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Evaluation of drug physical form during granulation, tabletting and storage

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Abstract

An active pharmaceutical ingredient (API) was found to dissociate from the highly crystalline hydrochloride form to the amorphous free base form, with consequent alterations to tablet properties. Here, a wet granulation manufacturing process has been investigated using in situ Fourier transform (FT)-Raman spectroscopic analyses of granules and tablets prepared with different granulating fluids and under different manufacturing conditions. Dosage form stability under a range of storage stresses was also investigated.

Despite the spectral similarities between the two drug forms, low levels of API dissociation could be quantified in the tablets; the technique allowed discrimination of around 4% of the API content as the amorphous free base (i.e. less than 1% of the tablet compression weight). API dissociation was shown to be promoted by extended exposure to moisture. Aqueous granulating fluids and manufacturing delays between granulation and drying stages and storage of the tablets in open conditions at 40 °C/75% relative humidity (RH) led to dissociation. In contrast, non-aqueous granulating fluids, with no delay in processing and storage of the tablets in either sealed containers or at lower temperature/humidity prevented detectable dissociation.

It is concluded that appropriate manufacturing process and storage conditions for the finished product involved minimising exposure to moisture of the API. Analysis of the drug using FT-Raman spectroscopy allowed rapid optimisation of the process whilst offering quantitative molecular information concerning the dissociation of the drug salt to the amorphous free base form.
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Keywords: Active pharmaceutical ingredient; Granulation; Tabletting; Storage; Raman spectroscopy; Process control

1. Introduction

Whilst several strategies exist for improving pharmaceutical powder flow, granulation remains one of the most popular approaches. Both dry and wet granulation methods have some advantages and disadvantages, but for drugs requiring relatively high loading, then the wet process is usually the method of choice (assuming adequate drug stability) as it can provide particles with superior processing characteristics. In the study reported here, a wet granulation process was optimised for a new chemical entity, Compound A, which is a hydrochloride salt of an amine (Fig. 1).

The hydrochloride salt, with a pK_a of 3.8, showed a tendency to dissociate in water to form the free base, typically found as an amorphous oil in water or a waxy solid when dry. Thus, attempts were made to acidify an aqueous granulation fluid; employing a binder so-

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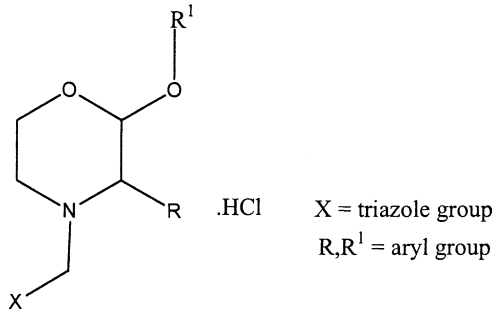

Fig. 1. Structural formula of Compound A.

lution with a pH of around 1.5 inhibited the dissociation but raised other processing problems. Alternative binder solutions were thus sought. Powders granulated using absolute ethanol, whilst acceptable, did not bind as effectively as those prepared from aqueous systems. Combining absolute ethanol with water in various ratios provided appropriate granule and drying properties, but concerns remained over possible dissociation arising from the use of a water-containing binder fluid. One further concern with the process arises from possible delays during processing and hence increased exposure times of the hydrochloride salt to the water in the granulating fluid. Clearly, during manufacturing cycles there may be occasions where granules are stored on a short-term basis prior to drying. Thus, the effect of holding time on the dissociation of the salt to the free base was of interest. Finally, in order to ensure that the process was optimised, a stability assessment of granules formed using different binder fluids was performed; since the free base was less stable than the salt form, early detection during processing could reduce the need to wait several months whilst stability studies were performed.

Various analytical techniques were used in attempts to discriminate between the hydrochloride salt and the free base. One particular difficulty arose from the relatively low levels of dissociation found in most of the samples (typically less than 1% of the tablet compression weight), and from the presence of other excipients in the granules. Thus, techniques such as X-ray diffractometry that assess the degree of crystalline material in the samples as a measure for the dissociation to the amorphous free base were ineffective and chromatographic separations were equally ineffective as the salt and base forms were indistinguishable. However, using differential scanning calorimetry it is possible to confirm the presence of the hydrochloride salt, which possesses a strong melting endotherm at 238 °C, but the amorphous free base can only be assumed by the absence of this feature. Due to the structural similarities of the base and the hydrochloride, infrared spectra of the two forms were nearly identical differing only by the presence of an N–H stretching mode around 3400 cm^{-1} seen in the hydrochloride and not the free base. The spectrum of the base showed considerably broader spectral features than that of the hydrochloride and so detection of low levels of base within the hydrochloride data was impossible.

Raman spectroscopy is a tool that is becoming more widely used in pharmaceutical research studies (Bugay, 2001). Generating data complementary to that from infrared spectroscopy, the technique provides unique capabilities in that minimal sample preparation is required, data can be collected rapidly and non-destructively and water tends to have minimal interference with the vibrational modes from most drugs. Whilst most literature reports focus on the use of Raman spectroscopy to characterise a drug, it is a technique that has been shown to provide accurate quantitative results for powder blends (Deeley et al., 1991; Tudor et al., 1993; Langkilde et al., 1997; Niemczyk et al., 1998a, b), for determining the amorphous content of a powder (Taylor and Zografi, 1998) and in determining drug form in tablets (Taylor and Langkilde, 2000). This technique is also attracting interest for in-process monitoring and control (Wang et al., 2000; Lewis, 2001), but the potential for using Raman spectroscopy as a tool in process development has yet to be fully exploited.

Here, we report an application of Raman spectroscopy to quantify the hydrochloride to free base dissociation during development of a granulation formulation, considering binder fluid selection, holding time prior to granule drying and granule stability under various stressed conditions as well as determining the degree of dissociation in tablets.

2. Materials and methods

2.1. Active pharmaceutical ingredient (API) powders

Compound A was synthesised as the hydrochloride salt. The free base was prepared by stirring this salt

in a mixture of 0.2 M phosphate buffer (pH 9) and chloroform (1:1, v/v) for 4 h. The organic layer was then recovered, washed with pH 9 buffer, then twice with water before drying over anhydrous sodium sulphate. The solvent was then evaporated using a stream of nitrogen. Final drying under vacuum provided a white amorphous solid with formation of the free base confirmed by the loss of a melting endotherm previously given by the hydrochloride salt at 238 °C.

2.2. Granules

Granules containing 4 and 20% (w/w) Compound A were prepared. Other excipients included within the formulation were butylated hydroxyanisole, microcrystalline cellulose (Avicel PH101), hydroxypropyl cellulose (Klucel EXF), croscarmellose sodium (Ac-di-sol), lactose monohydrate and magnesium stearate. Absolute ethanol and 96 and 90% (v/v) ethanol/purified water binder fluids were used.

2.3. Active tablets

Tablets containing both 10 and 50 mg of API (as 10.7 and 53.4 mg of the hydrochloride salt) in 250 mg compression weights were prepared.

2.4. Placebo tablets

Analytical placebos were necessary and they were made to contain the same proportions of excipients as within the active tablets.

2.5. Preparation of standards

Binary mixtures of the hydrochloride and free base forms of Compound A were prepared. For development of the Raman method, binary mixtures of 25:75, 50:50 and 72:28% (w/w) hydrochloride:free base were prepared. For determinations of API form within tablets, low levels of base were expected and hence a calibration set comprising relatively low free base compositions was utilised ranging from 97.5 to 80% hydrochloride. Additionally, two mixtures whose content was unknown to the operator were prepared for validating the calibration curve.

2.6. Pharmaceutical processing

Granules and tablets with both 10 and 50 mg drug loadings were prepared according to the following scheme. A solution of butylated hydroxyanisole was prepared in the granulating fluid (ethanol or ethanol/ water solutions). Batches of microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, lactose monohydrate and Compound A were blended in a high shear mixer/granulator (Fukae Powtec).

The powder blends were granulated with the butylated hydroxyanisole solutions, adding further granulating fluid if necessary. The wet granule sublots were screened and dried in a fluid bed dryer (Aeromatic Strea-1) with an inlet temperature of 40 °C. A sample of the dried granule sublots was then analysed for dissociation with the remainder being tabletted.

Prior to tabletting, the granules were milled using a cone mill, and then lubricated with sieved magnesium stearate using an Apex drum blender. The lubricated granules were tabletted using a Manesty F3 Press. Finally, the tablets were film coated using an aqueous suspension of hydroxypropyl cellulose, hydroxy propyl methylcellulose, talc and titanium dioxide in an Aeromatic Strea-1 with an inlet temperature of approximately 60 °C. Analytical placebo granules and tablets were prepared in the same manner using the same proportion of excipients but without the active ingredient.

2.7. Raman spectroscopy

FT-Raman spectra were obtained using a Bruker FRA 106 Raman module on an IFS 66 optics bench. Sample excitation was effected using an Nd:YAG laser operating at 1.064 μm and the scattered radiation from the samples was collected with a liquid nitrogen-cooled germanium diode detector, with an extended spectral bandwidth covering the range 50–3500 cm^{-1}. The laser power at the sample was approximately 400 mW, spectra are the average of 200 scans and all spectra were collected at 4 cm^{-1} resolution. Wavenumber positions, calibrated against an internal laser, had an accuracy greater than ±1 cm^{-1}, and the spectral response was corrected for white light. For analysis, powder/granule samples were

placed into a stainless steel sampling cup whereas tablets were analysed directly.

2.8. Data manipulations

Data manipulations used commercially available OPUS spectroscopic software, version 2.0, from Bruker Analytische Messtechnik GmbH. To minimise potential errors arising from variations in laser power or sample packing efficiency, peak intensities from spectral modes originating from the free base and the hydrochloride were expressed as ratios.

2.9. Stability testing

Tablets (both 10 and 50 mg loadings) were stored for up to 11 weeks in a variety of environments; 5 °C/50% relative humidity (RH), 40 °C/20% RH and 40 °C/75% RH. Samples were stored in HDPE bottles with induction-sealed child resistant closures (closed) or exposed to the stability environment (open). In addition to the Raman analyses, stability samples were tested for moisture content by Karl Fischer titration, the mean hardness was determined and mean disintegration times recorded. Also, dissolution profiles and assays of API content and degradation products for the initially prepared and the stored samples were obtained.

2.10. Dissolution testing

Dissolution profiles were obtained for 250 mg tablets containing 50 mg of Compound A following storage under a variety of conditions. The dissolution medium was 900 mL of 0.01 M HCl in USP vessels stirred at 50 rpm by paddles. Aliquots of the dissolution medium were taken at 5, 10, 15, 20, 30 and 45 min.

3. Results and discussion

As would be expected for two materials that differ only by the presence or absence of a hydrochloride group, the Raman spectra of the two API forms are extremely similar (Fig. 2). Spectral features for the highly crystalline hydrochloride are better resolved than those for the amorphous free base, as seen in the C–H stretching modes observed around 2800–3200 cm^{-1}. There are also some expected subtle spectral changes in the modes below 200 cm^{-1} which arise from lattice packing arrangements. However, both these spectral regions contain no clear spectral modes to allow easy identification or quantification of the base or hydrochloride.

Closer examination of the “fingerprint region” of the spectra, between 1700 and 500 cm^{-1} where spec-

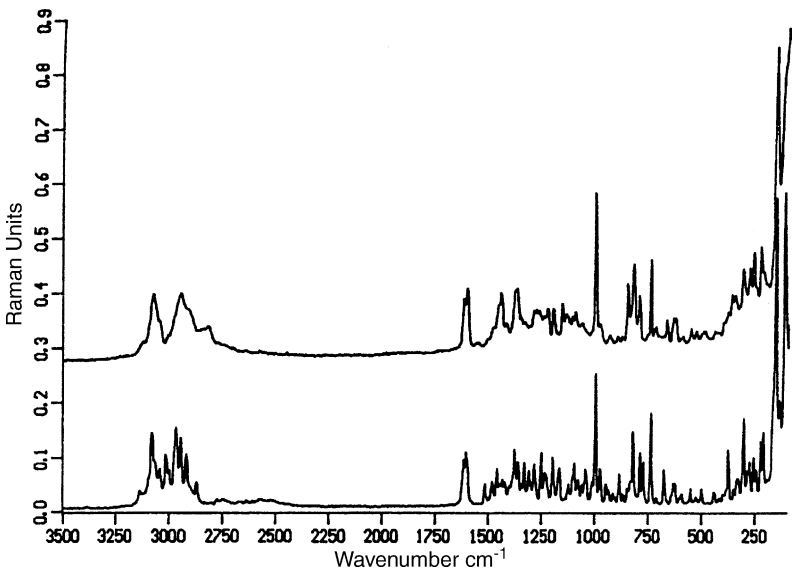

Fig. 2. FT-Raman spectra of Compound A as the free base (top) and the hydrochloride salt (bottom).

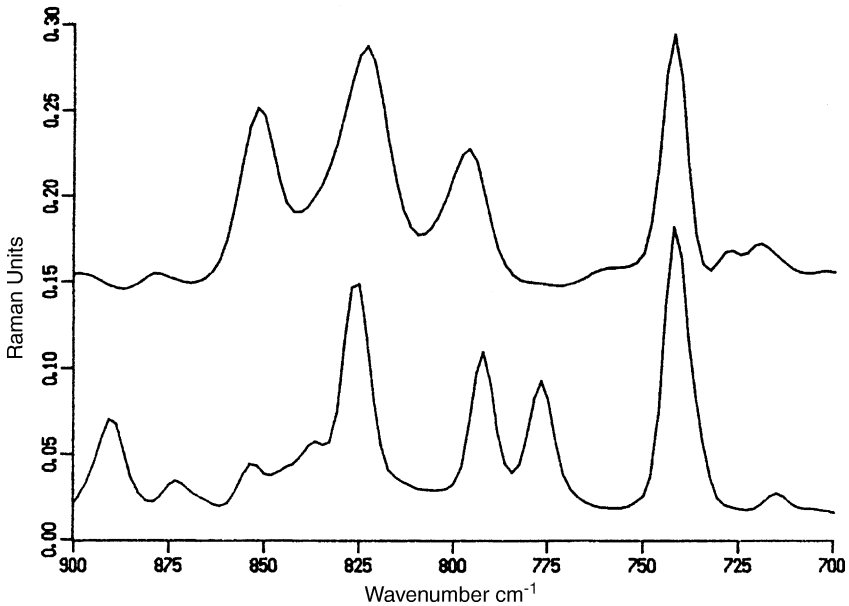

Fig. 3. Expansion of the 700–900 cm^{-1} region of the FT-Raman spectra of Compound A showing the characteristic peak at 852 cm^{-1} from the free base (top) and the 777 cm^{-1} peak from the hydrochloride salt (bottom).

tral modes arise largely from functional group stretching and deformation modes, shows that there are features between 700 and 900 cm^{-1} which are characteristic for the two API forms (Fig. 3). Under ideal circumstances, it would be desirable to have spectral modes that have no interference from either excipients or the other API form. In practice, this is not possible for Compound A. The Raman spectrum of the hydrochloride form is somewhat richer than that of the free base, and the vibrational modes tend to be sharper; the salt is highly crystalline whereas the free base is considerably less ordered. Several spectral modes arising from the hydrochloride are not seen in the Raman spectrum of the free base and could therefore be used to indicate the presence of the salt form. For the present study, the mode at 777 cm^{-1} was thus chosen as the marker peak for the hydrochloride form of the API.

Unfortunately, and again as expected, the free base spectrum has no vibrational mode that was not present in the hydrochloride data yet the assay requires determination of a small amount of base within the hydrochloride. A compromise was thus necessary, and the mode at 852 cm^{-1} was selected as the marker for the free base; although present in the spectra of both forms, this mode is only a relatively weak feature in the spectrum of the hydrochloride form.

Initial Raman method development used gross mixtures of the two API forms; binary systems of hydrochloride to base compositions 25:75, 50:50 and 72:28% (w/w) were used. Subsequently, a calibration data set was generated using mixtures of salt to base over the range 80:20–97.5:2.5% (w/w). Two samples of the calibrants were analysed, and the peak intensity ratio $I_{777/852}$ (the intensity of the peak at 777 cm^{-1} divided by the intensity of the peak at 852 cm^{-1}) was determined. The mean intensity ratio was plotted against composition and yielded a linear relationship with a correlation coefficient (R^2) of 0.978. At the time of the investigation, there was limited amount of the API available for these studies and hence the calibration range was limited to the expected practical hydrochloride: base compositions. Similarly, for the method to be employed within a quality control environment, validation of the calibration data with calculation of standard errors of prediction would be necessary (e.g. Mark, 2000), but require considerable amounts of material. However, and within these constraints, further confidence in the calibration data was obtained from analysis of two “unknown” compositions with

duplicate samples from each mixture analysed. Using the calibration curve, the predicted compositions were 97.5 and 97.0% for the "unknown" prepared with 97.0% hydrochloride and were predicted to be 89.6 and 84.5% for a 90.0% prepared "unknown". The most likely source for the variation seen in these data is sample inhomogeneity, previously identified as the biggest contributor to Raman assay errors for mixture quantification (Taylor and Zografi, 1998; Findlay and Bugay, 1998; Campbell Roberts et al., 2002).

The intention of the present study was to examine the value of Fourier transform (FT)-Raman spectroscopy in process development and for estimating API form content within the dosage form. Thus, whilst it is demonstrated above that relatively low amounts of base in hydrochloride could be estimated in a simple powder mixture, the practical situation necessitates assay during processing and in dosage forms.

FT-Raman spectra of 50 mg tablets with the hydrochloride salt as the API form were nearly identical to placebo formulations (Fig. 4), demonstrating that the most intense spectral modes originate from the many excipients present in the formulation. However, there are small yet characteristic features from the API present at approximately 1615 and 1002 cm^{-1} in the active tablet. Conversely, expansion of the spectral data shows that a mode at 476 cm^{-1} is found in the placebo tablet and does not originate from the active drug.

Normalising the spectral intensities to this mode, and subtracting the signal of the placebo from that of the active tablet, yielded an excellent quality spectrum for the API present in the tablet without the interference of the excipient modes (Fig. 5). It is important to note that the data in Fig. 5 were obtained using an analytical placebo, containing the excipients in the same relative proportions to those found within the active tablet. As expected, spectral subtractions using clinical placebos (equal weight to the API-containing tablet, prepared by increasing the lactose monohydrate and microcrystalline cellulose content) were unsuccessful.

Following these spectral manipulations, the nature of the API form (free base or hydrochloride) within the tablet could be determined using the approach employed previously for the powder mixtures. The subtracted data showed no evidence that the API was present as the free base—indeed the subtraction spectrum and that from the hydrochloride were superimposable. It is difficult to specify the level of accuracy for this type of determination as multiple data manipulations have been performed, and spectral quality tends to diminish with such manipulations.

As an indication of the level of discrimination possible in the samples, API was clearly detectable in

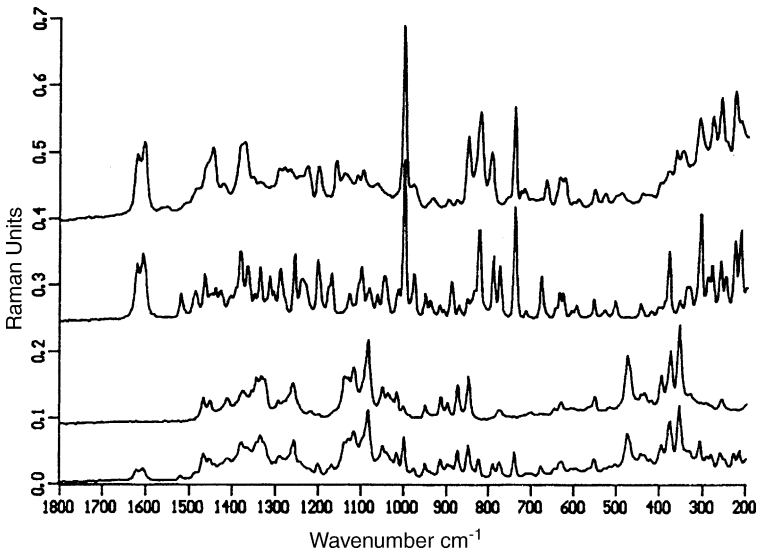

Fig. 4. FT-Raman spectra of, from top to bottom, Compound A as the free base form; Compound A as the hydrochloride salt form; analytical placebo tablet; tablet containing 20% loading of Compound A.

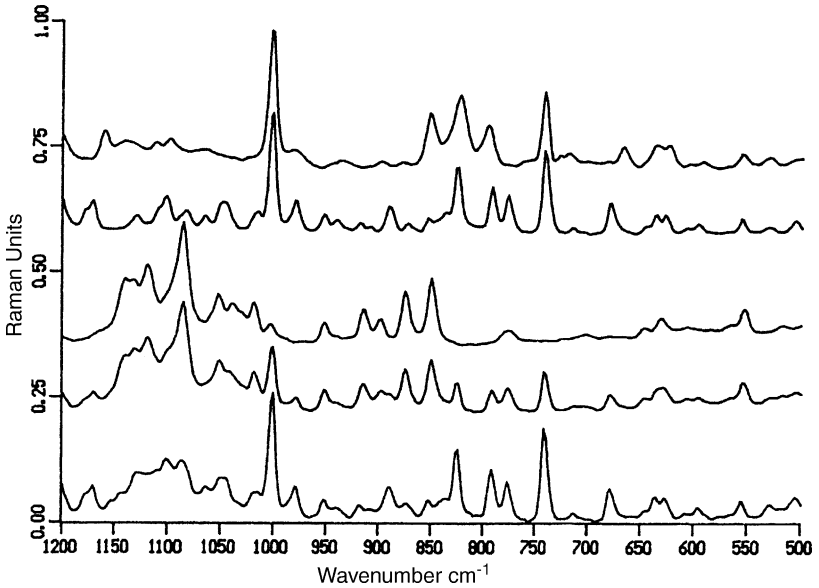

Fig. 5. Expansion of the 500–1200 cm^{-1} region of the FT-Raman spectra of, from top to bottom, Compound A free base; Compound A hydrochloride; analytical placebo tablet; 20% loading active tablet; spectral subtraction of analytical placebo from active tablet showing drug present as the hydrochloride.

tablets prepared with a loading of 10 mg in 250 mg compression weight. Determination of the amounts of base formed in these samples was problematic; typically, under worst case scenarios, up to ∼10% of free base may have formed from the hydrochloride salt, equivalent to ∼1 mg of the amorphous base in the 250 mg tablets, i.e. around 0.4% of the total tablet weight. The method developed here was unable to demonstrate this level of discrimination between the two API forms. In contrast, with a drug loading of 50 mg base could be determined, and semi-quantified, showing that a limit of quantitation lower than 2% of free base in the total tablet weight was achieved for the amorphous material. Considering the spectral similarities between the API forms, and that the free base rather than the somewhat more distinct hydrochloride was the form being determined, then this lower limit correlates well with literature reports using Raman spectroscopy to quantify drug actives. For example, Taylor and Zografi (1998) found a limit of estimation around 1%, for determining of amorphous indomethacin in crystalline samples. More recently, Raman spectroscopy has been used to show the solid state form of a range of drugs (e.g. polymorphs of ranitidine, the hydrate state of theophylline) in capsules and tablets (Taylor and Langkilde, 2000); again, drug levels of down to 1% can be assayed in situ in the tablets. Clearly, the precision and accuracy of such determinations depend on numerous factors, including the scattering efficiencies of the solid state forms, the presence of clear spectral markers for the two forms, the accuracy and precision of the calibration data and sample homogeneity. However, it is apparent that Raman spectroscopy can be used to quantify drug levels within tablets in situ, whilst also providing a capability to estimate drug integrity—polymorph content, amorphous content, hydration state and salt form.

The above approach was extended to optimise a suitable manufacturing process that would minimise the risk of forming the amorphous base form. For this optimisation, a simple assessment of the presence or absence of the base in granules and tablets was sufficient. As described above, the salt was known to dissociate to the base in aqueous media. However, for granule properties, an aqueous granulating fluid was desirable. Thus, the effects of a range of granulating fluids on the integrity of the hydrochloride were examined. Granulating with absolute ethanol, or 96 or 90% ethanol/water binder fluids caused no detectable dissociation of the drug (Fig. 6A). In all cases, the re-

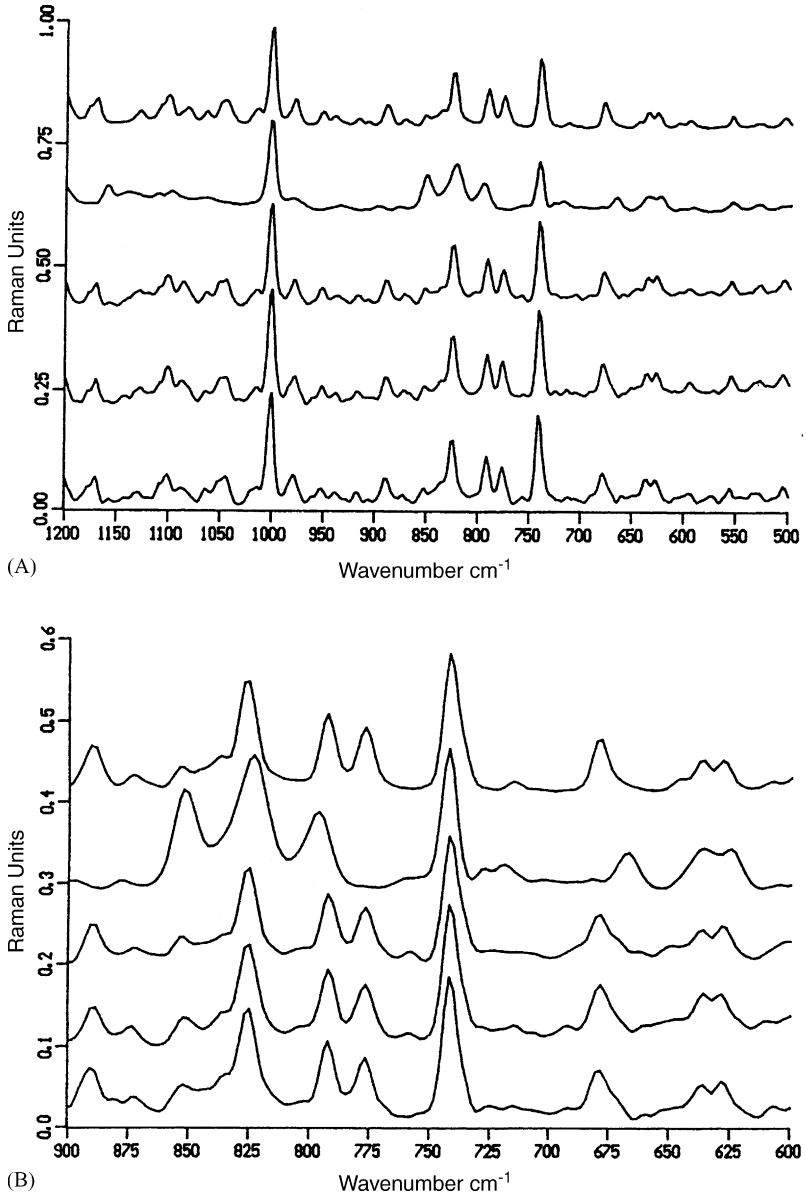

Fig. 6. FT-Raman spectra of, from top to bottom, Compound A hydrochloride form; Compound A free base form; spectral subtraction of placebo from active granules prepared using absolute ethanol; spectral subtraction of placebo from active granules prepared using 96% ethanol; spectral subtraction of placebo from active granules prepared using 90% ethanol. Granules prepared with (A) no delay between granulating and drying and (B) a 4-h delay between granulating and drying.

sultant spectrum after subtracting the placebo signal from that of granules containing the API was superimposable on the data from the pure hydrochloride salt. However, the granulation process also needed to be robust since manufacturing delays could occur between granulation and drying. Thus, the effects of holding the granules for 4 h prior to drying on the drug form were probed. The spectra (Fig. 6B) clearly show that for granules prepared using absolute ethanol no dissociation occurred. However, there was some modification

to the API with a 4-h delay prior to drying when the granulation fluid contained water; most clearly seen by the increased intensity of the 852 cm^{-1} peak which is largely attributable to the free base form of the drug. Subtraction of the Raman signal given by the pure hydrochloride form from that of the API in the granules leaves a spectrum of the base in the granules, and can be used to clearly demonstrate drug dissociation after the delay. Using the above methodology, approximately 4 and 7% of the API content of the tablets was present as the base when using the 96 and 90% ethanolic granulating fluids, respectively. Considering the compression weight of 250 mg, semi-quantification of amorphous material comprising around 4% of the drug content (i.e. around 2 mg of the 50 mg active content) shows that the limit of quantification is indeed lower than the 2% described above, and is probably nearer to 1% of the drug in the total tablet weight.

From the above results, and considering other factors, such as the tabletting quality of the granules, an absolute ethanol binder fluid was selected. 50 mg tablets prepared from these granules were stored under a variety of conditions. 10 mg loaded tablets were similarly prepared but, as with the granules, subsequent Raman analysis was insufficiently sensitive to determine the base content of these tablet although the hydrochloride drug was clearly distinguishable.

In addition to spectroscopic analyses, several tests were performed to assess tablet quality after storage, summarised in Table 1. As can be seen, there are no significant differences in tablet properties after storage for up to 11 weeks at 5 °C and a relative humidity of 50%; tablet hardness, mean water content and disintegration time were comparable to the initially prepared samples. Similarly, tablets stored at 40 °C/20% RH and those stored at 40 °C/75% RH were stable for up to 11 weeks with hardness, moisture content and mean disintegration times invariant to those of the initially prepared and tested samples. However, the above samples were stored in "sealed" containers (HDPE bottles with induction-sealed, child resistant closures). When the tablets were stored open in the aggressive storage conditions (40 °C/75% RH), change in the physical properties of the tablets were recorded. Though the mean disintegration time had fallen slightly from 5 to 3 min, there was a small increase in mean tablet hardness after 3 weeks storage in the open conditions. After 11 weeks of such storage, the mean tablet hardness had risen dramatically, from 13.7 to 22.7 kp, and the mean disintegration time had risen to 6 min. No significant differences in moisture content were apparent under any of the storage conditions.

It is clear that exposing the tablets to a high humidity and elevated temperature for extended time periods has introduced some physical changes to the tablet properties. The nature of these physical changes remains unclear. It is feasible that, since moisture induces dissociation to the amorphous free base, this material may act as an additional binder in the tablets. Alternatively, crystal bridges may form from the amorphous material so providing greater tensile strength in the tablets. Interestingly, despite the clear difference in tablet hardness for samples stored in the open at 40 °C/75% RH, no differences were detected in the dissolution profiles of the tablets from any storage conditions; >95% dissolution was seen in less than 20 min for all tablets.

The hypothesis that the open storage of tablets at high temperature and humidity induced dissociation of the salt to the free base form of the drug was evaluated using Raman spectroscopy as for the granules. One ad-

Table 1
Some physical stability data for tablets containing Compound A after storage

Test time (weeks)	Storage conditions (°C/% RH)	Mean disintegration time, range (min)	Moisture content (%)	Mean hardness (kp)
Initial	–	5, 5–6	3.38	13.7
3	40/20	5, 5–6	3.09	14.1
3	40/75	5, 5–5	3.29	13.6
3	40/75 open	3, 3–4	3.45	15.7
11	5/50	5, 5–5	3.19	14.2
11	40/20	5, 4–5	3.24	14.3
11	40/75	4, 4–4	3.72	14.0
11	40/75 open	6, 5–7	3.26	22.7

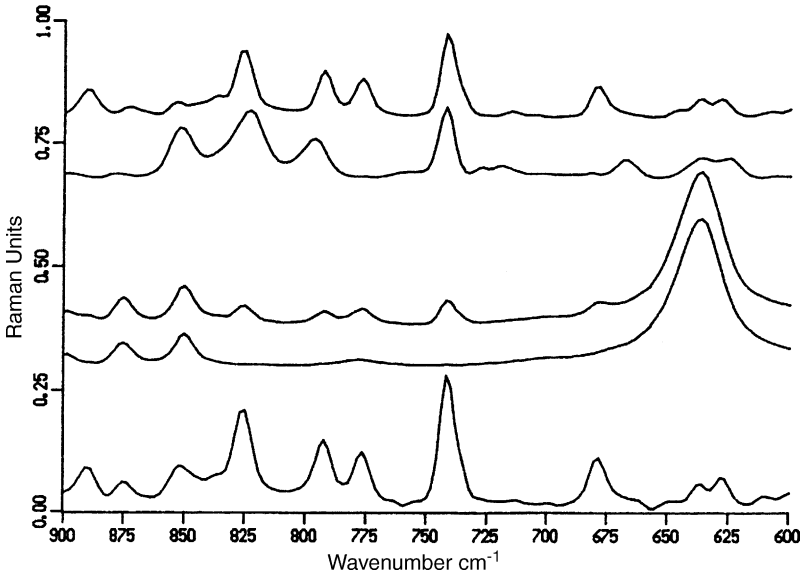

Fig. 7. FT-Raman spectra of, from top to bottom, Compound A hydrochloride form; Compound A free base form; tablet containing Compound A stored under open conditions at 40 °C/75% RH for 11 weeks; analytical placebo tablet; spectral subtraction of analytical placebo signal from tablet containing Compound A.

ditional complication present in analysis of the tablets arose from the film coat applied to the tablets which was obviously absent from the granules. Although analytical placebo tablets were again used for the spectral manipulations, variations in coat thickness could introduce some errors to the spectral subtractions.

Fig. 7 shows the characteristic Raman bands in the wavenumber range 900–600 cm^{-1} of the two API forms, the 40 °C/75% RH open tablet stored for 11 weeks, the placebo tablet and the "subtracted" spectrum. Evidently, from the peak at 852 cm^{-1} in the subtraction data, the tablet contains appreciable amounts of the free base. Using our previous data, it would appear that up to 20% of the API has undergone dissociation under these extreme storage conditions. A similar analysis for the 11 week samples under the other (closed) storage conditions, 40 °C/75% RH, 40 °C/20% RH and 5 °C/50% RH, all showed no evidence for the presence of the free base.

As only the samples stored open at elevated temperature and high humidity were found to alter after 11 weeks storage, tablets taken from storage after 7 and 3 weeks were analysed by Raman spectroscopy as above. For the 7-week stability samples, again clear evidence for dissociation was found with approximately 10% of the API present as the free base. The data from the 3-week stability samples was less conclusive with a suggestion of a very small amount of free base within the sample, though the low signal from the base compared to the noise introduced by the spectral manipulations precluded any semi-quantitative analysis. The presence of the free base in the open stability samples correlates well with the observations of increasing tablet hardness on storage. The mechanism by which the tablets harden is unclear. However, the dissociation of the hydrochloride salt to the base clearly affects the physical properties of the tablets.

4. Conclusions

We have demonstrated that it is possible to determine the nature of an API in both tablet and granule formulations. Despite the chemical and hence spectroscopic similarities between the two forms, it is possible to determine the amorphous free base in the crystalline hydrochloride salt form to levels below 1% of

the total tablet weight. This determination has allowed a pharmaceutical process to be developed so that minimal dissociation of the salt form is introduced. Avoidance of water in the granulation fluid and ensuring rapid drying of wet granules eliminates the formation of the amorphous drug form. The potential for subsequent drug dissociation under a range of storage conditions has been examined and showed that only the extremes of exposure to (open) elevated temperature and humidity induces significant levels of drug dissociation to occur, which leads to subsequent alterations in physical properties of the tablets.

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