COMPATIBILITY SCREENING OF SOME DILUENTS WITH NEWER FLUOROQUINOLONE: MOXIFLOXACIN. HCl

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ABSTRACT

Differential Scanning Calorimetry was used as a screening technique for assessing the compatibility of Moxifloxacin hydrochloride with some currently employed pharmaceutical diluents. The data was supported by isothermal stability studies (IST) carried out at ambient conditions and at 50°C for the period of six months. Stability of drug in solution state in presence of diluents and the influence of pH were also investigated. DSC results revealed incompatibility of drug with neosorb, dextrose anhydrous and pearlitol on the basis of enthalpy loss and absence of melting endotherm of drug. Compatibility was predicted with microcrystalline cellulose, emcompress, dicalcium phosphate anhydrous, lycatab, lactochem fine powder and lactopress spray dried on the basis of DSC thermograms. In present work the ranking of diluents in decreasing order of stability obtained from IST and the results obtained from DSC were compared and correlated.

Keywords: Moxifloxacin hydrochloride, DSC, isothermal stability studies, compatibility, enthalpy, diluents

INTRODUCTION

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of a preformulation stage during the development of solid dosage forms[1]. Potential physical and chemical interactions between drugs and excipients can affect the chemical nature, stability and bioavailabilty of drugs and consequently their therapeutic efficacy and safety[2]. Successful compatibility studies require a good experimental design that furnishes the necessary information with minimum number of experimental efforts. For the preformulation screening investigation thermal analysis can be applied to provide information on physicochemical properties of substances with respect to compatibility by forecasting future problems of safety prior to the final solid dosage form[3].

Differential scanning calorimetry is frequently a preferred thermal analytical technique because of its ability to provide detailed information about both the physical and energetic properties of substance[4]. DSC is fast becoming an indispensable tool for rapidly investigating the physicochemical incompatibility between an active principle and pharmaceutical excipients. Though DSC can not replace chemical methods for quantitative determination of drug concentration in long term stability tests, it gives fast and adequate data to classify acceptable and unacceptable excipients through the appearance, shift or disappearance of endothermic or exothermic peaks as well as variations in the relevant enthalpy values, in DSC profiles of drug excipient mixtures[5].

DSC offers certain advantages such as requirement of small sample size and fast results but there are certain limitations also[6]. At times interpretation of results can be difficult, particularly when simultaneous reaction occurs and to avoid misinterpretation of DSC results, it must be emphasized that the interactions observed at high temperature may not be always relevant at ambient conditions[7].

In present study, compatibility of moxifloxacin hydrochloride (Fig.1) with some directly compressible diluents was investigated using DSC.

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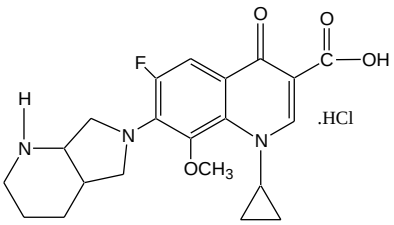

Fig. 1. Structure of Moxifloxacin HCl

Moxifloxacin.HCl is a fourth generation, 8-methoxy novel fluroquinolone antibiotic, with broad-spectrum of activity against anaerobic and aerobic bacteria[8-9]. The results of compatibility screening were supported with isothermal stability studies carried out at ambient conditions and at 50°C, for a period of six months. Influence of excipients on stability of drug in liquid state, along with changes in pH was also determined. The IST stability data was subjected to statistical analysis on the basis of which excipients were ranked in decreasing order of stability. An attempt was made to correlate the results of DSC studies with data obtained from IST studies.

MATERIALS AND METHODS

Materials

Moxifloxacin hydrochloride (MF) was obtained as gift sample from Cipla Ltd., Mumbai, India. Microcrystalline cellulose pH101 and pH102 (Chemsfield Ltd., Nagpur, India), Emcompress (JRS, USA) Neosorb, Lycatab and Pearlitol (Roquette Inc. USA), Lactochem Fine powder (lactochem FP) and Lactopress spray dried (lactopress SD) (Borculo Domo ingredients, The Netherlands), Dicalcium phosphate anhydrous (Merck Ltd., Mumbai, India) and Dextrose anhydrous (Cipla Ltd., Mumbai, India) were received as generous gift samples. All other chemicals and reagents used were of A.R. grade.

Preparation of solid binary system for Isothermal stress studies

Physical mixtures of MF (#100 mesh) with each selected diluent (#100 mesh) were prepared in 1:1 w/w ratio by simple blending of components in mortar for 10 minutes at room temperature. After uniform mixing, the admixtures were wetted with 95% ethanol until a paste was obtained and mixed for further10 minutes to ensure complete wetting. The paste was then dried in vaccum oven (Simeco, Kolkata, India) at 50 °C for 1 hour at 500 psi. After drying, admixtures were mildly grounded and divided into two equal parts for further studies. Control samples of pure drug, with and without solvent were also prepared in similar manner. The 1:1 w/w ratio was selected to maximize the likelihood of observing any interaction [10].

Storage and analysis of samples

The dried admix were stored in two sets of amber colored bottles, with tight fitting screw caps and sealed with adhesive tape. One set of bottles was kept at ambient conditions (30±2°C), while the other set was stored in oven (Spectrum, India) with temperature adjusted at (50±2°C). For blends stored at ambient conditions samples were withdrawn from the bottles at the interval of 15 days till 2 months and afterwards every 45 days, till 6 months. Similarly samples were withdrawn from bottles stored at 50°C, at 0,8,15,22,30,45,60,90,135,180 days and analyzed spectrophotometrically for drug content. The blends were also examined for any unusual color change. All the analysis was performed in duplicate.

For analysis of samples, 20 mg of admix was weighed (10 mg in case of pure drug), and diluted with 100mM HCl (pH 1.4) to obtain 10 mcg/ml concentration. The samples were analyzed at 295 nm against 100mM HCl as blank. Drug content was determined from the calibration curve prepared within the range of 2-35 mcg/ml of drug solution. The method was found to be linear with studied range (R=0.999).

For content estimation and data acquisition UV-visible spectrophotometer from Shimadzu, Japan, supported with UV probe 2.01-version software, was used.

Stability study in liquid state

Seymaur and Milton method[11] was applied for the study loss of MF with excipients in liquid state. 1gm of diluent was added to 100 ml of MF solution (strength 10mcg/ml in 100mM HCl). Series of such solution with other diluents were also prepared in iodine flask and kept in water bath shaker (Remi equipments Ltd., India) at a speed of 50 rpm for 48 hrs. The temperature of the water bath was maintained at 30°±2C. Aliquots from these flasks were withdrawn at regular interval, filtered (Whatman filter paper no.2) and analyzed for changes in absorbance (λmax 295 nm) and changes in pH (μ pH system, Systronics, India). Solution of

pure drug was prepared to serve as control and subjected to analogous condition.

Differential scanning calorimetry

For thermal analysis of drug and drug-diluents mixtures, DSC Q10 V9.4, Build 287, from TA instruments, USA, equipped with TA universal analysis 2000 software was used for acquisition and analysis of data. Individual samples (drug and diluents) as well as freshly prepared admix of drug and selected diluents (#100) were weighed directly in DSC aluminium pan and scanned in the temperature range of 30 -350°C (at heating rate of 20°C/min) under an atmosphere of dry nitrogen (50ml/min). An empty pan with lid placed in it was used as reference. Mettler AB-264 balance (Mettler, Switzerland) was used for weighing of samples. All the analysis was performed in duplicate.

RESULTS AND DISCUSSION

Isothermal stability study

The stability of a formulation depends among other factors on compatibility of the active components with the excipients. The excipients can affect the solid-state stability of drug in various ways by either chemical reaction between the drug and excipients or indirectly by sorption of moisture or catalysis[12]. The primary factors that may have a critical influence on the stability of drug substances in the presence of excipients are the chemical nature of excipient, drug to excipient ratio, moisture, microenvironmental pH of drug excipient mixture, temperature and light[13]. Heat and water play a critical role in the stability of a drug substance leading to degradation[14]. Infact, reaction with water may modify the properties of the active ingredient and such a reaction may be facilitated by the excipients, which is often the vehicle of water into the formulation[15].

Unless incompatibility is evident, it is necessary to carry out stability study[16]. van Dooren has recommended the use of DSC in combination with short-term stress studies in order to interpret DSC curve more easily[17].

In the isothermal stability study of MF with excipients, solvent was incorporated during sample preparation, to facilitate occurrence of drug excipient solid-solid interaction, if any during the period of storage[18]. This preparation method results in intimate contact between drug and excipient compared to conventional mixing and hence degradation rates can be expected to be higher than in ordinary powder blends[19].

The blends remained physically stable and no caking, liquefication, discoloration, odour or gas formation was observed during the period of storage except in case of blends of neosorb, DCP-anhyd. and emcompress. Neosorb, being hygroscopic, gained moisture. It is reported that hygroscopic nature of neosorb (sorbitol) makes it deleterious for many active ingredients [20]. Discoloration was observed in the blends of DCP-anhyd. and emcompress within one week of storage of samples, at both storage conditions.

On the basis of percent drug remaining for the samples stored at ambient conditions, stability was in the order of MCC (AVICEL PH101)> DCP-anhyd. > lactochem FP > pearlitol > MCC (AVICEL PH102) > lycatab > lactopress SD > dextrose-anhyd. > emcompress > neosorb. Similarly for the samples stored at 50°C, the stability order was slightly altered with lactochem FP taking the lead in terms of percent drug remaining. The order of stability was lactochem FP > DCP-anhyd. > MCC (AVICEL PH101)> lactopress SD > MCC (AVICEL PH102)> lycatab> dextrose-anhyd. > pearlitol > neosorb> emcompress. Although the stability in each case was comparatively higher at 30°C than at 50°C in both instances, the drug alone and the drug in combination with diluents appears to follow zero order and first order decomposition.

Ranking of the adjuvants with respect to increased interaction in terms of % drug remaining (considering the absence of interaction as 100%) at the end of six months at ambient condition and at 50°C is presented in Table 1.

Stability study in liquid state

The kinetics of drug decomposition in solid dosage form is often more complex than in solution and the rate of breakdown may show unusual time dependency however, in solution state degradation takes place most rapidly[21]. Stability of a drug substance in solution mainly depends on its molecular environment and its pH profile[22]. Infact, changes in microenvironmental pH of drug in presence of excipient can accelerate the formation of degradation products[23]. The result (Table 2) indicates that there was no significant adsorption, absorption or degradation of drug in presence of excipients, the drug being stable in presence of excipients. The slight change in pH of drug solution

Table 1. Influence of diluents on relative stability of MF after six months of storage at 50°C and 30°C and quantification of first order decomposition rate constant

Drug/diluent	50 °C					RT~30 °C				
	Relativestability		$KX10^{-5}$	* r	K Ranking	Relativestability		$KX10^{-5}$	# r	K Ranking
	% DR	R				% DR	R			
MF (C)	100.00	C	-4.54	0.9269	C	100.00	C	-6.17	0.9736	C
MF (R)	100.14	R	-4.77	0.9580	R	100.08	R	-6.14	0.9524	R
Lactochem FP	99.78	1	-4.98	0.9586	2	100.20	3	-5.81	0.9745	5
DCP-anhyd.	99.68	2	-4.86	0.9557	1	100.36	2	-4.82	0.9827	1
MCC (AVICEL PH101)	99.49	3	-5.75	0.9841	3	100.57	1	-4.82	0.9827	2(1`)
Lactopress SD	99.42	4	-5.88	0.9571	4	99.92	7	-6.92‡	0.9773	10
MCC (AVICEL PH102)	99.39	5	-5.98	0.9700	6	100.05	5	-5.80	0.9776	4(3`)
Lycatab	99.26	6	-5.94	0.9659	5	99.95	6	-6.11	0.9897	6
Dex-anhyd.	99.21	7	-6.29	0.9468	7	99.91	4	-5.80	0.9776	3
Pearlitol	99.15	8	-6.50	0.9864	8	100.10	8	-6.53	0.9647	7
Neosorb	99.09	9	-6.64	0.9279	9	99.60	10	-6.53	0.9351	8(7`)
Emcompress	98.68	10	-6.70	0.9453	10	99.48	9	-6.60	0.9804	9

(C) : Control (MF) under same storage conditions (treated as 100% at the end of six months).
(R) : Reference (MF prepared by kneading method) under same storage conditions.
***** r limiting (50°C): correlation coefficient at n=10 & P<0.05.
r limiting (30°C): correlation coefficient at n=8 & P<0.1 except in ‡ where P<0.5.
DR : drug remaining at end of six months.
R : ranking of diluents based on relative stability.

was observed immediately after addition of excipients to drug solution, however there afterwards the pH of the solution largely remains unchanged during the entire period of study. This indicates that the diluents used have no buffer capacity and would not be expected to affect stability of MF on basis of pH. Only in case of emcompress and DCP-anhyd. which are alkaline excipient, there was change in pH from 1.4 to 3.6, which might be one of the probable cause for discoloration of blends of MF with these diluents. In a previous study by El. Shattawy, nalidixic acid showed interaction with emcompress, due to its incompatibility with an alkaline vehicle[24]. Overall the rate of MF degradation in the medium increases as pH moves toward alkaline region.

Differential scanning calorimetry

The thermogram of MF showed two endothermic peaks, first dehydration peak at 105°C and second melting peak of drug at 259°C with enthalpy values of 71 J/g and 87 J/g respectively. Table 3 and Table 4 record thermal parameters of drug, diluents and their binary mixtures.

The thermogram of MCC (AVICEL PH101) and MCC (AVICEL PH102) showed a lone shallow endotherm in the scanned region, which corresponds to loss of adsorbed moisture. Thermogram of MCC (AVICEL PH101) with MF retained the thermal features of both MF and MCC (AVICEL PH101) (Fig. 2A), the DSC profile being a mere addition of the thermal features of individual components, ruling out any probability of incompatibility. This is also evident from IST studies. In the thermogram of admixture of MF with MCC (AVICEL PH102) (Fig. 2B), endotherm corresponding to melting of drug was present at 258°C. As expected some changes in height to width ratio, peak shape and enthalpy values were seen because of possible differences in mixture sample geometry. However since thermal features of both drug and MCC (AVICEL PH102) were retained, probability of any incompatibility was ruled out. The stability of MF in presence of MCC (AVICEL PH102) is also corroborated from the isothermal stability data.

The DSC thermogram of DCP-anhyd. displayed a gradual endothermic shift in baseline without any transition being apparent. In thermogram of binary

Table 2. Stability of MF in presence of diluents in liquid state (Effect on pH and drug content).

Drug/diluent	pH		Drug content	
	0hrs	48hrs	0 hrs	48 hrs
MF (C)	1.42	1.40	100.88	100.00
MCC (AVICEL PH101)	1.70	1.74	97.68	97.13
MCC (AVICEL PH102)	1.68	1.64	98.86	98.56
DCP-anhyd.	3.12	3.16	101.93	101.59
Emcompress	2.62	2.66	100.32	100.39
Neosorb	1.52	1.48	100.88	100.39
Dex-anhyd.	1.44	1.42	102.04	101.59
Pearlitol	1.54	1.56	98.75	98.04
Lactopress.SD	1.72	1.70	101.24	100.83
Lactochem.FP	1.70	1.70	101.77	101.09

mixture of DCP-anhyd. with MF (Fig. 2C) the thermal feature of MF with peak melt transition at 257°C was visible.

In the DSC thermogram of emcompress a broadened transition due to loss of water followed by the melting endotherm with maximum peak of transition at 195°C was recorded. In the DSC thermogram of admixture of MF with emcompress (Fig. 2D), the characteristic endothermic features of drug as well as emcompress were preserved. van Dooren and Duphar had proposed that if the DSC thermogram of a binary mixture is a simple superimposition of the individual traces, an incompatibility is highly unlikely[17]. Drug content analysis carried out at the end of six months at both conditions revealed the stability of drug, in admixture of emcompress and DCP-anhyd.

However, the discoloration of MF with emcompress and DCP-anhyd. during IST studies may be attributed to interaction between an alkaline excipient with that of drug. An investigation of the pH of drug solution in presence of both emcompress and DCP-anhyd. showed the change of pH from 1.4 to 3.6. Discoloration and change of appearance depends on the amount of water added, whilst the single components may also change in organoleptic properties during storage. The bearing of the visual observation on the ultimate conclusions about possibility of incompatibilities is only slight. The concentration of remaining active ingredient being a more decisive factor in such cases[17].

In the thermogram of lactochem FP and lactopress SD, an endothermic peak with transition starting at 146°C was observed which corresponded to its dehydration and subsequent changing into anhydrous form. Two endothermic peaks followed the dehydration peak at 210°C and at 250°C respectively. In the DSC thermogram of admixture of

Table 3. Thermal parameters of MF and diluents used

Drug/diluent	Dehydration			Fusion		
	T_{onset} (°C)	T_{peak} (°C)	ΔH_{dehyd} (J/g)	T_{onset} (°C)	T_{peak} (°C)	ΔH_{fus} (J/g)
MF (C)	50.89	105.39	71.82	248.42	259.35	87.14
MCC (AVICEL PH101)	45.34	77.02	34.26	-	-	-
MCC (AVICEL PH102)	39.52	75.00	45.30	-	-	-
DCP-anhyd.	-	-	-	-	-	-
Emcompress	124.81	143.37	31.57	184.82	195.53	307.8
Neosorb	-	-	-	98.18	100.77	156.9
Dex-anhyd.	66.18	72.46	10.28	150.94	158.23	195.2
Pearlitol	-	-	-	165.67	168.61	289.9
Lactopress.SD	145.83	148.8	157.7	213.57	220.23	157.3
Lactochem.FP	146.63	149.97	150.9	210.91	219.00	163.5
Lycatab	30.22	67.22	166.3	-	-	-

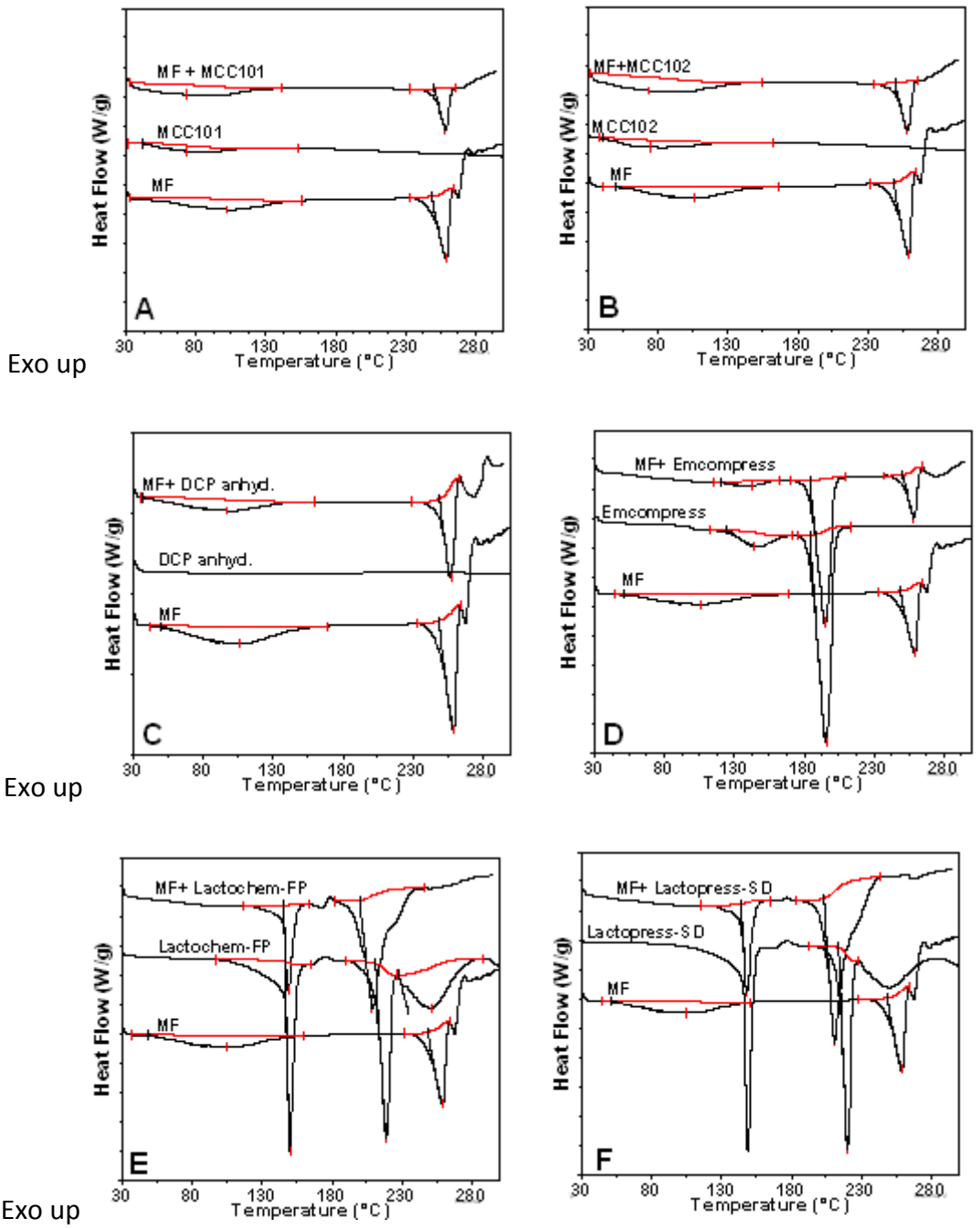

Fig. 2. (A-F) DSC curves of pure drug, diluents and their 1:1 w/w physical admixtures

lactochem FP with MF (Fig. 2E), the initial peak due to loss of bound water of lactochem FP was retained but the subsequent melting peaks at 219°C and 250°C, seems to have merged with melting endothermic peak of drug at 259°C, resulting in a new peak at 208°C, which was prior to the melting peaks of both lactochem FP and drug. Similar such thermal features were observed in case of lactopress SD (Fig. 2F). This behaviour indicates a strong solid-solid interaction, although not necessarily deleterious. Since melting peaks of lactochem FP and lactopress SD coincides with MF, in the resultant

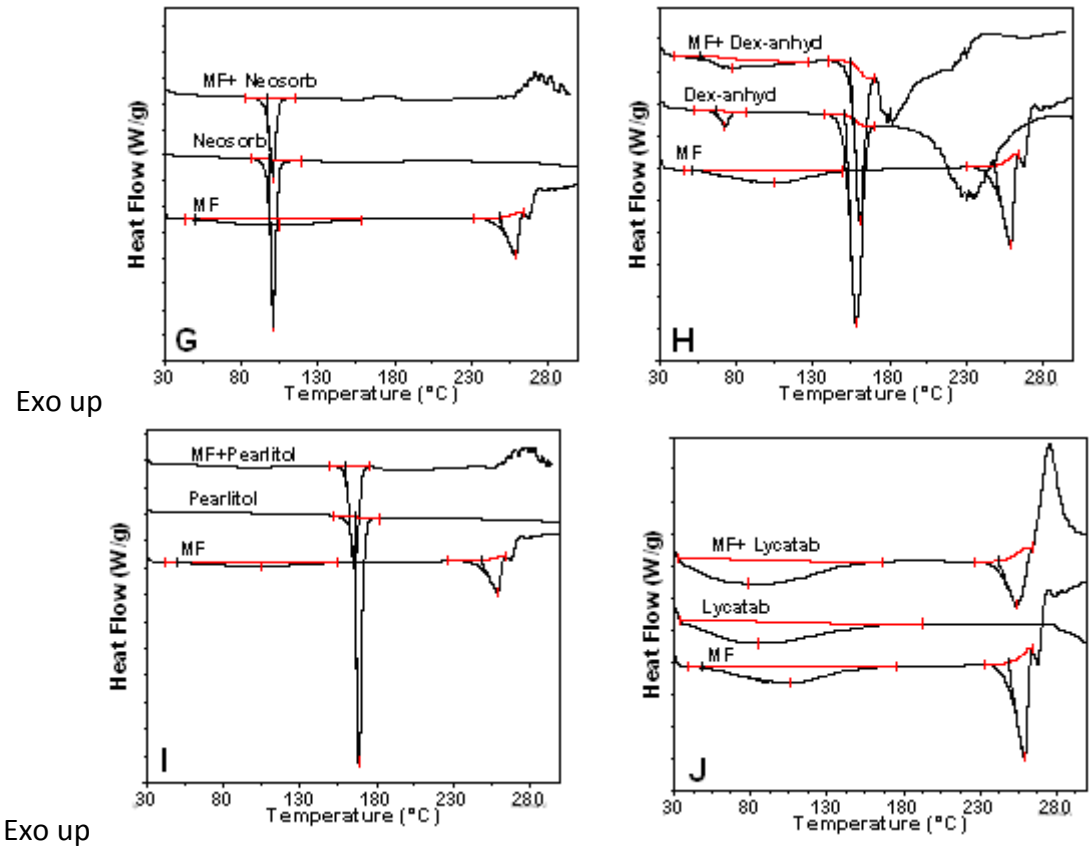

Fig. 2. (G-J) DSC curves of pure drug, diluents and their 1:1 w/w physical admixtures

Table 4. Thermal parameters of binary mixtures of MF with diluents.

Diluent	T_{onset} [a] (°C)	T_{peak} [b] (°C)	ΔH_{fus} [c] (J/g)	ΔH_{cal} [d] (J/g)	ΔH_{obsv} [e] (J/g)	% Change in enthalpy of (Admixture)	% Change in enthalpy of (MF)
MCC (AVICEL PH101)	250.51	258.54	46.95	96.61	130.13	34.69^{+}	7.75^{+}
MCC (AVICEL PH102)	249.36	258.45	52.36	102.13	133.01	30.26^{+}	20.17^{+}
DCP-anhyd.	248.48	258.68	59.69	79.48	94.69	19.12^{+}	36.99^{+}
Emcompress	250.49	257.20	50.81	250.51	269.95	7.76^{+}	16.616^{+}
Neosorb	*	*		157.93	92.30	41.55^{-}	
Dex-anhyd.	*	*		182.22	120.99	33.60^{-}	
Pearlitol	*	*		224.43	155.20	30.84^{-}	
LactopressSD	*	*		236.98	279.97	18.13^{+}	
LactochemFP	*	*		236.50	286.45	21.12^{+}	
Lycatab	242.53	254.59	59.18	162.63	225.38	38.58^{+}	35.82^{+}

a : Onset of melting endotherm of MF retained in binary mixture.
b : Peak maximum of melting endotherm of MF retained in binary mixture.
c : Enthalpy of melting endotherm of MF retained in binary mixture.
d : Enthalpy values calculated from the 1:1w/w percentage contribution of each ingredient in admixture.
e : Enthalpy values observed in DSC thermograms of admixtures.
* : Characteristic melting peak of MF was lost.
+ : Gain in enthalpy.
- : Loss in enthalpy.

compatibility studies of this drug are reported in literature. In present investigation moxifloxacin hydrochloride was found to be compatible with MCC (AVICEL PH101), MCC (AVICEL PH102), emcompress, DCP-anhyd. and lycatab on the basis of retention of fusion endotherm of drug while incompatibility was predicted with neosorb, dextrose-anhyd. and pearlitol in which the melting endotherm of drug was not found and a loss of enthalpy was observed in DSC thermograms. Changes in pH of drug solution in presence of emcompress and DCP-anhyd. were helpful in identifying the probable cause of discoloration in admixtures of these diluents with drug. Interaction in binary mixtures of lactopress SD and lactochem FP was ruled out on the basis of IST stability data, as interpretations based on thermograms of binary mixtures of these diluents with drug were inconclusive due to superimposition of thermal features of drug and diluent. Although the drug was found to be stable with all the diluents tested from the results of IST data, the ranking of diluents in decreasing order of stability on the basis of % drug remaining was quite in accordance with the results obtained from DSC data. Interestingly isothermal stability and liquid state stability results performed simultaneously were of considerable help in interpretation of DSC thermograms. Loss of characteristic endothermic melting feature is a clear indication of incompatibility as was evident from thermograms of neosorb, dextrose-anhyd. and pearlitol. It appears that retention of melting endotherm of drug; irrespective of slight changes in position is an indication of compatibility[28]. The results confirmed that DSC measurements allowed a fast and reliable screening of the excipient performances.

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Dedicated to: This manuscript is dedicated to Late Prof. G.M. Panpalia, Birla Institute of Technology, Mesra, Ranchi, Jharkhand. May god bless his soul.

REFERENCES

1. J.I. Wells, Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances, Ellis Harwood Ltd., UK (1988).
2. P. C. Mora, M. Cirri, P. Mura, Differential scanning calorimetry as a screening technique in compatibility studies of DHEA extended release formulations J. Pharm. Biomed. Anal. 42, 3-10 (2006).
3. M. L. Veuba, F. Veiga, J. J. Sousa, M. Eugenia, Compatibility Studies Between Ibuprofen or Ketoprofen with Cellulose Ether Polymer Mixtures Using Thermal Analysis, Drug. Dev. Ind. Pharm. 31, 943-949.
4. S.D. Clas, C. R. Dalton, B. C. Hancock, Differential scanning calorimetry: applications in drug development Pharm. Sci. Technol. Today. 2 , 311-320 (1999).
5. P. Mura, M. T. Faucci, A. Manderiolli, S. Furlanetto, S. Pinzauli, Thermal Analysis as a Screening Technique in Preformulation Studies of Picotamide Solid Dosage Forms Drug. Dev. Ind. Pharm. 24 747-755 (1998).
6. R. K. Verma, S. Garg, Compatibility studies between isosorbide mononitrate and selected excipients used in the development of extended release formulations J. Pharm. Biomed. Anal. 35, 449-458 (2004).
7. M. J. Hardy, Applications of thermal methods of analysis in the pharmaceutical industry.Anal. Proceedings. 19, 556-557 (1982).
8. E.V. Keutz, G. Schluter, Preclinical safety evaluation of moxifloxacin, a novel fluoroquinoloneJ. Antimicrob. Chemother. Suppl. B. 43, 91-100 (1999).
9. F. L. B. Guerra, C.S Paim, M. Steppe, E. E. S Schapoval, Biological assay and liquid chromatographic method for analysis of moxifloxacin in tablets. JAOAC International. 88, 1086-1092 (2005).
10. M. J. Akers, Preformulation testing of solid oral dosage form drugs. Methodology, management, and evaluation. Can. J. Pharm. 11, 1-10 (1976).
11. M. B. Seymaur, R. C. Milton. J. Pharm. Sci. 51, 1965 (1962).
12. H. H. El. Shattawy, G. E. Peck, D. O. Kildsig, Aspartame-direct compression excipients: preformulation stability screening using differential scanning calorimetry. Drug. Dev. Ind. Pharm. 7, 605 (1981).

13. S. Vaithiyalingam, I. K. Reddy, M. A. Khan, Aqueous-Based Cellulose Acetate Butyrate Dispersion: Screening of Process and Formulation Variables to Obtain Verapamil HCl-Controlled Release Beads Particul. Sci. Technol. 19, 131-144 (2001).
14. S. A. Botha, A. P. Lotter, Compatibility Study Between Atenolol and Tablet Excipients Using Differential Scanning Calorimetry Drug. Dev. Ind. Pharm.16, 1945-1954 (1990).
15. J. L. Sims, J. A. Carreira, D. J. Carrier, S. R. Crabtree, L. Easton, S. Hancock, C. E. Simcox, A New Approach to Accelerated Drug-Excipient Compatibility Testing Pharm. Dev. Technol. 8, 119-126 (2003).
16. H. Jacobson, G. Rier, Application of differential thermal analysis to compatibility and stability problems in penicillin-stearic acid mixtures J. Pharm. Sci. 58, 631-633 (1969).
17. A. A. van Dooren, B.V. Duphar, Design for Drug-Excipient Interaction Studies Drug. Dev. Ind. Pharm. 9 43-55 (1983).
18. P. Mura, M. T. Faucci, A. Manderiolli, G. Bramanti, L. Ceccarelli, Compatibility study between ibuproxam and pharmaceutical excipients using differential scanning calorimetry, hot-stage microscopy and scanning electron microscopy J. Pharm. Biomed. Anal. 18, 151-163 (1998).
19. N. Wyttenbach, C. Birringer, J. Alsenz, M. Kuentz, Drug-excipient compatibility testing using a high-throughput approach and statistical design Pharm. Dev. Technol. 10, 499-505 (2005).
20. H. H. El. Shattawy, Ampicillin-direct compression excipients: preformulation stability screening using differential scanning calorimetry. Drug. Dev. Ind. Pharm. 8, 819-831 (1982).
21. A. T. Florence, D. Attwood, Physicochemical Principles of Pharmacy, third ed., Macmilan Press Ltd., London, (1998).
22. J. T. Carstensen, Drug Stability: Principles and Practices, second ed., Marcel Dekker Inc., New York, (1995).
23. A. T. M. Serajjudin, A. B. Thakur, R. N. Ghoshal, M.G. Fakes, S.N. Ranadive, K R. Morris, S. A. Varia, Selection of solid dosage form composition through drug–excipient compatibility testing J. Pharm. Sci. 88, 696-704 (1999).
24. H. H. El. Shattawy, Nalidixic acid-direct compression excipients, preformulation stability screening using differential scanning calorimetry Drug. Dev. Ind. Pharm. 10, 491-504 (1984).
25. T. Sebhatu, M. Angberg, C. Ahlneck, Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry Int. J. Pharm. 104, 135-144 (1994).
26. E. S. Watson, M. J. O'Neil, J. Justin, N. Brenner, A Differential Scanning Calorimeter for Quantitative Differential Thermal Analysis Anal. Chem. 36, 1233-1237 (1964).
27. J. L. Ford, P. Timmins, Pharmaceutical Thermal Analysis: Techniques and Application, Ellis Harwood Ltd., New York, (1989).
28. A. Balasubramanium, G. M. Panpalia, Drug-adjuvant interaction study using DSC supported by isothermal method. Drug. Dev. Ind. Pharm. 27, 475-480 (2001).