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N,*N*′-dichloro-bis[2,4,6-trichlorophenyl]urea (CC2) and suspending agents used for the preparation of decontamination formulation against chemical warfare agents

A study of compatibility by thermoanalytical techniques

Fakhruddin Ahmed · P. K. Gutch · K. Ganesan · R. Vijayaraghavan

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Abstract *N*,*N*′-dichloro-bis[2,4,6-trichlorophenyl]urea, known as CC2, is used as a reactive chemical decontaminant of mustard agents. The present study was undertaken to establish the compatibility of CC2 with a number of commonly used suspending agents, using thermoanalytical techniques viz., thermogravimetry (TG) and differential scanning calorimetry (DSC) with the support of Fourier transform infrared spectroscopy (FTIR). The results demonstrated the applicability of TG and DSC as a fast screening tool for analysing the compatibility of drug with excipients at the early stages of a preformulation process. Methylcellulose, hydroxypropylcellulose, and betaine were found to be compatible with CC2.

Keywords *N*,*N*′-dichloro-bis [2,4,6-trichlorophenyl]urea · Suspending agents · Compatibility · DSC · TG · FTIR

Introduction

Decontamination is an important unavoidable part in protection against chemical warfare agents. The aim of decontamination is to rapidly and effectively render harmless or remove poisonous substances both on personnel and equipment. High decontamination capacity is one of the factors which may reduce the effect of an attack with chemical warfare agents. The most important decontamination measure naturally concerns the individual. If it is suspected that skin has been exposed to liquid agents, then it must be decontaminated immediately (within a minute). All experience confirms that the most important factor is time.

There are a large number of compounds and formulations that can be employed for the decontamination of chemical warfare agents [1–4]. Although many reactions can detoxify chemical warfare agents [5], only a few are feasible for practical neutralisation because the reactions must be simple and the reactants must be stable, cheap, and of relatively low molecular weight.

Chloramines are the chemicals incorporating a direct nitrogen–chlorine bond formed by the substitution of chlorine into an amide or amine group. They can generate positive chlorine which acts as oxidant. There are several chemical possibilities for such reagents, but only a few have acquired military significance. Since chloramines are milder chlorinating agents than bleaches, the formulations having chloramines as active ingredient have been developed for the skin decontamination, e.g. M258, M258A1 and M280 kits. Major limitation of these chloramines-based decontaminants is their pH and temperature dependence. Hence cannot be used at lower, especially sub-zero temperatures [6, 7].

A reactive chemical decontaminant, CC2 (Fig. 1), acts as an oxidant during the decontamination of sulphur mustard (SM). Positive chlorine generated from CC2 attacks on the lone pair of electrons on the sulphur atom of SM to generate chlorosulphonium ions. Subsequently, an elimination addition reaction sequence follows to generate non-toxic sulphoxide and its α-chloro derivative [8]. The other well-known decontaminants viz. *N*-chloro amines and DS-2 solution are highly corrosive [5]. The major advantage of CC2 over these reported decontaminants is its benign nature. Hence, CC2 could be used on human skin and other

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delicate surfaces. The efficacy of CC2 in the decontamination of SM has been proved experimentally [9–13]. Since, CC2 is insoluble in water, its aqueous suspension was prepared using various suspending agents for the present study.

A pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase [14]. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly through out the suspending vehicle with the aid of single or combination of suspending agents.

A pharmaceutical suspension, like other disperse systems, is thermodynamically unstable, thus, making it necessary to include in the dosage form, a stabiliser or suspending agent which reduces the rate of settling and permits easy redispersion of any settled particulate matter both by protective colloidal action and by increasing the consistency of the suspending medium [15–17]. Suspending agents may be (i) inorganic materials, (ii) synthetic compounds, or (iii) polysaccharides. Most suspending agents perform two functions, i.e. besides acting as a suspending agent they also imparts viscosity to the solution. Suspending agents form film around particle and decrease interparticle attraction.

But successful formulation of a stable and effective suspension depends on careful selection of the excipients. Although excipients traditionally have been thought of as being inert, excipients have shown that they can interact with the drug, preventing its absorption and bioavailability [18, 19]. During the formulation of new products or to reformulation of existing products, it is advantageous to have knowledge on any physical and/or chemical interactions between drug and excipients [20]. Drug–excipient interaction is an important exercise in the development of a stable dosage form [21]. The identification of possible incompatibilities between drug and excipients is one of the basic tasks to be dealt with in a pre-formulation laboratory. In this sense, devising a quick and accurate method to test and select the best candidates for stable dosage forms would constitute a real breakthrough in the pre-formulation pharmacy [22].

Thermoanalytical techniques measure changes in physical or chemical properties of the sample as a function of temperature. There are many possible applications in pharmaceutical industry, for example, identification, characterisation of active and inactive ingredients, routine analysis, quality control and stability study [23–25].

In recent years, applications of thermoanalytical techniques in the pre-formulation stages in formulation development have increased immensely. In particular, TG and DSC have been proposed as a rapid method for evaluating physicochemical interactions between components of the formulation and therefore selecting excipients with suitable compatibility [26–28].

The present study was undertaken to establish the compatibility of CC2 with a number of commonly used suspending agents, using thermoanalytical techniques with the support of Fourier transform infrared spectroscopy (FTIR).

Experimental

Materials

N,*N*′-dichloro-bis [2,4,6-trichlorophenyl]urea (CC2) was synthesized by the reported method [10], and active chlorine was determined by iodometric titration using standard sodium thiosulphate solution. Various suspending agents viz., methylcellulose (MC), hydroxylpropylcellulose (HPC), gum acacia (A), sodium lauryl sulphate (SLS), tetramethyl ammonium chloride (TMAC), cetyltrimethyl ammonium bromide (CTAB) and betaine were purchased from Sigma-Aldrich and Alfa-Aesar (USA).

Methods

Thermogravimetry (TG)

The TG/DTG measurement was performed on TGA-2950 (TA Instruments, USA), under nitrogen atmosphere with the flow rate of 40 mL/min. 5 mg of sample was placed in platinum pan and heated from room temperature to 900 °C at a heating rate of 10 °C/min. TG analysis has been performed using pure CC2, excipients and binary mixtures formed by CC2 with different excipients (1:1 mass ratio).

Differential scanning calorimetry (DSC)

The DSC measurement was performed in DSC-2920 cell (TA Instruments, USA), under nitrogen atmosphere with the flow rate of 50 mL/min. 2 mg of sample was weighed out and placed in a sealed aluminium pan and scanned from room temperature to 400 °C with heating rate of 10 °C/min. DSC analysis has been performed using pure CC2, excipients and binary mixtures formed by CC2 with different excipients (1:1 mass ratio).

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were recorded on a Nicolet IMPACT 410 FTIR apparatus using KBr discs in the range of 400–4000 cm^{-1}. FTIR analysis has been performed using pure CC2, excipients and binary mixtures formed by CC2 with different excipients (1:1 mass ratio).

Results and discussion

A pharmaceutical suspension, like other disperse systems, is thermodynamically unstable, thus, making it necessary to include in the dosage form, a stabiliser or suspending agent

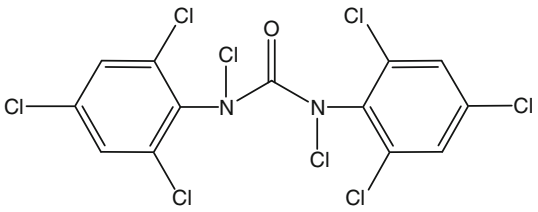

Fig. 1 Structural formula of CC2

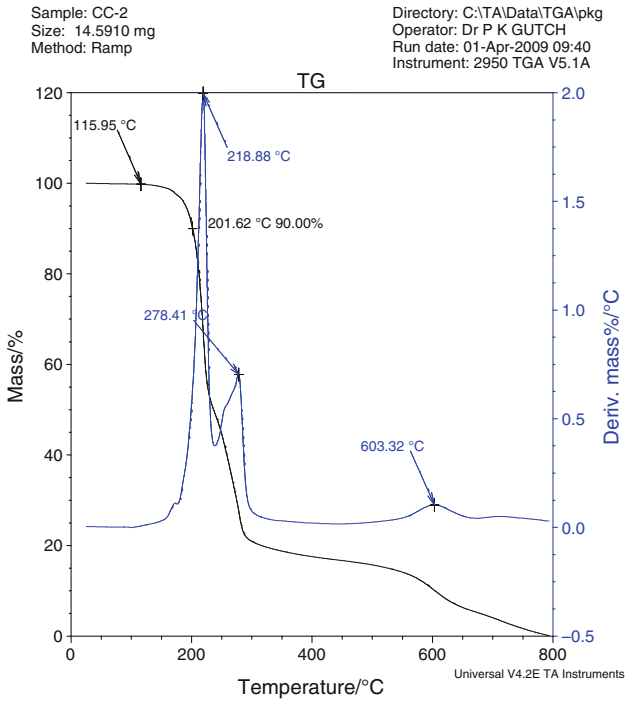

Fig. 2 TG curve of CC2

which reduces the rate of settling and permits easy redispersion of any settled particulate matter both by protective colloidal action and by increasing the consistency of the suspending medium [15, 16]. Suspending agents are used to prevent sedimentation by affecting the rheological behaviour of a suspension. An ideal suspending agent should have certain attributes: (1) it should produce a structured vehicle, (2) it should be compatible with other formulation ingredients and (3) it should be nontoxic. Generally used suspending agents in suspension include cellulosic derivatives (methylcellulose, carboxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl methylcellulose), synthetic polymers (carbomers, polyvinylpyrrolidone poloxamers and polyvinyl alcohol) and polysaccharides and gums (alginates, xanthan, guar gum, etc.) [29]. Most suspending agents perform two functions, i.e. besides acting as a suspending agent they also imparts viscosity to the solution. Suspending agents form film around particle and decrease interparticle attraction. A good suspension should have well-developed thixotropy. At rest, the solution is sufficiently viscous to prevent sedimentation and thus aggregation or caking of the particles. When agitation is applied, the viscosity is reduced and provides good flow characteristic from the mouth of bottle. Suspending agents also act as thickening agents. They increase in viscosity of the solution, which is necessary to prevent sedimentation of the suspended particles as per Stoke's law. The suspension having a viscosity within the range of 200–1500 milipoise is readily pourable [30].

Formulation of a pharmaceutical suspension requires knowledge of the properties of both the dispersed phase and the dispersion medium. The material for the formulation of suspensions should be carefully selected keeping in mind the route of administration, intended application, and possible adverse effects. One of the major concerns in designing new formulation is that the active ingredient should be compatible with all the excipients and packaging material components. Excipients are considered pharmaceutically inert, but physical and chemical interactions with an active component are possible. Incompatibilities will affect the efficiency

Table 1 Thermal stability of CC2 with various suspending agents by TG

S. No.	Sample	Initial decomposition/°C	10% Mass loss/°C	Final decomposition/°C	Residue/%
1	CC2 alone	116	190.72	793.85	7.077
2	CC2+Betaine	116	192.98	794.75	7.035
3	CC2+MC	126	192.54	790.45	8.045
4	CC2+HPC	110	192.04	790.46	7.454
5	CC2+A	53.36	197.43	792.72	7.096
6	CC2+TMAC	61.0	173.02	790.45	2.812
7	CC2+SLS	45.32	195.07	775.18	6.849
8	CC2+CTAB	117.0	217.74	793.85	1.416

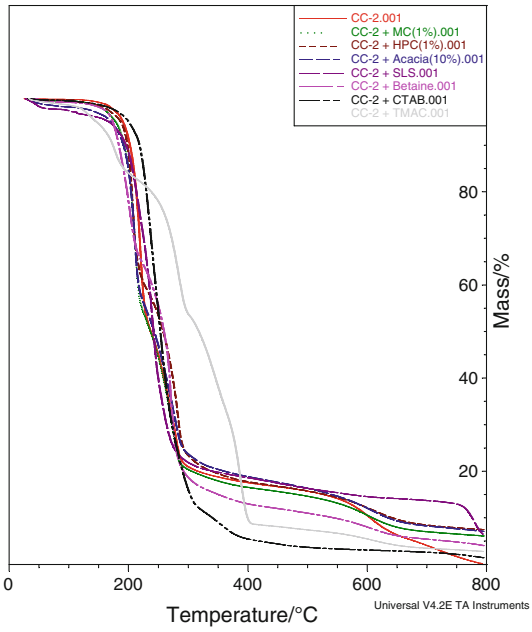

Fig. 3 TG overlay of CC2 and its binary mixtures

of the drug. The identification of possible incompatibilities between drug and excipients is one of the basic tasks to be dealt with in a pre-formulation study.

Thermoanalytical techniques measure changes in physical or chemical properties of the sample as a function of temperature [23]. Thermoanalysis has been used for the rapid evaluation of purity, kinetics decomposition and physical property of drugs [31–33]. Moreover, this technique provided an alert for compatibility problems and it was indicated the most favourable directions to pursue for a successful formulation [34–36]. Thermal analysis, mainly DSC, TG and DTG techniques, has been used for more than 30 years by pharmacists, applied for the characterisation of materials and preformulation [37]. TG and DSC analyses of CC2 and its binary mixture with different excipients were recorded, and the results were interpreted on the basis of mass% loss in TG and change or shifting of exothermic and endothermic peaks, comparison of phase transition and appearance of new peaks in DSC.

TG curve of pure CC2 was shown in Fig. 2, which indicates two step mass loss of pure CC2. CC2 was stable up to 116 °C, and 93% was decomposed at 800 °C. The residue left was only 7%. These results were compared with TG of binary mixtures of CC2 with various suspending agents viz., MC, HPC, Gum acacia, CTAB, TMAC, SLS and betaine. Thermal stability of CC2 and its binary mixture with various suspending agents were reported in Table 1,

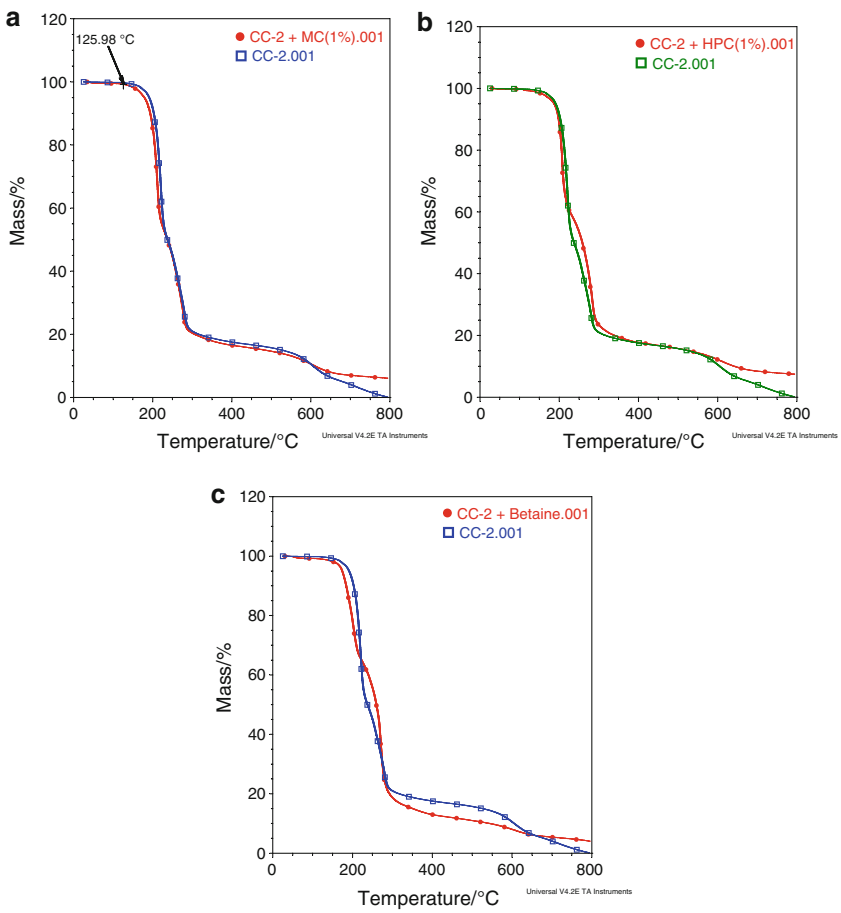

Fig. 4 TG overlay of CC2 and its binary mixture with **a** methylcellulose, **b** hydroxypropylcellulose, and **c** betaine

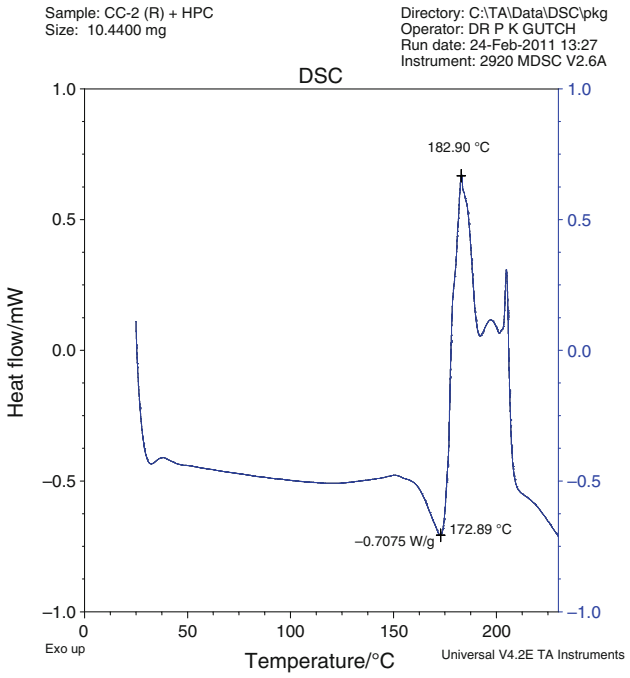

Fig. 5 DSC analysis of pure CC2

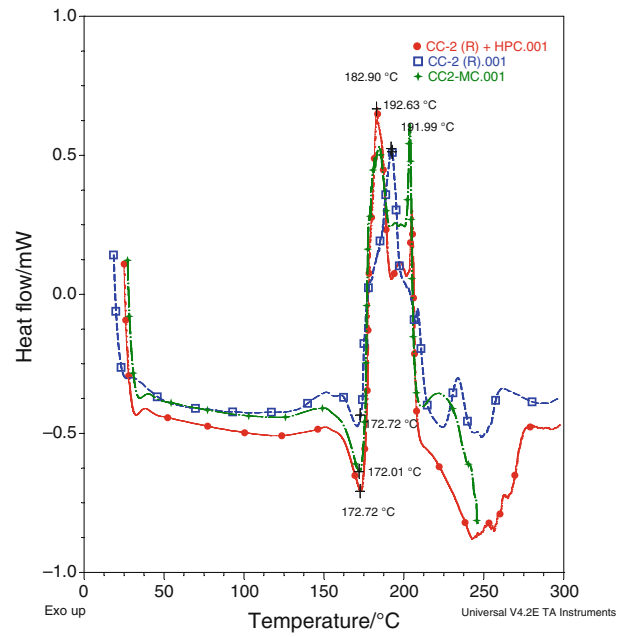

Fig. 6 DSC overlay of CC2 and its binary mixture with MC and HPC

and it is clear from this table that all binary mixtures were stable up to 197 °C. Only few changes were observed in case of binary mixture of CC2+TMAC and CC2+CTAB. The overlay of pure CC2 and its binary mixtures with methylcellulose (MC), hydroxylpropylcellulose (HPC), gum acacia (A), sodium lauryl sulphate (SLS), tetramethyl ammonium chloride (TMAC), cetyltrimethyl ammonium bromide (CTAB) and betaine is given in Fig. 3.

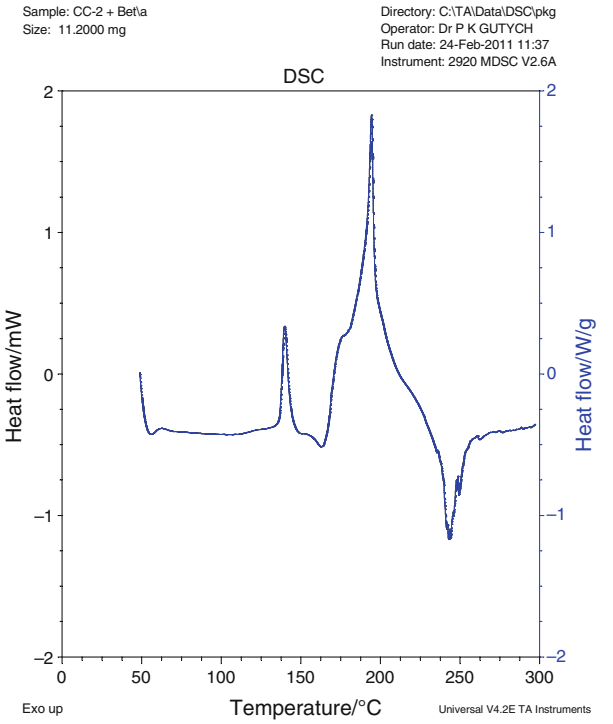

Fig. 7 DSC of binary mixture of CC2 and betaine

We have compared TG curve of pure CC2 with binary mixtures of CC2 and MC, HPC or betaine. TG curve overlay of most compatible excipients is given in Fig. 4a–c. Figure 4a shows TG of pure CC2 and binary mixture of CC2 and methyl cellulose, which indicates no chemical interaction at any temperature. Similarly, the TG of other suspending agents was also compared individually. No chemical interaction was observed in case of CC2+HPC and CC2+Betaine as shown in Fig. 4b and c, respectively. Hence, these excipients were found to be suitable for the preparation of decontamination formulation against mustard agents.

DSC analysis of CC2 is illustrated in Fig. 5. CC2 shows endothermic peak at 172.89 °C which corresponds to the melting temperature and it is followed by a sharp exothermic peak at 182.90 °C ascribed to crystallization temperature. Observed endothermic and exothermic peaks in DSC analysis of pure CC2 were compared with the binary mixtures of CC2 with MC, HPC and betaine. The overlay of DSC curve for pure CC2 and its binary mixtures with MC and HPC are given in Fig. 6, which shows no interaction between binary mixture of CC2 with MC and HPC. In DSC analysis of CC2 with betaine (Fig. 7), an additional exothermic peak at 137 °C was also observed.

The subsequent step of the present study was to analyse the FTIR spectra of pure CC2 (Fig. 8) and compare it with the binary mixtures of CC2 with various suspending agents (1:1 mass/mass) in order to identify a possible chemical

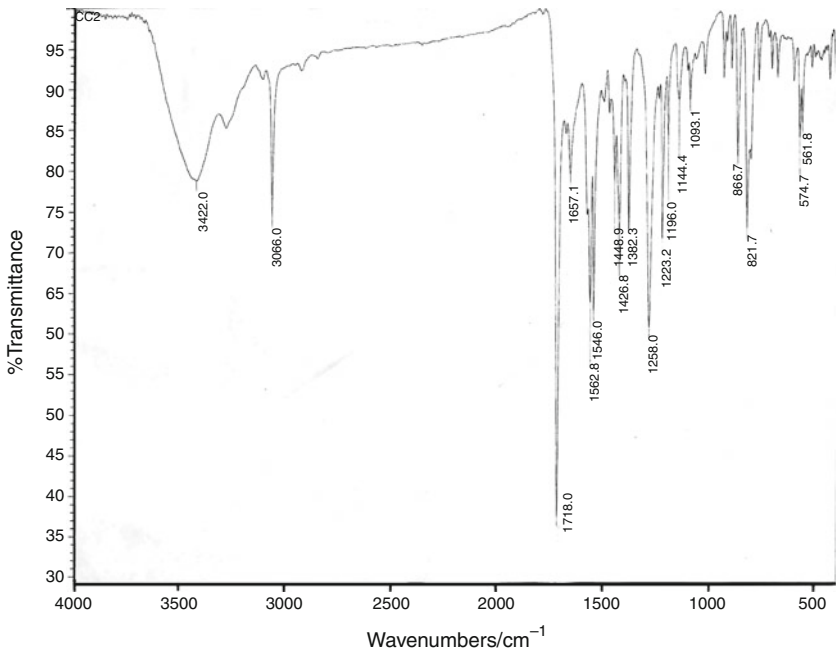

Fig. 8 FTIR spectra of CC2

interaction between them. The FTIR spectra (Fig. 8) of pure CC2 has shown bands at 3066(Ph–H), 1718(C=O) and 822(C–Cl) cm^{-1}. The FTIR spectra of CC2 and binary mixtures with MC, HPC and betaine did not show evidence of chemical interaction. Moreover, the spectra of binary mixtures did not show the absence or shift of fundamental absorption frequency bands. It explains the absence of chemical interactions between CC2 and suspending agents.

Conclusions

TG and DSC analyses of CC2 and its binary mixture with different excipients were recorded, and the results were interpreted on the basis of mass% loss in TG and change or shifting of exothermic and endothermic peaks and appearance of new peaks with respect to temperature in DSC. The results demonstrated that methylcellulose, hydroxypropylcellulose and betaine were compatible with CC2 and chosen for the preparation of decontamination formulation against mustard agents.

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