Journal of Thermal Analysis and Calorimetry, Vol. 73 (2003) 441–457

CHARACTERISATION OF SALTS OF DRUG SUBSTANCES

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Abstract

The properties of the solid-state of drug substances are critical factors that determine the choice of an appropriate salt form for the development of the pharmaceutical formulation. The most relevant properties may affect the therapeutic efficacy, toxicity, bioavailability, pharmaceutical processing and stability. The salt form must fulfil the needs of the targeted formulation, be suitable for full-scale production and its solid-state properties maintained batchwise as well as over time.

Comparison of the solid-state properties of different salt candidates may be quite complicated if each salt candidate exist as different solid phases: polymorphs, solvates or amorphous forms. Thermal analysis, microcalorimetry and combined techniques, X-ray diffraction, solubility, intrinsic dissolution, sorption-desorption and stability studies are basic techniques for the characterisation of the salt candidates. Some examples show the role of the salt form as well as the polymorphic form in the characteristics of the solid-state. Thermal analysis and combined techniques are efficient for the detection of unexpected phase transitions and for the comparison of the suitability of the salt candidates prepared for salt selection.

Keywords: characterisation of salts, intrinsic dissolution, microcalorimetry, pharmaceutical salt form, phase transitions, polymorphism affected properties, polymorphism in salt selection, salt candidates, salt selection, sorption-desorption, thermal analysis, thermal analysis combined techniques

Introduction

The properties of the solid-state of drug candidates are critical factors for the development of the pharmaceutical formulation. The most relevant properties may affect the therapeutic efficacy, toxicity, bioavailability, pharmaceutical processing and stability. An estimated half of all the drugs molecules used in medicinal therapy are administrated as salts [1], therefore the choice of an appropriate salt form is an important task of the development [1–6]. The salt form must be suitable for full-scale production and its solid-state properties maintained batchwise as well as over time.

The different salts are different entities with different behavior in solid-state and also in liquid and vapor state. Comparison of the solid-state properties of different salt candidates may be quite complicated if each salt form exists as different solid phases: poly-

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morphs, solvates or amorphous forms. Polymorphs have different crystalline arrangements but the same liquid and vapor phases. Solvates are new crystalline compounds formed with the solvent. In the amorphous phase there is no ordered structure of the compound. All physico-chemical characteristics of the solid-state are involved in the polymorphism and pseudo-polymorphism (solvate or hydrate formation). The main properties affected are melting and sublimation temperatures, heat capacity, conductivity, volume, density, viscosity, crystal hardness, crystal shape, color, refractive index, solubility, dissolution rate, stability, hygroscopicity, processability and solid-state reactions [7–13]. The consequences of polymorphism and pseudo-polymorphism are found in all steps of manufacture and storage of drug substances and drug products. This impact is so high that the International Conference on Harmonization (ICH) requires proper investigations and analytical methods for drug substance and drug products following a decision tree [14].

The parameters affected by the processing of the drug products: solvent, excipients, temperature, pressure and humidity are relevant in the choice of the salt form considering the different phases which may exist for each salt form.

Therefore the solid-state properties such as solubility, dissolution, melting, density, morphology, hygroscopicity, processability, stability, compatibility have to be studied taking into account thermodynamic and kinetic factors. For this task automated thermal analysis techniques, microcalorimetry coupled or combined with other techniques play an important role [15, 16] in addition to solubility, dissolution and stability studies [17–19].

Instrumentation

For the examples given in this paper, automated DSC-7 of Perkin Elmer, automated TGA-850 of Mettler, the TG-MS of Mettler, TGA7 of Perkin Elmer, the X-ray diffraction with heating cell or moisture control of Scintag, type XDS 2000 and the FT-IR with heating cell of Brucker IFS 55 have been used. The intrinsic dissolution experiments have been carried out according to USP 24 with the Vankel instrumentation. The hygroscopicity has been measured by DVS instrument of Surface Measurement Systems Ltd, or by a previous internal developed instrument. Scanning electron microscopy has been carried out with the instrument Jeol JSM 6300.

Properties in the solid-state

Melting point

The choice of the counter-ion allows modifying the characteristics of the drug molecule. A drug candidate with a low melting point is not suitable for purification, handling, processing. Table 1 gives examples of the influence of the salt form on the melting point measured by DSC. The influence of the counter ion on the thermal behavior is based on the thermodynamic phase diagram between the counter-ion and the drug substance. Figure 1 exemplifies binary mixtures of a stable compound with a congruent melting and a compound which dissociates on melting with incongruent

behavior. The phase diagrams allow understanding why some eutectics between the salt form and the molecule may be encountered as well as different salts in crystallization. These types of phase diagrams are also valid for the solvates.

Table 1 Influence of the salt form on the melting point

Salt form	Substance 1	Substance 2
	Melting point/°C	
Base	40	98
Hydrogen fumarate	156	196
Hydrogen maleate	139	161
Hydrogen malonate	115	72
Hydrogen tartrate	–	122
Hydrochloride	210	251
Oxalate	197	–
Pamoate	154	–

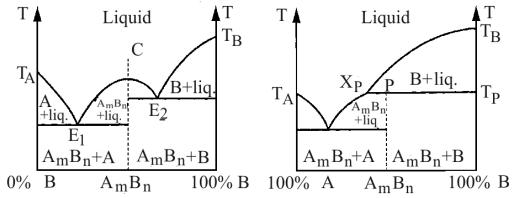

Fig. 1 Phase diagrams of binary mixtures of temperature *vs*. composition (e.g. mole fraction) of two chemical compounds, A and B, showing the following behaviour: left – formation of a compound with a congruent melting point at C, right – formation of a compound with an incongruent melting point at P

Morphology

Different salts may exhibit different morphology as exemplified in Fig. 2. Morphology depends also on the polymorph. The solvent of crystallisation and additives may be used for the modification of the morphology.

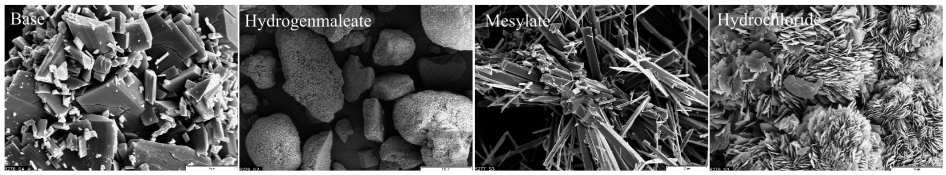

Fig. 2 SEM pictures showing different morphologies of several salt forms of a compound

Solubility/dissolution rate

The next property affected by the salt form is the solubility. As emphasised by Bastin *et al*. [6], the majority of the salts are developed to enhance the aqueous solubility of drug substances. In special cases, a retarding effect is suitable and insoluble counter-ion like pamoic acid or hydrophobic fatty acids are chosen. For albuterol, Jashani *et al*. [20] compared different salts, base, sulfate, adipate and stearate. All were crystalline. The densities were 1.15, 1.34, 1.22 and 1.07 g cm^{-3}. The solubilities were 15.7, 250, 353 and 0.6 mg mL^{-1}. Only the sulfate was found hygroscopic at relative humidity RH >93%. For inhaler performance in a high humidity environment, the hydrophobic stearate was found the best.

Metastable forms may have higher solubility giving wrong expectations for a salt form when the thermodynamic stable form is obtained with a lower solubility.

Figure 3 shows the effect of the equilibration time in order to obtain the equilibrium solubility of a drug molecule [21]. Therefore the solubility should be measured at different time and the insoluble analysed by DSC or X-ray diffraction. This point as well as the solubility profile *vs*. pH is discussed in several chapters of the reference [1]. Automated instrument has been developed for the determination of the pH solubility profile [19].

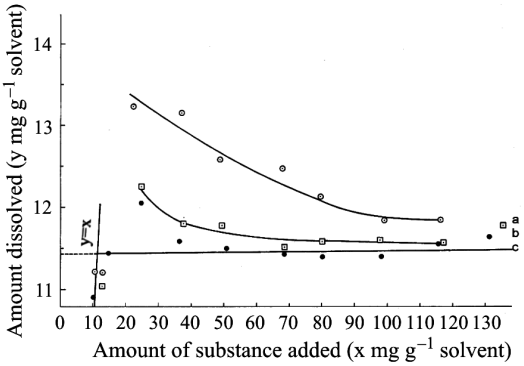

Fig. 3 Phase solubility analysis: transformation into a less soluble form depending on the time of equilibration a: 20 h, b: 63 h, c: 115 h [21]

In early development the measurement of the intrinsic dissolution is very useful since the dissolution rate is measured independently of the particle size. The influence of the salt form on the intrinsic dissolution rate measured at 50 rpm with the vankel instrument is demonstrated in Tables 2 and 3. Polymorphism has also its relevance as demonstrated in Table 4. If different salt forms with the same counter ion are possible, their IDR is also very relevant as demonstrated in Table 5.

The influence of the pH on the intrinsic dissolution rate (IDR) of a drug candidate is given in Fig. 4. When measuring salts there are differences among the salts as resulting from the behavior of the salts in solutions (Fig. 5).

Table 2 Influence of the salt form on the intrinsic dissolution rate of a poor soluble drug

Salt form	IDR/mg min^{-1} cm^{-2}	
	IDR in mg $min^{-1}cm^{-2}$ Buffer pH 5	IDR in mg $min^{-1}cm^{-2}$ Buffer pH 8
Base	0.014	0.0004
Hydrochloride	0.056	0.0016
Oxalate	1.359	0.0096
Tosylate	0.011	0.0032

Table 3 Influence of the salt form on the intrinsic dissolution rate of a soluble drug

Salt form	IDR/ mg min^{-1} cm^{-2}	
	IDR in mg $min^{-1}cm^{-2}$ HCl 0.1 N	IDR in mg $min^{-1}cm^{-2}$ Water
Base	2.61	–
Hydrochloride	1.09	4.04
Tartrate	1.78	–
Lactate	3.48	4.44
Succinate	3.38	–
Benzoate	10.85	–

Table 4 Influence of polymorphism on the intrinsic dissolution rate

Drug substance as base		Drug substance neutral	
Polymorph	IDR in water with 0.2% LDAO	Polymorph	IDR in water/ mg min^{-1} cm^{-2}
Amorphous form	0.048	Amorphous form	0.269
Form B	0.035	Form A	0.117
Form D	0.011	Form B	0.085

Table 5 Influence of the salt form and of the hydrate formation for a sodium salt of a drug substance

Salt form	IDR/ mg min^{-1} cm^{-2}	
	Water	Buffer pH 6.8
Monosalt Na	43.6	22.6
Monosalt monohydrate	17.6	16.5
Hemisalt	0.40	0.35

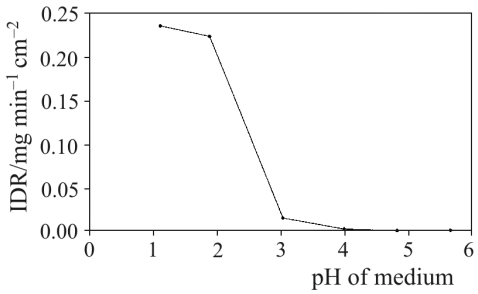

Fig. 4 Influence of the pH on the intrinsic dissolution rate with the same counter ion (HCl). pKa of the base is 6.9

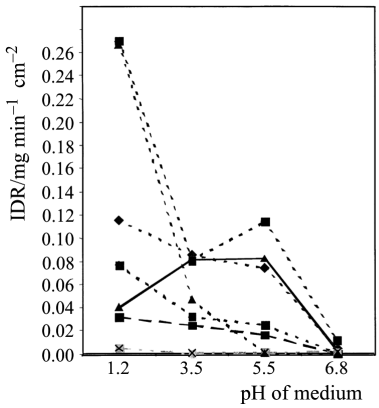

Fig. 5 Influence of the salt forms on the intrinsic dissolution rate in different buffers. -▲- – HCl, -◆- – Malonate, -■- – Maleate, -■- – Malate, –■– – Oxalate, -×- – Pamoate and -▲- – Base

Hygroscopicity/Interaction with water vapor

Water vapor is an omnipresent component of the atmosphere. The most excipients contain water. For solid dosage forms granulation in humid conditions are generally used. Therefore the study of the behaviour of substances in water vapor atmospheres is a prerequisite in the studies for the choice of the salt form. Some salts are deliquescent and cannot survive high humidities. At a given temperature, the ratio actual water vapor pressure/saturated vapor pressure at that temperature is called the relative humidity RH given as percentage of the saturation. The environmental humidity depends on the climatic zones. Sorption-desorption isotherms are measured as the mass change observed during the change of the relative humidity. Generally a hysteresis in the desorption is an indication of hydrate formation. But reversible desorption may also be observed for hydrates. X-ray diffraction during such studies is very fruitful [22]. Figure 6 shows the complexity of sorption-desorption of several salts of a drug candidate. The base and the hydrogen maleate salt were not hygroscopic while the

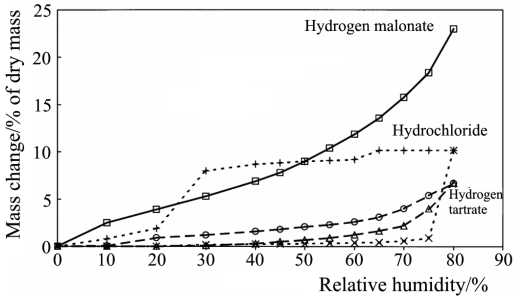

Fig. 6 Water vapour sorption isotherms of several salts of a basic investigational compound: – hydrogen malonate; (□ – sorption and desorption, water uptake 22%); – hydrochloride (X sorption+desorption, formation of hydrate occurs, corresponding to the plateau); – hydrogen tartrate (△ – sorption; ○ – desorption). The base and the hydrogen maleate are not hygroscopic, the water uptake is 0% until 90% relative humidity (RH)

hydrochloride transformed into a hydrate and the hydrogen malonate took until 22% water. The hydrogen tartrate was slightly hygroscopic.

In such studies the polymorphic form as well as the amorphous content of the samples used for the comparison of the salts is very important as exemplified in Figs 7 and 8. Figure 7 shows the different behaviours of two polymorphs of a hydrochloride [10] with an enantiotropic relationship. The high melting form, metastable at ambient temperature takes up water at lower RH value; the hydrate form loses water at RH values below 20%. A choice of the hydrated form was discussed. In fact a second polymorph of the hydrated form was also obtained in crystallisation studies in aqueous media.

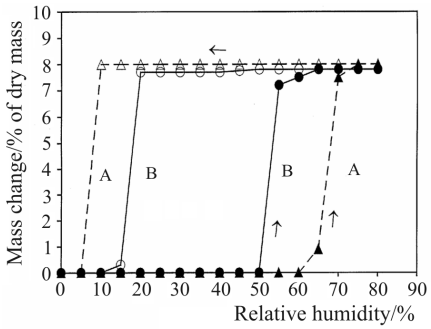

Fig. 7 Examples of water sorption-desorption isotherms of two polymorphs. The two polymorphs, A and B, transform into the same hydrated form. The metastable form B takes up water a lower RH than the stable form A. The hydrate form loses water at RH values below 20%

In Fig. 8, the salt form is not hygroscopic, but as resulting of milling the sample is partially amorphous and takes up moisture until a high level of humidity. The recrystallization is observed with lost of adsorbed water.

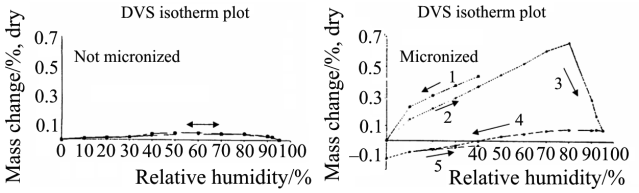

Fig. 8 Comparison of the behaviour of two samples in sorption-desorption experiment. Before milling, no change is observed. After milling the sample takes up water as resulting of the partial amorphisation during milling. Then an abrupt loss of water occurs resulting of the expulsion of water since the amorphous part crystallizes

Stability

The chemical stability behavior depends on the solid-state of the salt form [13] and also on the polymorphic form [23, 24]. The amorphous state is particularly critical for its chemical reactivity [25]. Microcalorimetry has been proposed for stability screening [26, 27]. An example of discriminative behavior between salt candidates is given in Fig. 9. Figure 10 exemplifies the influence of crystallinity. Table 6 gives 3 examples with the stability results of different polymorphs.

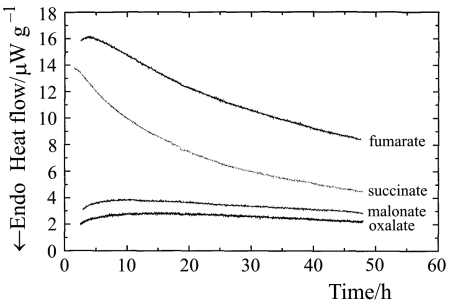

Fig. 9 Use of microcalorimetry for the study of the stability behaviour of 4 salts candidates of a drug

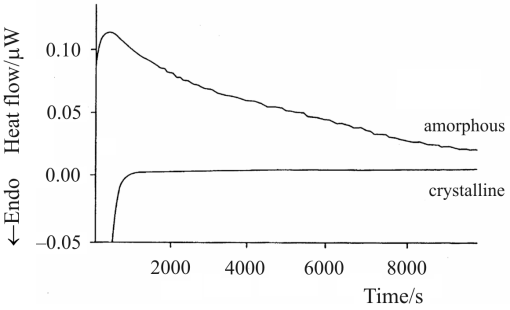

Fig. 10 Discriminative stability behaviour between amorphous and crystalline forms of a drug candidate

Table 6 Influence of polymorphism on the stability behaviour in solid-state

Examples	Degradation (HPLC)	
Example 1	1 month at 80°C (oxygen/water)	
Crystalline form A	No degradation	
Crystalline form B	0.5–1.5% degradation	
Amorphous form	2–3.5% degradation	
Example 2	2 weeks at 50°C	Exposition 1200 kluxh
Monohydrate A	No degradation	10%
Monohydrate B	12%	23%
Example 3	1 week at 70°C	Exposition 300 kluxh
Crystalline form	10%	2%
Amorphous form	80%	38%

Phase transitions

Polymorphic phase transitions

The process of transformation of one polymorph into another is a phase transition, which may occur on storage or during processing. If the phase transition is reversible, the two polymorphs are enantiotrops. If the phase transition is irreversible, the two polymorphs are monotrops and only one form is stable whatever the temperature. In case of solvates, the phase transitions are more complex since several compounds are involved. If a physical property of a crystalline substance is plotted *vs.* temperature, a sharp discontinuity occurs at the melting point. For amorphous substances, there is no melting point, and a change of slope occurs at the so-called glass transition temperature T_g. Below this temperature, the amorphous phase has certain properties of a crystalline solid (e.g. plastic deformation) and is termed 'glassy'. Above this temperature, the substance retains some of the properties of a liquid, e.g., molecular mobility, and is termed 'rubbery'. Above this temperature, the increase in molecular mobility facilitates spontaneous crystallization into the crystalline form with an exothermic enthalpy change after the glass transition. The amorphous state is thermodynamically unstable. The glass transition temperature, T_g, is lowered by water or other additives, facilitating crystallization.

All thermodynamically 'unstable' forms may behave like stable forms outside the phase diagrams for kinetic reasons. They are therefore called 'metastable' forms and may behave like stable forms. Therefore a limited polymorphic study is part of the salt selection. In the example of Fig. 10, the hydrochloride and the base were amorphous. The crystalline form of the base was obtained during the polymorphic study of the salt selection: After equilibration of a suspension the crystalline form

was obtained in the solid phase. The base which could be obtained crystalline and as result was chemically more stable was chosen for future development. The impurities may inhibit the transformation and the metastable form may not transform, giving rise to wrong selection. As the purification increases with the first batch the thermodynamic stable form appears. We had such an example for a drug candidate. The salt form had a better morphology for micronization. It was never possible to manufacture again this metastable form and the thermodynamic stable form had a needle shape habit and was difficult to be milled. In another case, the hydrochloride was rejected because of its hygroscopicity, the besylate was chosen. During development several forms including hydrates were identified for the besylate and a stable anhydrous hydrochloride could be obtained. In the last case from 12 salts showing hygro-

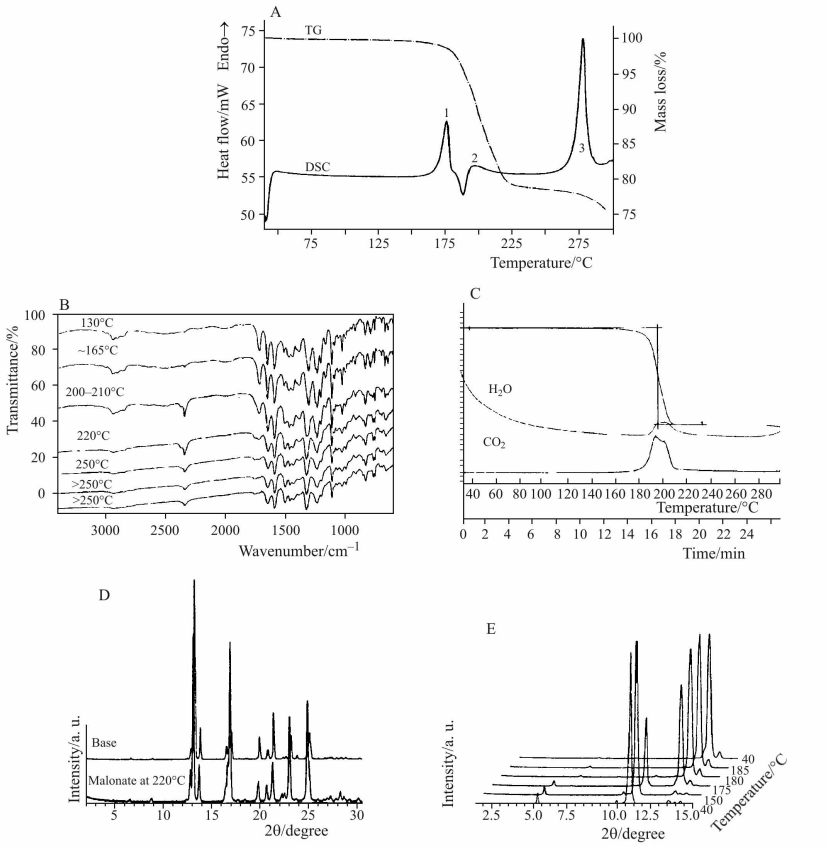

Fig. 11 Use of thermal analysis and combined techniques for the study of the thermal behaviour of a malonate salt. A: DSC and TG curves. B: FT-IR in the heating cell, bands of the base and of CO_2 appear. C: TG-MS experiment demonstrating the formation of water and CO_2 by decomposition of malonic acid. D: Comparison of the X-ray diffractograms of the base and of the compound obtained until 220°C. E: Temperature resolved X-ray diffraction scans following the decomposition

scopicity and polymorphic behavior, the base was chosen. Deeper polymorphic study revealed 3 forms of the base.

Another consequence of polymorphic transition is the chemical result of the stress testing if during this stress a polymorphic change occurs giving erroneous results (e.g. hydrate formation with high moisture, polymorphic change for testing at high temperatures).

Phase transitions observed by thermal analysis and combined techniques

The use of combined techniques is very efficient to understand results of pre-screening due to the very low amounts which can be studied with a lot of information. Figures 11 and 12 exemplify the use of TG-MS and combined techniques with X-ray diffraction or FT-IR for proper interpretation of the DSC curves. Figure 11 deals with a malonate salt [16]. The DSC scan with a dual melting would be wrongly attributed to a polymorphic behaviour if the TG curve had done parallel. The high amount of lost found by TG showed a decomposition which was easily attributed to the lost of malonic acid by TG-MS, FT-IR and X-ray diffraction with heating cell. The base was

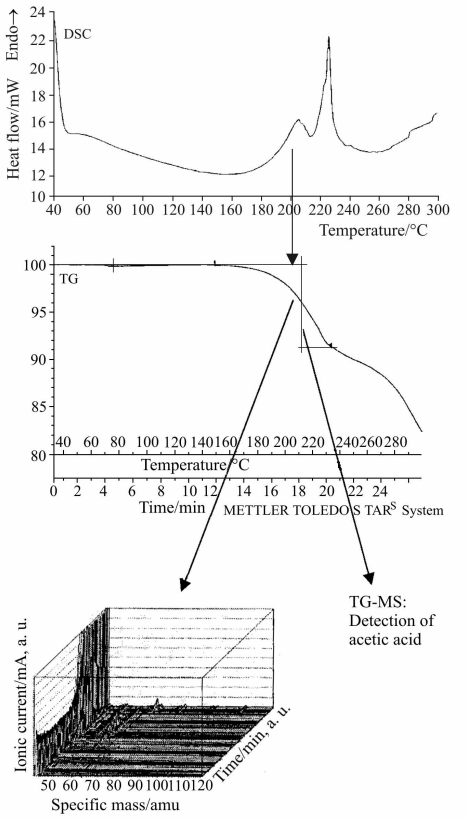

Fig. 12 Use of TG-MS for the interpretation of the DSC scan of an acetate which loses acetic acid by melting (pKa of the base 7.2)

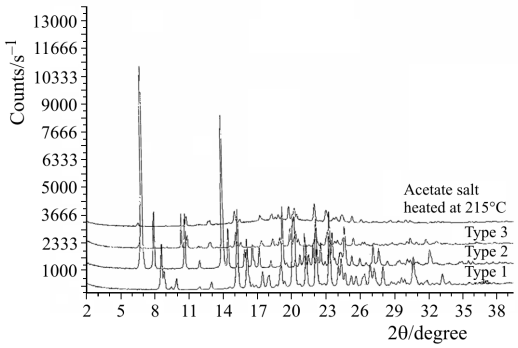

Fig. 13 Comparison of the base obtained in DSC (Fig. 12) with the 3 different polymorphs of the base

the product formed after recrystallization. The last DSC peak is the melting peak of the base and is not the melting peak of a polymorph of the malonate.

In Fig. 12, the acetate converts to the base as demonstrated by TG-MS and X-ray diffraction of the product compared to the 3 different forms of the base (Fig. 13). TG-MS is generally very helpful when salt forms contain high amount of entrapped residual solvents which play a role in the solubility results or which are bound as solvate or hydrated forms.

Change of salt form

Dissociation of the salt forms is often observed by analysing the undissolved residue as demonstrated in Figs 14 and 15. Figure 14 deals with a bi-methanesulfonate dihydrate, which dissolved, in a parenteral formulation. Upon storage a precipitate was observed. The monomethanesulfonate anhydrous was less soluble and was more stable in the formulation. In the case of Fig. 15, the salt was a hydrochloride and the

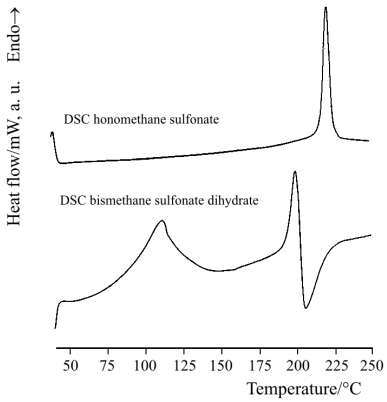

Fig. 14 Transformation of a soluble bi-methanesulfonate in the less soluble monosalt in a liquid formulation

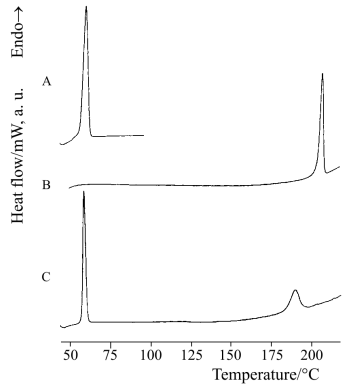

Fig. 15 Observation of the dissociation of a hydrochloride in the base in solubiliity experiments in water; A – DSC of the base, B – DSC of the hydrochloride and C – DSC of the insoluble crystals after vibration of an excess of hydrochloride with water

base was undissolved. In solubility experiments the amount of substance in solution increased with the amount of solid added resulting in a strong decrease of the pH, but the remaining base was undissolved and the solubility results completely erroneous.

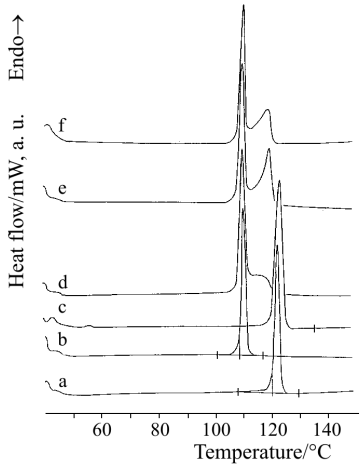

Fig. 16 DSC curves of mixtures of two salt forms of the base of an investigational drug substance with fumaric acid. a – fumarate salt (base:acid=1:1); b – fumarate salt (base:acid=3:2); c – mixture (1:1) of a and b, equilibrated in ethanol or 2-propanol; d – mixture (1:1) of a and b, ground; e – mixture (1:1) of a and b, placed directly in the sample pan; f – mixture (1:1) of a and b, equilibrated in ethyl acetate

Figure 16 shows the advantage of DSC for the study of the relative stability of two salts of fumaric acid with the drug substance in alcoholic solutions [28].

Figures 17 and 18 are example of the observation, which can be done when a phase transition occurs during the intrinsic dissolution experiment. The IDR curve of the hydro-

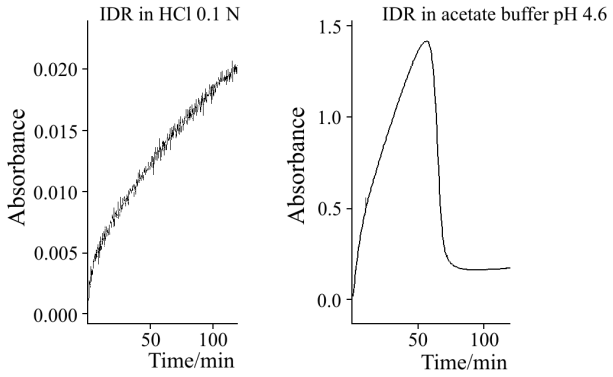

Fig. 17 UV absorbance measured curves during IDR experiment of a hydrochloride salt in HCl 0.1 N and acetate buffer. During the experiment in acetate buffer the hydrochloride transforms into a less soluble compound demosntrated to be the acetate (Fig. 18)

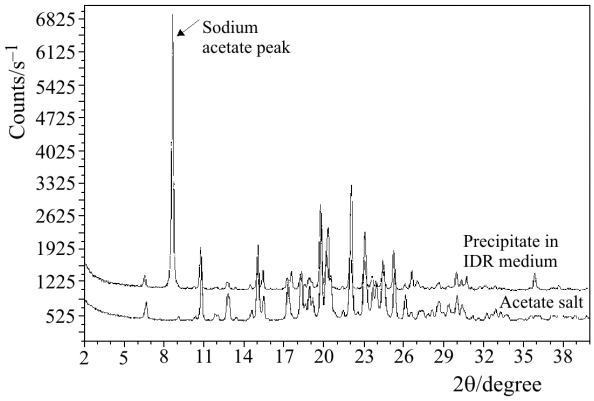

Fig. 18 Comparison of X-ray diffractograms of the acetate salt and the precipitate obtained in acetate buffer (Fig. 17)

chloride salt in HCl 0.1 N is a current behaviour. In acetate buffer the IDR is high and with the time an abrupt decrease of the curve is observed as result of a phase transition in a new entity. The X-ray diffraction (Fig. 18) confirms the formation of the acetate salt form. This salting out effect of buffers should be investigated in the salt selection.

The last example deals with a hydrochloride, which partially transforms into the base (pKa=4.9) in a gelatine capsule [28]. Figure 19 shows the mixture of drug substance with lactose after storage at 40°C/75% RH in accelerated conditions as required by ICH [29]. Needles sticking to the gelatine wall were growing in these storage conditions. The DSC curves of some needles are identical with the DSC of the base (Fig. 20). FT-IR microscopy could confirm the findings.

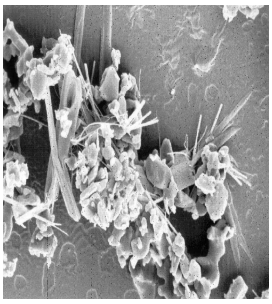

Fig. 19 SEM of a powder formulation in a gelatin capsule. After storage in accelerate conditions, needles appear due to the partial dissociation of the hydrochloride salt into the base

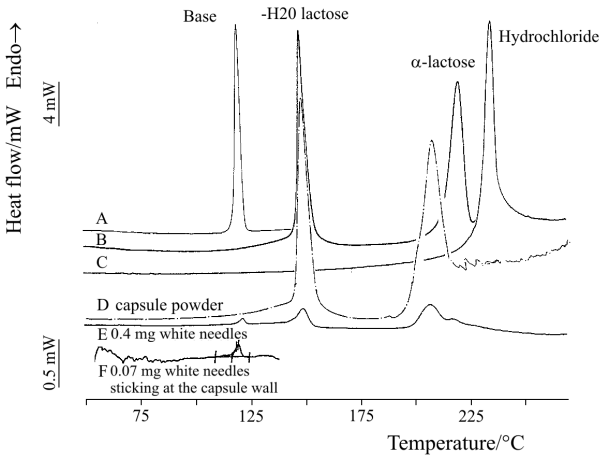

Fig. 20 DSC study of the mixture lactose, hydrochloride salt. Needles are pure base

Conclusions

The selection of the salt candidate requires a proper characterisation of the solid-state including chemical analysis, polymorphic behaviour and feasibility in different solvents as well as targeted studies for the dosage form. The decision takes into account several criteria. An example of a selection is given in Table 7. The 6 candidates were feasible and of good crystallinity. Three salt candidates showed a polymorphic behavior in the selected study. Two were hygroscopic. The selected hydrogen maleate had a solubility of 0.8%, was not hygroscopic, was monomorphic and was acceptable for stability and compatibility with excipients.

Thermal analysis, microcalorimetry and combined techniques play an important role in such studies for helping the manufacture of samples, for discriminating hydrates, solvates and amorphous samples from stable forms and for the characterisation of suitable salt forms.

Table 7 Results of screening of salts of a drug

Item	Base	hfu	hml	ch	hta	hmo
Melting/°C	98	196	161	251	121.5	71.7
DSC purity	99%	99%	>99.9%	–	–	–
Hygroscopicity	no	no	no	yes	yes	no
X-ray	cryst.	cryst.	cryst.	cryst.	cryst.	cryst.
Polymorphism behaviour	mono	mono	mono	poly	poly	poly
Feasibility	good	good	good	good	good	good
Solubility						
water	<0.01%	0.5%	0.8%	0.8%	>3%	>3%
HCl 0.1 N	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%
pH 1% water	8.3	3.6	4.6	5.9	3.9	4.2
Stability bulk						
96 h Xenon	0%	0%	0%	2–5%	0%	0%
1 week 70°C	0%	0%	0%	<2%	0%	10–20%
1 w.70°C/95 RH	0%	0%	0%	<2%	>20%	10–20%
Methanol	0%	0%	0%	10–20%	<2%	0%
water	>20%	>90%	>20%	>20%	>90%	>20%
Compatibility						
mixture 1	0%	>20%	0%	<2%	0%	0%
mixture 1/95 RH	>90%	>20%	>20%	>20%	>90%	10–20%
mixture 2	2–5%	<2%	<2%	0%	10–20%	2–5%
mixture 2/95 RH	5–10%	>20%	5–10%	10–20%	>20%	10–20%
Particle size 99%/μm	115	50	17	–	–	–

* * *

Many thanks to my colleagues for their contribution: M. Bellus, S. Garnier, C. Golbronn, M. Mutz, S. Pfeffer, P. Piechon and F. Zaman.

References

1 Handbook of Pharmaceutical Salts, Properties, Selection and Use, P. H. Stahl and C. G. Wermuth (Eds), IUPAC, Wiley-VCH, Verlag Helvetica Chimica Acta, Zürich 2002.
2 S. M. Berge, L. D. Bighley and D. C. Monckhouse, J. Pharm. Sci., 66 (1977) 1.
3 L. D. Bighley, S. M. Berge and D. C. Monkhouse, Salt forms of drugs and absorption. Encyclopaedia of pharmaceutical Technology, (Eds: J. Swarbrick, J. C. Boylan) Vol. 13, Marcel Dekker, New York 1996, p. 453.
4 P. L. Gould, Int. J. Pharm., 33 (1986) 201.

5 J. I. Wells, Pharmaceutical Preformulation, Ellis Horwood Series in Pharmaceutical Technology, Chichester 1988.
6 R. J. Bastin, M. J. Bowker and B. J. Slater, Organic Proc. Res. & Dev., 4 (2000) 427.
7 J. Haleblian, J. Pharm. Sci., 64 (1975) 1269.
8 D. Giron, Labo-Pharma, Probl. Techn., 307 (1981) 151.
9 S. R. Byrn, Solid State Chemistry of Drugs, Academic Press 1982.
10 D. Giron, Thermochim. Acta, 248 (1995) 1.
11 H. G. Brittain, 'Polymorphism in Pharmaceutical Solids', Ed., Marcel Dekker 1999.
12 D. Giron, S. T. P. Pharma, 4 (1988) 330.
13 W. D. Walkling, W. R. Sisco, M. P. Newton, B. Y. Fegely, H. N. Plampin and F. A. Chrzanowski, Acta Pharm. Technol., 32 (1986) 10.
14 International Conference on Harmonization (ICH), Guideline Specification Q6A 1999.
15 D. Giron, J. Therm. Anal. Cal., 64 (2001) 37.
16 D. Giron, J. Therm. Anal. Cal., 68 (2002) 335.
17 D. Giron and D. J. W. Grant, in Handbook of Pharmaceutical Salts, Properties, Selection and Use, Ch. 3 p. 42.
18 D. J. W. Grant and H. Brittain, Physical Characterization of Pharmaceutical Solids, (Ed.) H. G. Brittain, Marcel Dekker 1995, p. 321.
19 A. Avdeef, Pharm. Pharmacol. Commun., 4 (1998) 165.
20 R. N. Jashani and P. R. Byron, Int. J. Pharm., 130 (1996) 13.
21 D. Giron and C. Goldbronn, Analysis, 7 (1979) 109.
22 D. Giron, C. Goldbronn, M. Mutz, S. Pfeffer, P. Piechon and P. Schwab, J. Therm. Anal. Cal., 68 (2002) 453.
23 W. D. Walkling, B. E. Reynolds, B. Y. Fegely and C. Janicki, Drug Dev. Ind. Pharm., 9 (1983) 809.
24 D. Giron, Mol. Cryst. Liq. Cryst., 161 (1988) 77.
25 B. C. Hancock and G. Zografi, J. Pharm. Sci., 86 (1987) 1.
26 M. Anberg, C. Nyström and S. Castensson, Int. J. Pharm., 81 (1992) 153.
27 M. Koenigbauer, J. Pharm. Res., 11 (1994) 777.
28 D. Giron, PSTT, 1 (1998) 239, 262.
29 International Confederation of Harmonisation (ICH) Guideline 'Stability Testing of New Drug Substances and Products', ICHQ1A.