at 135 °C shifts to a lower temperature (131 °C) and the one at 200 °C disappears completely (Table 2). Additionally, a widening in drug melting peak can be observed. Those differences are maintained in the SM samples. The slight hygroscopic nature of both, βLAP and PRUV, justifies this behaviour [16].

Cyclodextrins (CDs) are cyclic oligosaccharides with lipophilic inner cavities and hydrophilic outer surfaces capable of interacting with a large variety of drugs giving non-covalent inclusion complexes [27]. βLAP can form inclusion complexes with different cyclodextrins giving an improvement in its solubility and dissolution rate [10,12]. Variations in the raw material thermal profiles or even the disappearance of the fusion peak of the drug in combinations of drug–cyclodextrin are often interpreted as an evidence of an inclusion complex formation. Cyclodextrins exhibit a broad endothermic effect ranging

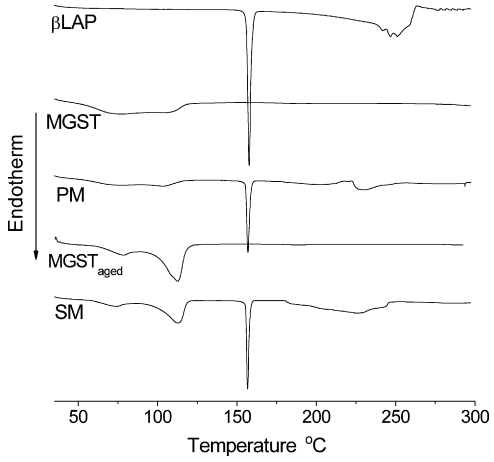


Fig. 4. DSC analysis of βLAP, MGST and βLAP–MGST combinations.

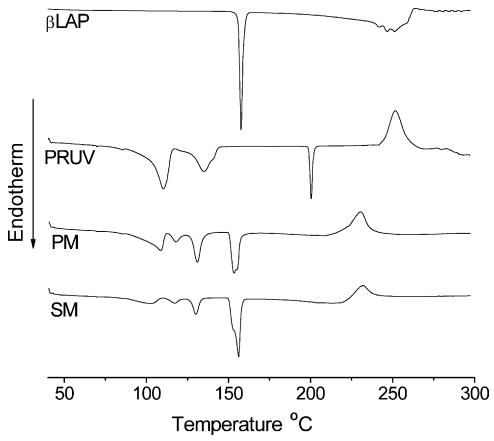


Fig. 5. DSC analysis of βLAP, PRUV and βLAP–PRUV combinations.

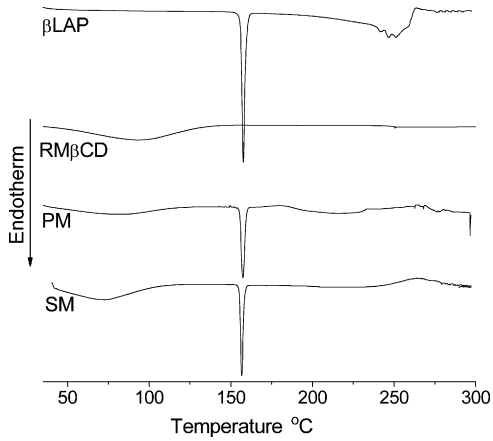


Fig. 6. DSC analysis of βLAP, RMβCD, βLAP–RMβCD combinations.

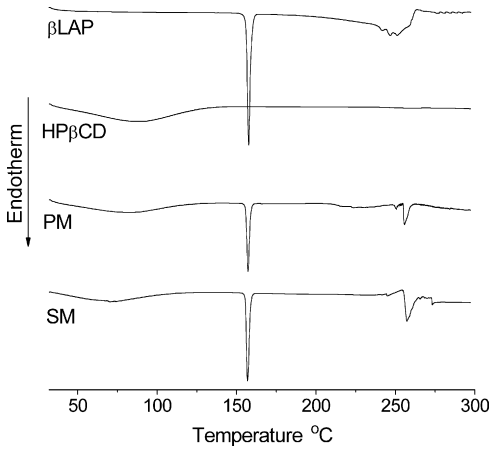


Fig. 7. DSC analysis of βLAP, HPβCD, βLAP–HPβCD combinations.

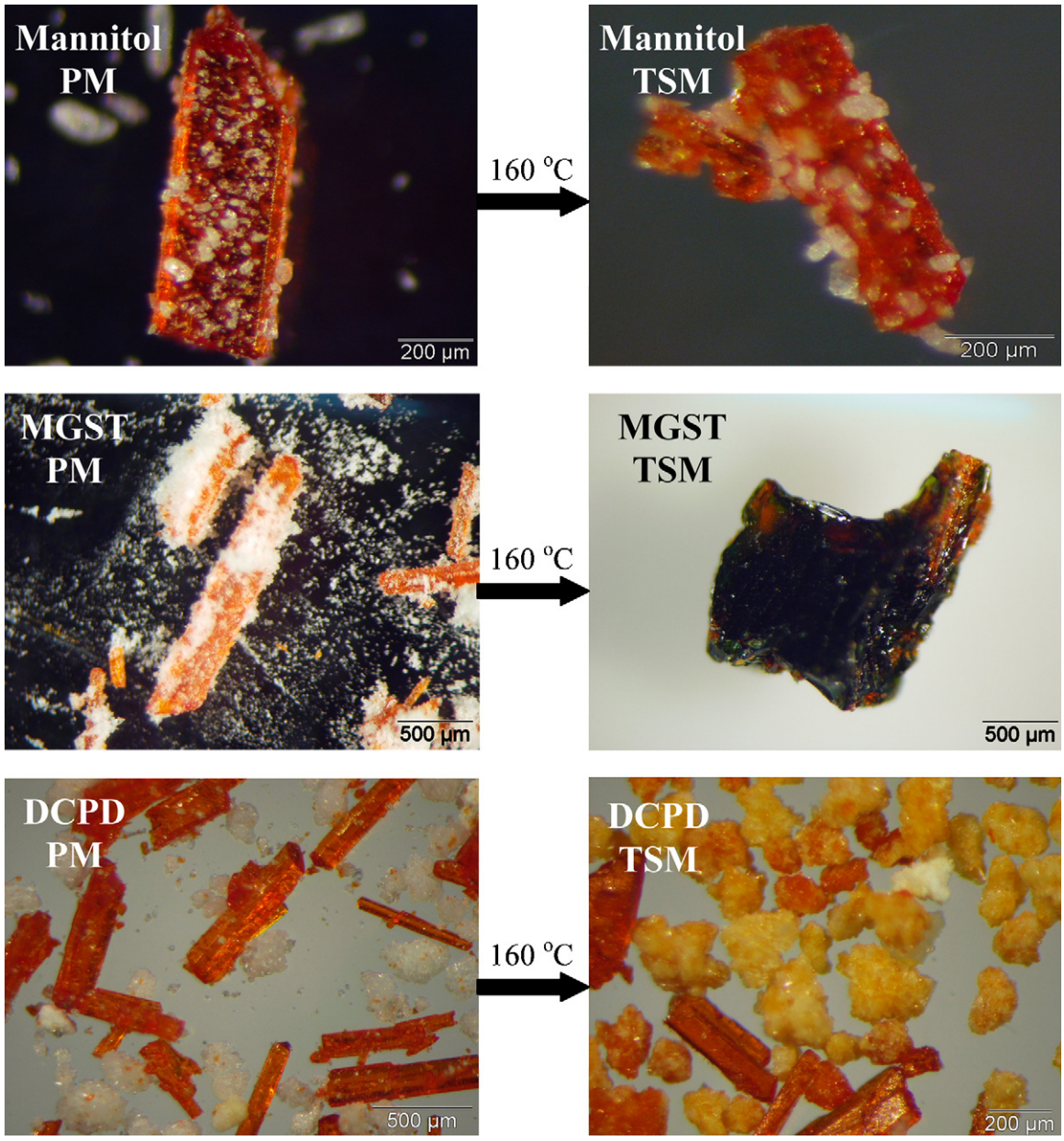
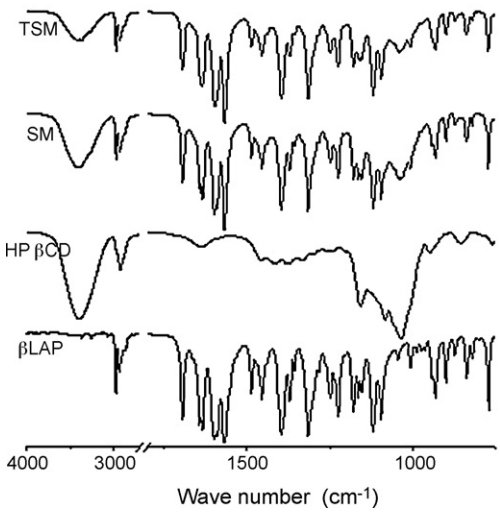


Fig. 8. OM micrographs of some of the mixtures indicated.



βLAP	HPβCD	SM	TSM
2977.9 (s)	-	2977.8 (m)	2977.8 (m)
2935.5 (m.b)	2927.6 (s.b)	2933.4 (m.b)	2935.3 (m.b)
1695.3 (s)	-	1695.2 (s)	1695.2 (s)
1643.2 (s)	-	1643.2 (s)	-
1635.5 (s)	1637.4 (m.b)	1635.5 (s)	1637.4 (s)
1598.9 (m)	-	1598.8 (m)	1596.9 (m)
1568.0 (m)	-	1568.0 (m)	1568.0 (m)
1487.0 (m)	-	1487.0 (w)	1487.0 (w)
1454.3 (m)	-	1454.2 (m)	1454.2 (m)
1396.4 (s)	-	1396.3 (s)	1396.3 (s)
1371.3 (s)	-	1371.2 (m)	1371.2 (m)
1315.4 (s)	-	1315.3 (s)	1315.3 (s)
1247.9 (m)	-	1247.8 (m)	1247.8 (m)
1153.4 (m)	1157.2 (m.b)	1155.3 (w.b)	1155.3 (w.b)
1118.6 (s)	-	1118.6 (s)	1118.6 (s)
1093.6 (s)	1081.9 (m.b)	1093.5 (m)	1093.5 (m)
-	1033.7 (s.b)	1033.7(w)	-

Fig. 9. FTIR spectra and data of βLAP, HPβCD and its mixtures SM and TSM. Bands are classified in function of its intensity as s (strong), m (medium), w (weak) and b (broad).

between 30 and 149 °C associated with water loss from inside the cavity (Table 2). Among the cyclodextrins studied, only HPβCD and RMβCD (Figs. 6 and 7) shows small modifications in the thermal profiles of the stressed samples (SM), mainly shifting at the melting peak of the drug and in the enthalpies associated to loss of water from the CDs, which could be indicative of the interactions. The βLAP–RMβCD mixtures (Fig. 6) show, additionally, an extra exothermic event at 178 °C, which was really small quantitatively (associated enthalpy 8 J g^{-1}) but was consistent. This could be associated to a strong interaction between the RMβCD and the melted drug and subsequently, the βLAP entrance into the empty CD cavity in an energetic favoured process that decreases the energy of the system. The RMβCD has been shown as the most useful βCD derivative in improving βLAP solubility [12].

3.2. FTIR, OM and HC-DSC compatibility confirmatory assays

Neither mannitol nor PRUV incompatibility with βLAP was confirmed from those additional experiments. No significant changes in the FTIR characteristic bands of the pure substances can be detected, even after heating at 160 °C (TSM samples). HC-DSC experiments show, on cooling, two exothermal events corresponding to the drug and excipient crystallization process. On the second heating, the endothermal events of the first heating remain unchanged. No sign of decomposition was detected by optical microscopy (as an example see mannitol/βLAP mixtures, Fig. 8). Results are in agreement with other author findings for mannitol [7,9,19] and PRUV [26]. The interaction detected by thermal methods can be explained on the basis of the proximity of the melting events of both components without significant physicochemical stability problems.

The same conclusion was achieved after additional research on RMβCD and HPβCD/βLAP samples. FTIR data (Fig. 9) and HC-DSC (Fig. 10) on HPβCD/βLAP and RMβCD/βLAP mixtures, respectively do not show significant changes on the characteristic behaviour of the pure substances even after thermal stress (TSM) or after a melting–crystallization–melting cycle. Interactions between those CDs and the drug suggested by the preliminary DSC results (Table 1) should be interpreted in terms of the inclusion of βLAP into the CD cavity and the formation of inclusion complexes, thus being a beneficial interaction with profitable repercussion in the βLAP hydrosolubility [12].

The DCPD/βLAP incompatibility was confirmed by FTIR data (Fig. 11). Accentuated changes were detected in the bands corresponding to the functional groups of the drug, especially in the TSM samples, which indicate chemical decomposition of βLAP. The OM results showed the intrinsic association between the compounds. The mixture (TSM) is composed of several βLAP crystals and also coloured excipient particles (Fig. 8).

The heating–cooling DSC results suggest that βLAP promotes DCPD dehydration at lower temperature, at the same time as the melted drug (Fig. 12). The DCPD water hydration (20.9%

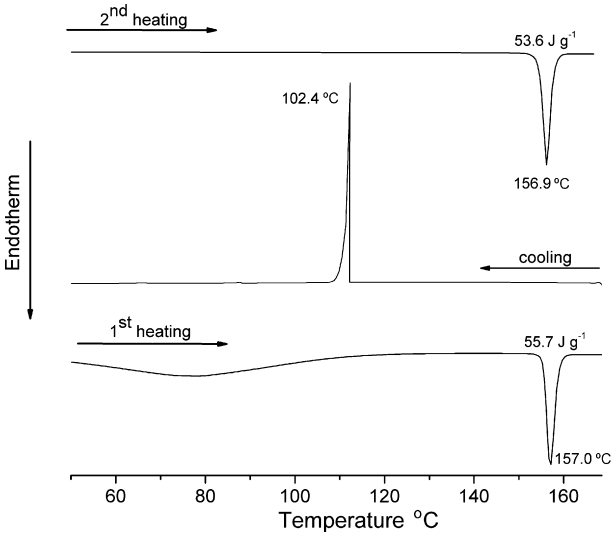
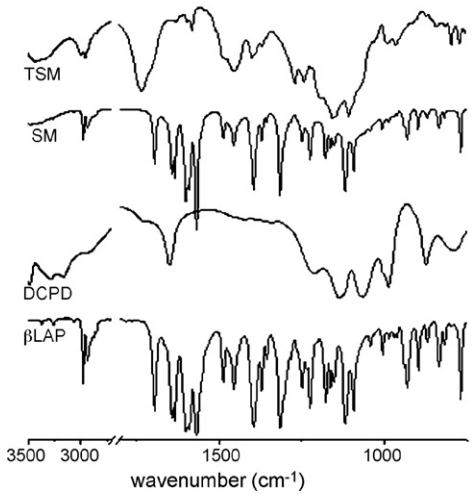


Fig. 10. HC-DSC of the βLAP–RMβCD PM binary system.



βLAP	DCPD	SM	TSM
2977.9 (s)	-	2977.8 (m)	2993.2 (w.b)
2935.5 (m.b)	-	2935.3 (w.b)	2952.7 (w.b)
1695.3 (s)	-	1695.3 (m)	1731.9 (s.b)
-	1649.0 (s.b)	-	-
1643.2 (s)	-	1643.2 (s)	-
1635.5 (s)	-	1633.5 (s)	-
1598.9 (m)	-	1600.7 (m)	1595.0 (w)
1568.0 (m)	-	1568.0 (s)	1579.5 (w)
1487.0 (m)	-	1487.0 (w)	1479.2 (w)
1454.3 (m)	-	1454.2 (w)	1450.3 (m.b)
1396.4 (s)	-	1396.3 (s)	1400.2 (w.b)
1371.3 (s)	-	1369.3 (s)	1369.3 (w.b)
1315.4 (s)	-	1315.3 (s)	-
1247.9 (m)	-	1247.8 (m)	1242.0 (w)
-	1211.2 (m.b)	-	-
1118.6 (s)	-	1118.6 (s)	-
-	1135.9 (s.b)	-	-
1093.6 (s)	-	1093.5 (m)	-
-	1064.6	-	-
-	987.4 (s.b)	-	-

Fig. 11. FTIR spectra and data of βLAP, DCPD and its mixtures SM and TSM. Bands are classified in function of its intensity as s (strong), m (medium), w (weak) and b (broad).

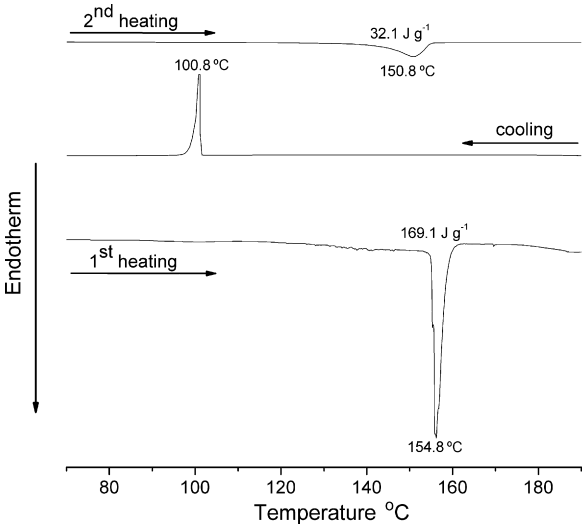
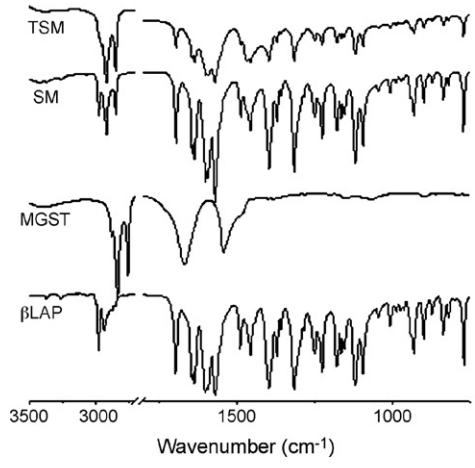


Fig. 12. HC-DSC of the βLAP–DCPD PM binary system.

of the DCPD weight) partially dissolves the βLAP and the basic environment from this [28] could decompose the βLAP, which are especially sensitive to an alkaline pH. This was verified on the second heating, by a broad drug melting peak, shifting to lower temperature and with a slight associated enthalpy, thus a clear sign of drug degradation. The DCPD is one of the most common diluents for tablets but it has been described as an excipient susceptible to dehydration at low temperature in the presence of water vapour, which is clearly relevant to the choice of conditions for processing and storage of the dosage forms [20]. Our results suggest great modifications in both βLAP and DCPD characteristics as a result of their incompatibility that would not recommend the use of DCPD in the development of βLAP solid dosage forms.

The MGST/βLAP interactions have also been confirmed by FTIR data (Fig. 13). The disappearance of different MGST bands (1579.5 and 1465.7 cm^{-1}) from both, SM and TSM FTIR spectra, suggests the decomposition of the excipient. Additionally,



βLAP	MGST	SM	TSM
2977.9 (s)	-	2977.8 (s)	-
2935.5 (m.b)	-	-	-
-	2918.0 (s)	2918.0 (s.b)	2919.9 (s.b)
-	2850.5 (s)	2850.5 (m)	2850.5 (m)
1695.3 (s)	-	1695.3 (s)	1695.5 (m)
1643.2 (s)	-	1643.2 (s)	1643.2 (w)
1635.5 (s)	-	1633.5 (s)	1633.5 (w)
1598.9 (m)	-	1598.8 (m)	1598.8 (w)
-	1579.5 (s.b)	-	-
1568.0 (m)	-	1568.0 (s)	1569.9 (w)
1487.0 (m)	-	1487.0 (m)	1487.0 (w)
-	1465.7 (s.b)	-	-
1454.3 (m)	-	1454.2 (m)	1454.2 (w)
1396.4 (s)	-	1396.3 (s)	1396.3 (m)
1371.3 (s)	-	1371.2 (s)	1371.2 (w)
1315.4 (s)	-	1315.3 (s)	1315.3 (m)
1247.9 (m)	-	1247.8 (m)	1247.8 (w)
1118.6 (s)	-	1118.6 (s)	1118.6 (m)
1093.6 (s)	-	1093.5 (s)	1093.5 (m)

Fig. 13. FTIR spectra and data of βLAP, MGST and its mixtures SM and TSM. Bands are classified in function of its intensity as s (strong), m (medium), w (weak) and b (broad).

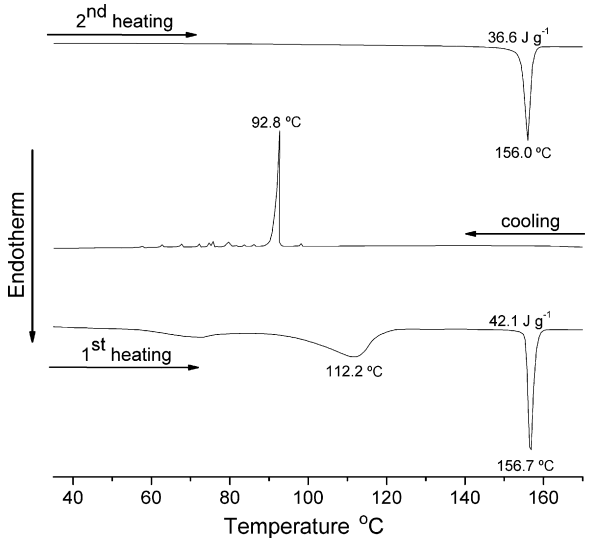


Fig. 14. HC-DSC of the βLAP–MGST PM binary system.

some modifications in the βLAP bands (2978 and 1568 cm^{-1}) assigned to the aromatic region of the drug, C–H and C–C, respectively, take place. The HC-DSC experiments (Fig. 14) corroborate the hypothesis of MGST degradation as in the second heating only the melting peak of βLAP, at lower temperature and associated enthalpy, can be observed and none of the MGST events. Heating up to 160 °C does not promote changes in the morphology of βLAP or MGST single systems but when heated together (Fig. 8) the sample becomes black as a consequence of the degradation of MGST. Lubricants are used in tablets at a ratio far lower than the one used in this study so, at the ratio 1:1 w/w greater MGST degradation would be expected on ageing. However, the interaction evidences between products suggest that MGST should be avoided in the βLAP formulations.

4. Conclusions

Six (magnesium stearate, PRUV, DCPD, mannitol, RMβCD and HPβCD) of the seventeen excipients studied presented thermal interactions with the βLAP. However, additional studies using FTIR, optical microscopy and heating–cooling DSC studies (HC-DSC) confirmed the incompatibility of βLAP with magnesium stearate and dicalcium phosphate dihydrate. Those excipients should be avoided in the development of solid dosage forms.

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