Drug Development and Industrial Pharmacy, 31:943–949, 2005

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500306153

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Compatibility Studies Between Ibuprofen or Ketoprofen with Cellulose Ether Polymer Mixtures Using Thermal Analysis

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ABSTRACT Differential scanning calorimetry (DSC) was used to investigate and detect incompatibilities between drugs such as: ibuprofen (IBU) or ketoprofen (KETO) with cellulose ether derivatives, which are frequently applied on controlled release dosage forms. Binary mixtures concerning methylcellulose (MC25) or hydroxypropylcellulose (HPC) with hydroxypropylmethylcellulose (HPMC) K15M or K100M in different ratios were prepared and evaluated by the appearance, shift, or disappearance of peaks and/or variations in the corresponding ΔH values. According to the DSC results, binary mixtures between those polymers were found to be compatible, but their mixture with IBU or KETO, promotes a solid–solid interaction mainly with 1:1:1 (w/w) ratio (drug-excipient). However, when the drug:excipient interactions were detected, they were not found to affect the drug bioavailability. DSC was successfully employed to evaluate the compatibility of the drugs with the selected polymers.

KEYWORDS Ibuprofen, Ketoprofen, DSC, Cellulose ether derivatives, Drug-polymer interaction, Thermal analysis

INTRODUCTION

The pharmaceutical development of solid dosage forms should imply a previous preformulation study of the drug and excipients. Since tablet and capsules oral sustained release dosage forms are commonly prepared by incorporating the drug in one or more gel forming agent(s), compatibility screening must be considered. In fact, for preformulation screening investigation, thermal analysis can be applied to provide information on physicochemical properties of substances, and, it is proved to be useful in the characterization of substances with respect to compatibility by forecasting future problems of stability prior to the final solid dosage formulation (Byrn et al., 1994; Verma & Garg, 2004). The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients

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which are added for administration improvement, promotion of consistent release, bioavailability of the drug, and predicting of degradation (Budavári et al., 1999).

Different methods can be applied in order to get structural information on a certain species as well as to understand interactions between the active agent and several distinct compounds (excipients and/or carriers). Among them, differential scanning calorimetry (DSC) has been widely used as a rapid thermal method for assessing the drug–excipient interaction because this method is fast, versatile, and uses only milligrams of sample (Smith, 1982). On the other hand, this technique, which allows a rapid evaluation of possible incompatibilities, may be deduced from the appearance, shift, or disappearance of peaks and/or variations in the corresponding ΔH values (Botha & Lotter, 1989).

The analysis of the DSC curves may predict an interaction but do not necessarily provide information about the nature of this event, only its likelihood when comparing the thermal behaviors of the drug and excipients alone with those of the physical mixture. Sometimes the interpretation of the thermal data is not always simple because when two substances are mixed, the purity of each is reduced and generally slightly lower melting points result and, therefore, a solid–solid interaction is weak or non-existent (Holgado et al., 1995). These considerations must be taken into account when DSC thermograms interpretations are performed. Some DSC studies (Botha & Lotter, 1989; De Villiers et al., 1999; Gordon et al., 1984; Mura et al., 1995, 1998, 1999, 2001) are reported in literature for the thermal analysis between ibuprofen (IBU) or ketoprofen (KETO) with different excipients. However, none of these studies involve ether polymer mixtures.

Cellulose ether derivatives were selected as the test material for the present study since they are one of the most frequently used excipients as the basis for controlled release hydrophilic in matrix systems. Methylcellulose (MC), hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC) K15M or K100M are a class of semisynthetic polymers obtained from a chemical reaction of the hydroxyl groups at positions 2, 3, and/or 6 of anhydroglucose residues of cellulose (Gómez-Carracedo et al., 2003; Kumar & Banker, 1993). Their popularity includes non-toxic nature, ease of compression, and their ability to accommodate a large load of drug (Ebube & Jones, 2004). In fact, Alvarez-Lorenzo et al. (2000) have reported that the properties of those polymers depend not only on the type of substituents, but also on the degree of substitution (DS), the average number of modified hydroxy groups per glucose residue, and the distribution of the substituents along the polymer chain. Although these polymers display a broad endothermic effect at 60–140°C corresponding to moisture loss, their chemical substitution levels are different from each other. They are available in a wide range of molecular weights and are classified on the basis of the viscosities of their 2% w/w aqueous solution.

Paying attention to previous considerations, the aim of the present study is to enable the successful use of thermal analysis by recognizing the physicochemical properties of drugs and excipients that affect drug performance in order to provide a rationale formulation design.

DSC was undertaken to establish the compatibility of IBU or KETO, two non-steroidal anti-inflammatory drugs (NSAIDs), with a polymer mixture usually compressed into tablets. This was achieved by comparing the DSC thermograms of the drug (IBU/

TABLE 1 **Cellulose Ether Polymers Grades**[a]

Polymer	Methoxyl %	Hydroxypropoxyl %	Viscosity (mPa.s)[b]	Brand®	Lot number
MC25	27.5–32	0	10–25	Methocel A	MFCD00081763
HPC	0	53.4–77.5	1500–3000[c]	Klucel HF	8174
HPMC K15M	19–24	7–12	6138–9030	Methocel K 15M	OG20012N31
HPMC K100M	19–24	7–12	16922–19267	Methocel K 100M	OB12012N11

[a]According to the supplier.
[b]Apparent viscosity, 2% aqueous solution at 20°C, mPa.s according to the supplier.
[c]Apparent viscosity, 1% aqueous solution at 20°C, mPa.s according to the supplier.

KETO) and each one of the investigated mixtures. The following work is, hopefully, allowing the selection of the polymers that can be more suitable on preparation of controlled release matrix tablets.

MATERIALS AND METHODS

Materials

Ibuprofen (IBU) batch no. 9907257 was purchased from Knoll, Nottingham, England. Ketoprofen (KETO) batch no. 043K0684 was purchased from Sigma-Aldrich Chemie, Germany. Polymers obtained were methylcellulose, Methocel® (MC25) Fluka, Buchs, Switzerland; hydroxypropylcellulose, (HPC) Klucel, HF, Wilmington, DE, USA. Hydroxypropylmethylcellulose, Methocel® (HPMC K15M) and Methocel® (HPMC K100M), was obtained from Colorcon, Dartford, England. Table 1 summarizes the properties of the cellulose ether polymers grades.

Preparation of Binary and Ternary Solid Systems

Physical mixtures (PM) of MC25 or HPC with HPMC (K15M or K100M) in a 1:1 (w/w) or 1:3 (w/w) ratios were prepared by previously sieving each component and subsequently mixing them in a glass mortar for 10 min. Concerning ternary physical mixtures, the drug (IBU or KETO) was prepared using the same methodology previously described. The composition of the binary and ternary mixture is shown in Table 2.

Differential Scanning Calorimetry Measurements (DSC)

Differential scanning calorimetry (DSC) measurements were performed using a Shimadzu DSC-50 with a thermal analyzer (Shimadzu TA-50, Tokyo, Japan). About 3 mg of either drug or polymer mixture, or 6 mg of the drug/polymer mixture 1:1 (w/w) were analyzed in sealed aluminium pans under nitrogen flow (20 mL/min), at a heating rate of 10°C/min, from 25 to 250°C. An empty sealed pan was used as reference. The equipment was calibrated with indium (99.98%, m.p.156.65°C, Aldrich®, Milwaukee, USA).

RESULTS AND DISCUSSION

It is well known that prior to the development of any dosage form with a new or old drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This

TABLE 2 Physical Binary and Ternary Mixtures of the Components

Code	Mixture components	Ratio drug–excipient (w/w)
A	MC25+HPMC K15M	1:1
B	MC25+HPMC K15M	1:3
C	HPC+HPMC K15M	1:1
D	HPC+HPMC K15M	1:3
E	MC25+HPMC K100M	1:1
F	MC25+HPMC K100M	1:3
G	HPC+HPMC K100M	1:1
H	HPC+HPMC K100M	1:3
I/I1	IBU/KETO	—
J/J1	IBU/KETO+MC25+HPMC K15M	1:1:1
K/K1	IBU/KETO+MC25+HPMC K15M	3:0.25:0.75
L/L1	IBU/KETO+HPC+HPMC K15M	1:1:1
M/M1	IBU/KETO+HPC+HPMC K15M	3:0.25:0.75
N/N1	IBU/KETO+MC25+HPMC K100M	1:1:1
O/O1	IBU/KETO+MC25+HPMC K100M	3:0.25:0.75
P/P1	IBU/KETO+HPC+HPMC K100M	1:1:1
Q/Q1	IBU/KETO+HPC+HPMC K100M	3:0.25:0.75

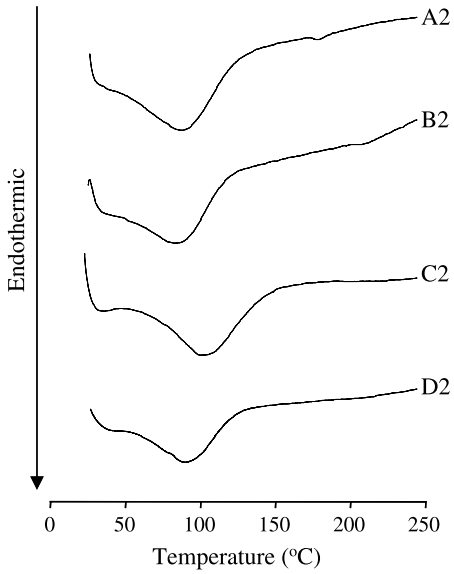

FIGURE 1 **DSC Curves of Individual Polymers. MC25 (A2), HPC (B2), HPMC K15M (C2), HPMC K100M (D).**

information will dictate many of the subsequent events and possible approaches in formulation development.

Hydrophilic polymers, as well as other excipients, contain reactive functional groups that may give rise to chemical and physical transformations. Thus, when studying new pharmaceutical formulations, it is important to verify the possibility of occurrence of incompatibilities between the components of the tablet. The evaluation of the DSC curves were analyzed according to the postulate by Van Dooren and Duphar (1983). In the first phase of the study, compatibility of polymer mixture was tested using the ratio mentioned in Table 2. Thermal curve of polymers MC25, HPC, HPMC K15M, and HPMC K100M has been recently investigated exhibiting a large broad endothermic effect over a temperature range of 30 to 100°C which may be due to water loss (Vueba et al., 2004). Actually, previous studies on cellulose reported the occurrence of endotherms above 100°C, which were attributed to dehydration (Ford, 1999; McPhillips et al., 1999). The DSC curves of the 1:1 and 1:3 (w/w) mixtures from binary systems MC25/HPMC K15M or MC25/HPMC K100M and HPC/HPMC K15 or HPC/HPMC K100M were very similar to those recorded for the DSC curves of MC25, HPC, HPMC K15M, and HPMC K100M (Fig. 1), where a large broad endothermic effect over a temperature range from 30 to 100°C was observed due to their dehydration (Fig. 2a,b). This hypothesis may suggest the absence of interaction between mixtures of the referred polymers since no other endothermic effect event was found.

The interactions between IBU/KETO and a distinct polymer mixture [1:1 or 1:3 (w/w)] were then investigated by DSC as shown in Figs. 3a,b and 4a,b. Peak temperature and enthalpy values of drug in various excipient mixtures are summarized in Tables 3 and 4. DSC trace of ibuprofen (Fig. 2a, I) displayed a single sharp endothermic peak at (T peak = 76.19°C, T onset = 68.26°C) corresponding to its melting point (Higginis et al., 2001) and the apparent heat of fusion was (ΔHf corr = 146.64 J/g); whereas, the thermal curve of ketoprofen (Fig. 3a, I1) showed a single

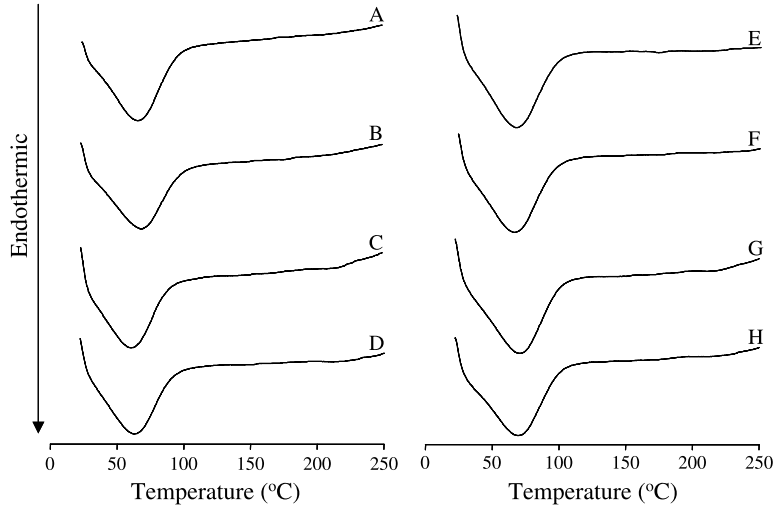

FIGURE 2 **A. DSC Curves of Binary Systems Containing Physical Mixtures of Polymers 1:1 (w/w) and/or 1:3 (w/w). MC25-HPMC K15M (A), MC25-HPMC K15M (B), HPC-HPMC K15M (C), HPC-HPMC K15M (D). b. DSC Curves of Binary Systems Containing Physical Mixtures of Polymers 1:1 (w/w) and/or 1:3 (w/w). MC25-HPMC K100M (E), MC25-HPMC K100M (F), HPC-HPMC K100M (G), HPC-HPMC K100M (H).**

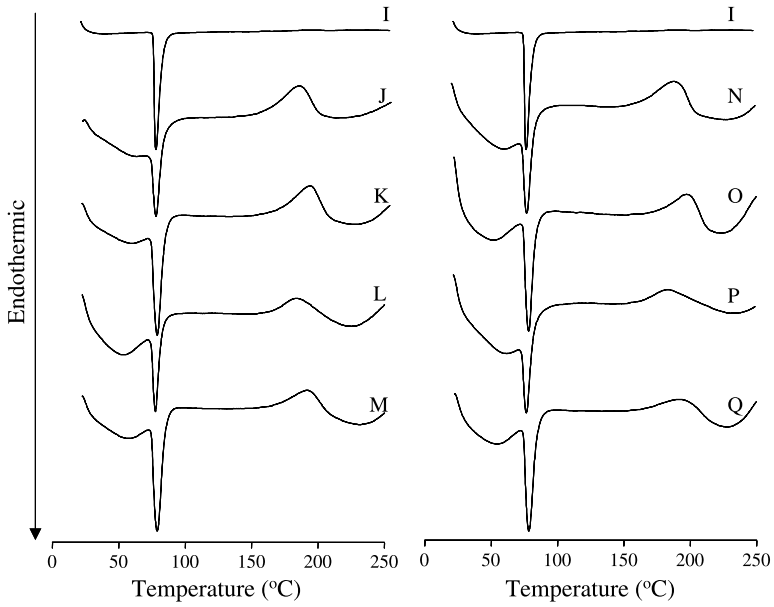

FIGURE 3 **A. DSC Curves of Ibuprofen (IBU) and Binary Systems Containing Physical Mixtures of Polymers 1:1 (w/w) and/or 1:3 (w/w). IBU (I), IBU-MC25-HPMC K15M (J), IBU-MC25-HPMC K15M (K), IBU-HPC-HPMC K15M (L), IBU-HPC-HPMC K15M (M). B. DSC Curves of Ibuprofen (IBU) and Binary Systems Containing Physical Mixtures of Polymers 1:1 (w/w) and/or 1:3 (w/w). IBU (I), IBU-MC25-HPMC K100M (N), IBU-MC25-HPMC K100M (O), IBU-HPC-HPMC K100M (P), IBU-HPC-HPMC K100M (Q).**

sharp endothermic peak that was detected at (T peak = 97.03°C, T onset = 88.53°C) the corresponding melting point of the drug (Liversidge, 1989) and the apparent heat of fusion (ΔHf corr = 124.57 J/g).

Regarding the 1:1 or 1:3 drug:excipient mixtures studied, the corresponding thermograms (Figs. 2a,b and 3a,b) were found not to be a simple superposition of those obtained for each component separately. In effect, there were slight changes in the peak shape. Reduction peak, as shown on termograms J, L, N, and P for ibuprofen and termograms J1, L1, N1, and P1 for ketoprofen, could be attributed to the mixing process that lowers the purity of each component in the mixture. Except in the case of J, K mixtures (Table 3)

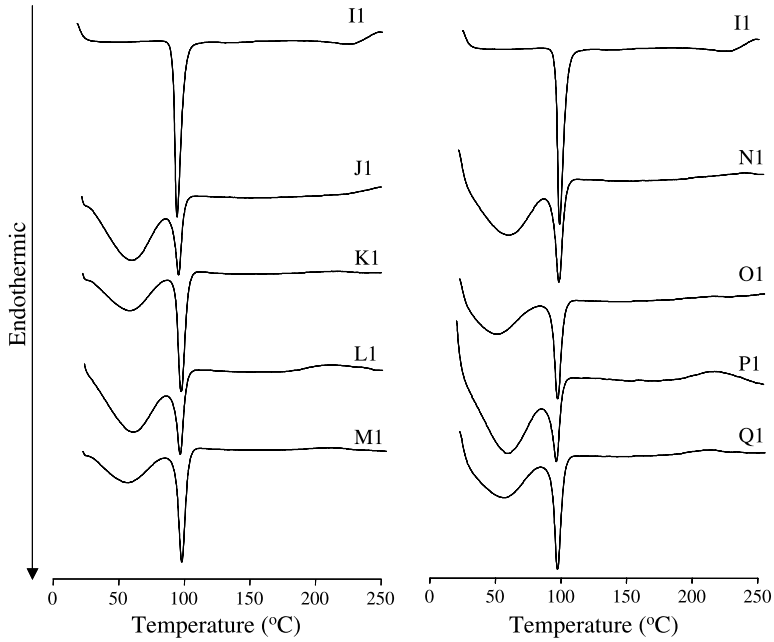

FIGURE 4 **A. DSC Curves of Ketoprofen (KETO) and Binary Systems Containing Physical Mixtures of Polymers 1:1 (w/w) and/or 1:3 (w/w). KETO (I1), KETO-MC25-HPMC K15M (J1), KETO-MC25-HPMC K15M (K1), KETO-HPC-HPMC K15M (L1), KETO-HPC-HPMC K15M (M1). B. DSC curves of ketoprofen (KETO) and binary systems containing physical mixtures of polymers 1:1 (w/w) and/or 1:3 (w/w). KETO (I1), KETO-MC25-HPMC K100M (N1), KETO-MC25-HPMC K100M (O1), KETO-HPC-HPMC K100M (P1), KETO-HPC-HPMC K100M (Q1).**

TABLE 3 Peak Temperature and Enthalpy Values of IBU in Various Drug–Polymer Mixtures

Code	Ratio (drug–excipient) (w/w)	*T* peak (°C)	*T* onset (°C)	*T* endset (°C)	ΔHf corr (J/g^{-1})[a]
I	—	76.19	68.26	84.88	146.64
J	1:1:1	78.09	72.94	84.84	92.83
K	3:0.25:0.75	78.73	72.00	86.33	81.10
L	1:1:1	77.94	71.35	86.37	66.37
M	3:0.25:0.75	78.95	72.09	87.31	94.12
N	1:1:1	78.10	75.55	83.35	72.94
O	3:0.25:0.75	78.92	71.91	87.27	92.39
P	1:1:1	77.71	71.38	83.34	66.34
Q	3:0.25:0.75	78.97	72.84	86.77	84.69

[a] ΔHf corr = ΔHf obs/% IBU in sample $\times$ 100. [From Verma and Garg, 2004.]

and N1, O1 mixtures (Table 4), interestingly enough, was to observe for ibuprofen–polymer mixture and for ketoprofen–polymer mixture, the ΔHf corr (J/g^{-1}) obtained in 1:1:1 (w/w) ratio (drug-excipient) was higher than those containing a (3:0.25:0.75) ratio (Tables 3 and 4). This may be attributed to the amount of the drug preserved in the majority of cases. On the other hand, according to the results shown in Tables 3 and 4, there was a significant reduction in the enthalpy values in 1:1:1 (w/w) ratios (drug–excipient) for the mixture of both drugs with the polymer mixtures. The appearance of this points toward a possible solid–solid interaction but not necessarily an incompatibility. It is suggested that before using this ratio 1:1 (w/w) in the formulation, it is necessary to confirm by utilizing other techniques.

In general, in all cases, the thermograms of both drugs were well retained at 76.19°C (+2°C) for ibuprofen (Table 3) and 97.03 (−2°C) for ketoprofen (Table 4), indicating that the drug is compatible with cellulose ether polymer mixture. In reality, there is a clear downward shift of the dehydration excipient signal relative to the free polymer mixture, probably due to the presence of a non-negligible drug:excipient interaction. Actually, polymers with hydrophilic groups such as hydroxyl, have various strengths of interaction with water (Hatakeyama & Hatakeyama, 1998; Nokhodchi et al., 1997). The mechanical properties of cellulose ethers are affected by this interaction (Nokhodchi et al., 1996a, 1996b). Water can gel the polymer or form stable bridges through hydrogen bonding resulting, for instance, in the production of strong compacts. The thermal properties of polymers and water are both influenced by this interaction. So, it is possible to emphasize that this could be responsible for a loosening of the water–polymer binding strength, due to a certain competition from the drug ionizable groups (e.g., carboxylates).

CONCLUSIONS

In the preformulation stability screening, in order to formulate a ibuprofen or ketoprofen controlled dosage form from the DSC thermograms of the mixtures studied, it was possible to detect some drug:excipient interactions that were found to affect mainly the corresponding hydration/dehydration processes. However, compatibility between those drugs

TABLE 4 Peak Temperature and Enthalpy Values of KETO in Various Drug–Polymer Mixtures

Code	Ratio (drug–excipient) (w/w)	*T* peak (°C)	*T* onset (°C)	*T* endset (°C)	ΔHf corr (J/g^{-1})[a]
I1	—	97.03	88.53	105.69	124.57
J1	1:1:1	95.63	88.36	103.19	63.94
K1	3:0.25:0.75	97.68	90.34	107.43	89.45
L1	1:1:1	96.02	89.63	102.73	58.30
M1	3:0.25:0.75	97.51	86.97	107.98	74.10
N1	1:1:1	96.99	88.93	103.42	89.35
O1	3:0.25:0.75	97.50	90.75	103.99	73.82
P1	1:1:1	95.01	89.27	101.03	34.41
Q1	3:0.25:0.75	97.32	90.48	104.71	66.33

[a] ΔHf corr = ΔHf obs/% KETO in sample $\times$ 100. [From Verma and Garg, 2004.]

and the polymer mixture were observed. The present study demonstrates the successful application of the DSC technique to assess compatibility investigation of drugs and excipients, namely, those used in the development of controlled release systems.

ACKNOWLEDGMENTS

M. L. Vueba acknowledges PhD fellowship from Gabinete de Relações Internacionais da Ciência e do Ensino Superior (GRICES) and Fundação para Ciência e Tecnologia (FCT) for financial support (Portugal).

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