Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt

Differential scanning calorimetry to investigate the compatibility of ciprofloxacin hydrochloride with excipients

M. FATHY, M. A. HASSAN and F. A. MOHAMED

The compatibility between ciprofloxacin hydrochloride (CFX) and some excipients was evaluated using differential scanning calorimetry (DSC). Physical mixture, coground mixture, compressed mixture and kneaded mixture were prepared to study the effect of sample manipulation. In addition, the samples of physical mixture were also accelerated at 55 °C for three weeks to obtain more reliable conclusions. Different types of excipients currently used in tablet or capsule formulations namely, calcium phosphate dibasic dihydrate (Emcompress®), magnesium stearate lactose, sorbitol, mannitol, croscarmellose sodium (Ac-Di-Sol®), sodium carboxymethyl starch (Primojel®), microcrystalline cellulose (Avicel® PH 101, Emcocil®) were examined. The DSC scan of CFX displayed two endothermic peaks probably as a result of a fusion process followed by a decomposition process. CFX appeared to interact with sorbitol, mannitol, Ac-Di-Sol, Primojel, Avicel PH 101 and Emcocil.

1. Introduction

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients [1]. Because the drug has intimate contact with the excipients, assessment of possible interactions between an active substance and different excipients is an important part of the development of dosage forms. A number of techniques can be used to indicate the interaction in drug-excipient systems, including chromatography (HPLC and TLC), infrared spectroscopy (IR) and differential scanning calorimetry (DSC).

In the last decade, DSC has found increasing use in detection of incompatibilities in drug-drug and drug-excipient interaction [2–9]. DSC is one of the valuable tools in the preformulation study to temporarily replace the long-term stability test and gives fast and reliable information about possible interactions. The interactions were deduced from DSC curves by observing changes in thermal events such as disappearance of melting peak, appearance of a new peak, changes in peak shape, peak onset or peak maximum temperature and/or variation in the corresponding ΔH values [10–12].

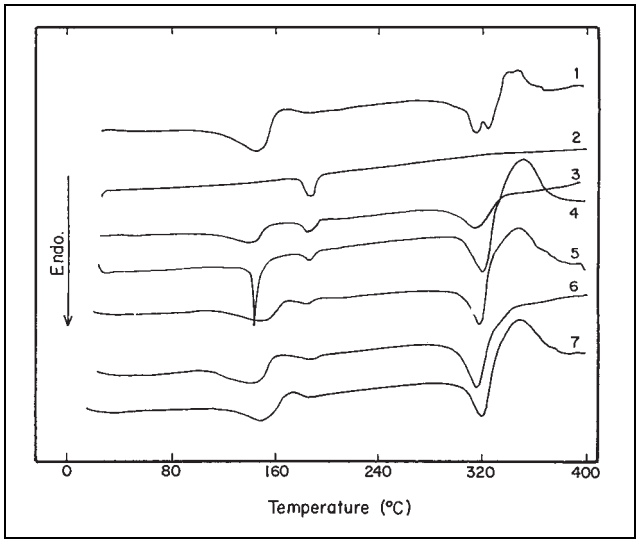

Fig. 1: DSC thermograms of ciprofloxacin HCl (CFX) and Emcompress. 1, CFX; 2, Emcompress; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

Ciprofloxacin, CFX, (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-yl quinoline-3-carboxylic acid) is a DNA gyrase inhibitor used as an antimicrobial agent. The efficacy of CFX has led to its use in the treatment of various bacterial diseases [13–15]. CFX as hydrochloride salt is used in preparations for oral and ophthalmic administration while the base or lactate are used for intravenous infusion.

This study was undertaken to determine the thermal behavior of CFX hydrochloride and to establish the compatibility of the drug with a number of commonly used tablet and capsule excipients. A 1 : 1 mixture of drug and excipient was prepared and the thermal properties thereof evaluated using DSC. Although this ratio is not likely to be used in practice, 1 : 1 mixtures were studied to maximize the likelihood of observing possible interactions. Different treatments for the physical mixtures were performed to simulate stress the drug is faced during its manufacture in oral dosage forms. Coground mixture, compressed blend, kneaded mixture and accelerated samples (at 55 °C for three weeks) were prepared and analysed using DSC.

2. Investigations, results and discussion

2.1. Thermal behavior of ciprofloxacin hydrochloride

In relation to the drug thermal study, The DSC scan of CFX hydrochloride (Trace 1, Figs. 1–9) showed two endothermic peaks; The first one corresponding to a fusion process (m.p. 315.1 °C) and the second one corresponding to a decomposition process (325.1 °C). In this study, the total enthalpy based on the total area under the endothermic peaks, 58.56 J/g, was considered. This value should be considered as approximate, due to the difficulty of exactly evaluating the endothermic melting peak, being this one immediately followed by the other endothermic peak due to decomposition. Moreover, an shallow peak starting at 111.8 °C with a maximum at 145.3 °C could be attributed to the water evaporation.

2.2. Compatibility studies

Trace 2 of the Figs. 1–9 indicated the DSC thermograms of different excipients. Different types of endothermic peaks could be noticed such as shallow and broad peak (Emcompress, Mg stearate), sharp peak (lactose, mannitol, sorbitol), exothermic peak (Ac-Di-Sol, Primojel) and

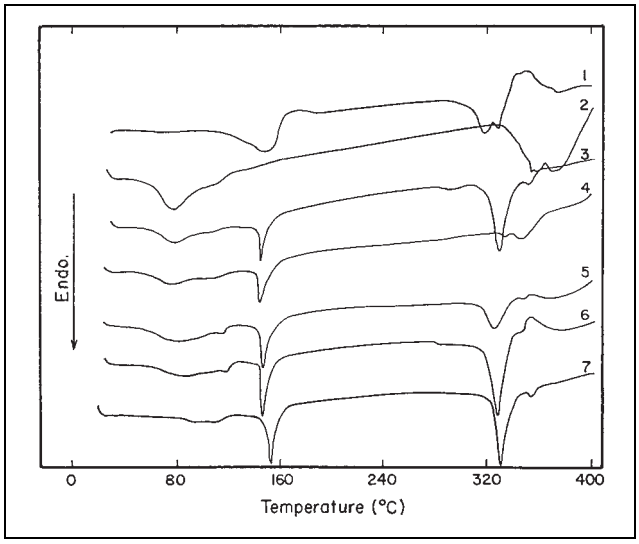

Fig. 2: DSC thermograms of ciprofloxacin HCl (CFX) and Mg stearate. 1, CFX; 2, Mg stearate; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

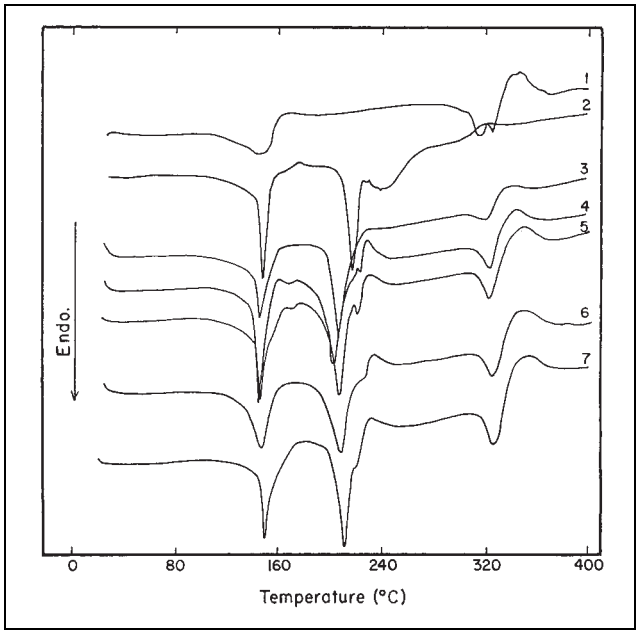

Fig. 3: DSC thermograms of ciprofloxacin HCl (CFX) and lactose. 1, CFX; 2, lactose; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

broad peak (Avicel PH 101 and Emcocil). The DSC trace for Mg stearate (Fig. 2, trace 2) showed two shallow, broad endotherms in the region of 50–110 °C corresponding to different hydrated states or pseudo-polymorphs [3]. Lactose (Fig. 3, trace 2) showed two sharp endothermic peaks; the first started at 132.7 °C with a peak at 147.2 (ΔH 59.37 J/g) and the second started at 204 °C with a peak at 217.3 °C (ΔH 72.23 J/g). The characteristic broad endotherms between 40 and 140 °C observed for celluloses (Avicel PH 101 and Emcocil) could be attributed to the loss of residual water from these polymers [10]. It is probable that similar dehydration reactions occurred in Ac-Di-Sol and Primojel.

Traces 3, 4 and 5 (Figs. 1–9) were the thermal curves of 1 : 1 physical mixture, coground mixture and kneaded product of CFX with each excipient, respectively. Compressed samples and accelerated ones (55 °C for 3 weeks) were shown in traces 6 and 7 respectively. Thermal parameters of the pure components were displayed in Table 1 and those of CFX after mixing with excipients were collected in Table 2.

In case of Emcompress-CFX, Mg stearate-CFX and lactose-CFX mixtures (Figs. 1–3), the characteristic endotherms of the drug and excipient were always present and no extrathermal effects were observed, either after sample manipulation or aging. Some different appearances found in peak shape and height-to-width ratio could be attributed to possible geometric differences in the mixture samples [11]. Lactose is known to undergo a non-enzymatic browning reaction (generally known as the Maillard reaction) with amines. The reaction is believed to occur mainly in primary amines [16]. This is not applicable to CFX since it has a secondary amine group. It seemed that

Table 1: Thermal parameters of ciprofloxacin HCl (CFX) and various excipients used

Sample	T_{onset} (°C)	T_{peak} (°C)	ΔH (J/g)
CFX	301.8	315.1	58.58[a]
Emcompress	178.4	187.3	18.08
Mg stearate	96.4	105.4	13.21
Lactose	204.4	217.3	72.23
Sorbitol	88.0	98.2	108.07
Mannitol	159.3	167.0	239.59
Ac-Di-Sol	272.0[b]	297.0[b]	128.77[b]
Primojel	270.1[b]	278.6[b]	254.47[b]
Avicel PH 101	292.6	322.5	123.92
Emcocil	297.0	330.3	268.21

a: Total ΔH while that of first peak = 14.58 J/g
b: Exothermic

Table 2: Thermal parameters of ciprofloxacin HCl (CFX) in various mixtures with excipients

Excipient	Peak temperature (°C)					Enthalpy (J/g)				
	Physical Mix.	Coground Mix.	Kneaded Mix.	Compressed Mix.	Aged Mix	Physical Mix.	Coground Mix.	Kneaded Mix.	Compressed Mix.	Aged Mix
Emcompress	315.8	320.5	318.4	314.8	318.8	39.55	67.55	50.37	88.26	55.21
Mg stearate	326.1	322.2	323.1	323.3	326.4	86.64	38.78	39.33	88.20	64.71
Lactose	319.8	324.0	321.9	322.0	323.4	27.79	27.34	30.76	52.63	66.37
Sorbitol	295.6	306.5	303.4	293.2	303.2	87.69	60.84	84.22	57.17	52.38
Mannitol	306.4	305.6	294.4	296.4	302.7	70.22	49.42	85.61	56.39	75.13
Ac-Di-Sol	268.9	290.0*	315.5*	297.6*	299.2*	8.45	24.99*	21.51*	39.4*	46.79
Primojel	312.0	282.8*	322.7	292.9	297.3*	13.27	39.55*	44.37	17.47*	74.32*
Avicel PH 101	315.0	314.0	320.1	315.0	320.4	6.30	8.84	3.43	2.71	9.58
Emcocil	320.5	–	318.7	316.2	320.4	2.22	–	4.31	3.5	4.49

* Exothermic
– No peak detected

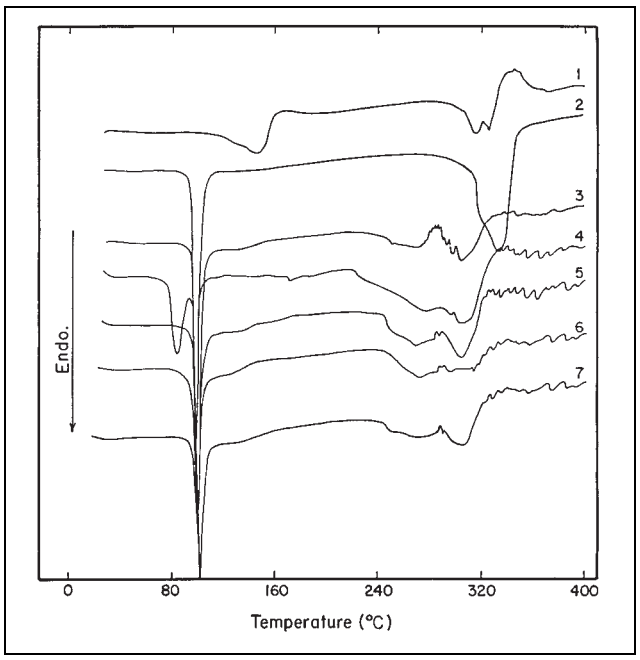

Fig. 4: DSC thermograms of ciprofloxacin HCl (CFX) and sorbitol. 1, CFX; 2, sorbitol; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

no interaction has occurred between CFX and Emcompress, Mg stearate or lactose.

When two substances are mixed, the purity of each could be reduced and generally slightly lower melting points appear in the DSC thermograph. If the solid-solid interaction is extremely week or non-existent, the reduction of the melting point is usually inconsequential. On the other hand, any large shift in melting point signifies that a strong solid-solid interaction has occurred, although it does not necessarily indicate an incompatibility [17]. It was noticed that in the case of sorbitol, two peaks were observed, sharp one at 98 °C for melting and broad and large began at 320.6 with a peak at 332.6 °C for its decomposition (Fig. 4, trace 2). This could overlap with the endothermic peak of CFX. However the DSC traces of CFX-sorbitol mixtures (Fig. 4, traces 3–7) showed a complicated large endothermic peaks. The peaks were largely shifted by more than 10 °C compared to the pure CFX in all samples regardless of the method of preparation. This large shifts in peak temperature are most probably indicative of a some physicochemical interaction between the two components. CFX and sorbitol are likely to be incompatible. Same findings were detected in case of CFX-mannitol mixtures (Fig. 5). Mannitol (Fig. 5, trace 2) exhibited a prominent sharp melting endotherm with a peak temperature of 167 °C and large broad peak occurred at 303.9 with a peak at 324 °C. Mixing of CFX and mannitol led to a decrease in peak temperatures of CFX by more than 10 °C which is an evidence for incompatibility. This appeared in all samples regardless of the way of treatment. From the above results, it seemed that some interactions have occurred between CFX and sorbitol or mannitol.

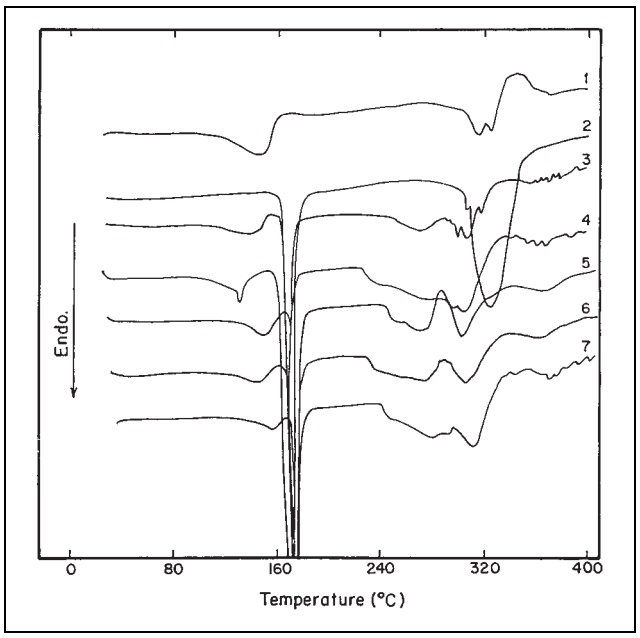

Fig. 5: DSC thermograms of ciprofloxacin HCl (CFX) and mannitol. 1, CFX; 2, mannitol; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

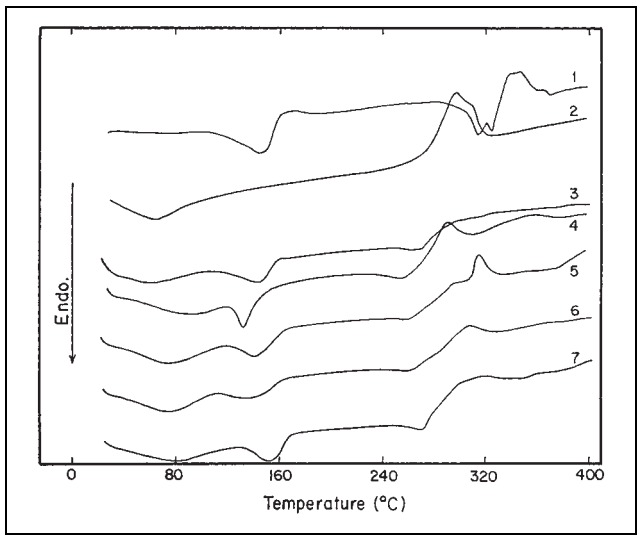

Fig. 6: DSC thermograms of ciprofloxacin HCl (CFX) and Ac-Di-Sol. 1, CFX; 2, Ac-Di-Sol; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

Fig. 6 showed the thermograms of CFX-Ac-Di-Sol mixtures. Trace 2 of fig. 6 displayed that Ac-Di-Sol has an exothermic peak starting at 272.1 with a peak at 297.6 °C.

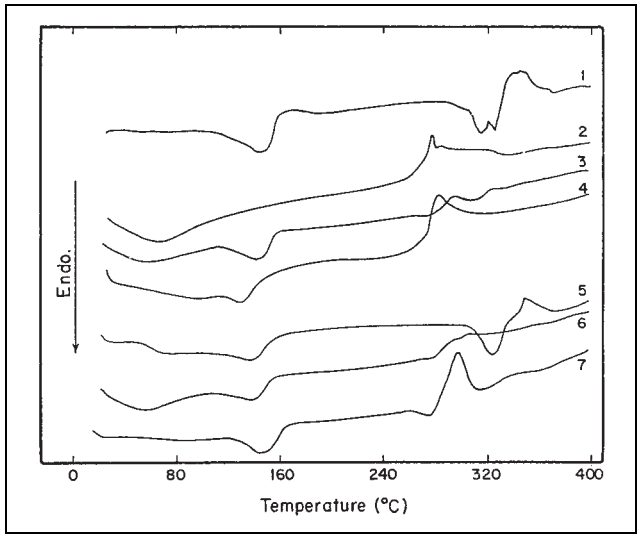

Fig. 7: DSC thermograms of ciprofloxacin HCl (CFX) and Primojel. 1, CFX; 2, Primojel; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

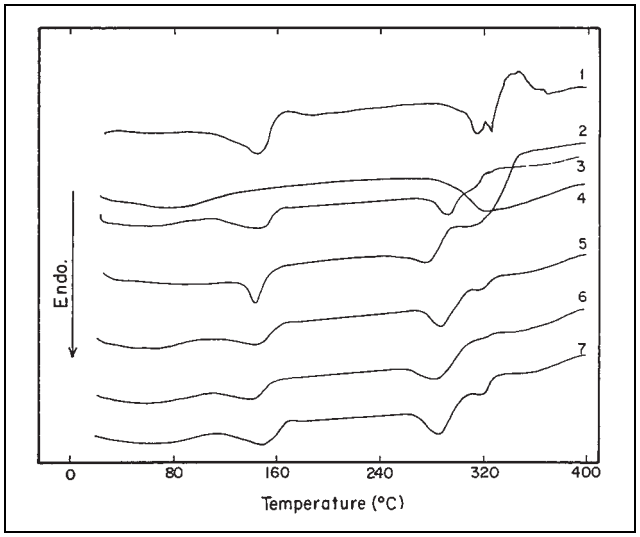

Fig. 8: DSC thermograms of ciprofloxacin HCl (CFX) and Avicel PH 101. 1, CFX; 2, Avicel PH 101; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

The combination of CFX with Ac-Di-Sol (Fig. 6, traces 3–7) exhibited no characteristic features of CFX indicating an incompatibility between CFX and Ac-Di-Sol. The thermograms of CFX-Primojel were depicted in Fig. 7. Primojel also showed an exothermic peak at 278.6 °C. A small shallow endothermic peak could be noticed in case of the physical mixture, kneaded mixture and compressed mixture. However, this changes in the melting behavior of CFX was more evident when the drug was exposed to more stress conditions as in case of coground and aged mixture where CFX peak disappeared completely.

Celluloses (Avicel PH 101 and Emcocil) (trace 2 of Figs. 8 and 9) displayed endothermic peaks at 322.5 and 330 °C, respectively. Despite the interference of the celluloses peak with that of CFX, two peaks could be observed near this region. The first peak was at 20 to 40 °C less than the melting point of CFX. The second peak was almost at the position of CFX peak, but it appeared very shallow. This significant changes in the thermal behavior of the mixture could indicate some type of interaction between CFX and Avicel PH 101 or Emcocil.

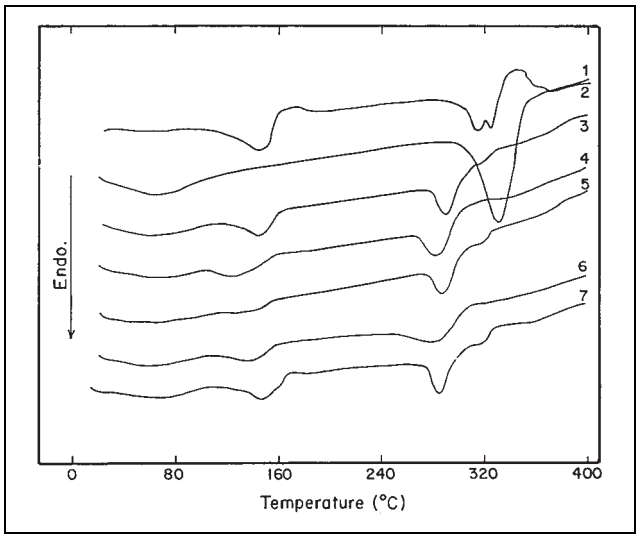

Fig. 9: DSC thermograms of ciprofloxacin HCl (CFX) and Emcocil. 1, CFX; 2, Emcocil; 3, physical mixture; 4, coground mixture; 5, kneaded mixture; 6, compressed mixture; 7, aged physical mixture

In conclusion, interpretation of the thermal data, according to appearance, shift or disappearance of endothermic or exothermic peaks and/or variations in the corresponding enthalpy, prevailed that Emcompress, magnesium stearate and lactose seemed to be compatible with CFX. Sorbitol, Mannitol, Ac-Di-Sol, and Primojel showed some interaction with the drug. CFX might interact with microcrystalline cellulose (Avicel PH 101, Emcocil).

3. Experimental

3.1. Materials

Ciprofloxacin hydrochloride monohydrate was obtained from Sigma Chemical Co., St. Louis, MO, USA. The following excipients were examined: Calcium phosphate dibasic dihydrate (Emcompress®); magnesium stearate; lactose; sorbitol; mannitol (Cooperation Pharmaceuttique Franscaise-France); croscarmellose sodium (Ac-Di-Sol®); sodium starch glycolate (Primojel®); microcrystalline cellulose (Avicel® PH 101 and Emcocil® (Seppic-France);

3.2. Preparation of samples

Physical mixtures of CFX and each excipient were prepared in a 1 : 1 w/w ratio by gently mixing in agate mortar with a spatula at room temperature. Coground mixtures were obtained by grinding a portion of each physical mixture with a pestle for approx. 10 min. Kneaded mixtures were prepared by slurring a portion of each physical mixture with ethanol and grinding thoroughly to obtain a paste which was dried in an oven at 50 °C to a constant weight. The solid was sieved and the fraction <100 μm was used. Compressed blends were prepared by compression a portion of each physical mixture (100 mg) with Carver Lab. Eq. (Model 3392, Carver Inc., USA) at a force of about 7500 psi. The tablets obtained were then crushed and sieved, then the fraction <100 μm was used. Isothermal stress test was carried by storing the physical mixtures in an oven at 55 °C for 3 weeks.

3.3. DSC

Thermal analysis using a DSC method was carried out on ciprofloxacin hydrochloride, the individual excipient and mixed systems of CFX and excipient, employing an automatic Shimadzu thermal analyzer. Samples (3–5 mg) were weighed in a flat bottomed aluminum pans. Temperature calibrations were made using indium as a standard. An empty pan, sealed in the same way as the sample was used as reference. All samples were run at a rate of 10 °C/min, from 25 °C to 400 °C in atmosphere of nitrogen.

References

1 Indrayanto, G.; Mugihardijo; Handayani, R.: Drug Dev. Ind. Pharm. **20**, 911 (1994)
2 Van Tonder, E. C; Lotter, A. P.; Botha, S. A.: Drug Dev. Ind. Pharm. **16**, 2125 (1990)
3 Durig, T.; Fassihi, A. R.: Int. J. Pharm. **97**, 161, (1993)
4 Gerber, J. J.; Lotter, A. P.: Drug Dev. Ind. Pharm. **19**, 623 (1993)
5 Venkataram, S.; Khohlokwane; Wallis, S. H.: Drug Dev. Ind. Pharm. **21**, 847 (1995)
6 Holgado, M. A.; Fernandez-Arevalo, M.; Gines, J. M.; Caraballo, I; Rabasco, A. M.: Pharmazie **50**, 195 (1995)
7 Malan, C. E. P.; de Villiers, M. M.; Lotter, A. P.: Drug. Dev. Ind. Pharm. **23**, 533 (1997)
8 Mura, P.; Faucci, M. T.; Manderioli, A.; Furlanetto, S.; Pinzauti, S.: Drug Dev. Ind. Pharm. **24**, 747 (1998)
9 Al-Gohary, O. M.: Pharm. Ind. **60**, 168 (1998)
10 Botha, S. A.; Lotter, A. P.: Drug Dev. Ind. Pharm. **16**, 331 (1990)
11 Lin, S. Y.; Han, R. Y.: Pharmazie **47**, 266 (1992)
12 Mura, P.; Manderioli, A; Bramanti, G.; Furlanetto, S.; Pinzauti, S.: Int. J. Pharm. **119**, 71 (1995)
13 Frances, C.; Veiga, M. D.; Espanol, O. M.; Cadorniga, R.: Int. J. Pharm. **77**, 193 (1991)
14 Tuncel, T.; Bergisadi, N.: Pharmazie **47**, 304 (1992)
15 Fawaz, F.; Guyot, M.; Lagueny, A. M.; Devissaguet, J. Ph.: Int. J. Pharm. **154**, 191 (1997)
16 Duvall, R. N.; Koshy, K. T.; Pyles, J. W.: J. Pharm. Sci. **54**, 607 (1965)
17 Budavari, Z; Zelko, R.; Racz, I; Marton, S.: Pharmazie **54**, 861 (1999)

Received June 7, 2002
Accepted July 12, 2002

Ass. Prof. M. Fathy
Department of Pharmaceutics
Faculty of Pharmacy
Assiut University 71526
Assiut
Egypt
Fathy@mailcity.com