Journal of Pharmaceutical and Biomedical Analysis 55 (2011) 424–428

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Solid state compatibility studies with tablet excipients using non thermal methods

Karin Liltorp[a], Trine Gorm Larsen[b], Birgitte Willumsen[b], René Holm[a,*]

[a] Preformulation, H.Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark
[b] Analytical Development Products, H.Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark

ARTICLE INFO

Article history:
Received 3 December 2010
Received in revised form 9 February 2011
Accepted 10 February 2011
Available online 17 February 2011

Keywords:
FTIR
Solid-state interaction
Compatibility magnesium stearate

ABSTRACT

Compatibility between two new active pharmaceutical ingredients (API) and several pharmaceutical excipients used in solid formulations has been investigated by FT-IR and HPLC following storage under two different conditions. Compatibility was investigated by storage at isothermal stress conditions for (i) 3 days and subsequently analysed by FT-IR and (ii) 12 weeks of storage and analysis by HPLC.

For the majority of the examined excipients a large degradation measured by HPLC after 12 weeks storage was also detected by FT-IR following storage at isothermal stress conditions for 3 days, i.e. there was a general agreement between the results obtained by the two protocols. Further, the FT-IR method showed clear incompatibility with three excipients where no degradation products were detected by HPLC, but where a significant decrease in the API quantified by the HPLC assay, was observed.

The accelerated method thus showed a clear advantage: incompatibility found after 12 weeks using HPLC was seen after 3 days with FT-IR. Furthermore, FT-IR provides an insight into structural changes not seen with HPLC. This is exemplified by the desalting of a hydrogen bromide salt of one of the two compounds, which might lead to changes of the intrinsic dissolution rate and potentially affect the bioavailability of the API.

1. Introduction

Pharmaceutical quality by design (QbD) is a systematic, scientifically based, holistic and proactive approach to pharmaceutical development [1], where selection of excipients following compatibility investigation is the first step towards the final pharmaceutical formulation. However, no general well defined principles for testing and selecting suitable excipients exist. This despite the fact that unfavourable combinations of drugs and excipients may alter both the stability and the bioavailability of the drug in the formulation [2,3]. Consequently, a thorough drug-excipient compatibility study is a very important part of QbD and in general for the development of a stable pharmaceutical formulation [1,3].

The collection of real-time stability and compatibility data is time-consuming and expensive, so obtaining rapid and reliable information about possible drug–excipient interactions is highly desirable. Differential scanning calorimetry (DSC) is the most commonly used method for assessing incompatibility between formulation components and the drug described in the literature, as it is fast, versatile and requires little sample [3–15]. However, thermal techniques lead to complex data interpretation that may be misleading. Moreover, interactions observed at high temperatures during DSC experiments may not be relevant at normal storage temperatures [3,8,12,13,16]. In addition, the observation of solid–solid interactions may indicate other things than incompatibility [12,16]. As water plays an essential role for interactions, DSC experiments should include humidity control [4,17] which is not usually the case. If an incompatibility is observed by DSC, additional confirmatory experiments are often required [6,9–11,15,17–19]. Therefore evaluating the compatibility directly by the methods normally used in the confirmatory experiments could be more relevant and beneficial from both an economical and time perspective.

Isothermal stress testing (IST) is a frequently used method in compatibility evaluations and involves storage of the drug-excipient blends with or without moisture at elevated temperature and subsequent investigation or determination of the drug content by a suitable method [2]. The methods used to detect incompatibility following IST include HPLC [2,5,8,13], XRPD [7,11,14,18,19], FT-IR [6,9,10,14,19,20], MS [15] and microcalorimetry [18].

Fourier Transform infrared spectroscopy (FT-IR) is a simple technique for the detection of changes within excipient-drug mixtures.

Abbreviations: API, active pharmaceutical ingredient; DSC, differential scanning calorimetry; FT-IR, Fourier transform infrared spectroscopy; HPLC, high-pressure liquid chromatography; IST, isothermal stress testing; MS, mass spectrometry; QbD, quality by design; XRPD, X-ray powder diffraction.

* Corresponding author. Tel.: +45 3630 1311; fax: +45 3643 8242.
E-mail address: rhol@lundbeck.com (R. Holm).

0731-7085/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2011.02.016

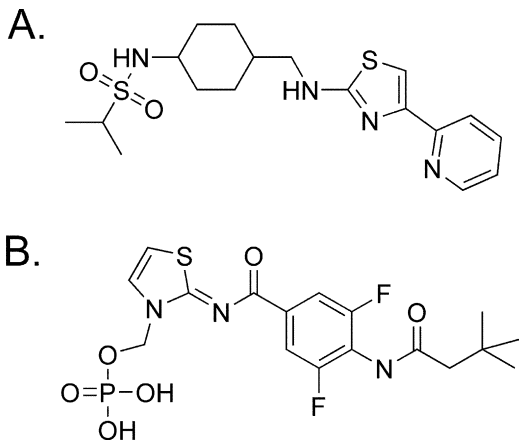

Fig. 1. Chemical structures of (A) Lu AA44608; propane-2-sulfonic acid {4-[(4-pyridin-2-yl-thiazol-2-ylamino)-methyl]-cyclohexyl}-amide and (B) Lu AA47070; phosphoric acid mono- {2-[(Z)-4-(3,3-dimethyl-butyrylamino)-3,5-difluoro-benzoylimino]-thiazol-3-ylmethyl} ester.

Disappearance of an absorption peak or reduction of the peak intensity combined with the appearance of new peaks give a clear evidence for interactions between the excipient and the drug investigated. As a first approach, changes are unwanted and excipients interacting with the drug should be avoided if possible in the final formulation. Deeper insight into the mechanism of interaction can be obtained by the use of FT-IR, as the method allows assignment of the peaks and thereby provides valuable information about possible chemical changes. Compared to the other analytical methods used in compatibility studies, FT-IR has some clear advantages including: (i) it is non-disruptive, as no preparation of the samples is needed, (ii) recording does not influence the result, and (iii) changes in crystal structure may be detected, i.e. desalting, hydrate formation or polymorphic changes.

The different methods for compatibility testing can only provide a rough indication for the selection/deselection of excipients, as the composition of the final formulation may be different from the one tested in the compatibility study and because the reaction kinetics may be different under the stress conditions used [21]. The purpose of the current study is therefore to evaluate an accelerated stress method and to compare it to a traditional long-term method–3 days versus 12 weeks by the use of FT-IR and HPLC, respectively.

2. Materials and methods

2.1. Materials

The chemical structures of the two active pharmaceutical ingredients are shown in Fig. 1, denoted Lu AA44608 (where the HBr salt was used) and Lu AA47070. Both compounds were produced by H.Lundbeck A/S (Valby, Denmark). Calcium hydrogen phosphate anhydrate was purchased from Budenheim (Budenheim am Rhein, Germany), talc from Scheruhn Industrie-Mineralen (Hof, Germany), maize starch from Roquette (Le Strem, France), lactose from DMV International (Veghel, The Netherlands), crospovidon (Kollidon VA64) and copovidon (Kollidon CL) from BASF (Ludwigshafen, Germany), PVP from Sigma–Aldrich (St. Louis, MO, USA) primojel from DMV-Fonterra Excipients (Veghel, The Netherlands), magnesium stearate from Peter Greven Fett Chemie (Bad Münstereifel, Germany), AcDiSol and micro crystalline cellulose from FMC (Philadelphia, PA, USA) and HPMC from Dow (Midland, MI, USA). All excipients were used as received. Water was obtained from a Millipore water purification system. All other chemicals used were of analytical grade or higher and used as received.

2.2. FT-IR experiments

10 mg API was mixed with 10 mg excipient. The mixtures were grounded thoroughly using a hand mortar. FT-IR spectra were recorded on a Spectrum1000 from Perkin Elmer (Beaconsfields Bucks, UK) equipped with an ATR diamond. After recording a background spectrum, 1–2 mg of the mixture was placed on the diamond. 4 scans were recorded of each sample with a resolution of 4 cm^{-1}. The mixtures were subsequently placed in a sealed glass container with a relative humidity kept around 96% using a saturated K_2SO_4 solution [22]. The glass container was placed in an oven at 50 °C and after 3 days of storage a FT-IR spectrum was recorded again.

2.3. HPLC experiments

Three different samples were prepared and stored at 60 °C for 12 weeks before analysis: (1) 2 mg pure API; (2) 10 mg pure excipient and (3) 10 mg of excipient mixed with 2 mg of API. 15–20 μl water was added and the vials closed with a teflon-lined cap. Samples of each excipient, each mixture and the pure API were analysed initially, and following storage by HPLC. The HPLC system comprised an L-7100 pump, an L-7300 column oven, an L-7400 UV detector, an L-7200 autosampler and a D-7000 interface, all equipment from Merck. Incompatibility was identified by observation of chromatographic changes compared to the changes in the chromatograms and in the recovery of the compound.

Samples with Lu AA44608 were diluted with mobile phase, sonicated for 10 min and centrifuged for 10 min at 4000 rpm before the HPLC analysis. The analysis was performed on an Xbridge C18 column, 150 mm × 4.6 mm ID, 3.5 μm particles from Waters (Milford, MA, USA). An isocratic HPLC method at 40 °C was used, with a flow rate of 1.0 ml/min and an injection volume of 25 μl. The mobile phase consisted of water/acetonitrile (77/23) with 1 ml formic acid/l and the samples were analysed by UV detection at 247 nm.

Lu AA47070 samples were diluted with water/acetonitrile (50/50), sonicated for 10 min and centrifuged for 10 min at 4000 rpm before HPLC analysis. The analysis was performed on a Sunfire C18 column, 150 mm × 4.6 mm ID, 3.5 μm particles from Waters (Milford, MA, USA). A gradient method was used (100% A to 17% A in 20 min, hold for 2 min, immediately switch to 100% A and hold at 100% A for 8 min) at 40 °C, with a flow rate of 1.0 ml/min and an injection volume of 50 μl. Mobile phase A consisted of water/acetonitrile (80/20) + 1 ml trifluoric acid/l and mobile phase B consisted of water/acetonitrile (20/80) + 1 ml trifluoric acid/l. The samples were analysed by UV detection at 255 nm.

3. Results and discussions

3.1. Characterisation of the compounds

Lu AA44608 has a single pK_a-value, determined to be 4.8 and a log P (and log $D_{7.4}$) of 3.1. The solubility of the free base in water (pH 8.0) and in buffer (pH 7.4) is approximately 1 μg/ml. The hydrogen bromide salt transforms into the free base in aqueous solution. The compound melts with T_{ons} around 184 °C, and is not hygroscopic absorbing less than 0.1% water at 95% relative humidity at ambient temperature. The compound in solution is very sensitive to light but stable when exposed to acidic conditions and oxygen.

Lu AA47070 is a phosphate pro-drug of the pharmacological active compound [23]. The low pK_a value of the acid is 2.2, and the pK_a value of the second acid is 5.9, determined by titration. Attempts to determine the log D profile by titration failed due to the very low lipophilicity of the compound. The solubility in aque-

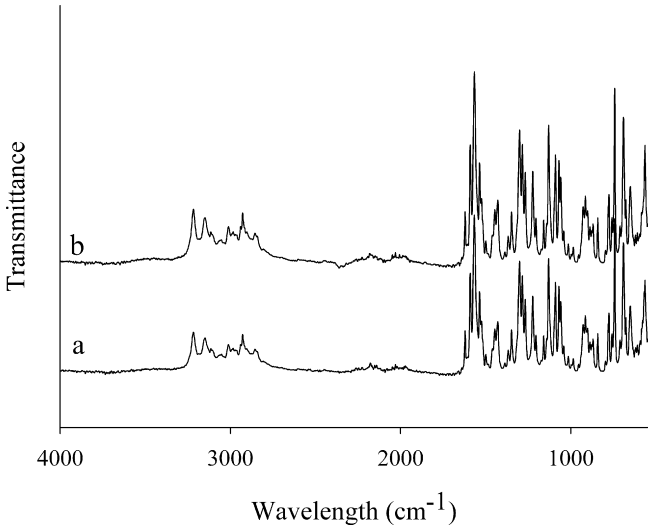

Fig. 2. FT-IR spectrum for Lu AA44608 HBr from the IST experiment; (a) before and (b) after exposure to 50 °C and RH 95% for 3 days.

ous solution is 0.8 mg/ml at pH 2.9. The compound decomposes upon heating at approximately 200 °C without prior melting. The compound is not hygroscopic absorbing less than 0.6% of water at 95% relative humidity at room temperature. As Lu AA47070 is a phosphate ester pro-drug a dephosphorylation might be a degradation risk, however stress studies in solution at pH 7 measured at 50 °C showed a half life of the compound of more than 1600 h [23]. The compound was therefore considered sufficiently stable to be investigated.

3.2. Compatibility study with Lu AA44608 HBr

The IST experiment with Lu AA44608 HBr revealed no changes in the FT-IR spectrum, as demonstrated by the spectra for the API before and after exposure to 95%RH for 3 days at 50 °C (Fig. 2). No changes in the peak positions or in their relative intensities were observed. Similar observations were seen when Lu AA44608 was combined with calcium hydrogen phosphate anhydrate, mannitol, lactose monohydrate, MCC, maize starch and talc indicating that the compound is compatible with all these excipients.

For the binary mixtures with excipients containing a carboxylic group (AcDiSol, primojel and magnesium stearate) changes in the FT-IR spectra were observed, as exemplified with the spectrum obtained for magnesium stearate, see Fig. 3. The most pronounced change was the appearance of a new peak at ~3270 cm^{-1}. This peak was also observed in the spectrum of the free base of the compound. Several other peaks, characteristic of the free base, appeared in the mixture after 3 days, including peaks at 1340, 1373, 1255 and 906 cm^{-1} suggesting that the changes correspond to a desalting of the hydrogen bromide salt. The appearance of an IR peak at 1705 cm^{-1} in the magnesium stearate/Lu AA44608 spectrum might be attributed to the formation of stearic acid [24], which may have been formed through the interaction with the released HBr. Generally, Lu AA44608 seems to be incompatible with excipients containing a carboxylic acid, which would be expected to affect dissolution rate. This effect could be based upon two possible mechanisms (i) the intrinsic dissolution rate of the hydrogen bromide salt is expected to be higher than of the free base or (ii) the hydroxyl group on Lu AA44608 could react with the stearic acid formed. Though this incompatibility was observed a formulation containing magnesium stearate was evaluated in a long term stability study. Lower dissolution rates were observed in a formulation containing Lu AA44608, MCC and magnesium stearate. The

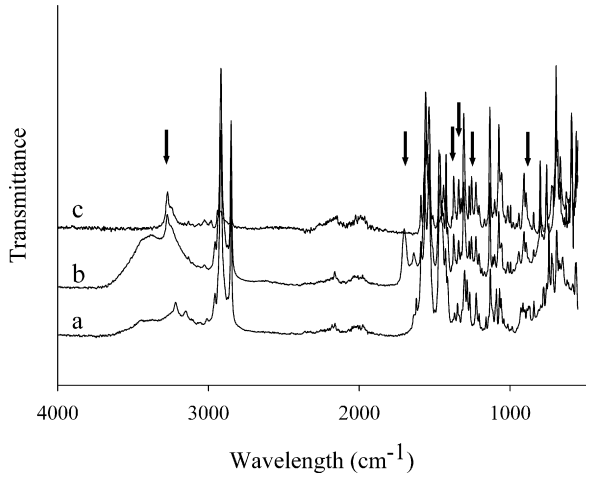

Fig. 3. FTIR spectra of Lu AA44608 HBr-Mg stearate; (a) before and (b) after exposure to 50 °C and RH 95% for 3 days; (c) Lu AA44608 free base. Arrows indicate where the changes in the spectrum are observed. For further information, see the main text.

released amount of Lu AA44608 decreased significantly in the dissolution study following 6 months of storage at 25 °C/65%RH (data not shown).

For the mixture of Lu AA44608 HBr and PVP several changes, including hydration, were observed in the FT-IR spectra before and after storage, see Fig. 4. An increasing peak ~1650 cm^{-1}, assigned to the C=O group of the excipient, and changing intensity of peaks at ~1300 and ~1170 cm^{-1}, assigned to SC=O stretching in Lu AA44608, suggests an interaction through hydrogen bonding between the sulfonamide group of Lu AA44608 and the pyrrolidon in PVP. Similar changes at ~1300 and ~1170 cm^{-1} were observed for copovidon, although to a lesser extent, i.e. the same changes are seen for the two excipients containing the same functional group.

HPLC analysis of the samples showed hydrogen phosphate, mannitol and talc to be compatible with Lu AA44608, whereas significant changes where seen after storage with HPMC and copovidon, in accordance with the results from the FT-IR experiments (Table 1). However, incompatibility was found by the HPLC method for lactose, MCC and maize starch was found by the HPLC method, which was in contrast to the results from the FT-IR method. This could either be due to a non-optimised extraction method of Lu AA44608 from the mixture, or reflect that these 3 excipients absorb the added water in the vial, leading to a higher aqueous

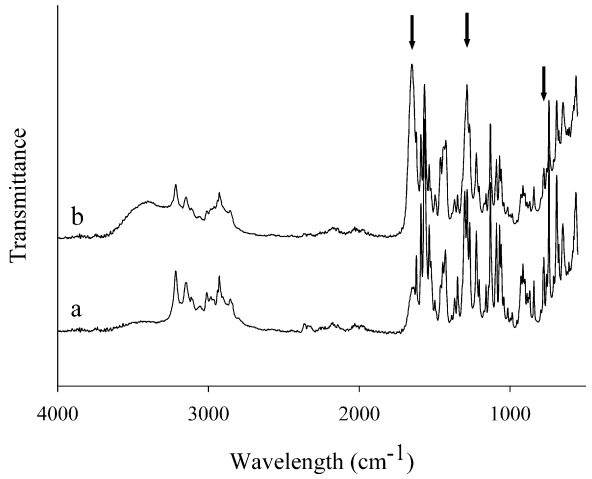

Fig. 4. FTIR spectra of Lu AA44608 and PVP 1:1; (a) before and (b) after exposure to 50 °C and RH 95% for 3 days. Arrows indicates where the change in the spectrum are observed. For further information, see the main text.

Table 1
FT-IR and HPLC results from the compatibility study with Lu AA44608 HBr.

Excipients	HPLC		FT-IR	
	Degradation	Retrieval (%) after 12 weeks	Structural changes after 3 days	Hygro-scopic
Lu AA44608 HBr	Insignificant	95	Insignificant	No
$CaHPO_4$ anhydrate	Insignificant	65	Insignificant	No
Mannitol	Insignificant	92	Insignificant	No
Lactose monohydrate	Some	71	Insignificant	No
Microcrystalline cellulose (MCC)	Minor	84	Insignificant	No
Maize starch	Some	76	Insignificant	No
Copovidon (Kollidon VA64)	Major	62	Some	Yes
Polyvinylpyrrolidon (PVP)	Major	25	Some	Yes
Hydroxypropylmethylcellulose (HPMC)	Major	39	Minor	Slightly
AcDiSol	Insignificant	55	Some	No
Primojel	Insignificant	47	Some	No
Magnesium stearate	Insignificant	15	Major	No
Talc	Insignificant	37	Insignificant	No

activity during the storage than in the FT-IR study, where the water is absorbed from the air. The FT-IR method showed incompatibility with AcDiSol, primojel and Mg stearate, although no degradation products were seen in the chromatograms. However, the retrieval was fairly poor (from 15 to 55%) i.e. not all of the API was released from the precipitate and is therefore not present in the solution used for analysis. This could suggest a chemical interaction between the hydroxyl group in Lu AA44608 and the formed stearic acid seen in the FT-IR experiment. This reaction would lead to a very low soluble ester.

Water is easy to detect by FT-IR, hence hygroscopicity can be observed. An increase in the intensity of the broad peaks originating from water at 3300 cm^{-1} (strong), 1630 cm^{-1} (medium) and 560 cm^{-1} (strong) was used to determine the hygroscopiciity of the mixtures, see Table 1. In general, a larger risk of interactions would be expected for the hygroscopic mixtures, as water will catalyse reactions, which to some extent is in accordance with the observed results in Table 1.

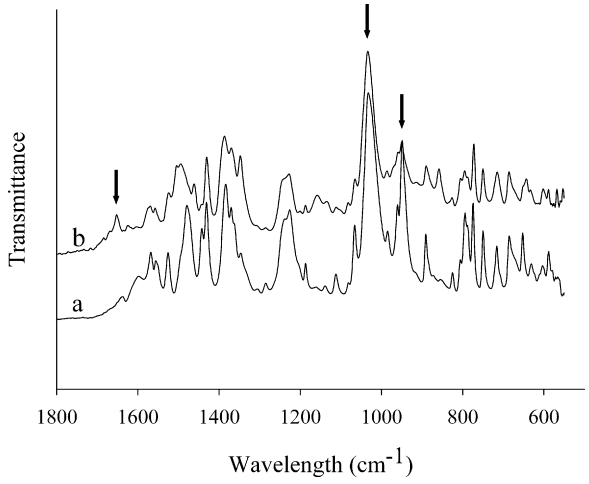

Fig. 5. FT-IR spectra of Lu AA47070 and AcDiSol 1:1; (a) before and (b) after exposure to 50 °C and RH 95% for 3 days. Arrows indicate where the changes in the spectrum are observed. For further information, see the main text.

3.3. Compatibility study with Lu AA47070

With the FT-IR protocol incompatibility was only observed for mixtures of Lu AA47070 and AcDiSol, primojel and copovidon (Fig. 5 and Table 2). After 3 days, major changes were observed in the spectra from the AcDiSol and primojel mixtures, with the appearance of several new peaks throughout the spectrum, indicating major structural changes affecting various functional groups. As Lu AA47070 has several conjugations in its molecular structure, the peak positions are different from generic values, making peak assignment more difficult. A possible explanation for these observations could be an acid/base reaction between COO^-Na^+ from AcDiSol/primojel and the phosphate group of Lu AA47070. Two of the peaks arising from interaction may originate from PO_4 (1030 and 948 cm^{-1}) and new peaks in the C=O stretching region (1670–1650 cm^{-1}) are observed, both supporting the acid/base hypothesis. Minor changes were seen with copovidon combined with visual changes, indicating an incompatibility. The HPLC method also found Lu AA47070 incompatible with AcDiSol and copovidon, whereas no change was seen with copovidon, though the recovery of Lu AA47070 was lower after 12 weeks of storage.

As demonstrated by these two examples, the use of IST and FT-IR analysis was able to find major incompatibilities for two chem-

Table 2
Comparison of FTIR and HPLC results for Lu AA47070.

Excipients	HPLC		FT-IR	
	Degradation	Retrieval (%) after 12 weeks	Structural changes after 3 days	Hygro-scopic
Lu AA47070	Insignificant	93	Insignificant	No
$CaHPO_4$ anhydrate	Some	87	Insignificant	No
Mannitol	Insignificant	93	Insignificant	No
Lactose monohydrate	Insignificant	93	Insignificant	No
Microcrystalline cellulose (MCC)	Insignificant	92	Insignificant	No
Maize starch	Insignificant	93	Insignificant	No
Copovidon (Kollidon VA64)	Some	84	Minor + visual changes	Yes
Hydroxypropylmethylcellulose (HPMC)	Some	85	Insignificant	Slightly
AcDiSol	Major	39	Major	Slightly
Primojel	Major	34	Major	Yes
Magnesium stearate	Insignificant	93	Insignificant	No
Talc	Some	81	Insignificant	No

ically very different APIs. For Lu AA44608 HBr 2 of 3 excipients showing major degradation in the HPLC method were identified after 3 days by FT-IR. In addition, FT-IR detected incompatibility for 3 extra excipients, where HPLC showed no degradation, but major changes in API recovery, i.e., the data from the FT-IR could be more unequivocally interpreted as showing incompatibility than the HPLC results, as the latter could be a reflection of the extraction method. For Lu AA47070, the IST/FT-IR method identified problematic excipients, although it is not known if these compatibility problems would also be reflected in a real pharmaceutical formulation stored under normal conditions. FT-IR therefore seems to provide fast answers to excipient selection and deselection and could further provide valuable information in situations where dissolution or stability problems arise during storage, as with the suggested interaction between Lu AA44608 and stearic acid formed from magnesium sterate.

Discrepancy between the results from different methods in compatibility studies are frequently seen [22] and could, in the present case, be explained by differences in the amount of water in the two situations, which is essential for drug decomposition [25]. Adding water directly into the vial, as was done for the long-term experiment, leads to larger risk of reaction for the non hygroscopic mixtures, whereas exposing the sample to high humidity might more closely mimic real storage conditions and could explain the lack of interaction for the non hygroscopic mixtures (Tables 1 and 2).

4. Conclusions

This study has demonstrated that IST/FT -IR can detect potential compatibility problems between an API and pharmaceutical excipients after only 3 days of storage. The method provided some insight into the reaction mechanisms by allowing the assignment of the bands in the spectra, which provides the preformulation and formulation scientists with information about which chemical groups to avoid in the excipients.

Acknowledgement

Kirsten Lech-Rasmussen is acknowledged for linguistic support.

References

[1] L.X. Yu, Pharmaceutical quality by design: product and process development, understanding, and control, Pharm. Res. 25 (2007) 781–791.
[2] A.T.M. Serajuddin, A.B. Thakur, R.N. Ghoshal, M.G. Fakes, S.A. Ranadive, K.R. Morris, S.A. Varia, Selection of solid dosage form composition through drug-excipient compatibility testing, J. Pharm. Sci. 88 (1999) 696–704.
[3] R.K. Verma, S. Garg, Selection of excipients for extended release formulations of glipizde through drug-excipient compatibility testing, J. Pharm. Biomed. Anal. 38 (2005) 633–644.
[4] G. Bruni, L. Amici, V. Berbenni, A. Marini, A. Orlandi, Drug-excipient compatibility studies: search of interaction indicators, J. Therm. Anal. Calorim. 68 (2002) 561–573.
[5] G.C. Ceschel, R. Badiello, C. Ronchi, P. Maffei, Degradation of components in drug formulations: a comparison between HPLC and DSC methods, J. Pharm. Biomed. Anal. 32 (2003) 1067–1072.
[6] J. Kerc, S. Srcic, U. Urleb, A. Kanalec, B. Kofler, J. Smid-Korbar, Compatibility study between acetylcysteine and some commonly used tablet excipients, J. Pharm. Pharmacol. 44 (1992) 515–518.
[7] A.A.S. Araújo, S. Storpirtis, L.P. Mercuri, F.M.S. Carvalho, M.D.S. Filho, J.R. Matos, Thermal analysis of the antiretroviral zidovudine (AZT) and evaluation of the compatibility with excipients used in solid dosage forms, Int. J. Pharm. 260 (2003) 303–314.
[8] C.E.P. Malan, M.M. de Villiers, A.P. Lötter, Evaluation of compatibility of tablet excipients with albendazole and closantel using DSC and HPLC, Drug Dev. Ind. Pharm. 23 (1997) 533–537.
[9] S. Thumma, M.A. Repka, Compatibility studies of promethazine hydrochloride with tablet excipients by means of thermal and non-thermal methods, Pharmazie 64 (2009) 183–188.
[10] S.G. Late, A.K. Banga, Thermal and non-thermal methods to evaluate compatibility of granisetron hydrochloride with tablet excipients, Pharmazie 63 (2008) 453–458.
[11] M. Tomassetti, A. Catalani, V. Rossi, S. Vecchio, Thermal analysis study of the interactions between acetaminophen and excipients in solid dosage forms and in some binary mixtures, J. Pharm. Biomed. Anal. 37 (2005) 949–955.
[12] P. Mura, A. Manderioli, G. Bramanti, S. Furlanetto, S. Pinzauti, Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients, Int. J. Pharm. 119 (1995) 71–79.
[13] C.E.P. Malan, M.M. de Villiers, A.P. Lötter, Application of differential scanning calorimetry and high performance liquid chromatography to determine the effects of mixture composition and preparation during the evaluation of niclosamide-excipient compatibility, J. Pharm. Biomed. Anal. 15 (1997) 549–557.
[14] A. Marini, V. Berbenni, S. Moioli, G. Bruni, P. Cofrancesco, C. Margheritis, M. Villa, Drug-excipient compatibility studies by physico-chemical techniques – The case of indomethacin, J. Therm. Anal. Calorim. 73 (2003) 529–545.
[15] F. Monajjemzadeh, D. Hassanzadeh, H. Valizadeh, M.R. Siahi-Shadbad, J.S. Mojarrad, T.A. Robertson, M.S. Roberts, Compatibility studies of acyclovir and lactose in physical mixtures, Eur. J. Pharm. Biopharm. 73 (2009) 404–413.
[16] A.A. van Dooren, Design for drug–excipient interaction studies, Drug Dev. Ind. Pharm. 9 (1983) 43–55.
[17] W.-T. Cheng, S.-L. Wang, S.-Y. Lin, Effect of moisture content on the solid-state interaction at the interface between magnesium stearate and captopril, Appl. Surf. Sci. 255 (2008) 2782–2786.
[18] E.A. Schmitt, K. Peck, Y. Sun, J.-M. Geoffroy, Rapid, practical and predictive excipient compatibility screening using isothermal microcalorimetry, Thermochim. Acta 380 (2001) 175–183.
[19] M. Laszcz, B. Kosmacinska, B. Smigielska, M. Glice, W. Maruszak, A. Groman, H. Beczkowicz, L. Zelazko, Study on compatibility on imatinib mesylate with pharmaceutical excipients, J. Therm. Anal. Calorim. 88 (2007) 305–310.
[20] J. Sims, J. Carreira, D. Carrier, S. Crabtree, L. Easton, S. Hancock, A new approach to accelerated drug-excipient compatibility testing, Pharm. Dev. Tech. 8 (2003) 119–126.
[21] D.C. Monkhouse, A. Maderich, Whither compatibility testing? Drug Dev. Ind. Pharm. 15 (1989) 2115–2130.
[22] H. Nyqvist, Saturated salt solutions for maintaining specified relative humidities, Tech. Prod. Mfr. 4 (1983) 47–48.
[23] A.G. Sams, G.K. Mikkelsen, M. Larsen, M. Langgaard, M. Howell, T.J. Schrøder, L.T. Brennum, L. Torup, E.B. Jørgensen, M. Kreilgaard, B. Bang-Andersen, Discovery of Lu AA47070: a phosphonooxymethylene prodrug of 4-(3,3-dimethyl-butyrylamino)-3,5-difluoro-N-thiazol-2-yl-benzamide, a potent and selective hA2A receptor antagonist, J. Med. Chem. 54 (2011) 751–764.
[24] E. Fukui, N. Miyamura, A.M. Kobayashi, A.K. Bansal, Effect of magnesium stearate or calcium stearate as additives on dissolution profiles of diltiazem hydrochloride from press-coated tablets with hydroxypropylmethylcellulose acetate succinate in the outer shell, Int. J. Pharm. 216 (2001) 137–146.
[25] J.T. Carstensen, A. Li Wan Po, The state of water in drug decomposition in the moist solid state: description and modelling, Int. J. Pharm. 83 (1992) 87–94.