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Thermal analysis of some diclofenac salts with alkyl and alkylhydroxy amines

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Abstract

A range of diclofenac salts was prepared with a variety of alkyl, hydroxyalkyl and alkyl hydroxyalkyl linear amines, and characterized by thermal analysis (DSC, TGA, and HSM). Another seven similar salts, previously described, were also prepared for a more careful analysis and comparison. The aim of this paper is a deeper knowledge of this class of compounds, previously poorly examined and that have, on the contrary, proved to offer complex situations in the solid state, as resulted by thermal analysis. The whole class of these salts presents a variety of behaviours, ranging from the formation of hydrates to polymorphs and hydrate polymorphs in the solid state. The salts with diethanolamine, triethanolamine, *N*-ethyl monoethanolamine and TRIS bases crystallize anhydrous. All the salts demonstrated thermal instability at temperature above the melting point, showing a dramatic loss of weight. In each case the TGA profile indicates that it corresponds to the base content inside the salt: this event is associated with a broad endotherm in the DSC thermogram that follows or overlaps with that of the melting endotherm. Prolonged heating in the oven of salts with very volatile amines causes decomposition, even at low temperatures, leaving the starting acidic diclofenac as residue. Different phases, in the case of polymorphs, were revealed, registering melting/re-crystallization by hot stage microscopy, as in the case of the salts with triethylamine and *N*-methyl monoethanolamine; while in the case of the salt with monoethanolamine evidence was obtained by means of DSC. The relationship between the structure of the starting bases and solid-state nature of these diclofenac salts studied is briefly discussed.

Keywords: Diclofenac salts; Alkyl and hydroxyalkyl amines; Thermal analysis; Thermal instability; Hydrate; Polymorph

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) represent interesting substrates for the study of pharmaceutical salts: they are weak acids, poorly soluble in their unionized form and most of them are commercially formulated as sodium salt to improve solubility in water. They are also suitable for studying the influence of counterions on the technological properties of solid pharmaceutical salts, as well as the therapeutical performance of the active agent. In fact there is an increasing number of pharmaceutical salts that are studied or formulated with cations other than sodium, such as that of aliphatic amines. The use of aliphatic amines appears promising as salt forming agents for acidic drug, since this class of compounds offers a wide choice of structural parameters that prove useful to achieve different physical, chemical, technological and, possibly, pharmacokinetic behaviour of the final salt form [1,2]. Many examples can be encountered in the literature of NSAID salts having an ammonium cation of various structures, e.g. ketorolac trometamine [3], ketoprofen lysine [4], meclofenac monoethanolamine and choline [5], ibuprofen *tert*-butyl amine [6], naproxen betaine and arginine [7,8], salicylic acid diethylamine [9,10]. Diclofenac in particular has been studied with a variety of aliphatic amines with the aim of preparing salts with improved solubility: the solubility of diclofenac has in fact represented a problem since its appearance on the pharmaceutical market, and it is currently formulated mainly as sodium salt, but also as potassium, diethylamine and *N*-(2-hydroxyethyl)pyrrolidine salt. Many diclofenac salts with a variety of amines were tested for solubility [11–13] and the factors affecting their solubility were examined [14–17]. However, the behaviour of diclofenac salts with *N*-(2-hydroxyethyl)pyrrolidine and diethylamine [12,13,18,19] that form hydrate and hydrate polymorphs of different degrees of hydration in the solid state; or in aqueous

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solution, where micelle-like aggregates form [11,12,20–23] and the easiness of dehydration of some alkaline diclofenac salts [22–25] suggested that complex behaviours could be common to most diclofenac salts. Moreover, the crystal characterization of a number of diclofenac salts with amines [13,18,26–32] indicated that formation of hydrate and polymorphs could be rather common among these compounds: this suggested the need for a serious examination of the nature of the solid-state of new, but also of old and poorly described [11,14] diclofenac salts in order to reveal the formation of hydrates and/or the presence of polymorphs, before starting solubility measurements and other pre-formulation tests, and define the stable form as a function of the experimental conditions or the most suitable for technological purposes (e.g. formulations).

In order to advance our understanding of diclofenac salts, a number of salts were prepared and examined. The study includes mainly aliphatic amines, as salt forming agents, containing varying numbers of hydroxy groups and represents an extension of previous papers investigating diclofenac salts in the attempt to select a highly soluble salt for this drug. The choice of this class of bases originated from the possible relationship between solubility and melting point of the salts and cation hydrophilicity. However, previous results revealed the complexity of the system represented by diclofenac salts and suggested a more in-depth examination in order to obtain reliable knowledge of their behaviour in the solid state and solution. We therefore prepared 13 diclofenac salts and compared some of them with the same salts, previously described, and characterized them with thermal analysis in order to highlight the nature of their solid state. Some salts of this series have been previously prepared and examined only by traditional techniques, such as the melting point [11,14]: this last parameter, which suffers from subjectivity, often offers incorrect and partial information on the nature of the solid and ignores possible transitions caused by temperature scanning. It is therefore expected that thermal analysis, in terms of differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and hot stage microscopy (HSM) represents a better investigation tool for the salts of this series, as demonstrated by the results previously obtained for the diethylamine, 2-(dimethylamino)ethanol and TRIS diclofenac salts of this series previously re-examined [12,13,19].

Here, therefore, we examine, by thermal analysis, a group of diclofenac salts with a large variety of linear aliphatic amines (carrying hydrophilic and/or hydrophobic substituents at the N atom) in order to highlight the nature of their solid state, as a function of the substituents around the N atom of the cation. This paper is part of a project where both linear and cyclic amines are used to prepare diclofenac salts, taking diethylamine and pyrrolidine, respectively as parent compounds for the two series, as references for an open or cyclic molecular structure.

2. Experimental

2.1. Materials

Diclofenac was a gift (IBSA, Lugano, Switzerland) of pharmaceutical grade. The following bases: monoethylamine (EtA), diethylamine (diEtA), triethylamine (triEtA); monoethanolamine (MEA), diethanolamine (DEA), triethanolamine (TEA), tris methylolamino methane (TRIS); *N*-ethyl monoethanolamine (EtMEA), *N*,*N*-diethyl monoethanolamine (diEtMEA), *N*-methyl monoethanolamine (MeMEA), *N*,*N*-dimethyl monoethanolamine (diMeMEA); *N*-ethyl diethanolamine (EtDEA) and *N*-methyl diethanolamine (MeDEA), were commercial samples of the highest purity grade available (Sigma–Aldrich, Milano, Italy) and used as received.

Throughout the paper the bases are identified with their acronym. All the solvents used for crystallization were of pharmaceutical purity grade.

2.2. Preparation of diclofenac salts

Salts were prepared separately dissolving equimolar amounts of acidic diclofenac and the appropriate base in acetone and then mixing the two solutions. The salts, according to their solubility in the solvent, either rapidly precipitated, or after cooling at −20 °C, or after concentration of the final solution, removing excess solvent at room temperature. Products, recovered by filtration under reduced pressure, were initially dried at ambient conditions for 24 h and examined by DSC. The salts were recrystallized both from an organic solvent (acetone or methanol) and/or from water, and thermograms were compared to show the presence of hydrate forms.

2.3. Scanning electron microscopy (SEM)

The morphology of the salts was examined by SEM. The salt particles were sputter-coated with Au/Pd using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (XL30 Philips, Eindhoven, NH) at 10 kV accelerating voltage, before taking the image.

2.4. Differential scanning calorimetry (DSC)

Thermal analysis was carried out employing an automatic thermal analyzer system (Mettler-Toledo 821e). The data processing system (Mettler 821e/500/847 thermo-cryostat) was connected to the thermal analyzer (Mettler-Toledo S.p.A., Novate Milanese, Italy). Holed aluminium pans were used for the experiment for all the samples. Temperature calibrations were made using indium as standard. An empty pan, sealed in the same way as the sample, was used as a reference. The thermograms were run at a scanning of 10 °C/min, from 30 to 320 °C, on 5–l0 mg powdered sample.

2.5. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was performed with a Mettler-Toledo automatic thermal analyzer system TGA/SDTA 851e/SF/l 100) (Mettler-Toledo S.p.A., Novate Milanese, Italy). Open alumina crucibles were used for analysis in the temperature range 30–320 °C at l0 °C/min scanning rate under nitrogen stream.

2.6. Thermomicroscopy (HSM)

Thermomicroscopy was carried out on hot stage apparatus (Mettler-Toledo S.p.A., Novate Milanese, Italy) mounted on Nikon UN2-PSE100 light microscope (Nital S.p.A., Firenze, Italy); samples were mounted in air or in silicone oil to detect the loss of water. Images were taken by a Nikon digital net camera DN100.

2.7. Powder X-ray diffraction (XRD)

To perform X-ray diffractometric analysis a Philips PW 3719 diffractometer was used, controlled by a computer. Experimental conditions: Cu Kα radiation ($X = 1.78896$ Å); 40 kV and 30 mA. Scanning interval: 5–50° 2θ; time per step: ls; graphite monochromator on the diffracted beam.

2.8. FT-IR

Spectra were recorded by a Nicolet FT-IR Nexus 470 connected to a Nicolet Continuum microscope: Experimental details: source global (SiC candle); beam splitter m-IR: KBr; detector: MCI (CdTe, doped by Hg) (Hg/Cd); spectral window: 4000–650 cm^{-1}; side resolution: 7–80 μm; spectral resolution: 4 cm^{-1}.

2.9. Karl Fischer titration analysis

KF titration analysis for determining water content was carried out on powdered samples using a KF titrator Mettler-Toledo DL38. The KF reagent (Hydranal Methanol dry Riedel-de-Haen) was standardized using Hydranal composite J Riedel-de-Haen. All determinations were carried out in triplicate.

3. Results and discussion

3.1. Characterization of diclofenac salts

Aliphatic linear amines used in the present study, starting from diethylamine, carry progressive structural variants, such as an increasing number of hydroxy groups (mono-, di- and tri-ethanolamine; TRIS), or a combination of ethyl (ethyl, diethyl, and triethylamine), methyl and ethyl and hydroxyethyl groups (methyl-, dimethyl-, ethyl-, diethyl-monoethanolamine; methyl-, ethyl-diethanolamine). From the structural point of view, this class of amines therefore represents a large range of different molecular structures and in turn can offer a variety of structural situations when the final salt is considered: some of these salts have been previously reported [12,19,13] or described to a limited extent [11,14,15,32], whereas in this paper we prepared and examined a larger range of diclofenac salts by modern thermal analysis. From this study it emerged that, even if it may be easy to prepare a diclofenac salt for different purposes, this class of salts needs careful examination to state the nature of the solid state and its transformations in the presence of water (as humidity or as dissolution as well as crystallization medium) and in the case of heating (for drying), before considering a given salt suitable for formulation or solubility studies.

The reaction of the formation of the salts, from acidic diclofenac and the bases, occurs rapidly and no problems were encountered in the preparation, since each base has a sufficiently high pK_a to react with the weakly acidic diclofenac. Salts were prepared in organic solvents to easily obtain nicely crystalline material. The formation of the salts was confirmed by the presence of characteristic bands in the FT-IR spectra concerning carboxylate and ammonium groups (not reported here).

Most salts examined at SEM display a platelet external habit, where plates are stacked on each other, often with regular and geometric boundary (Fig. 1).

3.2. DSC

Thermograms of all the salts examined are characterized at least by the presence of two endotherm peaks: one peak associated with melting in the range 100–200 °C. A second endotherm, broad and rounded, at a higher temperature in the range 180–230 °C, associated with the decomposition of the salt (see Figs. 2 and 4), is typical of these salts with organic bases, since it is not present in thermograms of diclofenac salts with alkaline cations. These last salts on the contrary display thermograms with a complex exotherm of oxidation of the organic moiety, starting from about 300 °C. In the cases where the melting point of the salt is encountered above l60–180 °C, overlapping between the two endotherms is observed, preventing reliable measurements of parameters associated with each thermal event (EtA, TRIS, MeMEA, and MEA salts). Most salts display thermal behaviour outside this simple scheme: some have an additional endotherm related to the formation of a hydrate at temperatures lower than 100 °C; some others present a complex thermogram, suggesting the occurrence of more than one thermal event, not adequately resolved or separated. In many cases the permanence of the sample inside a desiccator improves the shape of the endotherms or their splitting and allows observation of events that, in the presence of humidity or crystallization molecules, were masked by the melting. However, some events, such as polymorph transition (see Sections 3.4 and 3.6), not revealed by DSC traces, could only be observed by thermal microscopy.

Dehydration of hydrate salts in the oven leaves the sample in an (at least partially) amorphous state. This was documented by an irregular baseline of the X-ray diffractogram (not shown here) and by the fact that ΔH, associated with the melting, is lower as documented by the surface area of the endotherm peak.

All these different situations, not immediately solved with modem thermal analysis, make unreliable some previously reported descriptions of some of these salts [11,14,15], using the simple determination of a melting point. This last parameter is unable to describe the nature of the solid state of these compounds and also its documentation of purity of the salt must be considered with caution, when any unforeseen formation of hydrates or solvates makes the melting point dependent on the stoichiometry and nature of the crystallization solvent.

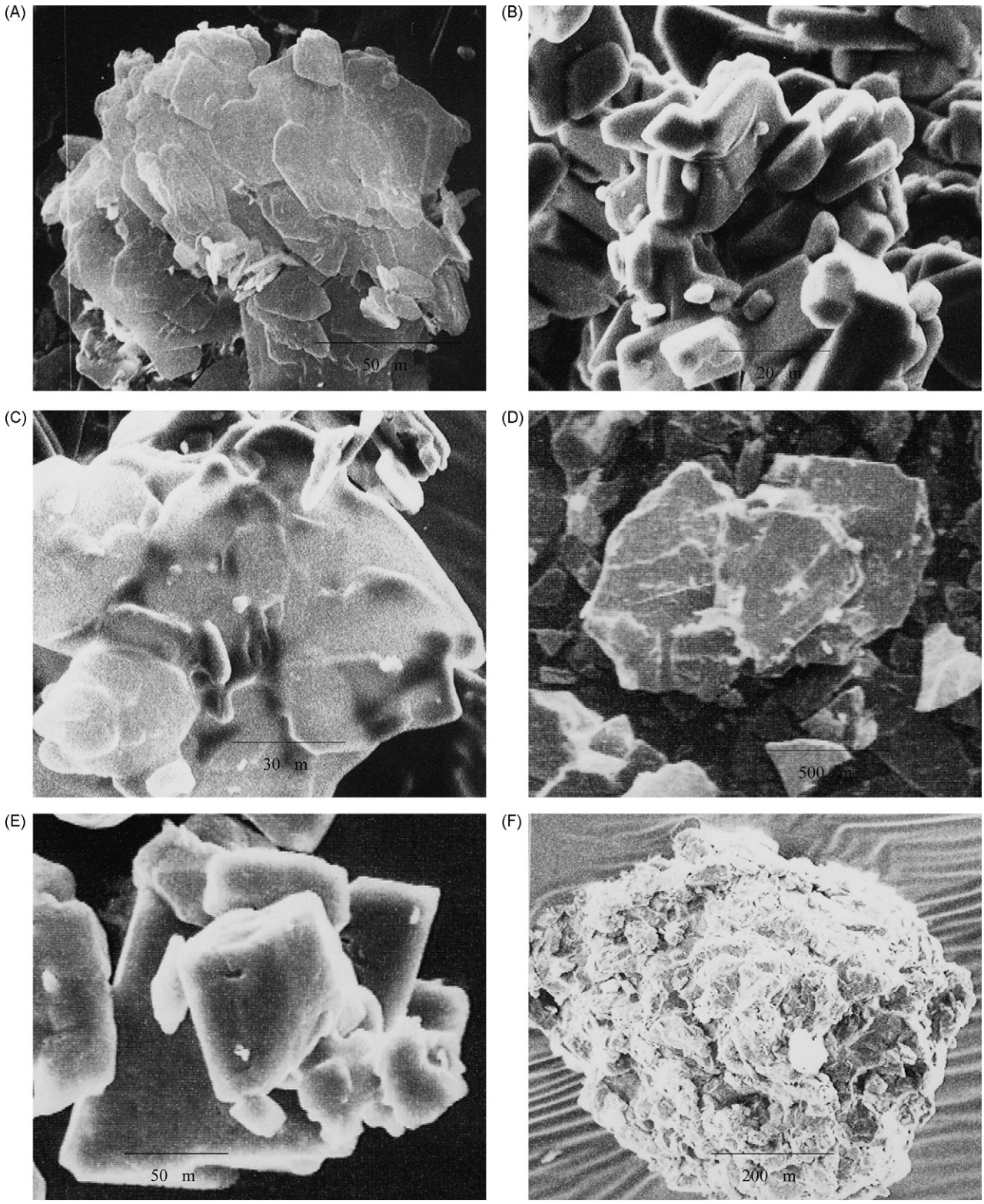

Fig. 1. SEM micrographs of diclofenac salts with (A) MEA, (B) DEA, (C) TEA, (D) diEtA, (E) MeMEA, and (F) triEtA.

The melting point of the studied salts was found to be in the range l00–200 °C, EtDEA and triEtA salts having values lower than 100 °C and TRIS salt higher than 200 °C. A low value was also displayed by EtMEA (101 °C) and MeDEA (102 °C) salts. The following sections will outline how uncertain the determination of the melting point of these compounds could be without any previous indication of the nature of the solid state. The complexity of the system was not revealed by simple parameters that could not distinguish between different thermal events that appear common to this series of salt, and previous papers

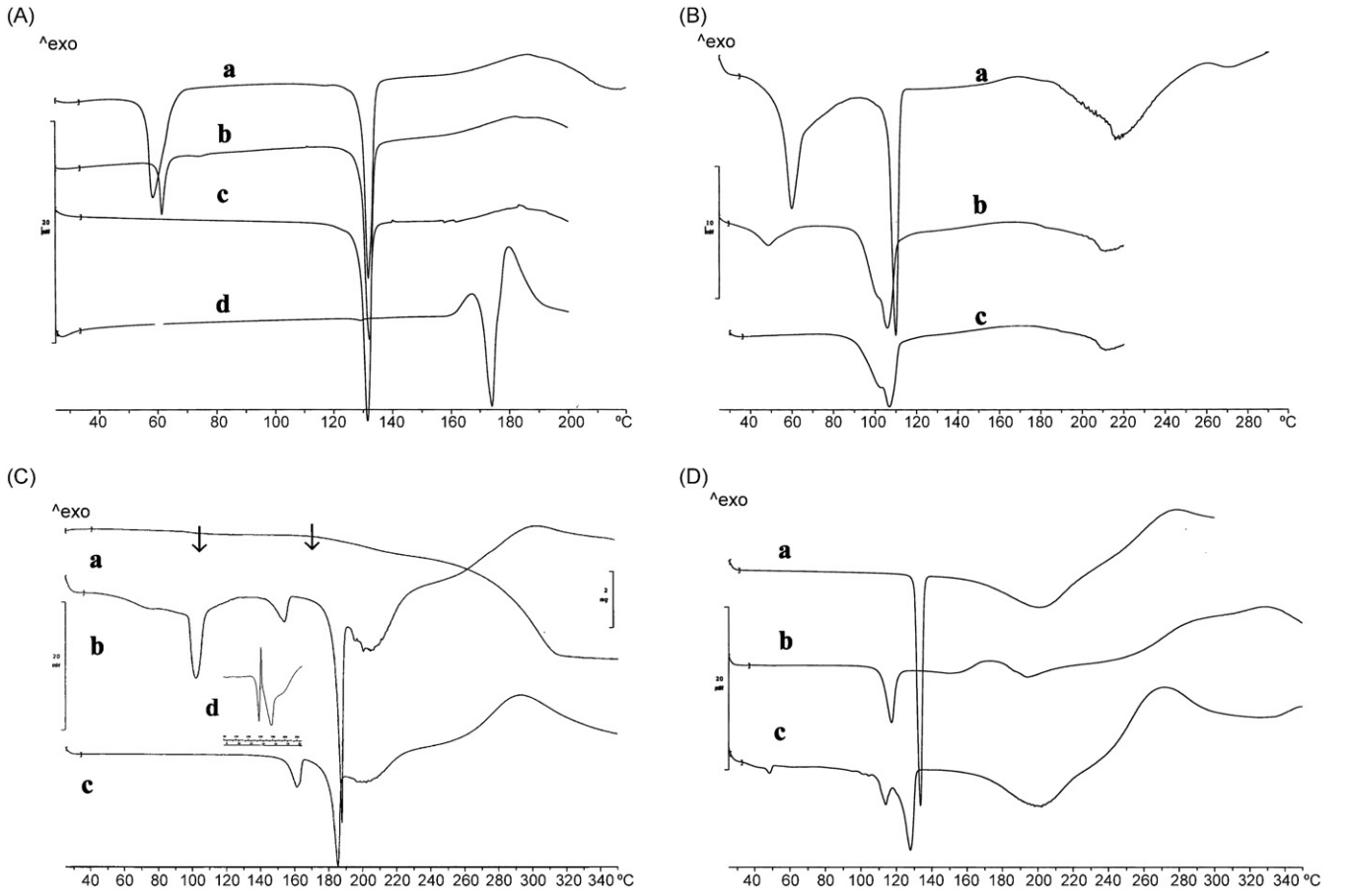

Fig. 2. DSC thermograms illustrating different situations for some diclofenac salts. (A) diEtA salt: (a) hydrate form; (b) hydrate form kept in a desiccator for 4 weeks; (c) dehydrated form in the oven at 60 °C for one night or form obtained by direct crystallization from ethyl acetate; (d) acidic diclofenac. (B) triEtA salt: (a) hydrate form; (b) hydrate form in a desiccator for 1 week; (c) hydrate form kept in a desiccator for 4 weeks. (C) MEA salt: (a) TGA profile: arrows indicate dehydration (at left) and decomposition (at right) of the salt; (b) hydrate form; (c) anhydrate form; (d) detail showing polymorph transition. (D) DEA salt: (a) form obtained by direct crystallization from acetone; (b) crystallized from water; (c) form obtained from acetone and equilibrated in water.

[11,14,15] reported data for some salts analysed as obtained from the crystallization medium, without any treatment.

3.3. TGA

Thermogravimetric profiles, obtained for all the salts, suggest a dominant thermal instability on heating of these diclofenac salts with volatile amines. Practically all the salts lose weight during melting: comparison of TGA with DSC profiles in the temperature range of endotherm associated with melting shows an appreciable weight loss up to 5.70% (diMeMEA). Obviously the loss is even larger when melting and decomposition endotherms overlap together (TRIS). DEA, TEA and MeDEA salts proved to be stable on melting. In the case of hydrates, the presence of water is documented by loss of weight in correspondence with the endotherm at a lower temperature in the thermograms and also by its disappearance after the sample had been kept in a desiccator over silica gel for a long time at room temperature or by Karl Fischer titration. The decomposition profile, associated with the broad endotherm at a higher temperature, often appeared to be stepwise, suggesting the occurrence of multiple thermal events together with the thermal dissociation of the salt (D^- = diclofenac anion; NH^+ = ammonium cation):

$$D^-{}^{\bullet}NH^+ \rightarrow DH + N\uparrow$$

The total weight loss is in most cases of the same order of magnitude as the base content inside the salt and is due to the evaporation of the free amine that leaves acidic diclofenac as residue. The odour of the amine is clearly noticed when TGA or DSC determinations are carried out in unsuitable conditions. Decomposition of the salt is easily observed in the case of gaseous or very volatile amines, when prolonged heating is previously carried out in an oven, though at a temperature lower than melting: the melting endotherm of diclofenac is evident in the thermograms of the final samples. The same was previously observed [25] with the NH_3 diclofenac salt and this fact can be a general behaviour of these salts, when the salt forming agent is a low boiling amine: it is therefore expected that heating the salt at the melting temperature causes its dissociation and free amine escapes from the sample mass.

3.4. Alkylamine salts

The N atom on EtA carries the simplest substituent within this series of bases and no hydroxy group is present, and this salt was thus prepared for comparison. The thermogram of the EtA/diclofenac salt presents an endotherm (about 190 °C) originated by the melting: the peak is asymmetric suggesting that also decomposition of the salt could occur due to volatility of the base, during the melting. A shoulder at the lowest temperature side of the endotherm can be clearly seen in the thermogram (not shown) and could be associated with the melting of acidic diclofenac, as a residue of a partial thermal dissociation of the salt. These thermal events occurring at temperatures close together hinder a simple description of this salt.

Increasing of the ethyl group number around the N atom increases complexity of the behaviour of these salts.

DiEtA diclofenac salt is present in commercial topical formulations and has been widely described in the solid state [12,13,19] and in solution [20]: its crystal structure has also been reported [33]: the salt is monohydrate (Fig. 2A). Using a very pure amine we were able to prepare a salt showing a DSC thermogram where dehydration and the melting endotherm are well separated at 58 and 131 °C, respectively (Fig. 2A, profile a). The first peak disappears after heating in the oven al 60 °C (Fig. 2A, profile c) or it takes longer when placed in a desiccator at room temperature (Fig. 2A, profile b): in both cases a simple thermogram is obtained with only one peak at 131 °C. When the salt is obtained from ethyl acetate (that is, from a non-aqueous anhydrous solvent), the endotherm at a lower temperature is absent and the salt can be obtained directly as an anhydrate, melting at the same temperature. After prolonged heating in the oven at 80 °C, only the melting endotherm of acidic diclofenac is present, as a residue of thermal dissociation of the salt (Fig. 2A, profile d).

TriEtA salt crystallizes as a monohydrate from aqueous acetone. The content of crystallization water decreases on aging at room conditions, as demonstrated both by thermogravimetric analysis and Karl Fischer titration. Loss of weight observed during TGA is accompanied in DSC thermogram by an asymmetric and large endotherm (from 38 to 58 °C); the narrow endotherm at 109 °C can be associated with the melting of the anhydrate form (Fig. 2B, profile a). The salt, kept in a desiccator at room tem-

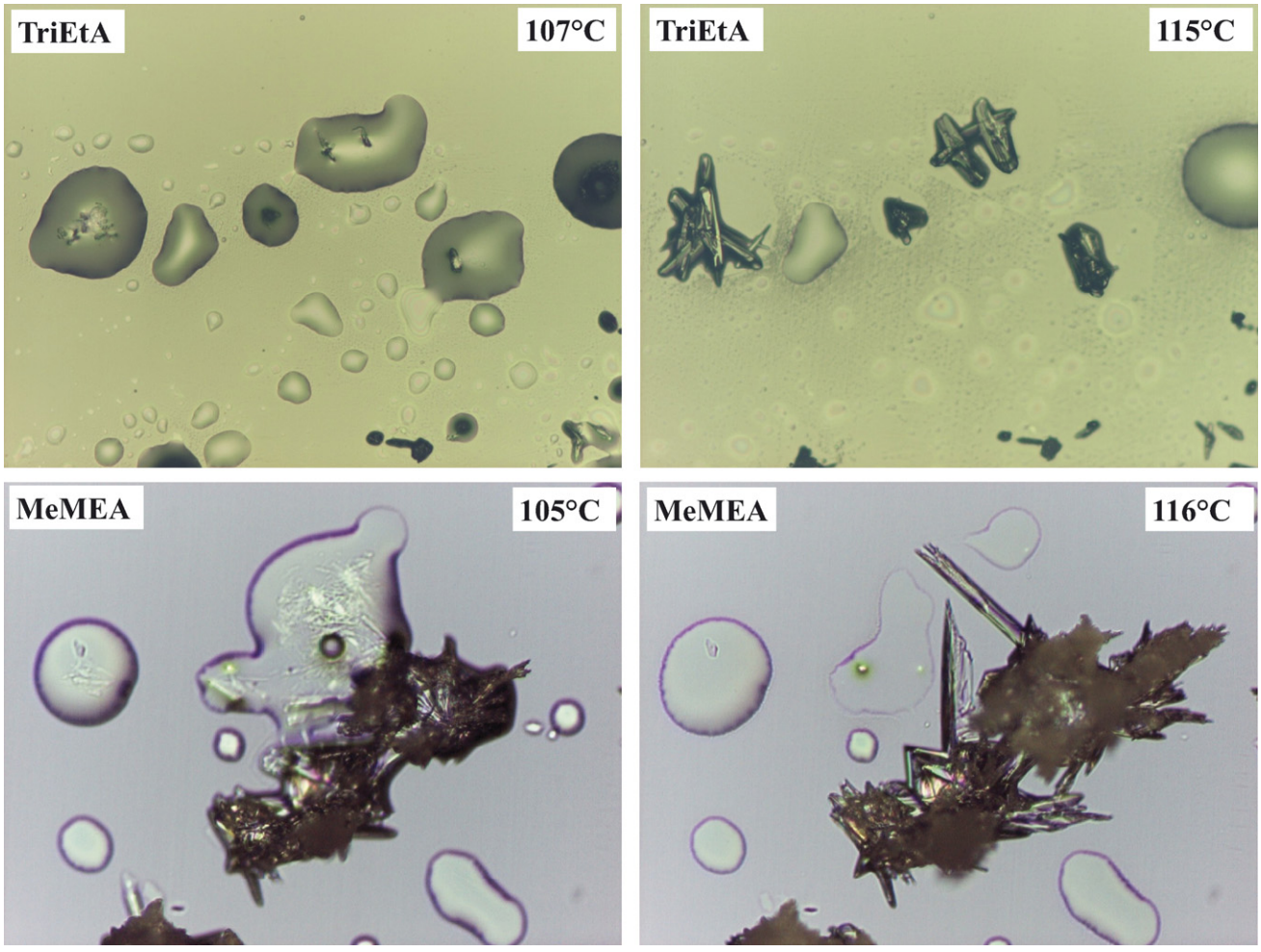

Fig. 3. HSM photographs. (Above) Behaviour of triEtA salt at different temperatures, showing melting of the metastable phase (107 °C), re-crystallization (115 °C) of the stable phase, melting at 125 °C. (Below) Behaviour of MeMEA salt at different temperatures, showing melting of the metastable phase (105 °C), re-crystallization (116 °C) of the stable phase, then melting at 155 °C.

perature, slowly dehydrates (Fig. 2B, profiles b and c), leaving the solid, at least partially, amorphous, since ΔH associated with melting, after this treatment, is only 40% of the starting value and the melting endotherm peak also reveals a complex structure, possibly suggesting thermal events different from simple meltdown (Fig. 2B, profile c). In fact, examination by thermomicroscopy (Fig. 3) made it possible to observe that, starting from about 107 °C, the melted phase shows increasing presence of centres of crystallization and at 116 °C well defined needles are visible grown from the molten phase. This phenomenon is, however, visible at HSM after dehydration of the salt in a desiccator, but cannot be noted from the thermogram profile, which shows only a splitting of the peak. It appears that the salt forms hydrate polymorphs, melting very close together: their characterization is under examination.

3.5. Alkanolamine salts

Bases, containing only hydroxyethyl moieties around the N atoms, form salts with diclofenac displaying very different behaviours from each other. These salts were previously characterized only by their melting point [11,14,15]: modern thermal analysis provided new and important details of the nature of the solid state.

MEA salt displays a thermogram with four endothermic peaks that, following TGA, HSM and DSC thermal cycles, were interpreted with the formation of a hydrate polymorph (Fig. 2C). The first endotherm peak, about 100 °C (Fig. 2C, profile b), is associated with the presence of one water crystallization molecule (4.20% by TGA measurement; 4.39% by KF titration), which is lost after heating in the oven al 60 °C (Fig. 2C, profile c). The second one is associated with melting of the anhydrate form, followed by a polymorph transition (Fig. 2C, profile d) to a more stable form, melting al 185 °C, with a melting endotherm overlapping the decomposition peak (at about 200 °C) (profiles b and c). TGA profile for MEA salt shows four steps for the weight loss. The first one is associated to dehydration that occurs in the temperature range 100–110 °C (Fig. 2C, profile a). The subsequent steps represent different degrees of decomposition that starts with the polymorph transition (1.83%, in the range 157–162 °C), continues with melting (4.34%) and terminates in correspondence of the broad endotherm (9.15%, in the range 190–230 °C). The sum of these weight loss exactly corresponds to the content of the base inside the MEA salt (15.29%), in the temperature range 110–230 °C, after dehydration. From Fig. 2C it can be appreciated that the position of the peaks change a little with the thermal history of the sample.

Attempts to obtain the high melting point form by direct crystallization failed, since the presence of water in the solvents during the synthesis of the salt could not be avoided, because water is always associated with the starting base, freely soluble in water and hygroscopic, like all the bases of this series: the presence of water accounts for the formation of the metastable form. The high melting form could not be obtained by thermal treatment of the dehydrated form: the TGA profile suggests loss of weight associated with each endothermic peak. The crystal structure of MEA salt with meclofenamic acid, a NSAID structurally related to diclofenac, suggested the formation of a monohydrate compound, stabilised, not only by anion/cation interactions but also by hydrogen bonds [5].

DEA salt does not form hydrates, but displays DSC thermograms with different peak temperature endotherms, when crystallized from acetone (139 °C, Fig. 2D, profile a) or from water (122 °C, Fig. 2D, profile b): when equilibrated in water, the thermogram of the highest melting form shows two different peaks (Fig. 2D, profile c), suggesting a transition from one to the other form mediated by the solvent. No signal of thermal transition is evident from the thermogram trace, due to close values of possible transition temperature and melting point. The structure of the salt obtained from acetone has been described [27]. The melting point previously reported for this salt concerns the form obtained from the organic solvent.

The salts formed with TEA or TRIS bases do not offer evidence by thermal analysis for hydrates or polymorphs: this fact explains why previous melting points [14] represented reliable values, even if determined by a simple technique. While TEA salt displays the most “normal” behaviour among this group (Fig. 4A, profile a), the TRIS salt melting endotherm overlaps with that of decomposition (Fig. 4A, profile b) [12]. It is interesting to note that, despite the high number of hydroxy groups in the cation, these last three salts do not form a hydrate: this fact suggests that OH groups can be involved in intramolecular hydrogen bonds rather than making them available to interact with water molecules, either of crystallization water or present in the dissolution medium: as a consequence a rather low solubility in water is expected. In fact the following solubility values were found in water [14]: 12, 16, 17, 4 mM for the MEA, DEA, TEA and TRIS diclofenac salts, respectively; these values are low, when compared with the solubility value 30 mM found for sodium diclofenac.

3.6. N-Alkyl-ethanolamine salts

EtMEA salt does not form hydrates or polymorphs and melts at 150 °C. The TGA profile suggests that decomposition starts during melting and terminates at about 250 °C, with a weight loss corresponding to the content of the base (Fig. 4D, profile d). On the contrary, the thermogram of the salt with MeMEA, having a shorter methyl chain and obtained from aqueous acetone, is rather complex (Fig. 4B, profile c). Beside the usual melting (170 °C) and decomposition peaks, two additional irregularly shaped endotherms, peaking al about 79 and 103 °C (Fig. 4B) are present in the DSC thermogram, after dehydration in oven or in desiccator (Fig. 4B, profiles a and b). Analysis of the results obtained also by TGA and HSM allows the following description of the thermal behaviour of the salt. The first endotherm, associated with a weight loss in TGA profile, suggests dehydration: the stoichiometry of the hydrate is difficult to assess only by TGA data, since loss of weight continues during the melting of the anhydrate form (associated with the endotherm above 100 °C) up to the complete decomposition of the salt. KF titration suggests a content of water close to a monohydrate stoichiometry. HSM reveals that, after melting, the anhydrate form undergoes a polymorph transition by recrystallization in

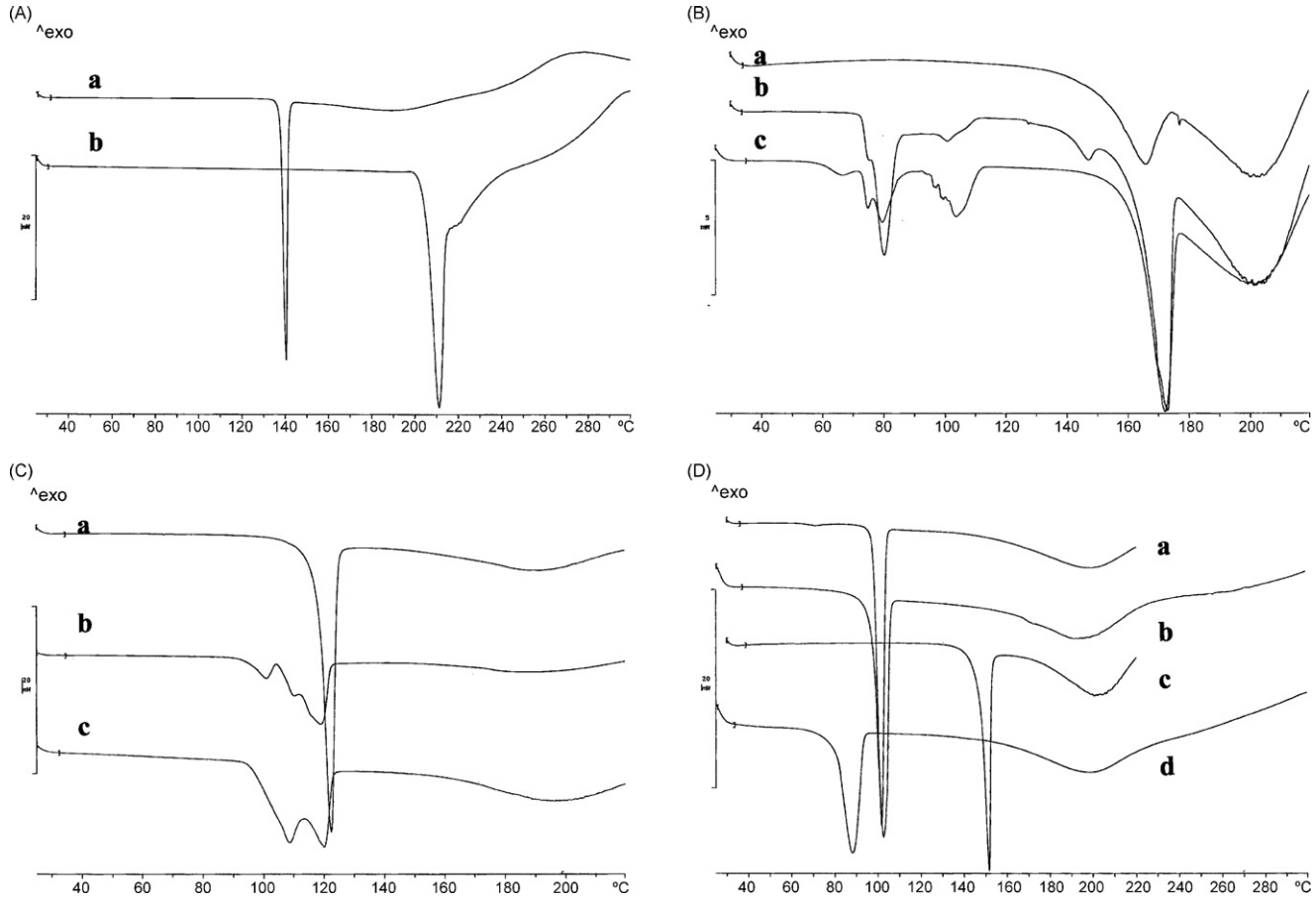

Fig. 4. DSC thermograms illustrating different situations for some diclofenac salts. (A): (a) TEA salt, and (b) TRIS salt. (B) MeMEA salt: (a) heated in oven at 100 °C for 1 day; (b) in a desiccator for 4 days; (c) hydrate form. (C) diMeMEA salt: (a) prepared from acetone; (b) 2 days in a desiccator; (c) 2 weeks in a desiccator. (D): (a) MeDEA salt; (b) EtMEA salt; (c) diEtMEA salt; (d) EtDEA salt.

the range 107–115 °C toward the stable form, melting at 172 °C (Fig. 3). This salt too is still under examination for the separation of the two forms.

DiMeMEA and diEtMEA diclofenac salts melt at low temperatures (122 and 101 °C, respectively) and a loss of weight on melting is registered by TGA. Since, as previously observed, loss of weight, starting with the melting, continues also in these cases up to complete dissociation, the idea that it could be associated with the presence of a hydrate must be considered with caution, if only this technique is employed. O'Connor and Corrigan [12] reported that this salt exists in two forms, one converting to the other on heating. The thermogram (Fig. 4C, profile a) of the salts suggests that the system is not simple: the two forms melt close together and, as in the other case, attempts are ongoing to obtain their separation (Fig. 4C, profiles b and c). On the contrary, the DSC thermogram of diEtMEA remains unchanged after any treatment and the salt melts at 101 °C (Fig. 4D, profile c).

The presence of two hydroxyalkyl substituents in the starting base simplifies the final salt, so MeDEA and EtDEA bases produce salts that melt al low temperatures and do not present any particular thermal behaviour (Fig. 4D, profile a and d, respectively). The thermograms do not change after a prolonged permanence in the desiccator or in a 75% RU container.

3.7. Structure of the diclofenac salts

All these results make it possible to interpret the role of different substituents carried by the salt-forming bases on the nature of the solid state of corresponding diclofenac salts. The structure of the molecule of diclofenac suggests the presence of different hydrogen bond-donor/acceptor groups: chlorine atoms, imino moiety and the carboxyl group. The acidic molecule forms a dimer in the solid state, where two carboxyl groups face together, while a chlorine atom is linked *via* a hydrogen bond with the imino group [31]. The result is a notable hydrophobicity of the molecule unable to display affinity for water and therefore poorly soluble. As a consequence of ionization or formation of a salt, the proton of the carboxyl is lost and hydrogen bonds can be provided by the presence inside the crystal lattice of water molecules of crystallization.

The crystal structure of some diclofenac salts of this study has been described [26–33] and it emerged that, beside the electrostatic interaction typical of ionic compounds, a network of hydrogen bindings between $>NH^+$ and OH groups of the cation and >NH and $–COO^-$ of the anion exists between the anion and cation of a structural unit: this constant presence of hydrogen bonds between the anion and cation in the diclofenac salts examined contributes to building a close contiguity between ions in the

crystal lattice [26,27,29,30]. The number of these bonds obviously increases with the increase of the hydroxyl group number of the bases (in the case of DEA salt, the network extends also to the neighbouring units [27], which in turn increases the melting point of the salt). This aspect, when present, could negatively affect the solubility in water: factors affecting the solubility of a series of diclofenac salts, in water or in solvents, have actually been described [11,14,15,18,19,34] and it emerged that diclofenac salts with organic bases cannot generally be considered as highly soluble compounds, at least with respect to similar salts of other NSAIDs. All the diclofenac salts studied so far form hydrates, with different degrees of hydration: this was the case of ammonia, alkaline and earth alkaline salts [35]. When the cation is an organic ammonium group, such as in the present cases, the situation changes. In the case of a substituent carried by the N atom lacking in hydroxy groups (diEtA, and triEtA), the crystal lattice is also built with water molecules. The salts display progressive complexity as the substituent number increases: EtA salt does not form a hydrate; diEtA can be obtained as a monohydrate, triEtA salt exists as hydrate polymorphs. The presence of one hydroxy group in the base is not enough to fulfil the demand of hydrogen bonds and stabilization of the crystal lattice of the salt: an additional water molecule of crystallization is needed for the MEA salt. All these hydrogen bonds, however, do not fix the structure of the salt, since MEA salt exists in different polymorph structures. The presence of a longer chain, such as an ethyl group in EtMEA salt, stabilizes the system and no hydrate and no polymorph are encountered for this salt. On the contrary, a shorter Me chain (in MeMEA salt) again makes the system instable (existence of hydrate polymorphs). Two methyl groups are not able to block the structure (again polymorphs are present), while two ethyl groups around the N atom in the monoethanolamine system produce only one simple diEtMEA salt form. An increase in hydroxy group number allows the formation of a close network of hydrogen bonds between anion and cation in the salts: the DEA salt shows two different forms, but very similar, having melting points very close together. The presence of a methyl or ethyl group allows the formation of only one salt form. As a consequence, the presence of three hydroxy groups further eliminates every complexity: only one form could be found for TEA and TRIS salts, melting at a high temperature. These ideas can be useful for foreseeing the presence of peculiar situations in the solid state when other salts of this series are prepared and considered.

4. Conclusions

Four main conclusions can be drawn from these results:

- Each pharmaceutical salt prepared for a given drug with different salt forming agents represents a “unicum”: its properties cannot be derived from those of the reacting compounds or from structurally related compounds. Unforeseen situations (hydrogen bonds, formation of hydrate, and polymorphism) can originate a final product that cannot be defined without a precise analysis of each single case.
- Diclofenac salts with aliphatic linear amines offer a variety of situations in the solid state, not always evident without specific and careful research even with modem thermal analysis. Application for commercial formulations of each salt needs a multifaceted study to reveal the nature of the solid state, the experimental conditions for its stability and which form could be suitable for a given formulation.
- Most of the diclofenac salts examined here form hydrates. Water crystallization molecules proved to be weakly bonded and different hydration grades can be encountered on aging of the sample in uncontrolled conditions.
- Most of the salts examined are thermally unstable and attention should be paid to the drying or dehydration conditions in order not to dissociate the salt form.

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