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Impact of downstream processing on crystal quality during the precipitation of a pharmaceutical product

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A B S T R A C T

In pharmaceutical industries, active pharmaceutical ingredients (API) are made of crystals whose properties must be controlled because they influence the end-use properties of the drug. Even if crystal quality is mainly determined during the precipitation step, downstream processing also has an influence. In this study, the influence of washing on the crystal size and shape was analyzed. For the API being considered, different impurities have to be removed from the final suspension by filter cake washing. The efficiency of the washing steps was measured by different types of characterization on the solid phase (differential scanning calorimetry, scanning electron microscopy, and size distribution) and on the remaining filtrate (concentration of impurities). A second component also coprecipitates with the API. A specific study has been carried out on the withdrawal of this by-product and on its impact on the evolution of the crystalline form during washing steps. It was found that three filter cake washings allow us to remove all the impurities and to obtain a pure crystalline form.

1. Introduction

Filter cake washing is a common process in the field of solid–liquid separation with the aim of removing impurities from the slurry; the impurities have to be removed until the product has reached a certain degree of purity. This is particularly the case in the pharmaceutical industry. Generally, the active pharmaceutical ingredient (API) crystals suspension is obtained by a crystallization process followed by filtration and drying processes. During filtration, impurities entrapped in the mother liquor around the crystals are displaced by clean washing liquor. Two mechanisms can be involved in washing: the dilution washing and the displacement process [1]. During the dilution washing process, the suspension is mixed with clean liquor to allow enough contact time and mass exchange due to convection by agitation. This is an efficient method but the main drawback is the high washing liquor consumption to achieve purification. On the contrary, the displacement process allows only a limited time of contact between the mother and washing liquor by pouring the liquid through the filter cake. The purification is then achieved through the displacement of the mother liquor by the penetrating washing liquor. In all cases, after filtration, dissolved impurities might be present in the remaining liquid or adsorbed on the particles surface [2,3]. That is

why multi-stage washing has often been done in order to obtain good purity.

The API considered in this study is produced by the precipitation of the sodium conjugate base of this API with hydrochloric acid. Sodium chloride (NaCl) is then formed as a by-product of the precipitation. According to the high solubility of NaCl in water (~360 g/L at 20 °C), it should not precipitate, but it is still present in the wet crystals after filtration. It must then be removed from the final crystals by washing and, in the case of our study, will play the part of a tracer which characterizes the efficiency of the washing steps. However, the studied API has a non-negligible solubility in water. Thus, dilution washing leads to API loss due to the partial dissolution of crystals in the wash liquor [4]. So, wash efficiency has to be studied. Furthermore, by removing impurities, the crystalline form of the API can also be changed. The eventual change of crystals during washing will be studied in this work.

This work could be a classical study on the evolution of the crystal quality during the washing process, but for the API being considered, sodium chloride is not the single impurity of the suspension. Indeed, due to an incomplete chemical reaction step preceding the precipitation of the API, a remaining reactant coprecipitates with the API, and was identified as leucine. The chemical equation could then be schematized as:

Sodium conjugate bases(of API and leucine) $+ HCl \rightarrow API + Leucine + NaCl$

Consequently, the objective of washing is not only to remove sodium chloride, but also to try to eliminate the leucine crystals by

studying the impact of the washing procedure on the structure of the crystals.

2. Materials and methods

2.1. Materials

Two types of initial API solutions were used in this study to perform precipitation: the industrial type (called "true" in the following sections), which contains impurities and by-products, and the synthetic type. The latter solution had been synthesized directly by dissolving the final API crystals, provided by Pierre Fabre Company, in a sodium hydroxide solution. The advantage of these experiments, in comparison with industrial solutions, is the control over the concentration of product, without the problem of reproducibility.

The automated reactor RC1 from Mettler Toledo (see Fig. 1) was chosen to perform the precipitation step by pouring the acid solution in the initial API solution. This reactor enables us to control the temperature, stirrer velocity and pumping rate, and to record pH values. It assures the reproducibility of the precipitation step, so that the study of the impact of a single parameter during precipitation could be carried out. All the precipitation experiments were carried out in the same conditions. Only temperature was varied.

After precipitation, the suspension is filtered on a sintered glassware filter (made of borosilicate, with a volume of 500 mL, a diameter of 9.5 cm and a diameter of pores of 10 μm (porosity 3)) from Robu-glas filter company. Two types of washing procedures were carried out. For the first one, the cake was removed from the filter and put back into the reactor at the chosen temperature with 150 mL of clean wash liquor (here demineralised water) during 15 min under stirring. The suspension is then filtered again. After preliminary studies which determined wash efficiency (see "Wash efficiency" section), it was decided to repeat this operation three times. For the second washing procedure, the same quantity of washing liquid was simply poured through the filtered cake.

Filtrates and some wet crystals were isolated at each step of washing in order to be analyzed. The final wet crystals were dried overnight in a ventilated oven at 50 °C.

Fig. 1. RC1 unit: stirred batch reactor equipped with two feeding pumps and temperature and pH sensors.

2.2. Characterization of the products

2.2.1. Liquid phase analyses

When a multistage dilution washing is performed, each filtrate was isolated in order to measure the efficiency of the considered washing step. As previously mentioned, the main by-product of the precipitation is sodium chloride (NaCl) and the objective of washing is to remove it. Which means that the purity of the final product is simply linked to the concentration of the entrapped NaCl. In order to quantify it, filtrate samples were analyzed in inductively coupled plasma (ICP) (Ultima 2, from Horiba Jobin Yvon) by dosing the concentration of sodium, and thus of sodium chloride.

2.2.2. Solid phase characterization

As the product studied is an API, constant crystalline quality has to be assured. In order to check the purity and the structure of the crystalline particles obtained, several characterizations were also made on the solid phase.

2.2.2.1. Crystal shape and size distribution. The shape of the crystals could give relevant information on the state of crystallinity after precipitation. It can also help in understanding size distribution measurements. The general shape of crystals was observed using a scanning electron microscopy (SEM). Crystals produced in the laboratory before and after washing steps were analyzed.

The particle size distribution was determined by using a laser sizer MasterSizer 2000 type from Malvern Instruments.

The results of the size distribution measurements are highly dependent on the fluid in which the crystals are suspended. When this fluid is a liquid, saturated aqueous solution of API has been chosen. Indeed, the product is slightly soluble in water (8 g/L at 20 °C). The choice of a saturated solution avoids the partial dissolution of crystals.

2.2.2.2. Crystalline form. To understand how washing steps could influence the crystalline form of final API particles, differential scanning calorimetry (DSC) (Q2000, from TA Instruments) measurements were carried out. The melting point of components can then be determined on samples before and after each washing step. The method chosen was scanning from 0 °C to 200 °C at a temperature rate of 5 °C/min, in sealed aluminium pans. However, in order to obtain a better resolution, some samples were also analyzed at a temperature rate of 1 °C/min.

2.2.2.3. Detection of residual presence of NaCl in crystals. After drying, some final crystals are also dissolved in demineralised water in order to determine the residual presence of sodium in crystals after the washing steps. This could characterize the final purity of API crystals after precipitation, washing and drying steps.

3. Results and discussion

3.1. Wash efficiency

Several parameters are used to characterize the wash efficiency and the mechanisms of washing [5]. The first parameter is the concentration ratio C^* which is the ratio of the concentration of the impurity, here sodium chloride, after (C) and before (C_0) washing (Eq. (1)) in filtrates. It will indicate the degree of purity.

$$C^* = \frac{C}{C_0} \qquad (1)$$

The second parameter is the wash ratio W which characterizes the specific amount of wash liquor required to wash the cake. It is the ratio of the volume of wash liquor V'_{wl} over the volume of the wet cake V_c (Eq. (2)). V_c has been experimentally obtained (160 mL) by
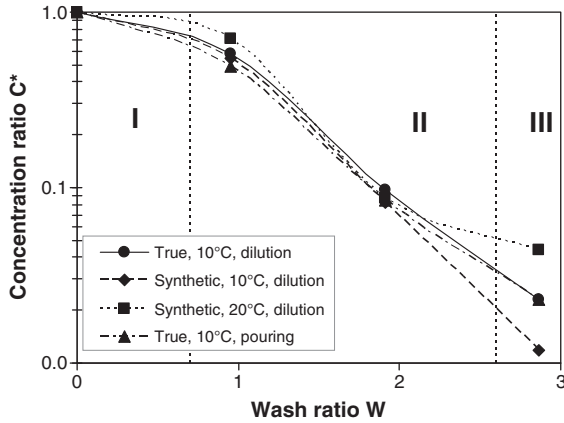
Fig. 2. Wash diagram of the API for different types of experiments carried out. Zone I, ideal displacement regime; zone II, dispersion regime; zone III, diffusion regime.

Fig. 3. SEM of crystals before washing.

measuring the height and the diameter of the cake in the filter. As variations were very small, it was considered as a constant. At each washing, the same volume of wash liquor ($V_{wl} = 150$ mL) is used. So, the volume of wash liquor V'_{wl} is the volume corresponding to the sum of the wash liquor added at each washing. The value of W increases after each washing as explained in the equation below:

$$W = \frac{V'_{wl}}{V_c} = \frac{\sum V_{wl}}{V_c} \tag{2}$$

By plotting the concentration ratio as a function of the wash ratio it is possible to compare different results in a wash diagram. In our case, the wash diagram was obtained in Fig. 2 for different types of experiments: true or synthetic experiments, different temperatures of precipitation (10 °C and 20 °C) and different types of washing (dilution washing in a vessel or directly in the filter). The operating conditions of these experiments are reported in Table 1.

The results in Fig. 2 show that the washing curve behaviour in each case is quite similar. This means that washing efficiency was similar in all cases studied, in particular, when two kinds of washing were carried out. Washing directly on the filter, thus with a small contact time of the solvent with the cake, is enough to remove impurities. The kinetics of dissolution of the impurity (here sodium chloride) is then fast and the main mechanism of washing is the displacement process whatever the origin of the initial solution.

In the case of washing directly on the filter by pouring the wash liquor, different regimes of washing can also be observed on the wash
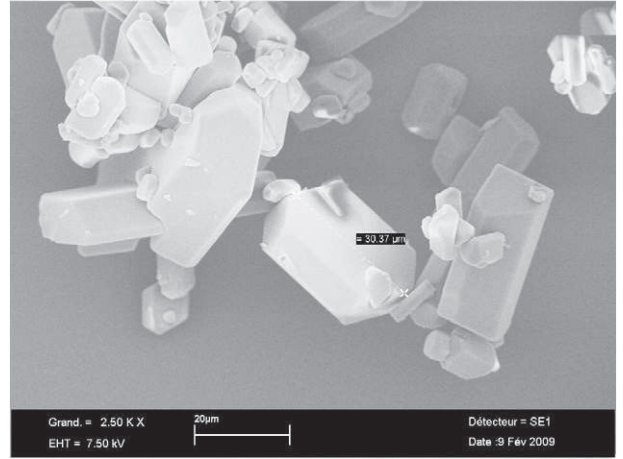
diagram. Indeed, to understand the mechanisms of washing, the wash diagram can be split into three regimes: the ideal displacement, dispersion and diffusion regimes [5]. In the first regime (Fig. 2, I), the mother liquor is displaced by incoming wash liquor as a piston flow. After that, the dispersion regime (Fig. 2, II) is predominant because the flow of the wash liquor is no longer homogeneous due to dispersion. The limit of this regime is obtained when the impurity concentration reaches a constant level after a certain quantity of wash ratio. This is the third regime, when wash effect disappears in the diffusion regime (Fig. 2, III). Adsorption of impurity on the API crystal surface can be this limiting factor and further washing would not improve purity by much.

A compromise also has to be chosen between purity and mass loss during washing because the API is rather soluble in water. Three washing steps allow us to remove a large portion of the sodium, and we can notice a stabilization of the concentration after the third washing step.

Moreover, the washed crystals were also analyzed by ICP after full dissolution in water. A proportion of less than 0.05% of sodium element was found in final crystals after three washings. A wash ratio of 3 is then sufficient to obtain a good purity.

3.2. Crystal quality

Beyond purity, crystal quality is paramount and properties built during the precipitation have to be kept during the following steps of washing, filtration and drying.
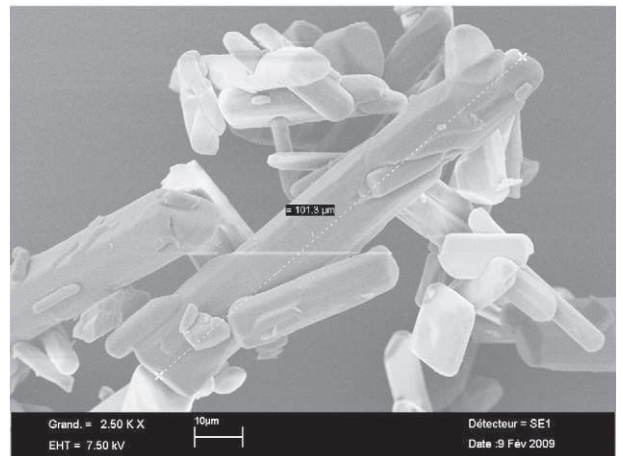
Table 1
Sodium concentration in filtrates for different washing experiments.

Type of initial solution	Temperature (°C)	Type of washing	Na concentration in filtrate (mol/L)	C^*	W
True	10	Dilution	0.776	1.000	0.00
			0.544	0.701	0.96
			0.068	0.087	1.91
			0.034	0.044	2.87
Synthetic	10	Dilution	0.859	1.000	0.00
			0.494	0.575	0.96
			0.084	0.097	1.91
			0.020	0.023	2.87
Synthetic	20	Dilution	0.783	1.000	0.00
			0.430	0.549	0.96
			0.064	0.082	1.91
			0.009	0.012	2.87
True	10	Pouring	0.833	1.000	0.00
			0.407	0.488	0.96
			0.070	0.084	1.91
			0.019	0.023	2.87

Fig. 4. SEM of crystals after washing.

Distribution granulométrique des particules

— Before washing, vendredi 16 janvier 2009 15:22:50
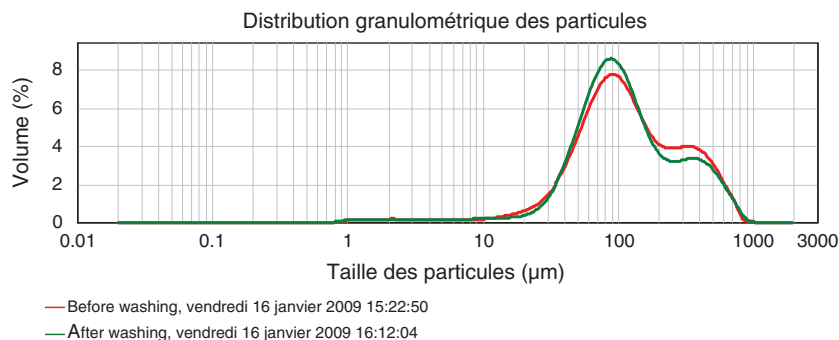— After washing, vendredi 16 janvier 2009 16:12:04

Fig. 5. Granulometric analyses of samples by the wet method.

Fig. 3 shows SEM pictures of crystals before washing of a true experiment sample. Crystals have smooth faces and defined edges. Furthermore, thin or large stick-like crystals and prismatic crystals can be observed in this picture. This could be linked with the formation of different crystals. In order to check the hypothetical presence of sodium chloride in the API crystals, complementary energy-dispersive X-ray (EDX) spectroscopy analyses were carried out on this sample in order to determine the sodium composition in the crystals. No sodium element was found. Thus different crystal shapes are not linked with the formation of sodium chloride.

On the contrary, crystals after washing steps, shown in Fig. 4, seem to be composed of only longer stick-like particles which are the known shape of the API. Furthermore, they have eroded edges and their faces are less regular. This means that washing has not only withdrawn sodium chloride, but has also dissolved one type of solid particles and rounded the surface of the produced crystals. Consequently, improving crystal purity by washing also has an impact on the crystal aspect.

Particle size distributions (PSD) were also measured on samples of true experiments before and after washing (Fig. 5). Size measurements results cannot be linked with an actual size of particle, but only give an idea of the PSD. It can be observed that the PSD is very large (from 1 to 1000 μm) and that agglomerates exist. Nevertheless, PSD curves are similar but are not representative of the actual elementary particles.

3.3. Crystalline form evolution after washing steps

Beyond the purity or shape of crystals, crystalline form is an important parameter that has to be controlled and which may change during washing. Fig. 6 shows the evolution of DSC spectra at each washing step for true experiments. The spectrum of the pure API has also been added for comparison purposes. Before washing, the peak was very large and a shoulder is clearly visible. After one washing step, the shoulder remains, but the onset point has shifted from 187.4 °C to 184.5 °C. The same phenomena can be observed in the last spectra of Fig. 6. After the third washing step, DSC peaks shifted to an onset point of 181 °C. This value is close to the onset point of the pure product. Another remark is that peaks were thinner after washing. This behaviour revealed a higher crystalline purity due to washing steps. The same phenomena are observed when the washing steps were performed with saturated solution of product.

In order to check a possible evolution of the solid particles into another form, maturation was performed in the reactor on the slurry of a true experiment before washing for 72 h. No influence on the DSC evolution of peaks was observed. So it seems that washing enables to remove impurities but also to move the product towards a unique crystalline form and has influence on crystalline purity. Therefore, the issue was to identify the impurity responsible for the DSC evolution and to explain how washing enables the evolution.
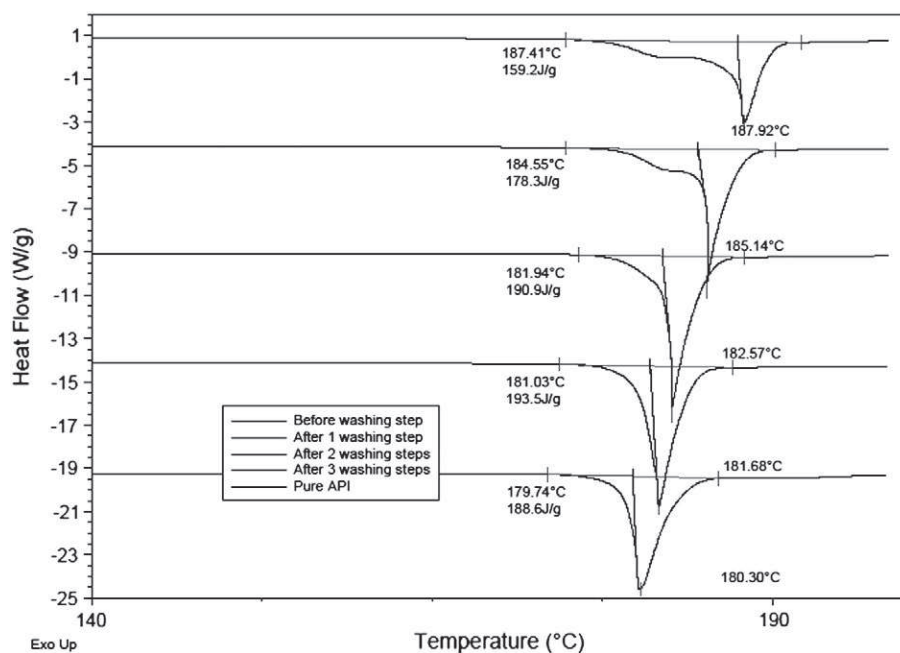

Fig. 6. DSC analyses of crystal samples after precipitation filtration and successive washing.

Table 2
DSC onset point of samples before and after washing, according to impurities added.

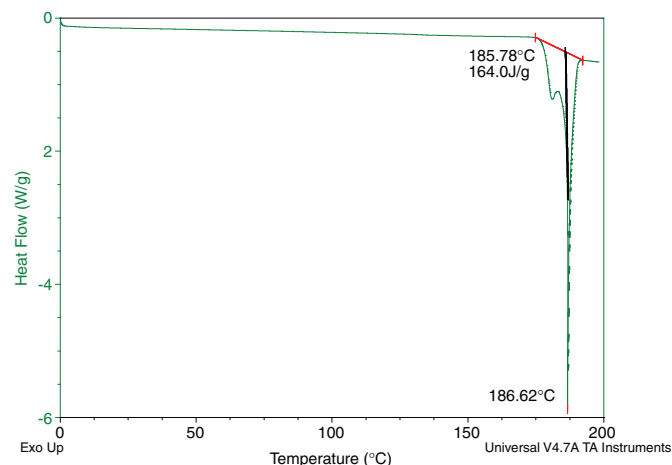| Impurity added		Before washing		After washing	
NaCl	Leucine	DSC peaks	T onset (°C)	DSC peaks	T onset (°C)
0%	0%	1	182.07	1	180.94
10%	0%	1	181.23	1	180.70
0%	5%	2	189.29	1	180.10
10%	5%	2	185.78	1	180.49

Fig. 7. Example of DSC spectrum before washing in the presence of leucine (10% leucine, 5% NaCl).

Considering the industrial process, leucine could be one possible by-product. So, in order to elucidate the crystalline product coprecipitated with the API, synthetic precipitation experiments were performed as previously but leucine was intentionally added as an impurity to the initial solution. Crystals before and after washing steps were then analyzed by DSC. Results are reported in Table 2 and an example is given in Fig. 7. When leucine was not added, only one peak is observed in DSC spectra before washing. However, in the presence of leucine, peaks before washing are wider and have shifted to higher temperatures. These spectra are similar to those obtained with true solutions. The behaviour of true solutions has then been well synthetically reproduced.

The DSC evolution was explained by the presence of leucine. Leucine acts as a doping component. Similar phenomena were observed by Srividya [6]. However, the melting point of pure leucine is 293 °C. This melting point cannot be observed by DSC because of the lower melting point of the API. It seems that a mixed precipitate was formed between leucine and the API in the conditions of our experiments. These results can be compared to the similar effects observed previously by Vemavarapu [7] for aspirin with salicylic acid. These two components form a eutectic with a modified melting point. In the case of the API studied in this work, a coprecipitation of leucine and API occurs, but leucine is removed during the washing steps. Thus, this is not an ordered solid solution, i.e., a new crystal form of the composite, but a solid solution of the two components.

In order to check this hypothesis, mixtures of dry pure crystals of leucine and API were performed in different ratios. They were not ground together but simply mixed with a spatula in order to avoid the formation of an amorphous product. Mixtures, for several molar ratios (from 0.5% to 20% of leucine), were analyzed on DSC and results are reported in Fig. 8.

The presence of leucine, even with a very low ratio of 0.5%, generates the same type of DSC spectrum as the one obtained for samples before washing steps. For higher leucine ratios, peaks are larger and the shift remains. However, no quantitative analyses can be obtained with these results because shifts do not seem to be proportional to the leucine ratio. DSC analyses are thus only a qualitative way to prove the withdrawal of leucine.

As simple physical mixtures reproduce well the behaviour of experimental samples and as washing removes leucine, we can conclude that leucine is not entrapped into the lattices of the drug host.

4. Conclusions

This paper deals with experimental investigations on filter cake washing as a unit operation in solid–liquid separation processes in the particular case of an industrial API. Wash efficiency, using sodium
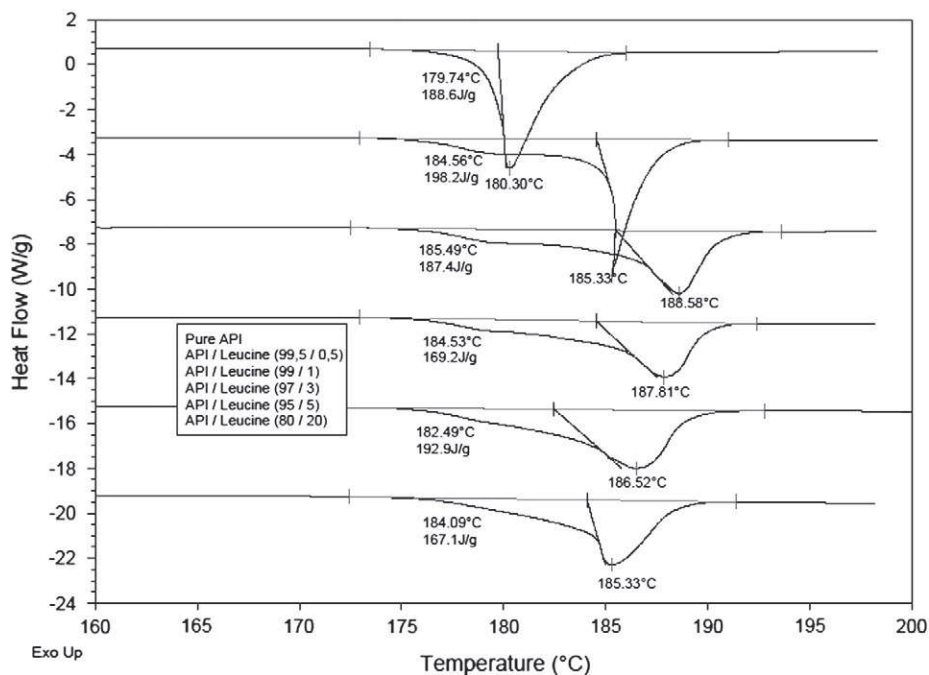

Fig. 8. DSC spectra of mixtures of API and leucine crystals in molar ratios.

chloride as a natural tracer, has thus been studied. Taking into account the partial dissolution of the API in the wash liquor, washing mechanisms were explained and a wash ratio equal to three has been proved to be a good compromise.

The particular study of the crystalline form also permitted to identify the coprecipitation of leucine with the API and its effect on the crystalline form. It was shown that washing procedure enables to dissolve leucine crystals and purify API crystals. X-ray analyses will be carried out in order to understand the evolution during washing steps and to link it with crystal structure.

Acknowledgements

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