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PREFORMULATION COMPATIBILITY STUDIES OF ETAMSYLATE AND FLUCONAZOLE DRUGS WITH LACTOSE BY DSC

S. R. Desai, M. M. Shaikh and S. R. Dharwadkar[*]

Department of Chemistry, The Institute of Science, 15, Madam Cama Road, Mumbai-400 032, India

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Abstract

Chemical compatibility of two drugs, namely, etamsylate and fluconazole was studied with lactose as excipient, employing differential scanning calorimetry (DSC) and X-ray diffraction (XRD) techniques. The DSC patterns recorded for the mixtures of both the drugs with the common excipient (lactose) indicated that fluconazole as well as etamsylate were incompatible with lactose at high temperatures. X-ray diffraction patterns recorded for pure drugs and lactose and the mixtures of individual drugs with lactose prepared at room temperature by intimate grinding of the components revealed incompatibility of both the drugs with lactose also at room temperature.

Keywords:compatibility, drugs, DSC, excipient, XRD

Introduction

Successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients used to facilitate release and bioavailability of the drug, and protect it from degradation [1].

Among the thermoanalytical techniques, DSC has been frequently employed in recent years for quick assessment of chemical compatibility of drug with excipients [2–6]. The present paper deals with the study of interaction of etamsylate and fluconazole with lactose using DSC and X-ray diffraction techniques.

Materials and methods

Among the selected drugs, etamsylate was procured from Biocon India Limited. Fluconazole (I) was procured from Dr. Reddy's Laboratories Ltd., India. Lactose [7] which was employed as excipient was obtained from Lactose (India) Limited. The purity of etamsylate [8] and lactose [9] were assessed with the help of British Pharmacopoeia

* Author for correspondence: E-mail: srdharwadkar@hotmail.com

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Akadémiai Kiadó, Budapest

2000. Purity of fluconazole was found to be 99.8% as analyzed by HPLC. The reverse phase HPLC system (Shimadzu, Model: LC 10 AT-vp) consisting of a solvent delivery pump and variable UV detector (set at 261 nm) was used for purity determination. A non-polar stationary phase (Lichrosphere C18, 10 μm particle size, 4×250 mm; Merck) column was used. The mobile phase consisted of 70% 0.05 M potassium dihydrogen ortho phosphate, 20% acetonitrile and 10% methanol. The flow rate of the mobile phase was maintained at 1.5 mL min^{-1}. The injection volume used was 20 μL. The fluconazole sample on drying in air oven at 105°C for three hours showed a mass loss of 0.3% which could be attributed to the loss of adsorbed moisture.

The DSC curves for drugs and excipient and their mixtures (in 1:1 ratio) were recorded on nearly 12 to 16 mg samples at the heating and cooling rates of 10°C min^{-1} in flowing nitrogen employing differential scanning calorimeter (Shimadzu, Model: DSC 60). The X-ray diffraction patterns of drugs, excipient and the 1:1 physical mixture were recorded using Philips X-ray diffractometer (Model: PW1710) employing CuK_α radiation. The scanning speed of 2° 2θ min^{-1} was used.

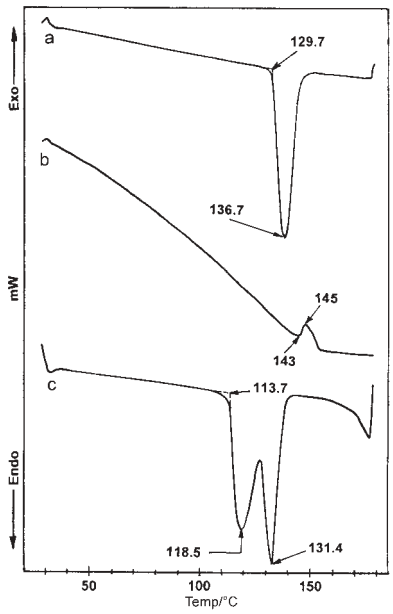

Fig. 1 DSC scans of a – etamsylate; b – lactose and c – 1:1 etamsylate–lactose mixture

Results

DSC observations

The DSC patterns for etamsylate, lactose and their 1:1 physical mixture are presented in Figs 1a–1c, respectively. Similar records for fluconazole, lactose and their 1:1 physical mixture are presented in Figs 2a–2c.

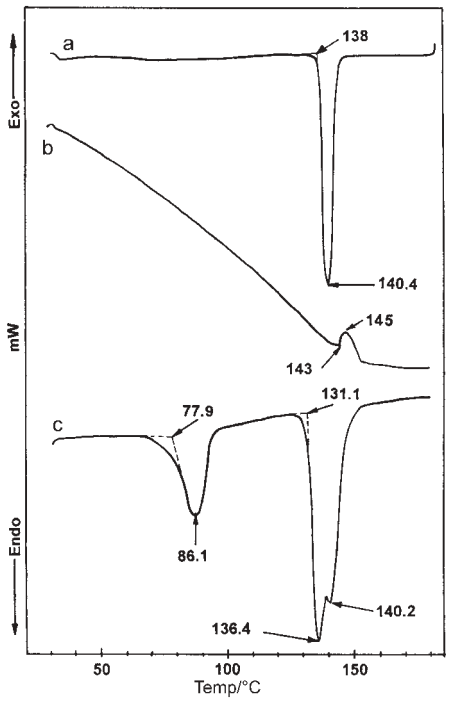

Fig. 2 DSC scans of a – fluconazole; b – lactose and c – 1:1 fluconazole–lactose mixture

In Fig. 1a a sharp endothermic peak is observed for etamsylate with the onset temperature of 129.7°C which is within the reported melting range (127–134°C) for the compound [8].

The DSC patterns for as received fluconazole (Fig. 2a) showed the prominent endothermic peak due to melting of the compound at 138.6°C which is also well within the reported melting range 138 to 140°C [10].

Table 1 Transition temperatures observed in DSC for etamsylate, fluconazole, lactose and the mixtures of etamsylate and lactose, and fluconazole and lactose

Material analysed by DSC	Peak temperature/°C				
Etamsylate	–	–	136.7	–	–
Fluconazole	–	–	–	140.4	–
Lactose	–	–	–	–	145.0*
E:L (1:1)	–	118.5	131.4	–	–
F:L (1:1)	86.1	–	136.4	140.2	–

*Exotherm

The DSC patterns of the mixtures of etamsylate and lactose, and fluconazole and lactose showed additional peaks, in addition to those recorded for individual drugs

and lactose. The peaks for individual drugs, excipient and the mixtures occurred at different temperature listed in Table 1.

It can be seen from this table that in the case of etamsylate–lactose mixture an additional prominent endothermic peak appeared at 118.5 and the main peak at 136.7°C in original etamsylate shifted to lower temperature of 131.4°C, probably due to solid solubility of lactose in etamsylate.

Similarly, the mixture of fluconazole and lactose showed additional peaks at 86.1 and 136.4°C respectively in addition to the peak corresponding to the melting of pure drug at 140.2°C indicating partial interaction of the drug with the excipient.

The additional DSC peaks observed for the mixtures which are not present in the DSC patterns recorded for pure drugs and excipients could have resulted from the chemical interaction of the drugs with excipients.

X-ray diffraction data

The X-ray diffraction patterns of etamsylate, lactose and etamsylate–lactose mixture and fluconazole, lactose and fluconazole–lactose mixtures prepared by physical grinding of the components intimately at room temperature are shown in Figs 3 and 4, respectively.

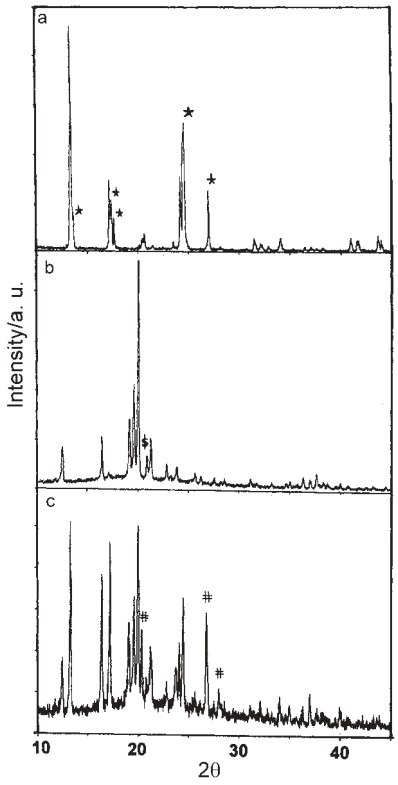

Fig. 3 X-ray diffractogram of a – etamsylate; b – lactose and c – 1:1 etamsylate–lactose mixture

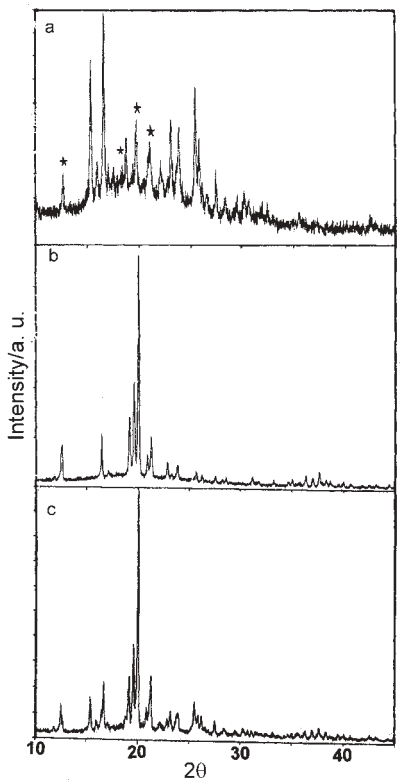

Fig. 4 X-ray diffractogram of a – fluconazole; b – lactose and c – 1:1 fluconazole–lactose mixture

The X-ray patterns presented in these figures reveal that some of the diffraction lines of moderate and lower intensities present in the parent components disappeared in etamsylate–lactose mixture and some new lines appeared in the mixtures prepared at room temperature (Table 2).

The X-ray pattern of fluconazole–lactose mixture prepared at room temperature showed no new lines in addition to those present in the X-ray patterns of pure fluconazole and lactose. However, the pattern showed absence of several lines present in the diffraction patterns of the pure components namely, fluconazole and lactose. This is shown in Table 3.

Discussion

The additional prominent DSC peaks in the mixtures of the drugs and excipients is a positive indication of chemical interaction of the drugs with excipients. Such interaction should result in the partial or complete disappearance of the reactant phases and appearance of new phases, which can be inferred from X-ray diffraction patterns. X-ray diffraction patterns of the mixture, prepared at room temperature, when com-

pared with those of its individual components showed appearance of new lines and disappearance of some of the lines present in the individual components.

The number of new lines appeared in etamsylate–lactose mixture are shown in Table 2. The same table indicates disappearance of some of the lines in the mixture which are originally present in the X-ray diffraction patterns of the individual components.

Table 2 X-ray diffraction data for etamsylate, lactose and etamsylate–lactose (1:1) mixture

Lactose		Etamsylate		Etamsylate:lactose=1:1 physical mixture	
2θ	%	2θ	%	2θ	%
12.49	14.18	–	–	12.50	27.58
–	–	13.49	100.00	13.34	97.78
–	–	13.66*	15.67	–	–
16.47	19.83	–	–	16.45	76.93
–	–	17.21	34.96	17.27	96.68
–	–	17.41*	23.36	–	–
–	–	17.65*	16.71	–	–
19.18	28.55	–	–	19.11	51.13
19.58	43.43	–	–	19.60	60.30
20.04	100.00	–	–	20.00	100.00
–	–	–	–	20.36#	49.55
20.90$	11.80	–	–	–	–
21.27	19.38	–	–	21.23	38.45
23.83	8.12	–	–	23.76	25.85
–	–	24.26	39.34	24.10	40.56
–	–	24.28	45.36	24.47	67.44
–	–	24.68*	60.67	–	–
–	–	–	–	26.73#	56.04
–	–	27.00*	29.98	–	–
–	–	–	–	28.01#	17.09

#Lines newly appeared in etamsylate:lactose=1:1 physical mixture
*Lines of etamsylate disappeared in etamsylate:lactose=1:1 physical mixture
$Lines of lactose disappeared in etamsylate:lactose=1:1 physical mixture

The XRD pattern of fluconazole–lactose mixture did not show the lines in addition to those present in the patterns of the individual components. However, number of lines present in the XRD pattens of the individal components were found missing in the similar pattern recorded for the mixture. The significant difference in the X-ray patterns of the drug–excipient mixtures compared to those of individual drugs and excipient indicates possible incompatibility of the drugs with the excipient, even at

Table 3 X-ray diffraction data for fluconazole, lactose and fluconazole–lactose (1:1) mixture

Lactose		Fluconazole		Fluconazole:lactose=1:1 physical mixture	
2θ	%	2θ	%	2θ	%
12.58	14.18	–	–	12.56	10.50
–	–	12.64*	17.24	–	–
–	–	15.41	77.98	15.43	13.20
–	–	16.00	24.13	15.99	4.50
16.47	19.83	–	–	16.45	8.30
–	–	16.66	100.00	16.68	19.30
–	–	18.40*	28.32	–	–
–	–	18.83	39.89	18.80	6.40
19.18	28.55	–	–	19.17	22.50
19.58	43.43	–	–	19.61	37.77
–	–	19.77*	42.14	–	–
20.04	100.00	–	–	20.04	100.00
20.90	11.80	–	–	20.90	11.70
–	–	21.12*	34.89	–	–
21.27	19.38	–	–	21.30	22.76
–	–	22.18	23.00	22.15	4.20
22.85	9.17	–	–	22.84	5.25
–	–	23.15	52.58	23.21	9.11
23.83	8.12	–	–	23.76	16.81
–	–	23.93	46.81	23.95	8.95
–	–	25.50	70.91	25.54	13.84
–	–	25.87	43.67	25.86	7.41
–	–	26.18	21.34	26.25	7.71
–	–	27.49	32.84	27.53	6.42
–	–	28.40	11.11	28.50	2.79
–	–	30.29	14.01	30.25	3.36

*Lines of fluconazole disappeared in fluconazole:lactose=1:1 physical mixture

room temperature. The presence of majority of the lines of the parent substances in the thoroughly ground mixture prepared at room temperature, however, suggests partial interaction of the drugs with the excipient at room temperature, which could increase with the increasing temperature.

Conclusions

DSC provides the useful means for quick assessment of chemical interaction of drug with excipient. Other techniques like XRD can further provide additional evidence for confirming the conclusions derived from DSC data.

The present study shows incompatibility of both the drugs with selected excipient at high temperatures as concluded from DSC and corroborated by XRD at room temperature.

If the drugs is compatible with excipient at high temperature it is necessarily compatible at room temperature. But if there is incompatibility at high temperature it may or may not be incompatible at room temperature. The mixtures, in such cases, should be investigated for the compatibility at room temperature by other independent measurements.

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