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RESEARCH PAPER

Compatibility Studies Between Carbamazepine and Tablet Excipients Using Thermal and Non-thermal Methods

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ABSTRACT

Proper formulation is an important aspect of any dosage form design. As a part of preformulation studies, differential scanning calorimetry (DSC) was used to investigate the physicochemical compatibility between Carbamazepine and various excipients commonly used in tablet manufacturing, supported by Fourier transform infrared (FTIR) and x-ray powder diffraction (XRPD) studies. Compatibility studies were conducted on samples kept at room temperature and at an elevated temperature of 55°C for 3 weeks. Carbamazepine was found to be compatible with all lactose-based components, such as Granulac 230®, Flowlac 100®, and Microcelac 100®. Differential scanning calorimetry studies indicated incompatibility with mannitol, microcrystalline cellulose, starch, and stearic acid. However, XRPD and FTIR studies implied that all the above excipients are compatible with Carbamazepine. X-ray powder diffraction demonstrated incompatibility with stearic acid for samples stored at 55°C for 3 weeks, indicative of formation of a solid solution. Thus, DSC being a thermal method of analysis should not be used singly to detect any inherent incompatibility. It has to be supported sufficiently by other non-thermal techniques, such as XRPD and FTIR.

Key Words: *Carbamazepine; Differential scanning calorimetry; FTIR; XRPD; Tablet excipients; Compatibility*

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INTRODUCTION

The stability of a formulation depends amongst other factors on the compatibility of the drug with the excipients. It is of significance to detect any possible physical or chemical interaction, since it can affect the bioavailability and stability of the drug (1). Unless incompatibility is evident, it is necessary to carry out a stability study that usually requires months or years. Thus, it is important to choose a method for the evaluation of the solid-state stability that gives fast and reliable information about the possible interaction. A number of techniques can be used to indicate the drug/excipient interaction. Differential scanning calorimetry (DSC) is one of the well-developed techniques used in detection of incompatibilities in drug/drug and drug/excipient interactions (2–5). Differential thermal analysis (DTA) is similar to DSC in many respects and analogous information about the same range of thermal events can be observed. However, DSC is far easier to use routinely on a quantitative basis, yields data which are inherently more quantitative and amenable to theoretical interpretation, and allows faster evaluation of possible incompatibilities between formulation compounds (6,7). Other non-thermal methods that have been used to indicate the drug/excipient interactions include diffuse reflectance spectroscopy (8), infrared spectroscopy (9), dissolution studies (10), and x-ray diffractometry (11,12).

In the present study, drug/excipient interaction studies were undertaken to establish the compatibility of Carbamazepine (CBZ), a potent anti-epileptic drug, with a number of commonly used tablet excipients. The techniques chosen for evaluation were DSC along with infrared (IR) spectroscopy and x-ray powder diffraction (XRPD).

MATERIALS

Carbamazepine was obtained as a gift from Natco Pharmaceuticals (Hyderabad, India). Table 1 shows the different classes of tablet excipients that were used in this study. The amounts of excipient and drug were based on the concentrations of drug and excipient which are likely to be present in the final dosage form. Granulac 230®, Flowlac 100®, and Microcelac 100® (Meggle GmbH, Germany) were obtained as gift samples from Uttam Pharma (Mumbai, India). Other tablet excipients, namely mannitol, starch, microcrystalline cellulose, were purchased from Loba Chemie (Mumbai, India) and used as received. Stearic acid purchased from Loba Chemie (Mumbai, India) was passed through a 100# sieve before it was used.

METHODS

Sample Preparation for Differential Scanning Calorimetry

The methodology suggested by Van Dooren and Duphar was adopted for DSC studies (13). Individual components and their mixtures were subjected to room temperature as well as an isothermal stress condition of 55°C for 3 weeks (Table 2). All mixtures were prepared by an arithmetic dilution method. Samples (5–10 mg) were accurately weighed and hermetically sealed in aluminum pans. Thermograms were obtained by using a Mettler

Table 1

Different Classes of Tablet Excipients Used

Sr. No.	Class	Excipient Used		Drug:Excipient Ratio[a]
1	Diluent	Lactose:	Granulac 230®	1:5
			Flowlac 100®	1:5
			Microcelac 100®	1:5
		Mannitol		1:5
2	Binder	Starch		3:1
3	Disintegrant	Microcrystalline cellulose		3:1
4	Lubricant	Stearic acid		5:1

[a]Drug:excipient ratio of 1:1 was taken in case of immediate mixture of sample for XRPD.
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Table 2

Sample Coding for Drug:Excipient Studies

	Individual Component		CBZ + Excipient Mixture	
Content	Room Temperature	55°C for 3 Weeks	Room Temperature	55°C for 3 Weeks
Carbamazepine	CBZ-RT	CBZ-55	—	—
Granulac 230®	G230-RT	G230-55	CBZG230-RT	CBZG230-55
Flowlac 100®	F100-RT	F100-55	CBZF100-RT	CBZF100-55
Microcelac 100®	M100-RT	M100-55	CBZM100-RT	CBZM100-55
Mannitol	Man-RT	Man-55	CBZMan-RT	CBZMan-55
Microcrystalline cellulose	MCC-RT	MCC-55	CBZMCC-RT	CBZMCC-55
Stearic acid	SA-RT	SA-55	CBZSA-RT	CBZSA-55

Toledo DSC 821 instrument, heating at a constant rate of 10°C/min, over a temperature range of 40–250°C. To maintain an inert atmosphere, N_2 was purged at a rate of 100 mL/min.

Sample Preparation for Fourier Transform Infrared Spectroscopy

Carbamazepine at room temperature and mixtures of drug and excipient kept at 55°C for 3 weeks were subjected to IR spectroscopy using a JASCO FTIR 5300 instrument (Table 2). Granulac 230 was taken as the representative sample of lactose-containing excipients. Pellets of samples were prepared after grinding and dispersing the powder in micronized IR grade KBr powder using an agate pestle and mortar, and scanned over a wave number range of 2000 cm^{-1} to 1000 cm^{-1}.

Sample Preparation for X-ray Powder Diffractometry

Individual components at room temperature and their mixtures kept at room temperature and at 55°C for 3 weeks were subjected to XRPD studies (Table 2). Granulac 230 was taken as the representative sample of lactose-containing excipients. The physical mixture of drug and excipient at room temperature was taken in the ratio of 1:1 as suggested by Erram and Tipnis (14). This ratio was used to maximize the likelihood of interaction taking place, and thus helps in easier detection of incompatibilities. The XRPD patterns of samples were recorded using a Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromated Cu Kα radiation (1.542 Å) and analyzed between 2θ angles of 0–45°. The voltage and current used were 30 kV and 30 mA, respectively. The range was 5×10^3 c/sec and the chart speed was kept at 100 mm/2θ.

RESULTS AND DISCUSSION

DSC Studies

Interactions in the sample are derived or deduced from DSC by changes in the thermal events, such as elimination of an endotherm or exotherm peak, or appearance of a new peak. However, some broadening of peaks leading to changes in the area, onset of peak, and changes in peak temperature occur simply due to mixing of the components without indicating any significant interaction. If all thermal features more or less remain the same, compatibility can be expected.

Figure 1a shows a DSC thermogram of pure Carbamazepine. The characteristic peak pattern indicates the β-form of Carbamazepine, which underwent thermal transition at 174°C (melting endotherm of β-form) and recrystallized into the α-form, which further melted at 191°C. Also, the $\triangle H_f$ for the β-form (−23.79 J/g) was in agreement with that reported by Behme and Brook (15). A similar thermogram was obtained for a Carbamazepine sample kept at 55°C for 3 weeks.

Thermograms (Fig. 1a) of all three lactose-containing excipients, namely Granulac 230, Flowlac 100, and Microcelac 100, show a similar peak pattern, both for samples at room temperature and at 55°C for 3 weeks. The peaks at 145°C and 217°C are the characteristic peaks of lactose.

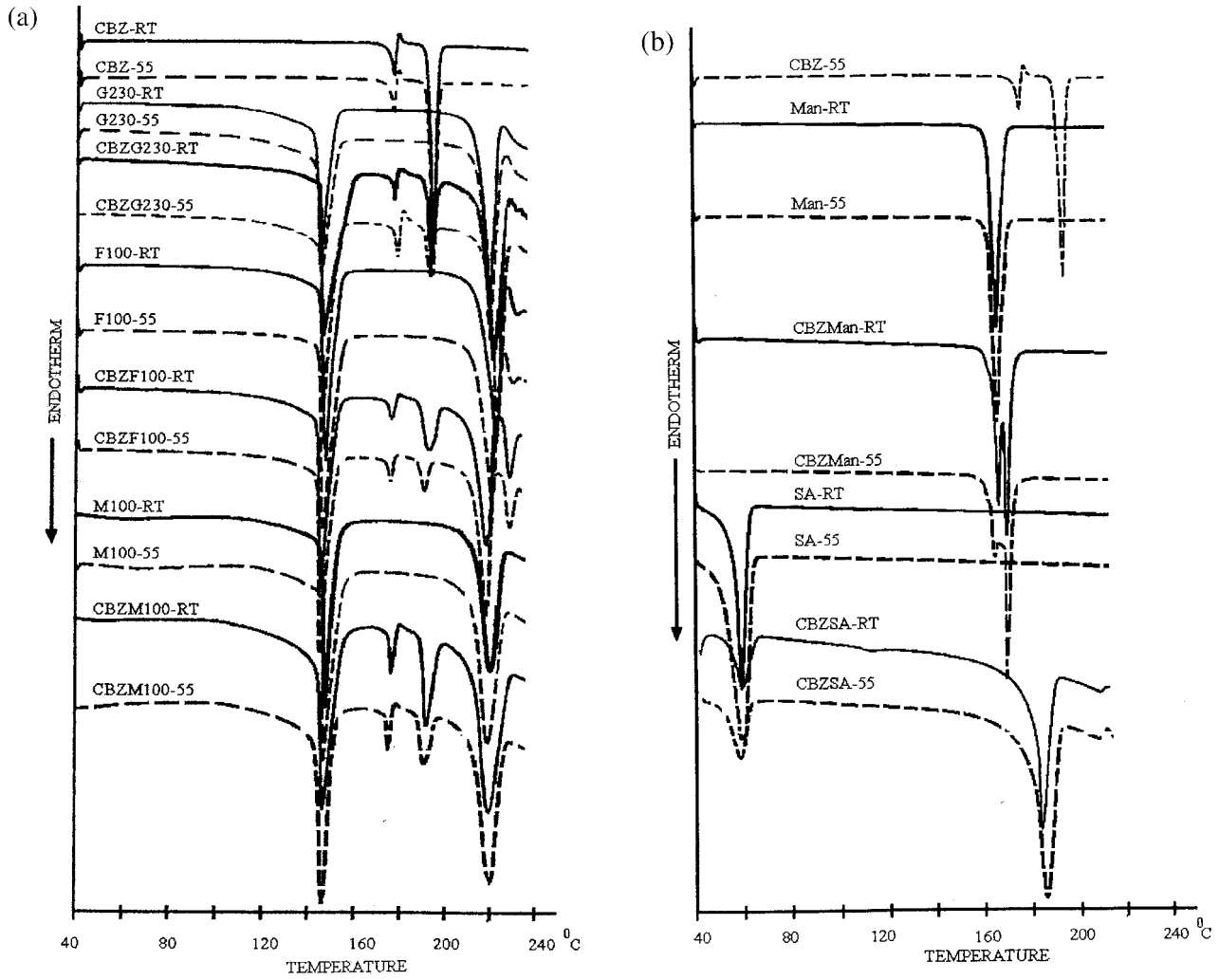

Figure 1. Differential scanning calorimetry thermograms of various samples kept at room temperature (—) and at 55°C for 3 weeks (- - -).

However, in a mixture with Carbamazepine the thermal transitions occurring at 174°C and 191°C were not affected, indicative of compatibility. Hirasawa et al. (16) have reported the formation of a solid dispersion of Carbamazepine with lactose, however, such transitions occur only when heated and melted together.

Thermograms of mannitol (Man-RT and Man-55) kept under the two different temperature conditions show a thermal transition (endotherm) occurring at 167°C, indicative of the melting of mannitol (Fig. 1b). This peak was not affected in case of both CBZMan-RT and CBZMan-55. The characteristic peak pattern (endotherms at 174°C and 191°C) of Carbamazepine, however, disappeared and a new endothermic peak at 170°C appeared in the thermogram. This could be attributed to the dissolution of Carbamazepine in the melt of mannitol. Similar observations were reported by Attia and Habib (17). They reported the formation of a solid dispersion of Carbamazepine with sugars such as mannitol, sucrose, and galactose.

Thermograms of stearic acid (SA-RT and SA-55) revealed a characteristic melting endotherm at 57°C (Fig. 1b). However, in case of a mixture with Carbamazepine, i.e., CBZSA-RT and CBZSA-55, the melting endotherms (174°C and 191°C) for Carbamazepine disappeared and a new peak at

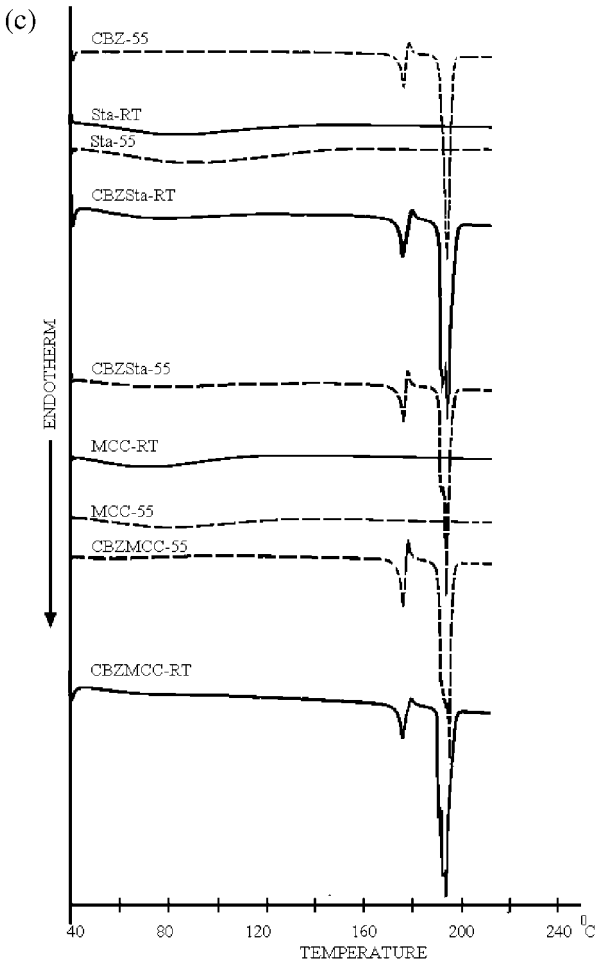

Figure 1. Continued.

183°C was observed. This could be attributed to the formation of a solid solution due to the dissolution of Carbamazepine in the melt of stearic acid.

Interesting findings were observed in case of starch (Sta-RT and Sta-55) and microcrystalline cellulose (MCC-RT and MCC-55) (Fig. 1c). No thermal transitions occurred in the temperature range under study for both the excipients (Fig. 1c). Though the melting endotherm of the β-form of Carbamazepine at 174°C and a subsequent small exothermic hump indicative of recrystallization to the α-form were not affected, there were additional shoulders in the α-peak of the drug:excipient mixtures (CBZSta-RT, CBZSta-55, CBZMCC-RT, and CBZMCC-55). Such findings have not been reported elsewhere. The additional shoulder in the α-peak has been cited only in the case of carbohydrate-based excipients, i.e., starch and microcrystalline cellulose (MCC). It is hypothesized that some interaction could be possible at elevated temperature during the DSC studies, or it could also be attributed to the interaction with the impurities which are likely to be present in the case of MCC and starch, both obtained from a natural source.

FTIR Studies

Samples kept at accelerated conditions and pure drug at room temperature were scanned in the region of 2000 cm^{-1} and 1000 cm^{-1}. Characteristic bands at 1680 cm^{-1} due to carbonyl stretching vibration in the primary amide group and at 1490 cm^{-1} due to $-NH_2$ bending vibration were reported by Hirasawa et al. (16). Infrared studies revealed that both characteristic bands at 1680 cm^{-1} and 1490 cm^{-1} were present in all spectra (Fig. 2), while no new bands or shift in characteristic peaks

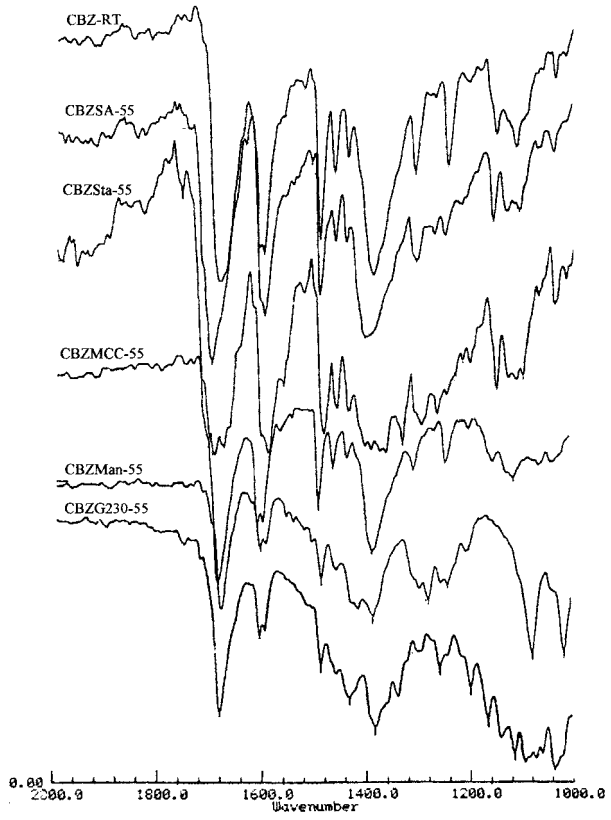

Figure 2. Fourier transform infrared spectra of Carbamazepine and sample mixtures kept at 55°C for 3 weeks.

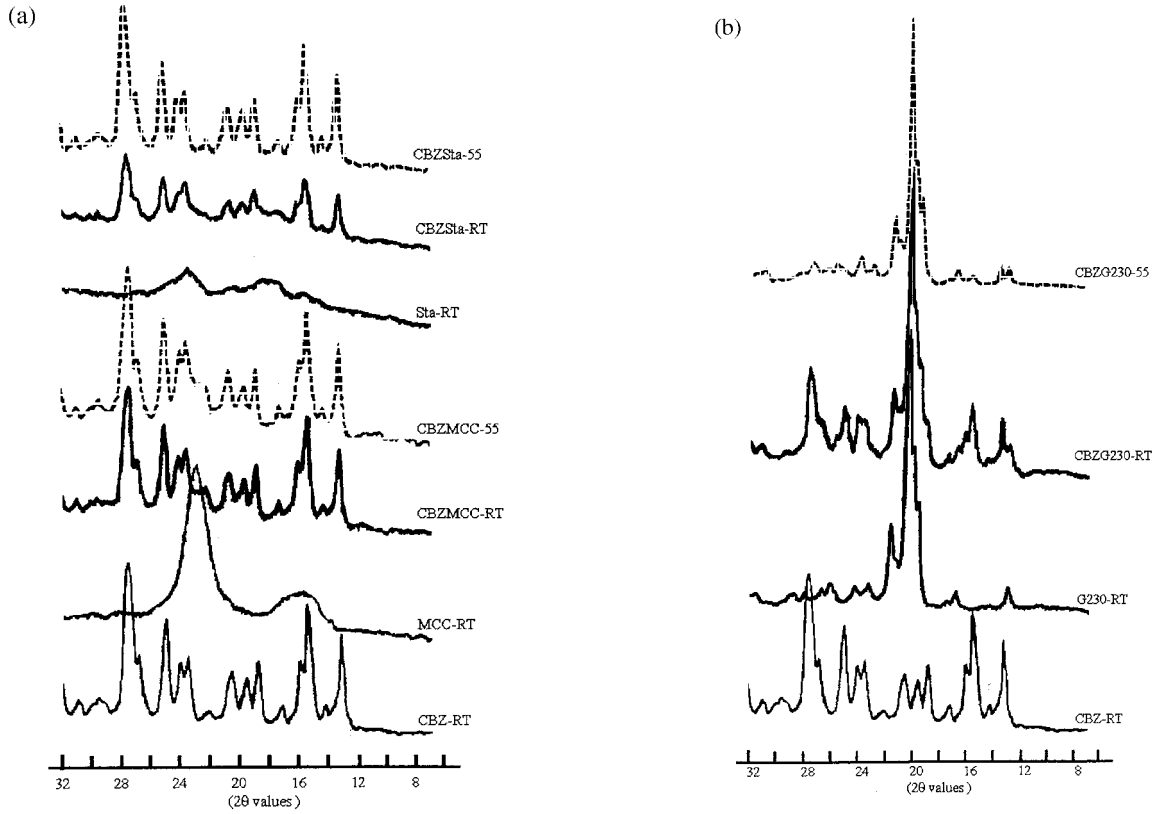

Figure 3. X-ray powder diffraction patterns of various samples kept at room temperature (—) and at 55°C for 3 weeks (- - -).

appeared except in the case of CBZSA-55. The band due to carbonyl stretching vibration of Carbamazepine in CBZSA-55 was broadened and shifted by $10\,cm^{-1}$ upward to $1690\,cm^{-1}$, while the band due to $-NH_2$ bending vibration was not affected. This indicated that stearic acid forms an intermolecular hydrogen with the C=O group in the primary amide group of Carbamazepine.

XRPD Studies

Earlier XRPD studies of Carbamazepine have reported that the peak at 8.8° 2θ is characteristic of the α-form and the peak at 13° 2θ is characteristic of the β-form (12). The XRPD of Carbamazepine (Fig. 3a) showed a characteristic peak at 13° 2θ, whereas the peak at 8.8° 2θ characteristic of the α-form was absent. This indicates that the sample is pure β-form. The characteristic peak at 13° 2θ was found to be present in XRPD patterns of all samples containing Carbamazepine, indicative of compatibility between drug and excipient, except for CBZSA-55 (Fig. 3a–c).

Interesting results were obtained for CBZSA-55. The XRPD pattern of the Carbamazepine:stearic acid mixture showed a characteristic peak at 13° 2θ. However, an additional peak at 8.8° 2θ was observed in case of the mixture kept at 55°C for 3 weeks, indicative of a conversion to the α-form. The earlier study by Suryanarayanan (12) reported the use of quantitative analysis by XRPD to study the effect of compression of Carbamazepine along with excipients such as MCC, starch, stearic acid, and silicon dioxide. The results indicated that Carbamazepine, when compressed in the presence of excipients, did not undergo any polymorphic transformation. However, in the present study, since the samples were exposed for a sufficiently long time to higher temperatures, a significant amount of change occurred, which could be detected by XRPD. This could be attributed to the melting of stearic acid at

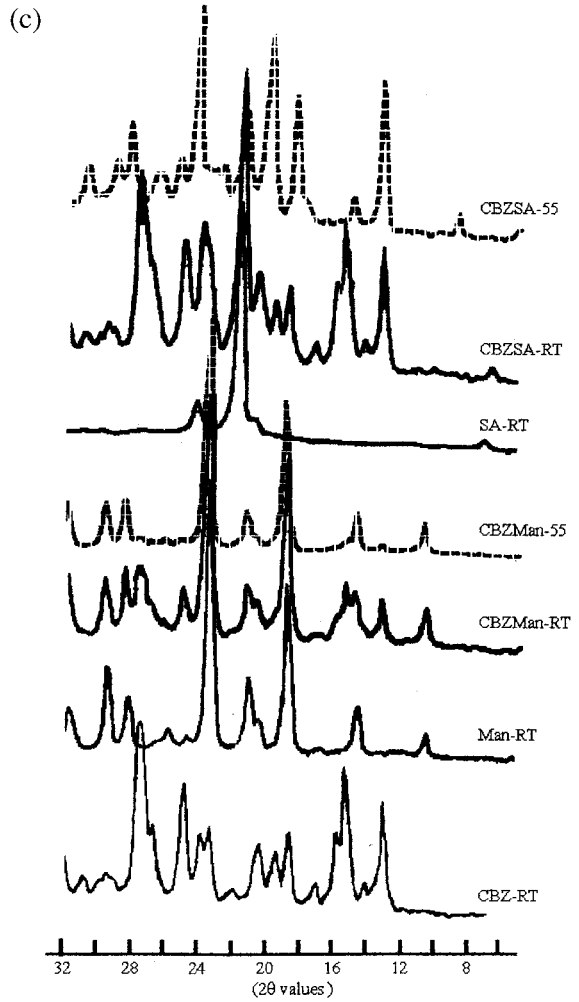

Figure 3. Continued.

55°C and subsequent solubilization of some amount of Carbamazepine in the melt of stearic acid, followed by recrystallization, when the mixture was brought to room temperature. Matthews et al. (18) have reported crystallization of Carbamazepine on the surface of tablets containing stearic acid stored at elevated temperatures. An alternative crystal growth mechanism to the more common water-mediated phenomenon was indicated. However, little was reported regarding the nature of the crystals. The present XRPD study thus helps to identify that polymorphic transformation of β-form to α-form occurs, if samples are kept at elevated temperature.

CONCLUSIONS

In this study DSC revealed the incompatibility of Carbamazepine with mannitol, starch, microcrystalline cellulose, and stearic acid. However, FTIR and XRPD studies helped to further analyze these interactions. Both these methods indicated that all excipients are compatible with Carbamazepine at room temperature and at 55°C, except for stearic acid, the XRPD pattern of which clearly revealed a polymorphic transformation of the β-form of Carbamazepine to the α-form.

In DSC, samples are subjected to a higher temperature range. Thus, this may pose a major drawback in identifying the interaction occurring at ambient conditions. The present study helps to provide factual support that degradation reactions, transformations, or interactions occurring at these temperatures may not take place at room temperature. Hence, DSC should not be used as the only tool for studying the drug/excipient interaction. The data obtained should be supported by other non-thermal tools like XRPD and FTIR to demonstrate any effective interaction.

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