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Thermal and non-thermal methods to evaluate compatibility of granisetron hydrochloride with tablet excipients

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Compatibility of granisetron hydrochloride with selected excipients was assessed using Differential Scanning Calorimetry (DSC) as a thermal screening technique. Non-thermal methods like Fourier Transform Infrared spectroscopy and Thin Layer Chromatography were used as complementary techniques to adequately support and assist in interpretation of DSC results. Some drug-excipient interaction was observed with β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, mannitol, and magnesium stearate in DSC studies. However, further evaluation of these incompatible excipients with non-thermal methods showed that these excipients were compatible with granisetron hydrochloride. Non-thermal methods were, thus, of help in interpreting DSC results and excluding all relevant pharmaceutical incompatibilities.

1. Introduction

The study of drug-excipient compatibility is an important process in the development of a stable solid dosage form. Interactions between drug and excipient can give rise to changes in bioavailability and stability, which in turn affects safety and/or efficacy of the drug. If carried out at an early stage, drug-excipient compatibility studies can be helpful in selecting excipients that could increase the probability of developing a stable formulation. There is a dearth of information on drug-excipient compatibility testing and any universally accepted procedure, despite the high importance of drug-excipient compatibility testing (Verma and Garg 2005).

Conventional isothermal stress procedures involve preparation of samples, storing the drug-excipient blends with or without moisture at high temperature and determining the drug content at definite time points using a suitable stability-indicating method (Serajuddin et al. 1999; Gu et al. 1990). But these procedures are very expensive and time-consuming (Mura et al. 1995). In recent years, differential scanning calorimeter (DSC) has been extensively reported in literature as a useful alternative method of predicting and/or investigating compatibility (Tomassetti et al. 2005; Mura et al. 1998; Malan and De Villiers, 1997). Good correlations were often obtained between DSC results and those of stability tests (Boscolo et al. 1990). DSC technique involves application of a heating or cooling signal to a sample and a reference. The difference between heat flow to a sample and to a reference was monitored against time or temperature, when substance undergoes any thermal event. During this thermal event, like melting, glass transition, or crystallization, any associated energy changes can be evaluated (Araujo et al. 2003). Thus, DSC allows rapid evaluation of possible interactions between the formulation components according to appearance, shift, or disappearance of endothermic or exothermic peaks and/or variations in the corresponding enthalpy (Lin and Han 1992).

Unfortunately, interpretation of the thermal data is not always plain and, to avoid misinterpretation and misleading of DSC results, it must be emphasized that the interactions observed at high temperatures may not always be relevant under room conditions (Verma and Garg 2005; Mura et al. 1995). Moreover, the presence of solid-solid interaction does not necessarily indicate pharmaceutical incompatibility (Van Dooren and Duphar 1983). Sometimes it might be even advantageous e.g. a more desirable form of drug delivery (Mura et al. 1995). Therefore, it would be prudent to use some non-thermal methods as complementary techniques to assist and support the interpretation of results obtained by the DSC technique, which is a thermal method (Mura et al. 1998; Mora et al. 2006).

The purpose of the present study was to investigate possible interactions between the selected excipient and granisetron hydrochloride as a part of an ongoing project of developing fast disintegrating tablets of granisetron hydrochloride. Granisetron hydrochloride is used as an antiemetic drug in the cancer chemotherapy and is very effective in the relief of nausea and vomiting associated with cancer chemotherapy (Chaturvedula et al. 2005). Effects of various formulation processing stress factors were evaluated using different sample treatments like physical mixing, co-grinding, and kneading. In order to investigate the possible interactions, DSC curves of drug and the excipient were compared with those of their mixtures of different sample treatments at their 50% w/w ratio. The 1 : 1 weight ratio will maximize the likelihood of observing

any interaction (Ford 1993). Non-thermal methods like Fourier Transform Infrared spectroscopy (FT-IR) and Thin Layer Chromatography (TLC) were used as complementary techniques to adequately support and assist in interpretation of DSC results.

2. Investigations, results and discussion

2.1 Differential Scanning Calorimetry studies

The endotherms of granisetron hydrochloride of the 1 : 1 physical mixture, co-ground mixture and kneaded mixture of each excipient were compared with the endotherm of granisetron hydrochloride alone to determine incompatibility between drug and excipient. Some changes or modifications in shape, peak temperature, area may arise simply from mixing of the components (Van Dooren and Duphar 1983; Watson et al. 1964). Therefore, these changes or modifications were not considered in determining incompatibility of the excipient with drug. Appearance of new peaks or disappearance of granisetron hydrochloride endotherm or major shift in the peak temperature were a major criteria in determining incompatibility of the respective excipient with drug.

Selected DSC scans of drug and drug-excipient mixtures of the various systems investigated are illustrated in Figs. 1–4. The thermal behaviors of pure drug, respective excipient and various systems of the drug-excipient mixtures investigated were compared in the DSC thermograms. The values of peak transition temperature (T_{peak}) and enthalpy values of granisetron after mixing with excipients are summarized in Table 1. In Figs. 1–4, trace (a) represents drug granisetron and trace (b) represents the respective excipient. Traces (c, d, e) are the thermograms of the 1 : 1 physical mixture, co-ground mixture and kneaded mixture of granisetron with each excipient, respectively.

The DSC thermal curve of granisetron hydrochloride showed a single endothermic peak at its melting point. At a scan rate of 10 °C min^{-1}, the observed peak temperature with the endotherm was 294.49 °C and the apparent heat of fusion was 511.4 J/g. Grinding and Kneading increased the surface of contact between drug and excipient. Generally, an increase in enthalpy (Table 1) of the overall thermal effect per unit mass of granisetron hydrochloride was observed because of increased surface of contact between drug and excipient by grinding and kneading as compared to physical mixture.

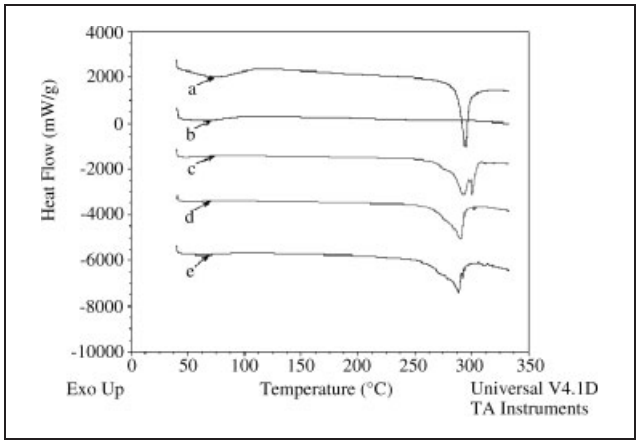

Fig. 1: DSC curves of granisetron hydrochloride (a), hydroxypropyl methyl cellulose (HPMC) (b) and 1 : 1 mixed systems of granisetron with hydroxypropyl methyl cellulose (HPMC) (1 c – physical mixture, 1 d – co-ground mixture, 1 e – kneaded mixture)

Hydroxypropyl methylcellulose exhibited a shallow broad endothermic in the 60–90 °C range in the DSC thermogram (Fig. 1 b), due to loss of water. The combinations of granisetron hydrochloride with hydroxypropyl methylcellulose, regardless of the method of sample preparation, reflected presence of same characteristic melting endotherm as the drug alone, suggesting compatibility. Some modifications, such as changes in shape or peak temperature, of granisetron hydrochloride melting peak were found with hydroxypropyl methylcellulose, but these changes arose simply from mixing of components (Van Dooren and Duphar 1983; Watson et al. 1964).

Ethyl cellulose was also found to be compatible with granisetron hydrochloride as it may be deduced from the thermograms. Ethyl cellulose did not show any peak in its thermogram. The 1 : 1 combinations of granisetron hydrochloride with ethyl cellulose showed the characteristic endotherm of granisetron hydrochloride in all the samples, indicating the absence of incompatibility. Small changes in area or peak temperature were observed but this could be attributed to mixing of the components (Van Dooren and Duphar 1983; Watson et al. 1964).

The thermogram of microcrystalline cellulose showed an endothermic peak in the range of 60–80 °C due to the loss of water. The DSC curves of 1 : 1 drug-excipient mixed systems displayed a single endothermic peak corre-

Table 1: Peak temperature and enthalpy values of granisetron hydrochloride after mixing with excipients

Excipients	Peak temperature (°C)			Enthalpy (J/g)		
	Physical mixture	Co-ground mixture	Kneaded mixture	Physical mixture	Co-ground mixture	Kneaded mixture
Hydroxypropyl methyl cellulose	293.27	290.85	288.95	155.7	123.0	98.95
Ethyl cellulose	292.93	290.64	300.38	124.7	141.4	281.2
Microcrystalline cellulose	289.25	291.44	288.54	92.87	101.3	107.4
Croscarmellose sodium	291.39	292.76	290.76	85.56	106.3	73.04
Copovidone	300.67	297.24	298.98	174.1	106.0	134.9
Crospovidone	302.66	295.26	294.54	157.5	131.3	130.3
β Cyclodextrin	–*	–*	–*	–*	–*	–*
2-Hydroxypropyl-β-cyclodextrin	295.50	287.34	286.10	101.4	20.94	5.22
Dextrose	288.72	288.58	291.29	26.06	46.64	75.46
Lactose SD	291.87	290.58	292.14	31.69	46.89	49.25
Mannitol	–*	–*	–*	–*	–*	–*
Magnesium stearate	281.55	285.59	283.53	77.86	84.21	96.66
Talc	300.39	299.02	298.48	81.75	83.56	114.4

* Endotherm of granisetron hydrochloride was not observed

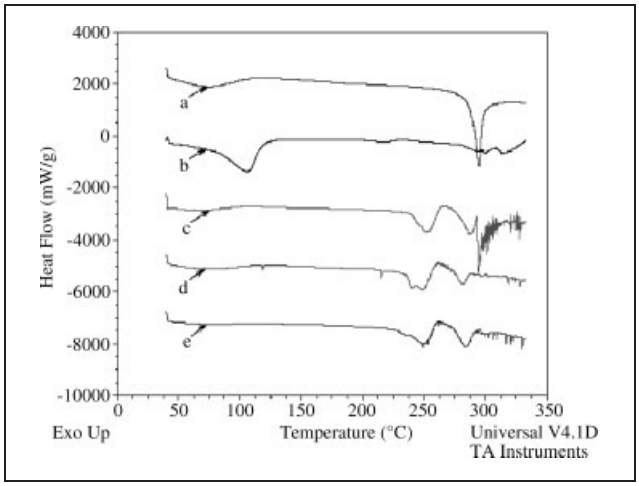

Fig. 2: DSC curves of granisetron hydrochloride (a), β-cyclodextrin (b) and 1 : 1 mixed systems of granisetron with β-cyclodextrin (c – physical mixture, d – co-ground mixture, e – kneaded mixture)

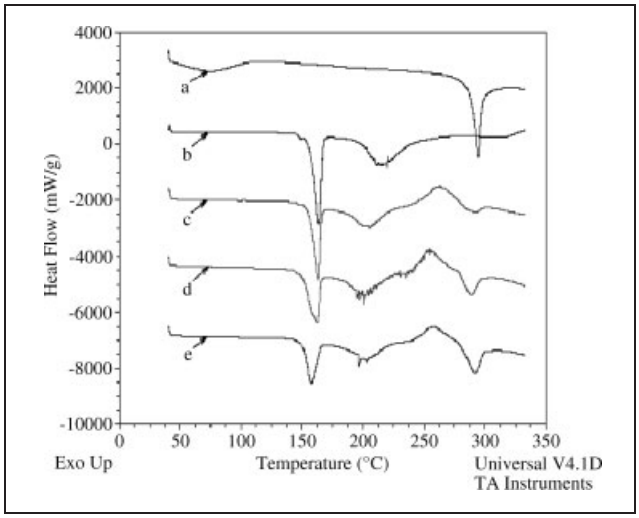

Fig. 3: DSC curves of granisetron hydrochloride (GRT) (a), dextrose (b) and 1 : 1 mixed systems of granisetron with dextrose (c – physical mixture, d – co-ground mixture, e – kneaded mixture)

sponding to granisetron hydrochloride. This indicates the absence of incompatibility.

The DSC curves of croscarmellose sodium, and crospovidone exhibited endothermic peak due to loss of water. The DSC curve of croscarmellose sodium also showed a small exothermic peak, which can be due to recrystallization of the some of the impurities associated with the excipient. Cellulose and its derivatives like croscarmellose sodium are obtained from the pulp of woody plants. This may incorporate some impurities in the final product, which was recrystallized in the DSC curve of croscarmellose sodium. In their 1 : 1 combinations with granisetron hydrochloride, the characteristic endotherm of the drug was always present, negating any possibility of incompatibility with these excipients.

The DSC curves of cyclodextrins namely, β-cyclodextrin (Fig. 2) and 2-hydroxypropyl β-cyclodextrin, showed some interesting results. Both excipients showed a broad endotherm in the range 60–100 °C due to loss of adsorbed moisture and they did not show any melting endotherm (Fig. 2b). The 1 : 1 w/w combinations of β-cyclodextrin showed an endothermic peak at around 254 °C. It also showed one extra endothermic peak at around 276 °C. It did not show any endotherm characteristic to the endotherm of the drug. Emergence of these extra endothermic peaks suggested that a strong solid-solid interaction has occurred. Therefore, these binary mixtures were then further evaluated with FT-IR and TLC studies to understand the nature of this interaction.

Characteristic endothermic peak of drug was visible with 1 : 1 mixtures of drug with 2-hydroxypropyl-β-cyclodextrin. It also showed one extra peak, which can be regarded as an interaction. Sample treatment caused marked reduction in peak area too, kneading sample showed highest reduction in peak area. Therefore, these blends were further evaluated with FT-IR and TLC to determine the true nature of the interaction.

The thermograms of dextrose is presented in Fig. 3. Granisetron hydrochloride was found to be compatible with dextrose and with spray dried lactose as well as, may be deduced from the thermograms. The thermal curve of dextrose gave a sharp endothermic peak at 163.77 °C (Fig. 3b). The thermal curve of spray dried lactose showed two distinct endotherm peaks corresponding at 144.35 °C and 217.11 °C. These endotherms were attributed to a loss of crystalline water and α-lactose monohydrate respectively (Gilani et al. 2004). In their 1 : 1 combinations with granisetron hydrochloride, the characteristic endotherm of the drug was always present. The results obtained in the case of spray-dried lactose were in contrast with the observations of Verma and Garg (2005) for the drug glipizide. This may indicate that glipizide is susceptible to a strong solid phase interaction with lactose because of its physico-chemical nature. This may not be true in the case of granisetron hydrochloride. No extra peaks in the thermal scans may indicate low possibility of incompatibility.

Mannitol showed a sharp endothermic peak at 169.58 °C as depicted in Fig. 4b. But its 1 : 1 mixtures with granisetron hydrochloride showed disappearance of drug endotherm (Fig. 4c, d, e). This can be considered as a strong solid phase interaction. Further evaluations of these systems were performed with FT-IR and TLC to confirm the incompatibility.

The thermogram of magnesium stearate showed an endothermic peak at 106.26 °C followed by a shoulder peak at a higher temperature, probably due to the presence of the corresponding palmitate salt impurity. The DSC curves of 1: 1 w/w drug-excipient mixed systems although dis-

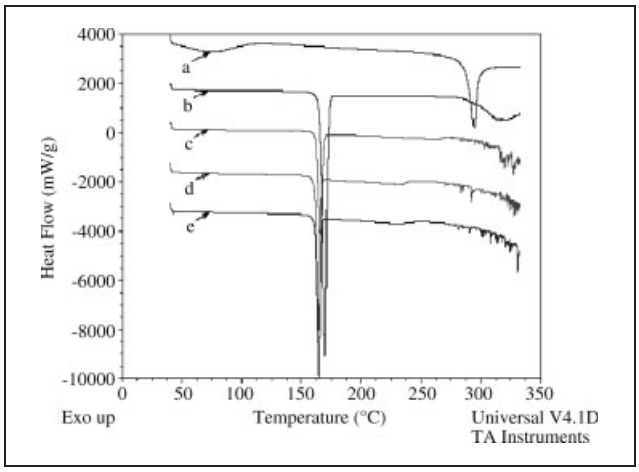

Fig. 4: DSC curves of granisetron hydrochloride (a), mannitol (b) and 1 : 1 mixed systems of granisetron with mannitol (c – physical mixture, d – Co-ground mixture, e – kneaded Mixture)

played a single endothermic peak due to melting of the drug, it was lowered by more than 9 °C in comparison with the melting points of the pure components. It was considered as a general incompatibility and was further evaluated with the help of FT-IR and TLC.
Granisetron hydrochloride was also found to be compatible with talc. The thermal curve of talc did not show any endothermic peak. In their 1 : 1 w/w combinations with granisetron hydrochloride characteristic endotherm of the drug was always present, indicating absence of incompatibility, although, some increase in peak area was observed, which can be attributed to mixing of components.

2.2. Fourier Transform Infrared (FT-IR) studies

The FT-IR scan of granisetron hydrochloride showed characteristic bands at 3221 cm^{-1} due to indazaole ring and at 2937 cm^{-1} due to the alkene group. It also showed bands at 2446 cm^{-1} and 1644 cm^{-1} characteristic to protonated tertiary amine group and C=O stretch respectively. It also showed a characteristic finger print region in 1500–1000 cm^{-1} range.
FT-IR spectra of different blends of the granisetron hydrochloride with β-cyclodextrin (Fig. 5) retained all characteristic bands of the drug indicating there was no change in structure of the drug. It also did not show any new bands indicating that β-cyclodextrin was compatible. It has been shown by several authors (Ventura et al. 2006; Rawat and Jain 2004) that cyclodextrins has a melting endotherm in the range (250–260 °C) where the extra peak was. Therefore, the extra peak can safely be attributed to an endothermic peak of an excipient, β-cyclodextrin. This may suggest that there was no incompatibility with β-cyclodextrin hydrochloride.
Similar kinds of results, as that of β-cyclodextrin, were observed in case of 2-hydroxypropyl β-cyclodextrin indicating that extra endothermic peak from DSC scan was an excipient peak. Cyclodextrins are good complexing agents; therefore modification of thermal behavior caused by the sample treatment may be due to the complexing abilities of cyclodextrins.
Characteristic bands of granisetron hydrochloride were seen in the FT-IR spectra of different mixtures of mannitol with the drug. Suggesting there is no change in the structure of drug in the presence of mannitol. Results obtained in DSC studies could be explained on the basis of amorphization of the drug. Amorphization involves formation of crystalline microaggregates of the drug and their considerable dispersion within the amorphous mannitol. This kind of behavior has already been reported for other drugs such as triamterene (Arias et al. 1995), ofloxacin (Okonogi et al. 1997), carbamazepine (Joshi et al. 2002) and meloxicam (Nassab et al. 2006), with positive effect on the drug solubility. Therefore, mannitol may be excluded as an incompatible excipient.

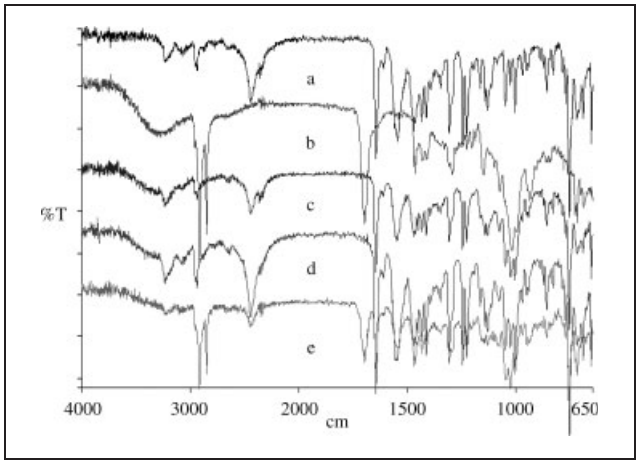

Fig. 5: FT-IR scans of granisetron hydrochloride (a), β-cyclodextrin (b) and 1 : 1 mixed systems of granisetron with β-cyclodextrin (c – physical mixture, d – co-ground mixture, e – kneaded mixture)

The FT-IR spectra of drug: magnesium stearate systems showed characteristic bands as that of the drug itself except some minor changes were observed for physical mixture and co-ground mixture in the finger print region. A similar effect was observed for drug ketoprofen (Mura et al. 1995; Botha and Lotter 1989) and was considered indicative of general incompatibility. These researchers postulated the formation of a simple eutectic mixture between magnesium stearate and drug. This may be reasonably hypothesized in the case of granisetron hydrochloride too.

2.3. Thin Layer Chromatography studies

In TLC studies, R_f value of granisetron hydrochloride alone was compared with the R_f value of granisetron hydrochloride of different drug excipient systems (Table 2). No significant change in the R_f value of the drug was observed with different systems of β-cyclodextrin. This further supported the claim that there was no change in the drug structure when β-cyclodextrin was mixed with granisetron hydrochloride. This may indicate that there was no pharmaceutical incompatibility with β-cyclodextrin. Similar kinds of results were seen with 2-hydroxypropyl-β-cyclodextrin confirming compatibility between drug and excipient. TLC studies further proved that mannitol was compatible with the drug as there was no significant change in the R_f value of the drug in different mixtures.

Table 2: R_f values of granisetron hydrochloride after mixing with excipients in the TLC study

Excipients	β Cyclodextrin	2-Hydroxypropyl-β cyclodextrin	Mannitol	Magnesium stearate
Granisetron	0.20	0.18	0.21	0.17
PM Granisetron*	0.21	0.19	0.19	0.18
Granisetron	0.22	0.20	0.21	0.19
CGM Granisetron**	0.22	0.20	0.21	0.16
Granisetron	0.15	0.18	0.18	0.18
KM Granisetron***	0.15	0.20	0.17	0.20

* PM – Physical mixture,
** CGM – co-ground Mixture,
*** KM – Kneaded mixture

In case of magnesium stearate, there was no significant change in the R_f values of these different systems as compared to that of the drug itself (Table 2). This suggested that there was no change in the structure and this is just a physical incompatibility.

2.4. Conclusion

Compatibility of different excipients was investigated with granisetron hydrochloride. The results confirmed that DSC could be used for the rapid assessment of drug-excipient compatibility or demonstration of drug-excipient interaction or incompatibility. However, DSC being a thermal method, DSC results should be interpreted with caution. Non-thermal methods such as FT-IR and TLC should be taken into consideration, wherever possible, to further assess the results predicted by DSC studies alone to support the conclusions. In the present study, FT-IR and TLC were successfully employed to assess the results obtained with DSC studies to ascertain compatibility of granisetron hydrochloride with different excipients, which could be used in the formulation of fast disintegrating tablets of granisetron hydrochloride.

No definite cases of pharmaceutical incompatibility were observed between granisetron hydrochloride and the majority of the excipients used in this study. However, based on DSC results alone, an interaction was suspected between granisetron hydrochloride and some of the excipients such as cyclodextrins, mannitol, and magnesium stearate. Results obtained with FT-IR and TLC studies ruled out any interaction possibility with mannitol and cyclodextrins. Eutectic formation can be a possible reason with magnesium stearate results and has been reported with other drug compounds.

3. Experimental

3.1. Materials

Granisetron hydrochloride was purchased from Ultratech India Ltd. (Bombay, India). The following chemicals and excipients were obtained and used as they are. β-Cyclodextrin and 2-hydroxypropyl-β-cyclodextrin (Wacker-Chemie, GmBH, Germany), hydroxypropyl methylcellulose and ethyl cellulose (Dow chemical company, Midland, MI), microcrystalline cellulose, croscarmellose sodium and spray dried lactose (FMC corporation, Newark, DE). Copovidone (ISP Technologies, Inc., Wayne, NJ), crospovidone (BASF, Ledgewood, NJ), dextrose and magnesium stearate (Fisher scientific, Fair Lawn, NJ), mannitol (Sigma-Aldrich co., St. Louis, MO), and Talc (Whittaker, South Plainfield, NJ).

3.2. Preparation of samples

The 1 : 1 weight ratio of granisetron hydrochloride and excipients was chosen because it maximizes the likelihood of observing any interaction (Ford 1993; Smith 1982). In order to examine the effect of sample manipulation and different surfaces of contact between drug and excipients, mixed samples for DSC studies were prepared in three different ways (physical mixture, co-ground mixture, kneaded product). Granisetron hydrochloride and all the excipients were passed through sieve number 40 before preparation of the samples.

Physical mixtures of granisetron hydrochloride and each excipient were prepared in a 1 : 1 w/w ratio by gently mixing in a mortar with a spatula at room temperature. Co-ground mixtures were obtained by grinding a portion of each physical mixture with a pestle for approximately 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 under vacuum at room temperature up to a constant weight; the solid was sieved and used for further experiments. Uniformity of the physical mixtures was verified by comparing thermograms obtained from three samples, all taken from the same mixture.

3.3. Differential Scanning Calorimetry (DSC) thermograms

DSC thermograms were obtained using a TA DSC Q100 differential scanning calorimeter (TA Instruments, New Castle, DE). Samples were scanned between 30 and 340 °C at a heating rate of 10 °C min^{-1} under nitrogen purge with a flow rate of about 50 ml min^{-1} The instrument was calibrated using indium as a standard (melting point 156.4 °C). Samples (2–6 mg) were weighed and hermetically sealed in standard aluminum pans.

3.4. Fourier Transform Infra Red (FT-IR) spectra

FT-IR spectra of drug and drug-excipient systems were recorded on a Perkin Elmer 16 PC FT-IR (Perkin Elmer, Waltham, MA USA). Samples were scanned in the range of 4000–650 cm^{-1} at a spectral resolution of 4.0 cm^{-1} and they were scanned at an average of 16 scans. Spectrum software was used for the analysis of all the spectra. Excipient spectra was not subtracted from the spectra of the drug with excipient.

3.5. Thin Layer Chromatography (TLC)

Thin layer chromatography was carried out to determine the R_f values of drug and drug-excipient systems. Respective sample was dissolved in a mixture of 1 : 1 chloroform and methanol. Solutions (20 μl) of the sample were placed on TLC plates. After separation of compounds, plates were placed into an iodine chamber to identify the spots. The R_f values were calculated using Eq. (1)

$$R_f = \frac{\text{Distance traveled by solute front}}{\text{Distance traveled by solvent front}}$$

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