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STUDY OF THE POLYMORPHIC BEHAVIOUR OF SOME LOCAL ANESTHETIC DRUGS

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Abstract

The local anesthetic drug tetracaine hydrochloride is described in the Europ. Pharmacopea with a melting point of 148°C or with a range of 134 to 147°C due to the melting points of two other forms. The polymorphic behaviour of tetracaine hydrochloride has been studied by using thermal treatments, storage at 92% r.h., crystallizations and equilibrations with saturated solutions. Samples were characterized by X-ray diffraction, IR, thermal analysis and elemental analysis. Since some findings were difficult to interpret, temperature resolved X-ray diffraction was used additionally for the understanding of the thermal behaviour of tetracaine hydrochloride. In this study the polymorphic behaviour of some other local anesthetic drugs is compared.

Ten different forms of tetracaine hydrochloride: six anhydrous crystalline forms, an amorphous form, a hemihydrate, a monohydrate and a tetrahydrate were identified. The relationships between all forms are given.

The heating curve of the commercial form 1 is very dependent on the heating rate. This anhydrous form 1 is the thermodynamic stable modification at ambient temperature. The form 2 is reversibly enantiotrope to form 1. The four other modifications called 3, 4, 5 and 6 are monotropes of form 1.

Only forms 1 and 5 are stable at ambient temperature. Form 1 is hygroscopic only at high humidity level of 92% r.h., form 5 is hygroscopic at 61% r.h. Both transform into the monohydrate.

No polymorphic forms of tetracaine base, dibucaine hydrochloride, procaine hydrochloride or prilocaine hydrochloride were found.

The commercial form of bupivacaine hydrochloride is a monohydrate. Thermal treatment at 200°C gives one anhydrous form. As demonstrated by temperature resolved X-ray diffraction two other forms are detected by heating and cooling processes between 100 and 170°C. Equilibrations and crystallization experiments show that solvates are easily obtained in different solvents.

Temperature resolved X-ray diffraction is a very efficient tool as a support to DSC for the identification of the transition processes and interpretation of thermal events and thermodynamic relationships. Equilibration experiments are very adequate to find out the thermodynamically stable form at ambient temperature (solvent mediated transitions).

Keywords: anesthetic drugs, bupivacaine hydrochloride, dibucaine hydrochloride, DSC, polymorphism, prilocaine hydrochloride, procaine hydrochloride, solvent mediated transitions, temperature resolved X-ray diffraction, tetracaine base, tetracaine hydrochloride, thermodynamic relationships

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Introduction

Polymorphism and pseudo-polymorphism may affect bioavailability, stability and processing [1–2]. For pharmaceutical purposes it is necessary to know thermodynamic relationships and to isolate different forms in order to be able to define the suitable form and to develop analytical methods for control of the polymorphic purity.

The local anesthetic drug tetracaine hydrochloride is described in the Europ. Pharmacopea with a melting point of 148°C or with a range of 134 to 147°C due to the melting points of two other forms. This behaviour was also shortly described [3–5]. In a previous study [6] three anhydrous forms and two hydrated forms were manufactured by using thermal treatments, storage at 61, 80 and 92% r.h., crystallizations and equilibrations with saturated solutions (solvent mediated transitions). They were characterized by X-ray diffraction, thermal analysis and elemental analysis. Since some findings were difficult to interpret, temperature resolved X-ray diffraction was used additionally for the understanding of thermal behaviour of tetracaine hydrochloride.

This article summarizes the findings of the polymorphic behaviour of tetracaine hydrochloride. The polymorphic behaviour of some other local anesthetic drugs: tetracaine base, bupivacaine hydrochloride, dibucaine hydrochloride, prilocaine hydrochloride and procaine hydrochloride is compared.

Experimental

Instruments: DSC: calibrated Perkin Elmer DSC-7 with robot system
TG: calibrated Perkin Elmer TGA 7
X-ray diffraction: XDS 2000 Scintag with auto sampler or with heating cell
FT-IR: calibrated Perkin Elmer FT-IR 1725-X.

Equilibration experiments were carried out by the phase solubility technique [7] by using 5 ml friction bottles with polyethylene stoppers, Mueller+Mueller, Germany, a vibration mixer Chemap, Switzerland and a water bath at 25.0°C. The solubility is measured by gravimetry after drying the saturated solutions in high vacuum drying oven (< 1.33 Pa).

Several commercial samples of tetracaine hydrochloride from Champion or Sigma were analyzed by DSC. Samples of other anesthetic drugs were purchased by Sigma or Aldrich.

The experiments were:

– DSC heating, cooling curves of commercial samples
– Isothermal tempering
– Storage at 61% r.h., 80% r.h. and 92% r.h. (saturated solutions according to [8]) and thermogravimetry
– Equilibrations of an excess of samples with saturated solutions of selected solvents
– Crystallizations in water and selected solvents
– Analysis of the samples obtained by X-ray, DSC, TG and for selected samples, elemental analysis and IR

– Use of temperature resolved X-ray diffraction with heating and cooling steps of selected samples

– Thermal microscopy.

Results

Tetracaine hydrochloride

The DSC curves of commercial batches of tetracaine hydrochloride show different behaviour depending on the heating rate. At heating rates ≥10°C min^{-1} two endotherms separated by an exotherm are observed. The proportions of the endotherms depend on the samples, the weight and the heating rate. At low scanning rate no exotherm or a very slight exotherm is observed and the first endotherm is smaller. In some curves this endothermic peak is split into two not well separated events.

Figure 1 shows some DSC curves of a commercial batch at different heating rates.

Figure 2 shows DSC curves of two batches at 5°C min^{-1}. Two peaks are overlapping in the first endotherm.

For better understanding, we use the numbering 1, 2 etc. for the polymorphic anhydrous forms. The commercial form is called form 1.

The DSC curves of samples heated for 1 h in the DSC pan at 120, 130 and 133°C are given in Fig. 3. The size of the second peak increases with the temperature of the tempering. The first peak disappears only after 1 h at 133°C.

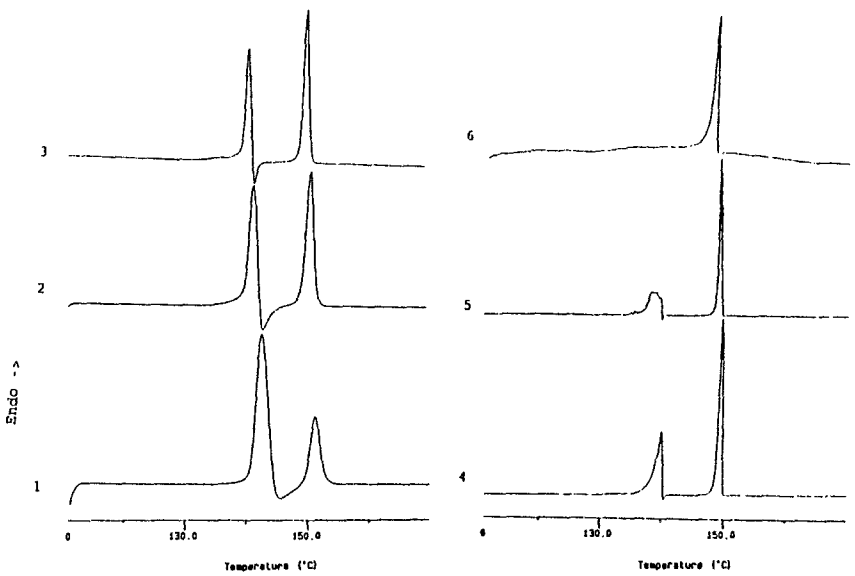

Fig. 1 Examples of DSC curves of tetracaine hydrochloride, commercial batch at different heating rates; 1: 20°C min^{-1}; 2: 10°C min^{-1}; 3: 5°C min^{-1}; 4:2°C min^{-1}; 5: 1°C min^{-1}; 6: 0.2°C min^{-1}

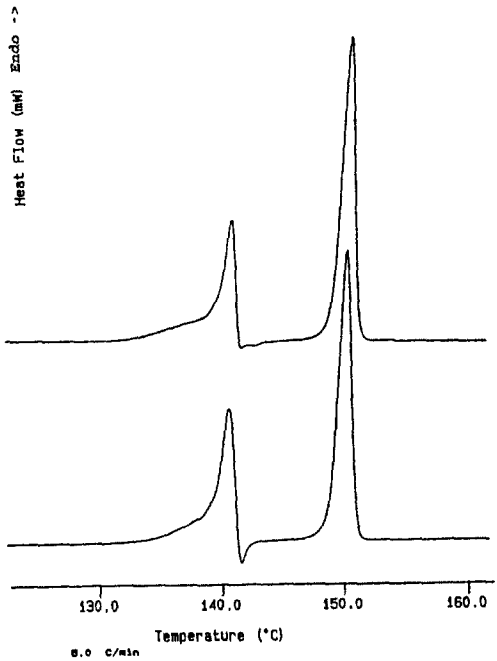

Fig. 2 Examples of DSC curves of two commercial batches of tetracaine hydrochloride at 5°C min^{-1} showing the splitting of the first peak into two overlapping thermal events

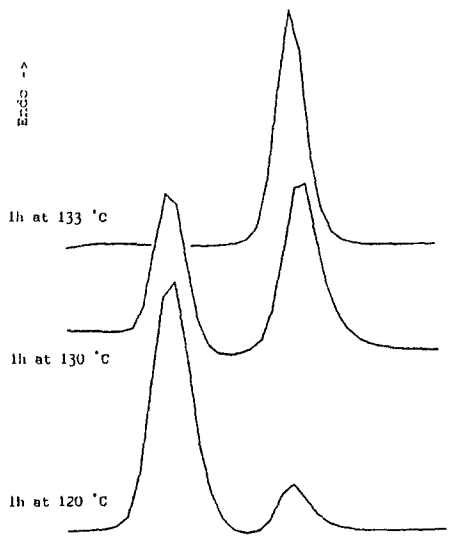

Fig. 3 DSC curves after tempering tetracaine hydrochloride commercial form (form 1) 1 h at 120, 130, 133°C

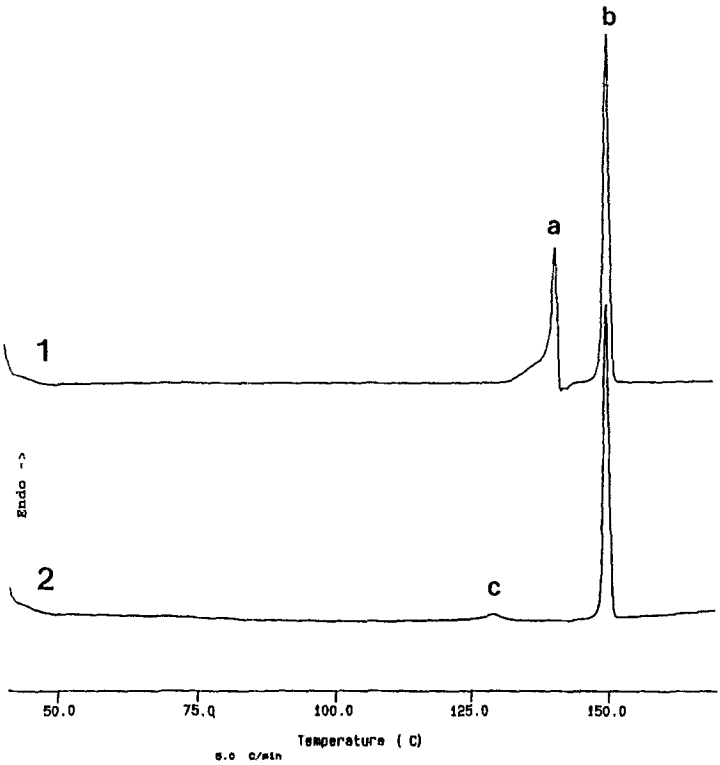

Fig. 4 DSC curves of forms 1 and 5 of tetracaine hydrochloride in the same scale at 5°C min^{-1}; 1: form 1; 2: form 5; a: melting forms 1+2; b: melting form 3; c: transition form 5 → form 3

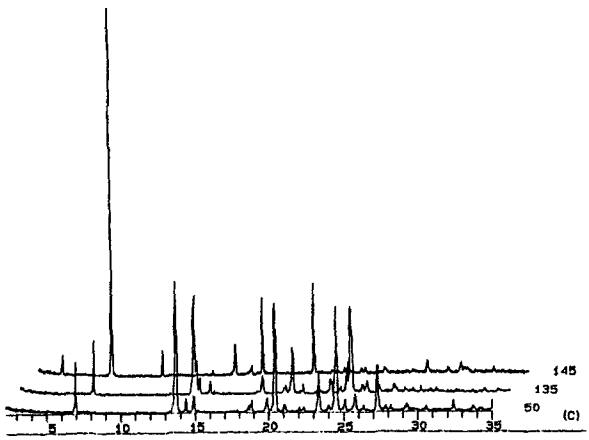

Fig. 5 Temperature resolved X-ray diffraction experiment 1; X-ray patterns at 50°C (form 1), 135°C (form 2) and 145°C (form 3)

Table 1 Results of temperature resolved X-ray diffraction. Experiments 1, 2, 3, 4, 5, 6, 7 with form 1, experiment 8 with form 5, experiment 9 with monohydrate

Experiment 1	Temperature/°C	50	70	100	110	135	145	
	Form	1	1	1	1+2	2	3	
Experiment 2	Temperature/°C	50	125	145	150	cooling		50
	Form	1	2	3	melt			4
Experiment 3	Temperature/°C	50	130	50				
	Form	1	2	1				
Experiment 4	Temperature/°C	50	125	50				
	Form	1	2	1				
Experiment 5, 6, 7	Temperature/°C	139	50		140	50	144	50
	Form		5			5		5
Experiment 8 with form 5	Temperature/°C	50	130	cooling		50	1–2 days RT	
	Form	5	3			6		5
Experiment 9 with monohydrate	Temperature/°C	50	75	110	130	145	150	50
	Form	mono	hemi	3	3	3	melt	6

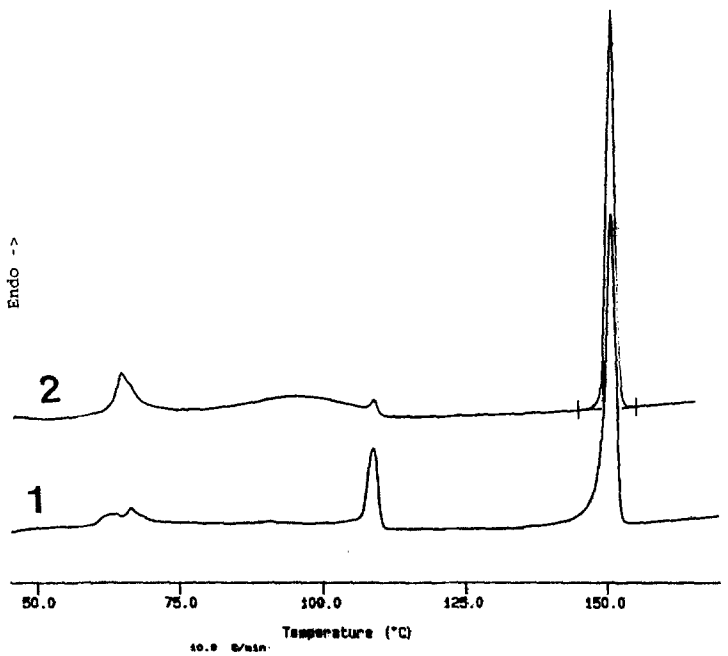

Fig. 6 DSC curves of tetracaine tetrahydrate (curve 1) and monohydrate (curve 2)

Table 2 Characteristics of crystalline modifications and hydrated forms of tetracaine hydrochloride

Characteristic	Form 1	Form 2	Form 3	Form 5	Tetra-hydrate	Mono-hydrate	Hemi-hydrate
Melting/°C	140	135–140	149–150 100 J g^{-1}	–	–	–	–
Solid transition	1↔2	2↔1		5→3 126°C 7 J g^{-1}	→ mono-hydrate 60°C	→ hemi-hydrate 75°C	→ 3 110°C
TG value/%	<0.05			0.3	18.6/20.4	6–8	2.5
Density/g cm^{-3}	1.209			1.200		1.211	
S1 in ethanol*	26			29/46		14	
S1 in isopropanol*	3			9/2		4	
S2 in ethanol**	26			26			
S2 in isopropanol**	2			2			

* S1 - solubility/mg ml^{-1} at room temperature after 5 min
** S2 - solubility/mg ml^{-1} at room temperature after 24 h

Table 3 Results of equilibriations experiments (solvent mediated transitions) at 25°C (no change means: same DSC and same X-ray diffraction as original samples)

	Water	Isopropanol	Ethanol	Ethyl acetate
Tetracaine ch				
Form 1	monohydrate	Form 1	Form 1	Form 1
Form 5		Form 1	Form 1	Form 1
Monohydrate		Form 1	–	monohydrate
Tetracaine b				
Commercial	no change	no change	no change	no change
Bupivacaine ch				
Monohydrate	no change	solvate?	change	change
Dibucain ch				
Commercial	no change	no change	no change	no change
Prilocaine ch				
Commercial	no change	no change	no change	no change
Procain ch				
Commercial	no change	no change	no change	no change

Tempering experiments of form 1 at 133, 139 and 140°C followed by cooling at room temperature give a new form (X-ray) with a characteristic DSC behaviour: a

new endothermic peak at about 126°C precedes the main melting endotherm. After tempering at 133°C, the first endotherm at about 140°C is present, but the samples tempered at 139–140°C do not have any peak of form 1 and are transformed totally into the new form (form 5) (Fig. 4).

Table 4 Results after storage at different relative humidities (no change means: same DSC and same X-ray diffraction as original samples)

	92% r.h.	80% r.h.	61% r.h.
Tetracaine ch			
Form 1	monohydrate	Form 1	Form 1
Form 5	monohydrate	monohydrate	monohydrate
Tetracaine base	no change		
Bupivacaine ch	monohydrate	not performed	monohydrate
Dibucaine ch	no change	not performed	not performed
Prilocaine ch	no change	not performed	not performed
Procaine ch	no change	not performed	not performed

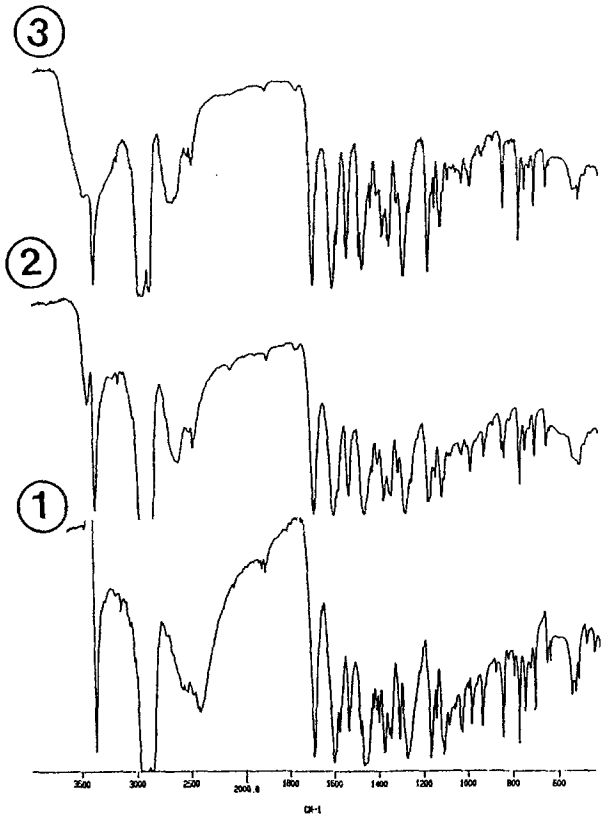

Fig. 7 IR spectra of tetracaine hydrochloride form 1 (1), form 5 (2) and tetrahydrate (3)

Table 5 Results of crystallization experiments (no change means: same DSC and same X-ray diffraction as original samples)

	Water	Isopropanol	Methanol	Ethanol	Ethyl acetate
Tetracaine ch	tetrahydrate	Form 1	Form 4	Form 1	Form 1
Bupivacaine ch	monohydrate	solvate?		solvate?	solvate?
Dibucaine ch	no change	no change	no change	no change	no change
Prilocaine ch	no change	no change	no change	no change	no change
Procaine ch	no change	no change	no change	no change	no change

Thermal microscopy observations are similar to DSC observations, but no clear interpretation of the complex behaviour in the temperature range 130–140°C is possible. Therefore X-ray resolved temperature experiments were undertaken.

The seven temperature X-ray resolved diffraction experiments with form 1, given in Table 1, demonstrate that the first endothermic peak (two overlapping peaks) observed in the DSC curves of form 1 corresponds to a reversible endothermic transition of the first form into a second form at 120–130°C followed by the melting of this form. With further heating a transformation to the high melting form 3 which melts at 149–150°C is observed.

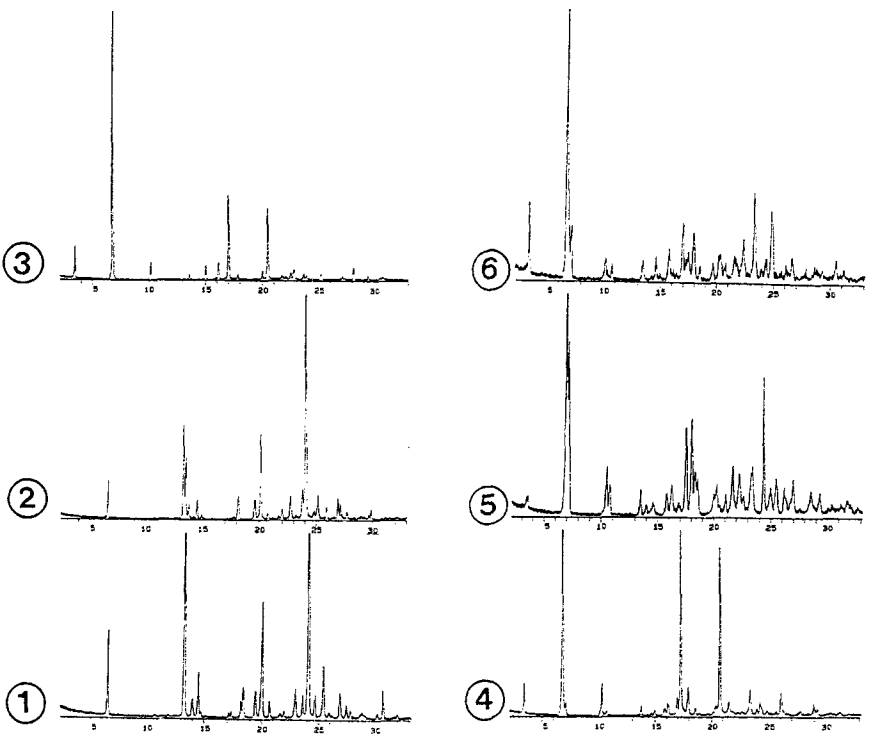

Fig. 8 X-ray diffractions of forms 1, 2, 3, 4, 5, 6 of tetracaine hydrochloride

Figure 5 shows the heating experiment 1 demonstrating the transformation 1, 2, 3.

By cooling at r.t. samples melted at 150°C an amorphous form or the metastable forms 4 and 6 have been obtained. After 1–2 days at r.t., form 6 transforms into form 5 (X-ray diffractions are given in Fig. 8).

Figure 4 gives the DSC curves of form 1 and form 5 at 5°C min^{-1}.

If a tempering of form 1 is made in the melting area 1+2 (133–140°C), the form 5 is obtained. This form is stable at least 3 years at r.t. The temperature resolved X-ray diffraction experiment (experiment 8 in Table 1) corresponding to the DSC curve of form 5 shows that the endotherm at 126°C is a transition into the high melting form 3. Form 6 is also obtained by cooling at r.t. the form 3 obtained after tempering the form 5 at 128–130°C.

At r.t. only anhydrous forms 1 and 2 are stable enough to allow their characterization (Table 2).

Results of equilibrations (solvents mediated transitions) of forms 1 and 5 are given in Table 3. They demonstrate that form 1 is the thermodynamic stable form at ambient temperature. Form 1 is not hygroscopic at ambient r.h. Form 5 on the contrary is hygroscopic at r.h. 61% (Table 4).

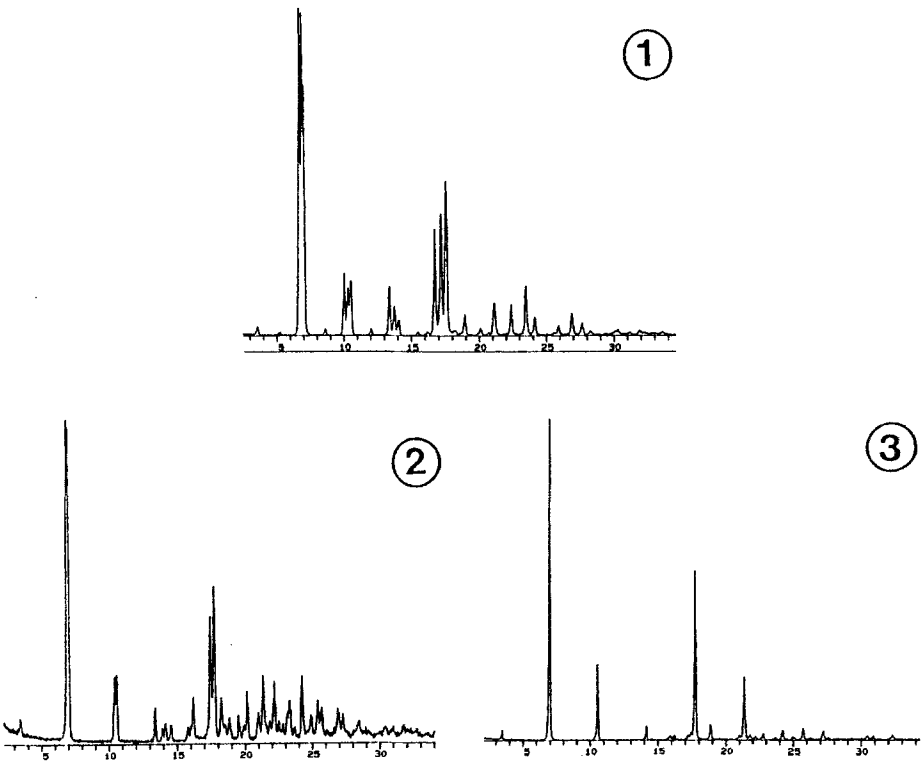

Fig. 9 X-ray diffractions of tetrahydrate (1), monohydrate (2) and hemihydrate (3) tetracaine hydrochloride

Results of crystallization experiments are given in Table 5.

After crystallization in water a tetrahydrate is obtained (Elemental analysis, TG, X-ray diffraction). This tetrahydrate loses water upon storage in ambient conditions

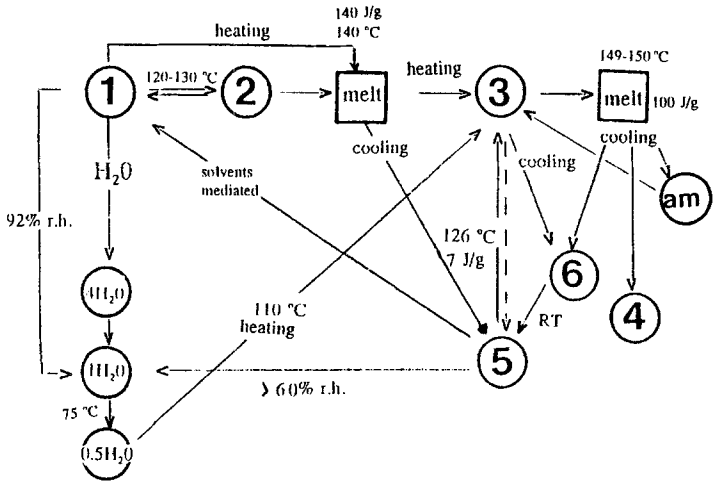

Fig. 10 Relationships between all forms of tetracaine hydrochloride

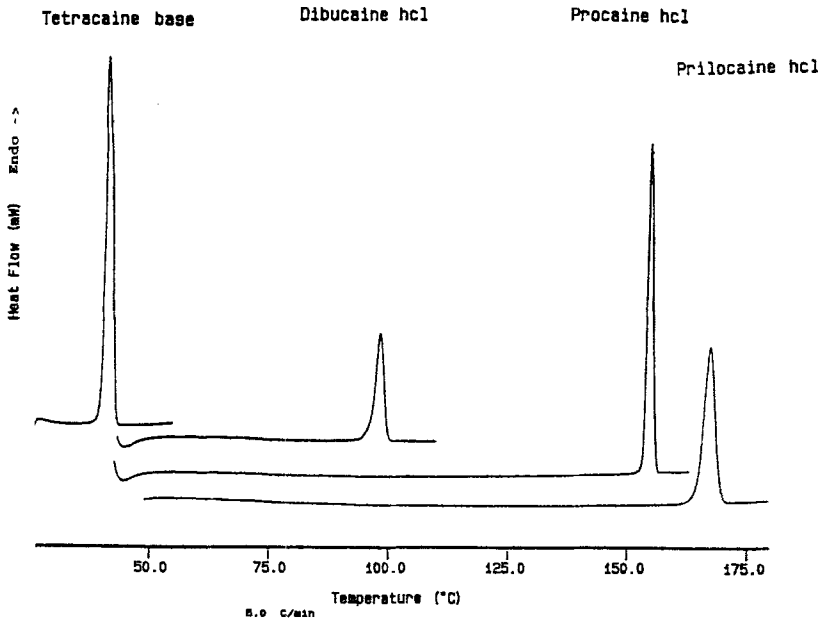

Fig. 11 DSC curves of tetracaine base, dibucaine hydrochloride, prilocaine hydrochloride and procaine hydrochloride at 5°C min^{-1}; tetracaine base : 41°C, 160 J g^{-1}; dibucaine hydrochloride: 97°C, 73 J g^{-1}; procaine hydrochloride: 154.5°C, 134 J g^{-1}; prilocaine hydrochloride 166°C, 124 J g^{-1}

(room temperature, appr. 50–60% r.h.) or under the influence of heat (DSC, TG) and transforms into a monohydrate. The same monohydrate is obtained by exposure of forms 1 and 5 at different r.h. as demonstrated in Table 4. By equilibration of the monohydrate in cyclohexane or after drying in vacuum the monohydrate transforms into a type 2 which is believed to be the hemihydrate. The temperature resolved X-ray diffraction experiment explains the DSC curves of the tetrahydrate and of the monohydrate (Fig. 6). At approx. 75°C, a transformation into the hemihydrate occurs. This hemihydrate transforms into the form 3 on subsequent heating. The transformation is complete at 110°C.

Table 2 gives the main characteristics of the forms of tetracaine hydrochloride. Figure 7 presents the IR-spectra of forms 1, 5 and of the tetrahydrate. Figure 8 shows the X-ray diffraction of the 6 crystalline modifications and Fig. 9 the X-ray diffraction patterns of the patterns 3 hydrated forms of tetracaine hydrochloride.

Figure 10 is the proposed diagram of the relationships between all forms detected. 6 crystalline anhydrous forms, an amorphous form, the hemihydrate, the monohydrate and the tetrahydrate have been identified.

From our experiments the interpretation is that form 1 and form 2 are enantiotropes. Form 5 and form 3 should be also enantiotropes. Forms 3, 4, 5, 6 are monotropes of form 1 at ambient temperature.

The thermogravimetric analysis or the loss on drying of the pharmacopea allows the exclusion of the hydrated forms in commercial samples. Since only forms 1 and 5 are stable at ambient temperature, the limit of detection of the X-ray diffraction was studied by using the peak of form 5 at $2\Theta = 18$ degrees. A limit of detec-

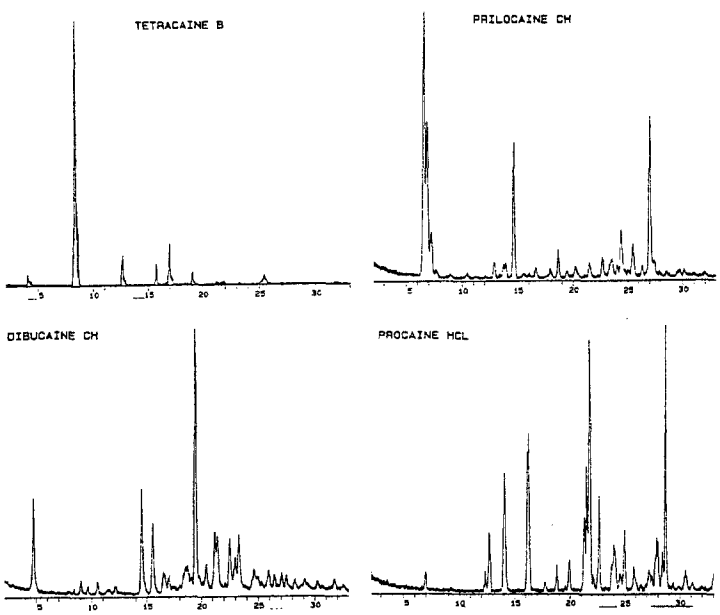

Fig. 12 X-ray diffractions of tetracaine base, dibucaine hydrochloride, prilocaine hydrochloride and procaine hydrochloride

tion of 2–5% was obtained. Additionally the absence of monohydrate and hemihydrate can be checked by the absence of peaks at 6.8–7.2 degrees (limit of detection 5%). Therefore excluding the amorphous part, a polymorphic content of form 1 of more than 95% in commercial samples can be concluded. 7 commercial batches were found >95% form 1.

Other anesthetic drugs

As demonstrated in the crystallization experiments, the equilibration experiments, the storage at 92% r.h. (Tables 3, 4 and 5, "no change" means same DSC curve and same X-ray diffraction as original samples) and the study of the DSC curves, no other polymorphic forms were found in this study for tetracaine base, dibucaine hydrochloride, prilocaine hydrochloride and procaine hydrochloride. For description of these substances see references [9–11]. DSC curves and X-ray diffraction patterns are given in Figs 11 and 12.

Commercial bupivacaine hydrochloride is a monohydrate. It is not thermally very stable. The corresponding DSC curves at 20°C min^{-1} and 10°C min^{-1} are given in Fig. 13.

The thermal treatment at 200°C gives an anhydrous form. As demonstrated by temperature resolved X-ray diffraction, two other forms are detected by heating and cooling processes between 100 and 170°C. X-ray diffraction patterns are given in

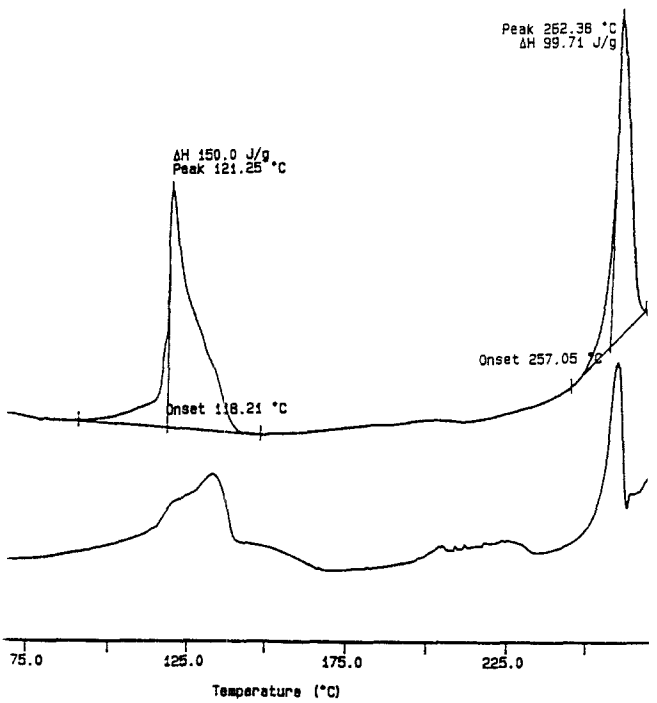

Fig. 13 DSC curves of bupivacaine hydrochloride monohydrate at 10°C min^{-1} and 20°C min^{-1}

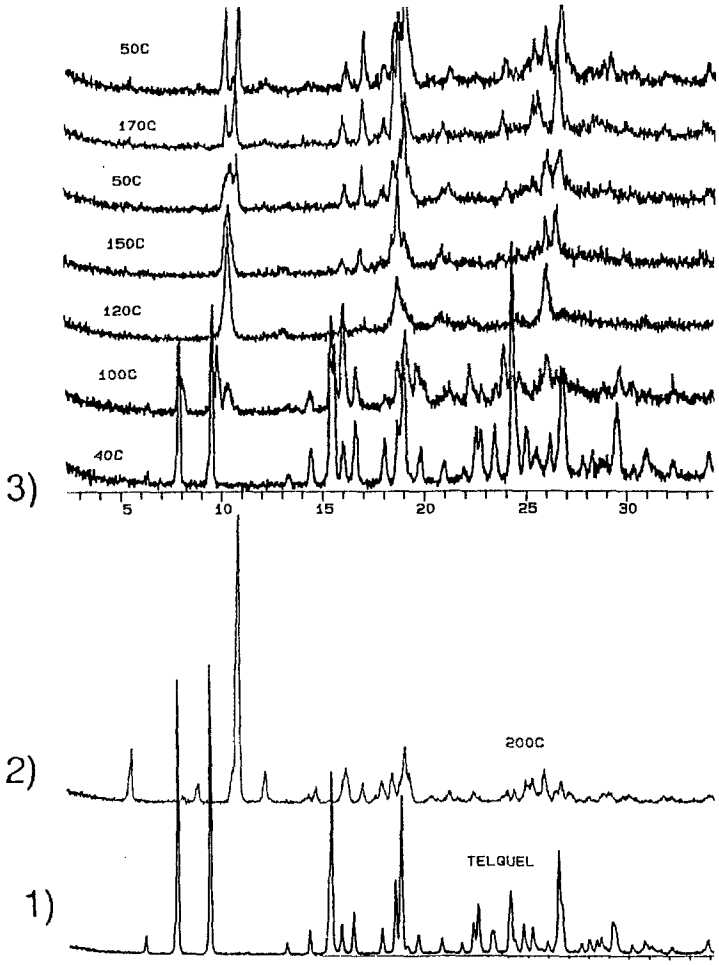

Fig. 14 X-ray diffractions of bupivacaine hydrochloride monohydrate and anhydrous forms 1: as is, 2: 200°C in pan and cooled at r.t., 3: temperature resolved X-ray experiment

Fig. 14. Equilibration and crystallization experiments show that solvates are easily obtained in different solvents (Tables 3 and 5) .

Conclusions

Tetracaine hydrochloride may exist in 6 crystalline modifications, one amorphous form and 3 hydrated forms.

The DSC curve of the commercial form 1 is very dependent on the heating rate. This anhydrous form 1 is the thermodynamic stable modification at ambient temperature. It undergoes a reversible enantiotropic transition into a form 2. This form melts and from the melt the form 3 is obtained. This form is the higher melting

form observed in literature [3, 4]. After melting of the higher melting form 3 and cooling two different crystalline forms: form 4 and form 6 and one amorphous form were observed .

The temperature of the solid–solid enantiotropic transition 1⇔2 is very close to the melting point of 2. Tempering at about 140°C from the melt and cooling at r.t. allows one to obtain the form 5. This form is stable at room temperature. Under heating this form 5 transforms into form 3. Under cooling the unstable form 3 gives the form 6. Form 6 transforms rapidly to form 5. All forms 3, 4, 5, 6 are monotropes of form 1. Dehydration of the tetrahydrate form occurs via the monohydrate. Heating this form produces form 3 via the hemihydrate.

Hydrated forms are obtained after exposure of form 1 at 92% r.h. or of form 5 at >61% r.h. or by crystallization in water.

Polymorphic purity of commercial tetracaine ch is best determined by X-ray diffraction, 7 commercial batches were found >95% form 1.

No polymorphic forms of tetracaine base, dibucaine hydrochloride or prilocaine hydrochloride were found. The commercial form of bupivacaine hydrochloride is a monohydrate. The thermal treatment at 200°C gives an anhydrous form. As demonstrated by temperature resolved X-ray diffraction experiments two other forms are detected by heating and cooling processes between 100 and 170°C. Equilibrations and crystallization experiments show that solvates are easily obtained.

Tetracaine hydrochloride and bupivacaine hydrochloride have a complex polymorphic behaviour. Temperature resolved X-ray diffraction is a very efficient tool as a support to DSC for the identification of the transition processes and for the interpretation of the thermal events and of the thermodynamic relationships. Equilibration experiments are very adequate to find out the thermodynamic stable form at ambient temperature (solvent mediated transitions).

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