Journal of Thermal Analysis and Calorimetry, Vol. 68 (2002) 647–655

POLYMORPHISM AND CYCLODEXTRIN INCLUSION OF SALBUTAMOL LAURATE

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Abstract

Salbutamol laurate is a novel salt form of the well-known bronchodilator salbutamol (albuterol). Its polymorphism and inclusion in (2-hydroxypropyl)-β-cyclodextrin were investigated by thermogravimetry, differential scanning calorimetry, infrared and powder X-ray diffraction techniques. Two polymorphic forms of the salt were identified. Conditions for inclusion complex formation between the salt and (2-hydroxypropyl)-β-cyclodextrin, namely prolonged co-grinding and kneading, were established by a combination of the above methods.

Keywords: cyclodextrin complex, polymorphs, salbutamol laurate

Introduction

Salbutamol (or albuterol, systematic name α^1-([(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol) is a selective β_2-adrenergic agonist widely used for the relief of reversible airway obstruction, status asthmaticus and other conditions that require the symptomatic relief of bronchospasm [1]. The drug has a relatively high water solubility and a poor partition coefficient across the membrane of the sublingual mucosa which limits its application as a sublingual dosage form for immediate relief of an asthmatic episode. Salbutamol laurate (Fig. 1), a salt resulting from the reaction between racemic salbutamol and lauric acid, was investigated here as part of a study aimed at developing a novel dosage form based on its inclusion complex with the host (2-hydroxypropyl)-β-cyclodextrin (HP-β-CD). A complex of this type should provide the lipophilic salbutamol laurate guest with a hydrophilic carrier for delivery of the drug to the membranes of the sublingual mucosa where it can be partitioned directly into the circulation for rapid action [2]. Here we report the preparation of this novel inclusion complex and its characterization by thermal, infrared and X-ray techniques. During the course of the study, salbutamol laurate was found to be dimorphic and we report briefly on that aspect. Examples of recent thermoanalytical studies treating cyclodextrin complexes with drugs include those on bifonazole [3], clofibric acid [4] and oxyphenbutazone [5].

1418–2874/2002/ $ 5.00

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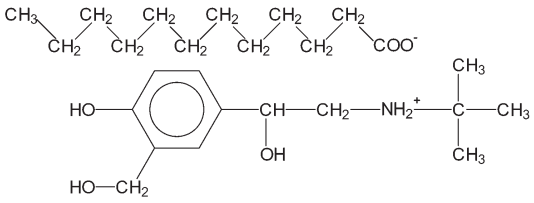

Fig. 1 Chemical structure of salbutamol laurate

Experimental

(2-hydroxypropyl)-β-cyclodextrin (DS:3.2) and two batches of salbutamol laurate were supplied by South African Druggists International (Port Elizabeth, South Africa). Each drug batch was characterised by the following methods: elemental analysis (duplicate determinations on a Carlo Erba elemental analyser Model 1106), TG and DSC (Perkin Elmer PC-7 Series, sample masses 5–15 mg, scan rates 5–20 min^{-1}, nitrogen purge 30 cm^3 min^{-1}), hot stage microscopy (Linkam THMS 600 hot stage coupled to a Linkam TP92 temperature control unit), SEM (Leica Stereoscan 440I instrument, accelerating potential 10 kV, probe current 75 mA) and PXRD (Philips PW1050/80 goniometer, CoK_α radiation, λ=1.790 Å, step scans of 0.1° 2θ, range 5–45° 2θ).

Kneading and co-grinding techniques were used in attempts to prepare complexes between salbutamol laurate (hereinafter SAL) and (2-hydroxypropyl)-β-cyclodextrin (HP-β-CD) using 1:1 and 1:2 drug:cyclodextrin molar ratios. Samples were prepared by the following methods: (a) manual co-grinding using a mortar and pestle (b) kneading in a mortar and pestle with small aliquots of water followed by drying in an oven at 60°C for 30 min (c) mechanical co-grinding using a Wig-L-Bug amalgamator for 1 h. The TG heating range was 30–150°C and heating rate 20°C min^{-1} with sample sizes: SAL 2–3 mg, 1:1 SAL:HP-β-CD samples 6–7 mg, 1:2 SAL:HP-β-CD samples 10–11 mg. The DSC heating range was 50–150°C and the heating rate 20°C min^{-1} with sample sizes: SAL 2.0–2.2 mg, 1:1 SAL:HP-β-CD samples 6.0–6.2 mg, 1:2 SAL:HP-β-CD samples 10.0–10.3 mg.

IR spectra of nujol mulls of both pure SAL and kneaded and co-ground materials were recorded on a Perkin Elmer 983 spectrophotometer over the range 600–4000 cm^{-1}.

Results and discussion

Polymorphism of salbutamol laurate

The two batches of SAL yielded comparable elemental analyses in agreement with those calculated for the unsolvated salt (batch 1: %C 68.33, %H 10.50, %N 3.40; batch 2: %C 68.50, %H 10.55, %N 3.33; calc. for $C_{25}H_{45}NO_5$: %C 68.30, %H 10.32, %N 3.19). Further evidence that the batches were solvent-free was obtained from TG which showed no significant mass losses over the range 30 to 300°C. No significant differences were detected in the peak positions and intensities of the principal IR

peaks for the two batches. PXRD gave the first indication of polymorphism (Fig. 2). The most intense peak (2θ=8.40°) is common to both batches but at higher angles there are significant differences in both peak positions and intensities. The batches were accordingly labelled polymorphic Forms 1 and 2.

The DSC traces are shown in Fig. 3 where each form was examined at three different scanning rates. Form 1 showed a single endotherm corresponding to fusion (peak at 115°C at 20°C min^{-1}) whereas Form 2 displayed two endotherms (peaks at 111 and 115°C at 20°C min^{-1}), the latter being completely resolved at a heating rate of 5°C min^{-1}. The first endotherm for Form 2 was interpreted as a phase transition from Form 2 to Form 1. HSM confirmed this transition by revealing a recrystallization process in the temperature range 100–114°C for Form 2, with simultaneous melting of both forms in the range 114–117°C. SEM images (×2000) of the SAL polymorphs showed distinctly different particle morphologies and textures. Form 1 consisted of platey crystals (size range 10–20 μm) whereas Form 2 had a more granular appearance (size range 200–500 μm). To eliminate any possible effects due to polymorphism, Form 1 of SAL was used exclusively for further experiments.

Complexation of SAL with HP-β-CD

DSC traces were recorded for all preparations and the melting endotherm for SAL was monitored (Table 1), its disappearance being taken as evidence for inclusion complex formation. This was based on the finding that when pure SAL was ground or kneaded, the melting endotherm persisted, though with slightly reduced peak temperature (by ~3°C) and reduced enthalpy of fusion (by ~20%). The amount of uncomplexed drug in the various preparations was estimated from the measured heat

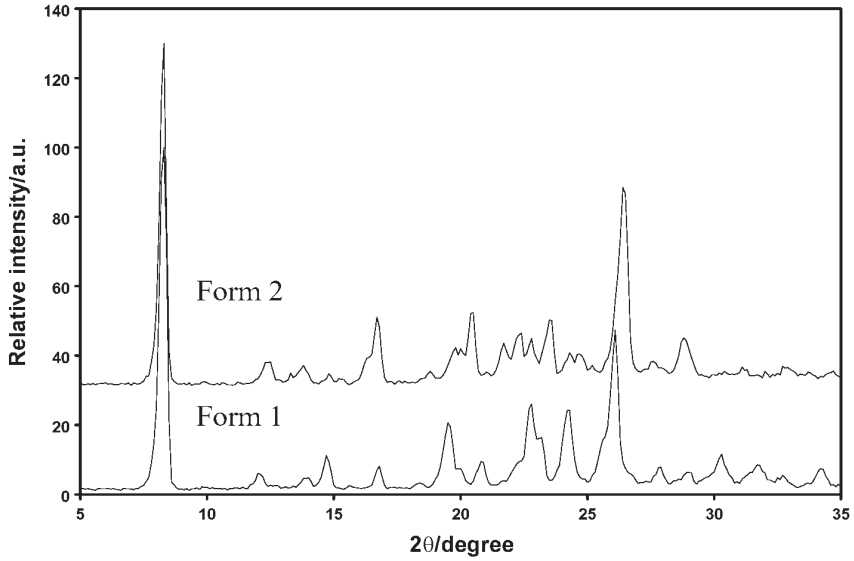

Fig. 2 PXRD patterns for two polymorphs of salbutamol laurate

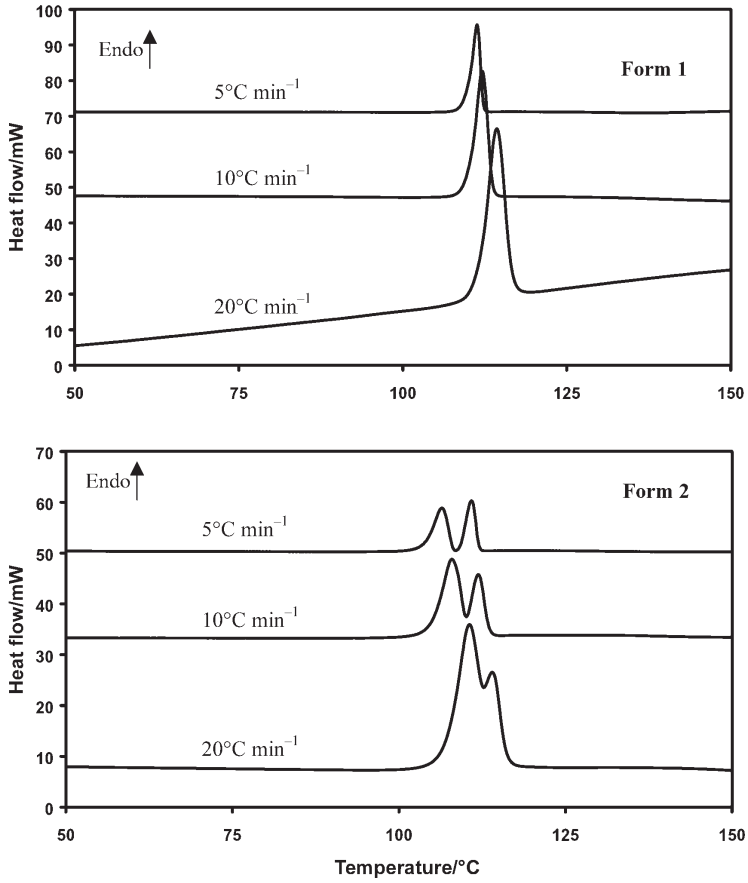

Fig. 3 DSC traces for the two polymorphs of salbutamol laurate

of fusion for the SAL endotherm. From the results in Table 1 it was concluded that for both the 1:1 and 1:2 drug:HP-β-CD preparations, all of the SAL is complexed after manual co-grinding for 30 min, and after kneading and mechanical co-grinding for 1 h. In Fig. 4, DSC traces are shown for SAL, HP-β-CD and for the physical mixture and kneaded 1:1 drug:HP-β-CD preparations (as representative). The SAL endotherm is absent in the trace for the kneaded preparation.

HSM was used to detect possible differences between complexed and uncomplexed preparations. On heating pure SAL (white powder), melting was observed at 114–115°C and the compound turned yellow at 170°C as decomposition commenced. HP-β-CD (white powder) showed no changes on heating until 280°C when it assumed the appearance of a viscous liquid. For physical mixtures as well as the drug/CD preparations in which uncomplexed drug had been detected by DSC, the white powder present became speckled with yellow patches from 170°C. In contrast, for the drug/CD preparations previously identified as complexes by DSC, the sam-

ples behaved homogeneously on heating, becoming uniformly light yellow at 170°C. Thus, HSM could distinguish between uncomplexed and complexed preparations and furthermore showed that the interaction between SAL and the host compound does not increase the decomposition temperature of SAL.

Table 1 DSC analysis of the SAL melting endotherm

Sample	Conditions	Peak range/°C	Onset temp./°C	Peak temp./ °C	Peak enthalpy/ J g^{-1} *	Uncomp-lexed. drug/% **
HP-β-CD	As found					
SAL	Raw material	112–126	114	117	103	100
	Co-grnd 10 min	112–126	114	117	103	100
	Co-grnd 20 min	105–121	112	114	87	100
	Co-grnd 30 min	103–120	112	114	84	100
	Kneading	104–121	112	114	85	100
1:1 SAL:HP-β-CD	Phys. mixture	109–125	113	117	88	85
	Co-grnd 10 min	106–121	110	114	80	78
	Co-grnd 20 min	100–118	103	110	58	67
	Co-grnd 30 min	–	–	–	–	0
	Kneading	–	–	–	–	0
	Mech. grnd 1 h	–	–	–	–	0
1:2 SAL:HP-β-CD	Phys. mixture	90–114	93	102	92	90
	Co-grnd 10 min	96–112	96	102	53	51
	Co-grnd 20 min	89–101	89	94	8	9
	Co-grnd 30 min	–	–	–	–	0
	Kneading	–	–	–	–	0
	Mech. grnd 1 h	–	–	–	–	0

*Peak enthalpy (J g^{-1}) corrected according to the fraction of drug in preparation (correction factor=[mass of drug+mass of CD†]/mass of drug)
**Percentage uncomplexed drug=peak enthalpy of drug endotherm in a preparation/average peak enthalpy of drug alone
†Mass of CD=mass of HP-β-CD (3.2 hydroxypropyls/CD) plus 10% water

TG traces were recorded for all preparations to quantify the water content. Results are shown in Table 2. SAL remained anhydrous when subjected to the same treatments used for complex preparation. In the case of pure HP-β-CD, physical mixtures and complexes of SAL and HP-β-CD, water was lost over a very wide temperature range (Table 2). This is reflected in the DSC traces for these species (Fig. 4), which show very broad endothermic effects in the corresponding temperature range. The calculated number of water molecules per HP-β-CD molecule for the host alone as well as for its complexes with SAL lies in a narrow range (~5.7–7.0). In the absence of structural data, it is there-

fore not possible to draw conclusions regarding possible displacement of water molecules from the apolar CD cavity on inclusion of SAL.

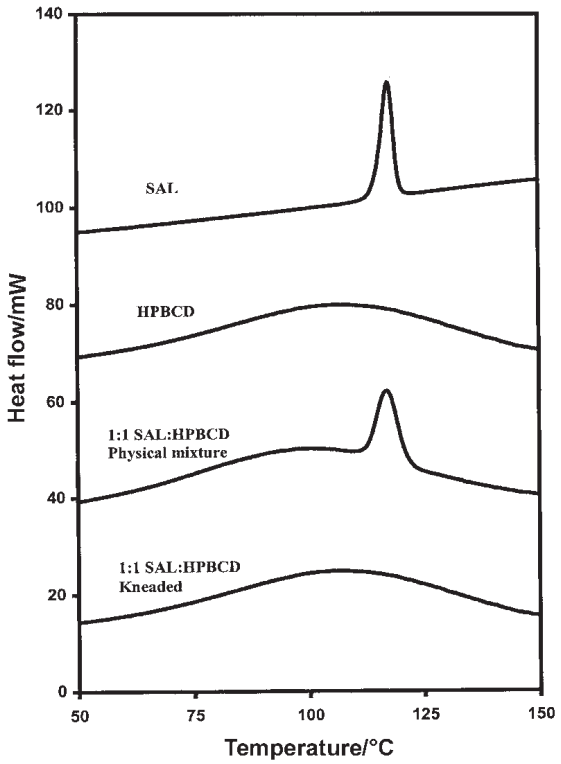

Fig. 4 DSC traces for SAL, HP-β-CD, a physical mixture and kneaded material

PXRD traces of all preparations were recorded and yielded results that were consistent with those from the DSC technique. The principal diffraction peaks for SAL (8.4, 19.6, 22.9, 24.5 and 26.4° 2θ) were not affected significantly when SAL was ground or kneaded. These peaks occurred at the same angular positions in PXRD traces of both the 1:1 and 1:2 SAL:HP-β-CD preparations obtained by co-grinding up to 20 min. However, under conditions of co-grinding exceeding 30 min, kneading, or mechanical grinding for 1 h, all diffraction peaks characteristic of SAL disappeared. Inclusion complex formation in the latter case was thus confirmed by this technique. Relevant PXRD traces are shown in Fig. 5. HP-β-CD is an amorphous material showing no sharp peaks in its PXRD pattern. An inclusion complex between SAL and HP-β-CD is likewise expected to yield a PXRD pattern characteristic of an amorphous substance. PXRD proved to be a sensitive technique for detection of uncomplexed SAL and the peak at 8.4° 2θ was particularly useful in this respect since it occurs at a position where the host HP-β-CD diffracts with negligible intensity.

Table 2 TG data for the various preparations of SAL and HP-β-CD

Sample	Conditions	Mass loss range/°C	M/mass loss/%	Water molecules/ HP-β-CD *
HP-β-CD	As found	30–130	7.2	5.7
SAL	Raw material	–	0	0
	Co-grnd 10 min	–	0	0
	Co-grnd 20 min	–	0	0
	Co-grnd 30 min	–	0	0
	Kneading	–	0	0
1:1 SAL:HP-β-CD	Phys. mixture	30–130	6.5	6.8
	Co-grnd 10 min	30–130	6.3	6.5
	Co-grnd 20 min	30–130	6.8	7.1
	Co-grnd 30 min	30–130	6.4	6.7
	Kneading	30–130	6.4	6.7
	Mech. grnd 1 h	30–130	6.2	5.7
1:2 SAL:HP-β-CD	Phys. mixture	30–130	7.5	6.9
	Co-grnd 10 min	30–130	7.7	7.1
	Co-grnd 20 min	30–130	7.6	7.0
	Co-grnd 30 min	30–130	7.6	7.0
	Kneading	30–130	7.4	6.8
	Mech. grnd 1 h	30–130	5.4	5.7

*Number of H_2O/CD=(%H_2O from TG)[M_rHP-β-CD+M_rSAL(SAL/HP-β-CD molar ratio)]/ ($M_r$$H_2O$)(100–%$H_2O$ from TG)

IR spectra were recorded for all preparations and seven of the strongest bands were monitored. Of these, five bands (at 1032, 1082, 1158, 1377 and 1458 cm^{-1}) were common to SAL and HP-β-CD, one was unique to HP-β-CD (947 cm^{-1}) and the last unique to SAL (1545 cm^{-1}) and assigned as the C–O asymmetric stretching band for a carboxylate salt. Only the latter band showed any significant variation, shifting to higher frequency for those preparations deemed to be complexes on the basis of the other techniques employed. Specifically, this band shifted from 1545 to 1551 cm^{-1} for the 1:1 co-ground (30 min) samples and to 1554 cm^{-1} for the 1:2 co-ground (30 min) samples. A significantly larger shift, from 1545 to 1661 cm^{-1} was recorded for the 1:2 kneaded and mechanically co-ground samples. Grinding of pure SAL did not result in any shift of this band and the significant shifts reported above are interpreted as further evidence of inclusion complex formation.

The possible mode of inclusion of SAL in cyclodextrins was investigated separately by manual docking of the minimum energy conformation of SAL into the cavities of β- and γ-cyclodextrin as model compounds using the Cerius 2 package [2]. For β-cyclodextrin, the best fit was obtained for complexation of the fatty acid residue

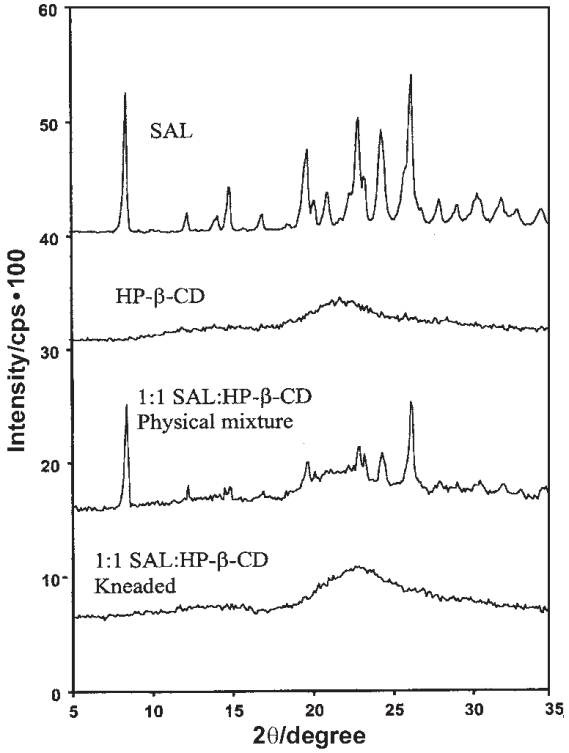

Fig. 5 PXRD traces for SAL, HP-β-CD, a physical mixture and kneaded material

rather than the salbutamol cation. For γ-CD, with a significantly larger cavity, the minimised energy structure corresponded to inclusion of both the guest anion and the cation in the cavity.

Conclusions

Thermal analysis and PXRD revealed that salbutamol laurate occurs in at least two polymorphic forms, one of which was found to transform into the other at 111°C, finally melting at 115°C.

Inclusion complex formation between salbutamol laurate and (2-hydroxypropyl)-β-cyclodextrin was achieved under conditions of manual co-grinding (t_{min}=30 min), kneading and mechanical co-grinding (t_{min}=1h) for both 1:1 and 1:2 drug:cyclodextrin stoichiometric ratios. This was inferred from a combination of DSC, HSM, PXRD and IR techniques.

* * *

We thank the University of Cape Town, the NRF (Pretoria) and S A Druggists International for financial assistance.

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