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Compatibility studies of aceclofenac with retard tablet excipients by means of thermal and FT-IR spectroscopic methods

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Abstract The compatibility of aceclofenac with various tableting excipients was investigated by means of differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR). The excipients applied in the direct pressing retard tablets were Carbopol 940, hydroxypropyl-methyl-cellulose, microcrystalline cellulose, Aerosil 200 and magnesium stearate. The ingredients alone and their 1:1 (w/w) binary mixtures were investigated before and after accelerated storage. An interaction was observed only between aceclofenac and magnesium stearate. The DSC and FT-IR examinations indicated formation of the magnesium salt of aceclofenac. For the other mixtures, there was no incompatibility between the components.

Keywords Compatibility · Aceclofenac · Magnesium stearate · DSC · FT-IR

Introduction

Compatibility of an active pharmaceutical ingredient (API) with excipients is one of the key factors influencing the stability of a formulation, because the excipients can interact with the active agent both chemically and physically. Chemical interactions between the API and the excipients result in a reduction of the quantity of the API, which can influence the absorption and therapeutic effect. Physical interactions can alter the physicochemical parameters of the components, e.g. the solubility, the dissolution rate and finally the bioavailability. Investigation of the incompatibility between the components of the dosage form is critical in the early stages of the development of a stable dosage form [1–3].

Differential scanning calorimetry (DSC) has been widely used to assess incompatibility between formulation components, because the method is fast and versatile, and requires only a small quantity of sample [1, 4–9]. However, caution needs to be exercised if the results of DSC alone are interpreted. Whenever possible, other techniques such as infrared spectroscopy (IR) and quantitative analysis after storage under stressed conditions should be utilized in conjunction with DSC [10]. As the thermoanalytical methods do not yield direct chemical information, Fourier transform infrared spectroscopic (FT-IR) investigations were used in this work.

Aceclofenac (ACE) ([[[2-[(2,6-dichlorophenyl)amino] phenyl]acetyl]oxy]acetic acid) is a non-steroidal anti-inflammatory agent with good tolerability and efficiency (Fig. 1) [11]. Its pharmacodynamic properties allow its application in retard solid dosage form for the treatment of rheumatoid arthritis, osteoarthritis and spondylitis. This API has a favourable side-effect profile [12–15].

A number of literature articles describe possibilities of producing retard preparations in solid or semisolid dosage forms [16, 17], or of increasing the bioavailability of this active ingredient, and some papers additionally reported on stability investigations. Mutalik et al. prepared and studied

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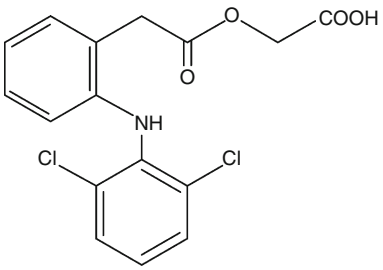

Fig. 1 Chemical structure of aceclofenac

several sustained release tablet formulations. The compatibility between the components was investigated by means of IR and DSC [13]. Patel et al. studied the possibilities of application of mixed surfactant systems in solid dispersions in order to increase the solubility of the API. The solid mixtures were characterized via IR and X-ray diffraction examinations [18]. Vadher et al. investigated the dissolution enhancement effect of co-ground mixtures of aceclofenac and a novel porous carrier. The method was suitable for the conversion of the crystalline API into the amorphous form and stabilization of the latter, which was confirmed by X-ray powder diffraction, DSC analysis and FT-IR [19].

Before the production of solid dosage forms, the compatibility between the API and the excipients must be investigated. In this paper, DSC and FT-IR studies were carried out to evaluate the compatibility of aceclofenac and several potential excipients for the direct pressing of retard tablets.

Materials and methods

Materials

Aceclofenac was used as received from Tecoland (New Jersey, USA). The examined additives in the retard tablets were Carbopol 940 (Noveon Consumer Specialties, Ohio, USA), hydroxypropyl-methyl-cellulose (HPMC, Vivapharm-JRS) (JRS Pharma, Weissenborn, Germany), microcrystalline cellulose (MCC, Vivapur-JRS) (JRS Pharma, Weissenborn, Germany), magnesium stearate (Peter Greven Industries, Venlo, The Netherlands) and Aerosil 200 (Evonik Degussa GmbH, Frankfurt am Main, Germany). Other materials, such as stearic acid and palmitic acid, were purchased from Reanal Co., Hungary.

Preparation of products and storage conditions

Binary component mixtures in 1:1 mass ratio were prepared in a porcelain mortar. The original components were investigated by means of DSC and FT-IR methods. The mixtures were investigated immediately after the preparation and after accelerated storage period (40 °C/75% RH/3 months). The mixture containing magnesium stearate was stored for an additional 3-month period.

Differential scanning calorimetry

A Mettler Toledo DSC 821^e thermal analysis system (Mettler Inc., Schwerzenbach, Switzerland) was used for thermal analysis of the drug-excipient mixtures. Data analysis was performed with the STAR^e thermal analysis program V6.0. Approximately 2–5 mg of aceclofenac, an excipient or their binary mixture was examined in the temperature range between 25 °C and 300 °C, in a normal covered 40 μL Al crucible (three pin holes were applied in the cover). The heating rate was 10 °C min^{-1}. Argon was used as carrier gas at a flow rate of 10 L h^{-1} during the DSC investigation.

Hot-stage microscopy

Microscopic observations of thermal behaviour of materials and their changes during heating were carried out with a LEICA Thermomicroscope (LEICA MZ 6, Germany). The samples were observed under the microscope by using a scanning speed of 2 °C min^{-1}. The magnification in the photographs was 59.7×.

Fourier transform infrared spectroscopy

FT-IR spectra of the API and its binary mixtures were recorded in the interval 4000–400 cm^{-1} with an Avatar 330 FT-IR apparatus (Thermo Nicolet, USA), at 4 cm^{-1} optical resolution. Standard KBr pellets were prepared from IR grade KBr and 0.5 mg of aceclofenac, or 1.0 mg of binary mixture. The spectra were recorded with the use of Omnic V6.1a software, and all spectral manipulations were performed with Thermo-Galactic's GRAMS/AI V7.00 software.

Results

Differential scanning calorimetry

The DSC findings on aceclofenac, the excipients and the binary mixtures after preparation and storage for 3 months or 6 months are presented in Figs. 2, 3, 4, 5, 6 and 8.

The DSC curve of aceclofenac exhibited one sharp endothermic peak at 153.1 °C, caused by the melting of aceclofenac. Chemical decomposition was not detected

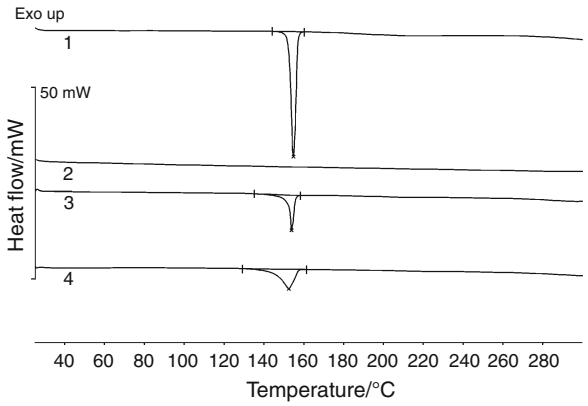

Fig. 2 DSC curves of aceclofenac, Aerosil 200 and mixtures. *1* aceclofenac, *2* Aerosil 200, *3* mixture before storage, *4* mixture after 3-month storage

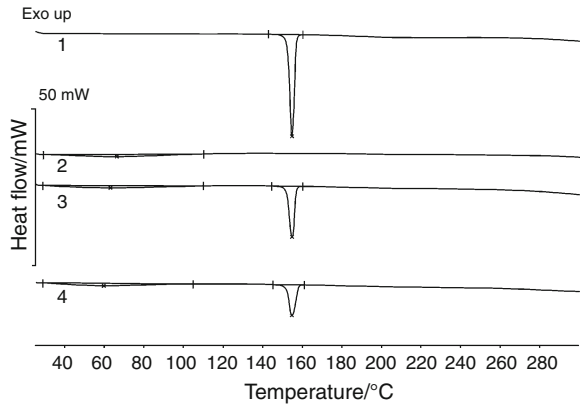

Fig. 3 DSC curves of aceclofenac, MCC and mixtures. *1* aceclofenac, *2* MCC, *3* mixture before storage, *4* mixture after 3-month storage

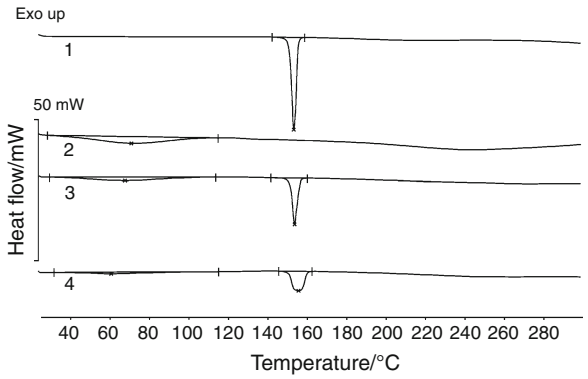

Fig. 4 DSC curves of aceclofenac, Carbopol 940 and mixtures. *1* aceclofenac, *2* Carbopol 940, *3* mixture before storage, *4* mixture after 3-month storage

after the melting; aceclofenac therefore has good thermal stability and does not contain crystal water.

There was no sign of any thermal event in the DSC curve of Aerosil 200. In the case of MCC, a broad

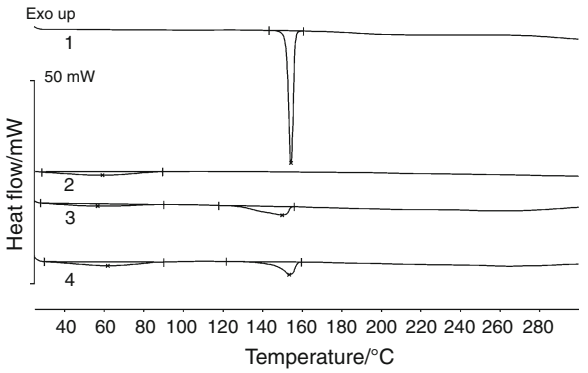

Fig. 5 DSC curves of aceclofenac, HPMC and mixtures. *1* aceclofenac, *2* HPMC, *3* mixture before storage, *4* mixture after 3-month storage

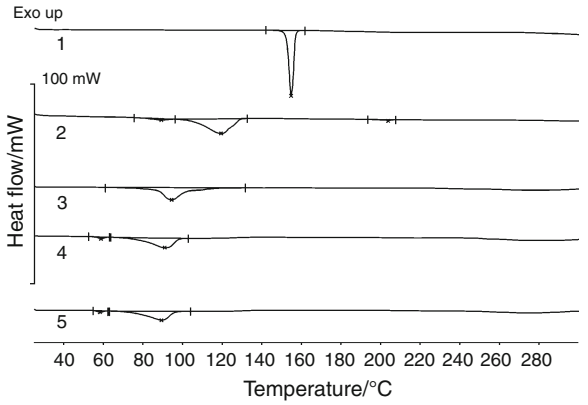

Fig. 6 DSC curves of aceclofenac, magnesium stearate and mixtures. *1* aceclofenac, *2* magnesium stearate, *3* mixture before storage, *4* mixture after 3-month storage, *5* mixture after 6-month storage

endothermic peak was detected between 30 and 100 °C, which denoted the presence of a small quantity of water content. Similar phenomena were observed for Carbopol 940 and HPMC. Magnesium stearate displayed three endothermic signals: a larger one with a peak temperature of 104.5 °C, and two smaller ones at 89.2 and 203.5 °C. None of the excipients gave any thermal signals near the melting peak of aceclofenac, and it was therefore possible to investigate the possibility of interactions between the components of the binary mixtures by DSC. The results of thermal analysis are presented in Table 1.

The onset, peak and endset temperatures and enthalpies of the 1:1 binary mixtures before and after storage for 3 months storage (in the case of magnesium stearate, storage for 6 months too are given in the Table 2).

After storage for 3 months, only one thermal signal was observed in the DSC curve of the binary mixture of aceclofenac and Aerosil 200. The enthalpy change corresponded to the ratio of the components, and the peak temperature was similar to that of aceclofenac, though a

Table 1 Onset, peak and endset temperatures and enthalpies of aceclofenac and tabletting excipients

Material	T_{Onset}/°C	T_{Peak}/°C	T_{Endset}/°C	Enthalpy/J g^{-1}
Aceclofenac	152.09	153.10	156.65	131.69
Aerosil 200	–	–	–	–
MCC	32.56	66.29	107.19	56.27
Carbopol 940	38.06	72.21	107.32	169.40
HPMC	31.88	59.62	87.00	52.24
Magnesium stearate, peak I	79.90	89.21	94.98	8.86
Magnesium stearate, peak II	104.49	118.92	127.35	167.02
Magnesium stearate, peak III	199.34	203.48	206.30	3.43

Table 2 Onset, peak and endset temperatures and enthalpies of 1:1 binary mixtures

Materials	I				II			
	T_{Onset}/°C	T_{Peak}/°C	T_{Endset}/°C	Enthalpy/J g^{-1}	T_{Onset}/°C	T_{Peak}/°C	T_{Endset}/°C	Enthalpy/J g^{-1}
ACE + Aerosil 200 (fresh)	–	–	–	–	151.94	153.21	155.79	46.60
ACE + Aerosil 200 (3 months)	–	–	–	–	145.18	152.04	157.23	64.87
ACE + MCC (fresh)	28.85	62.94	103.94	38.62	151.86	153.85	156.62	64.52
ACE + MCC (3 months)	32.90	59.60	99.63	43.46	151.87	154.13	158.02	56.40
ACE + Carbopol 940 (fresh)	37.43	68.94	102.48	66.18	152.60	154.19	157.67	72.50
ACE + Carbopol 940 (3 months)	43.70	62.10	96.47	24.83	152.04	155.10	159.11	65.18
ACE + HPMC (fresh)	28.42	56.96	84.96	27.80	128.14	150.01	154.52	45.48
ACE + HPMC (3 months)	30.39	62.09	87.47	53.88	148.32	153.28	157.93	48.12
ACE + Magnesium stearate (fresh)	–	–	–	–	86.83	94.07	102.79	135.01
ACE + Magnesium stearate (3 months)	55.84	58.61	61.16	4.55	77.31	90.76	97.76	114.74
ACE + Magnesium stearate (6 months)	55.68	57.94	60.60	5.13	75.57	89.12	95.61	124.29

small extent of peak broadening was seen for the binary mixture (Fig. 2).

The MCC containing physical mixture produced a broad endothermic peak between approximately 30 and 100 °C, demonstrating the water content in the product, similarly as for the original excipient. The enthalpy required for removal of the water corresponded to the weight ratio of the product, and there was no significant increase during storage. The other endothermic peak in the DSC curve was identified with the melting point of aceclofenac and the enthalpy corresponded to the 1:1 weight ratio of the components. Neither the enthalpy, not the peak temperature changed during storage for 3 months (Fig. 3).

Analysis of the Carbopol 940 containing mixture led to similar results as for the MCC containing product. Both the endothermic peak relating to the water content and the melting peak of aceclofenac were detected. The melting peak of the fresh mixture was slightly broadened after the 3-month storage. The storage did not alter the water content of the product either (Fig. 4).

Thus, the melting endotherm of aceclofenac was generally well preserved, with only slight changes in terms of broadening or shifting towards lower temperature. These small changes could be due to the mixing of the components, which lowers their purity and may not necessarily be indicative of potential incompatibility [5].

The HPMC containing mixture contained small amounts of water, similarly as for pure HPMC. The water content increased slightly during storage. However, a more appreciable change was detected in the endothermic signal of the aceclofenac. The endothermic peak was broadened and shifted to lower temperatures in the curves of both the fresh and the stored mixtures (Fig. 5). This phenomenon is presumably caused by some interaction between HPMC and aceclofenac in the mixture [13].

Major alterations were observed in the case of the magnesium stearate containing mixture. The endothermic peak at the melting point of aceclofenac disappeared, and the signals of magnesium stearate were changed. The freshly prepared sample gave a broad endothermic peak with an onset temperature of 86.8 °C, a peak temperature of 94 °C, and an endset temperature of 102.8 °C. This peak was fused with a smaller endothermic one with higher peak temperature. This smaller peak disappeared during storage and a new peak with low enthalpy appeared at 58.6 °C. The DSC curve did not change during the further 3-month

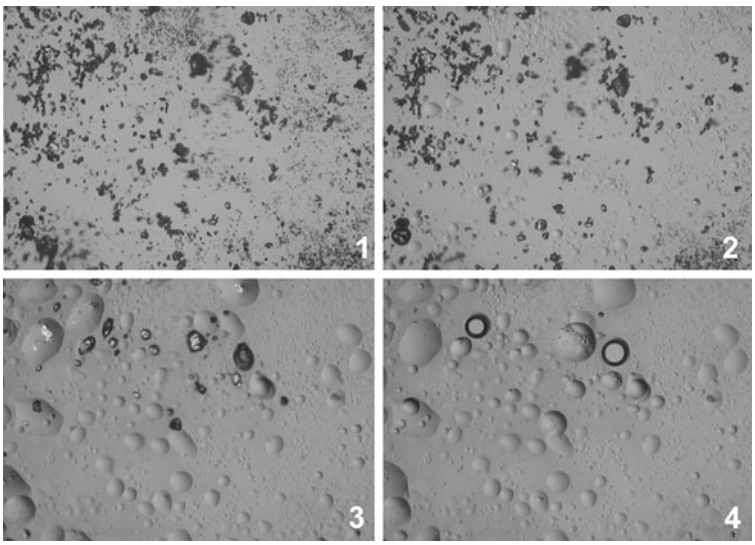

Fig. 7 HSM images of aceclofenac + magnesium stearate mixture. **1** 80 °C, **2** 90 °C, **3** 100 °C, **4** 120 °C

storage (Fig. 6). Hot-stage microscopy performed to investigate the events occurring during temperature increase indicated that the magnesium stearate melted first and the aceclofenac crystals then slowly dissolved in the melt (Fig. 7). This explained the disappearance of the melting endotherm of aceclofenac, and the modification of the peak of magnesium stearate.

The thermoanalytical investigations did not reveal any interaction between aceclofenac and Aerosil 200, MCC or Carbopol 940, whereas interactions may be assumed in the case of HPMC and especially magnesium stearate. The interactions of magnesium stearate with various APIs are a known phenomenon in the literature. Ceschel et al. described the incompatibility of magnesium stearate and acetylsalicylic acid. The decrease in the quantity of that API was measured by HPLC, and the main degradation products were determined [20]. Mura et al. reported that ketoprofen and magnesium stearate formed a eutectic mixture at a composition of about 50% (w/w). Such eutectic behaviour generally does not mean pharmaceutical incompatibility, even if it cannot always be overlooked, since it might cause difficulties with a given composition during processing. In this case, the interaction between the components did not cause any chemical change in the components [5].

As the commercial magnesium stearate used is a mixture of magnesium salts of different fatty acids (mainly stearic acid and palmitic acid, and minor proportions of other fatty acids), the main component fatty acids were studied. The DSC results are presented in Fig. 8. Both stearic and palmitic acids gave one endotherm peak at their melting points: 70.6 °C for stearic acid and 61.4 °C for palmitic acid. Since the new endothermic peak for the aceclofenac–magnesium stearate mixture corresponded to the melting temperature of palmitic acid, we assumed the appearance of this acid during the storage of the aceclofenac–magnesium stearate mixture.

Fourier transform infrared spectroscopy

For a better understanding of the chemical changes in the binary mixtures, FT-IR spectra of the binary mixtures of aceclofenac and the excipients were recorded immediately after preparation and after storage for 3 months, and the corresponding difference spectra were also calculated. The spectra of the fresh mixtures were subtracted from those of the stored ones, the ester carbonyl stretching band of aceclofenac at 1771 cm^{-1} being used as reference. The spectra were evaluated to assess the possible interactions of the components.

The IR spectrum of pure aceclofenac shows characteristic peaks at 966.21 cm^{-1} (O–H bending out of plane), 3,319.10 cm^{-1} (secondary amine N–H stretching or O–H stretching), 1770.40 cm^{-1} (–C=O stretching), 1,578.7 cm^{-1}, 1,508.1 cm^{-1} (aromatic –C=C stretching), and some prominent bands such as 1,344.2–1,257.4 cm^{-1} (–C–O stretching).

Most of the difference spectra demonstrated that the components of the binary mixtures did not influence each other appreciably under the given conditions or during storage. Slight shifts or slight changes in relative intensity, e.g. as seen in Fig. 9, cannot be considered indications of real interaction between the components, since the preparation of the fresh samples disturbed the physical state of the components and the storage period allowed them to return to the thermodynamically more stable state, which left minor changes in the spectra. Such phenomena were observed for the Aerosil 200, MCC or Carbopol 940 containing mixtures after storage.

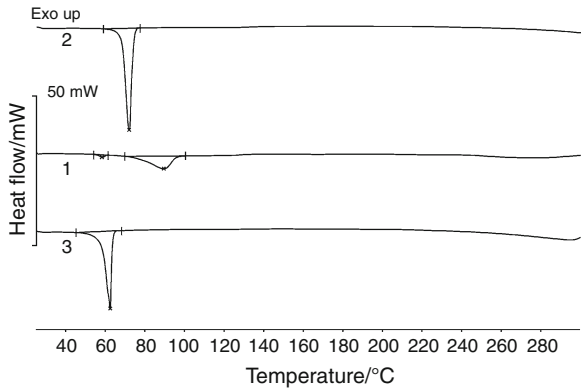

Fig. 8 DSC curves of aceclofenac, magnesium stearate mixture and fatty acids. *1* mixture after 6-month storage, *2* stearic acid, *3* palmitic acid

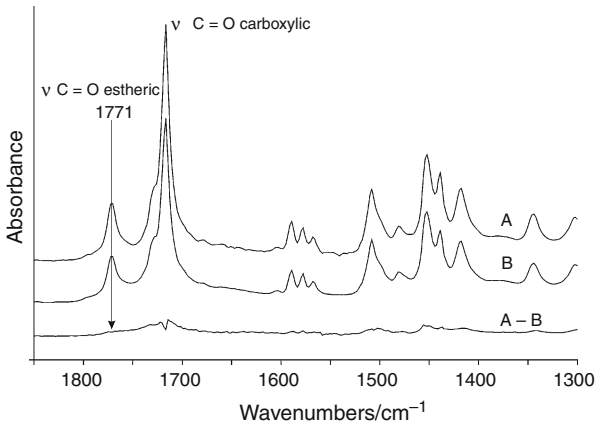

Fig. 10 FTIR spectra of HPMC containing mixtures. *A* freshly prepared mixture, *B* mixture after storage for 3 months, $A - B$ difference spectrum

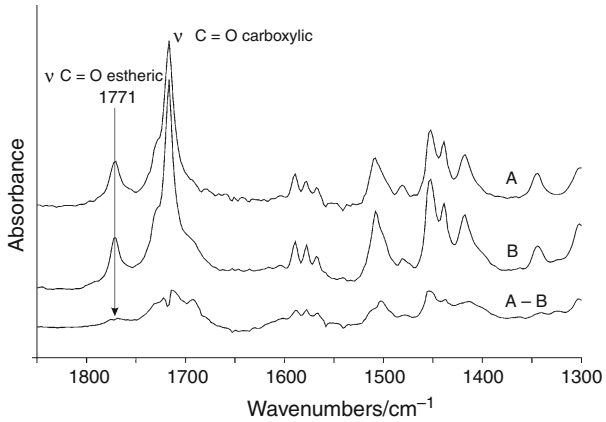

Fig. 9 FTIR spectra of Aerosil 200 containing mixtures. *A* freshly prepared mixture, *B* mixture after storage for 3 months, $A - B$ difference spectrum

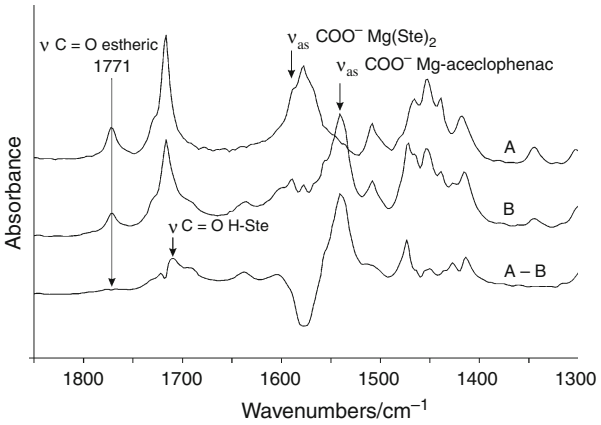

Fig. 11 FTIR spectra of magnesium stearate containing mixtures. *A* freshly prepared mixture, *B* mixture after storage for 3 months, $A - B$ difference spectrum

The DSC curve of the aceclofenac–HPMC binary mixture indicated a certain extent of physical interaction between the components, but the FT-IR examination ruled out any chemical change. The slight shifts and relative intensity changes were somewhat similar to those for the previous components (Fig. 10).

The only real exception was the mixture of aceclofenac and magnesium stearate, where strong peaks either developed or disappeared during the storage period, as shown in Fig. 11. The asymmetric stretching band of magnesium stearate at 1578 cm^{-1} was missing from the spectrum of the stored mixture, whereas a new band appeared at 1540 cm^{-1}. Since the 1:1 (w/w) mixture contains aceclofenac and magnesium stearate in a molecular ratio of 6:4, the total amount of the stearate ion can be replaced by the carboxylate group of aceclofenac, while some of the latter remains unreacted. The band at 1709 cm^{-1} in the difference spectrum, characteristic of free fatty acids, supports the above explanation of the spectral changes.

Conclusions

This study related to the compatibility of aceclofenac and excipients used for the preparation of retard tablets (1:1 w/w). The DSC curves and FT-IR spectra of aceclofenac, the excipients alone, and their fresh and stored binary mixtures were analyzed.

The DSC and FT-IR results indicated that the Aerosil 200, MCC and Carbopol 940 containing binary mixtures were stable, and that there was no incompatibility between aceclofenac and these excipients. The aceclofenac–HPMC mixture displayed some physical interaction according to the DSC results, but the FT-IR study ruled out any chemical change. However, chemical change did occur in the magnesium stearate containing mixture, which was detectable in both the DSC and the FT-IR curves. The absence of the endothermic peak of aceclofenac and the modification of the peak of the excipient indicated physical interaction between the components (the melted

magnesium stearate dissolved the aceclofenac). The changes in the FT-IR spectra revealed that the interaction of aceclofenac and magnesium stearate was accompanied by the formation of a small quantity of free palmitic acid and the magnesium salt of aceclofenac. The content of the magnesium stearate in solid dosage forms is generally very low (0.5–1%), and considerably less than the examined 1:1 ratio. Moreover, the tablet contains several other excipients, and thus the interaction identified between aceclofenac and magnesium stearate will probably not influence the stability of the product. Accordingly, application of the examined excipients gives a possibility to prepare a suitable retard solid product with appropriate stability.

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References

1. Thumma S, Repka MA. Compatibility studies of promethazine hydrochloride with tablet excipients by means of thermal and non-thermal methods. Pharmazie. 2009;64:183–9.
2. Crowley P, Martini L. Drug-excipient interactions. Pharm Technol Eur. 2001;13:26–34.
3. McDaid FM, Barker SA, Fitzpatrick S, Petts CR, Craig DQM. Further investigations into the use of high sensitivity differential scanning calorimetry as a means of predicting drug–excipient interactions. Int J Pharm. 2003;252:235–40.
4. Kiss D, Zelkó R, Novák Cs, Éhen Zs. Application of DSC and NIRs to study the compatibility of metronidazole with different pharmaceutical excipients. J Therm Anal Calorim. 2006;84:447–51.
5. Mura P, Manderioli A, Bramanti G, Furlanetto S, Pinzauti S. Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients. Int J Pharm. 1995;119:71–9.
6. Rezende RLO, Santoro MIRM, Matos JR. Stability and compatibility study on enalapril maleate using thermoanalytical techniques. J Therm Anal Calorim. 2008;93:881–6.
7. Araújo AAS, Storpirtis S, Mercuri LP, Carvalho FMS, Filho MS, Matos JR. Thermal analysis of the antiretroviral zidovudine (AZT) and evaluation of the compatibility with excipients used in solid dosage forms. Int J Pharm. 2003;260:303–14.
8. Zaccaron CM, Oliveira RVB, Guiotoku M, Pires ATN, Soldi V. Blends of hydroxypropyl methylcellulose and poly(1-vinylpyrrolidone-co-vinyl acetate): miscibility and thermal satibility. Polym Degrad Stab. 2005;90:21–7.
9. Schmitt EA, Peck K, Sun Y, Geoffroy J-M. Rapid, practical and predictive excipient compatibility screening using isothermal microcalorimetry. Thermochim Acta. 2001;380:175–83.
10. Verma RK, Garg S. Selection of excipients for extended release formulations of glipizide through drug–excipient compatibility testing. J Pharm Biomed Anal. 2005;38:633–44.
11. Hasan NY, Abdel-Elkawy M, Elzeany BE, Wagieh NE. Stability indicating methods for the determination of aceclofenac. Il Farmaco. 2003;48:91–9.
12. Chopra D, Sinha VR, Singh M. Thermal and isothermal methods in development of sustained release dosage forms of ketorolac tromethamine. J Chem. 2008;5:316–22.
13. Mutalik S, Naha A, Usha AN, Ranjith AK, Musmade P, Manoj K, Anju P, Prasanna S. Preparation, in vitro, preclinical and clinical evaluations of once daily sustained release tablets of aceclofenac. Arch Pharm Res. 2007;30:222–34.
14. Parfitt K. Analgesics, anti-inflammatory and antipyretics. In: Reynolds JEF, editor. Martindale the complete drug reference. 32nd ed. London: Pharmaceutical Press; 1999. p. 2–12.
15. Burrull M, Madridejos R, Gregori A, Busquets E. Non-steroid anti-inflammatory agents and gastrointestinal protection: adequate prescription in primary care? Aten Primaria. 1996;18:507–10.
16. Mutalik S, Anju P, Manoj K, Usha AN. Enhancement of dissolution rate and bioavailability of aceclofenac: a chitosan-based solvent change approach. Int J Pharm. 2008;351:279–90.
17. Tran TT-D, Tran PH-L, Lee B-J. Dissolution–modulating mechanism of alkalizers and polymers in a nanoemulsifying solid dispersion containing ionizable and poorly water-soluble drug. Eur J Pharm Biopharm. 2009;72:83–90.
18. Patel AR, Joshi VY. Evaluation of SLS: APG mixed surfactant systems as carrier for solid dispersion. AAPS Pharmscitech. 2008;9:583–90.
19. Vadher AH, Parikh JR, Parikh RH, Solanki AB. Preparation and characterization of co-grinded mixtures of aceclofenac and Neusilin US_2 for dissolution enhancement of aceclofenac. AAPS Pharmscitech. 2009;10:606–14.
20. Ceschel GC, Badiello R, Ronchi C, Maffei P. Degradation of components in drug formulations: a comparison between HPLC and DSC methods. J Pharm Biomed Anal. 2003;32:1067–72.