Thermal analysis of interactions between an oxime and excipients in some binary mixtures by differential scanning calorimetry and thermogravimetric analysis

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ABSTRACT

Thermal analysis methods are widely used in all fields of pharmaceutical sciences but especially in preformulation studies. These techniques are unique for the characterization of single compounds and mixtures. The information correlated with the thermodynamic phase diagrams is extremely helpful for rational preformulation studies and development of novel drug delivery systems. Excipients found compatible can be chosen for formulation development. Different excipients were checked and evaluated with obidoxime chloride by using thermal analytical techniques. All the binary mixtures represent the characteristic Obidoxime chloride peak. All the excipients found compatible compatible with Obidoxime chloride.

Keywords: Oxime, Differential scanning calorimeter (DSC), Thermogravimetry (TGA), Preformulation study, Melting point, Binary mixture.

INTRODUCTION

The nerve agents are organophosphorus compounds (OP). All OP compounds do not qualify as war gases and are not a threat, due to their differential toxicity. Some of the OP compounds that are less toxic to humans are used as insecticides. Agents that fall in the nerve agent category are tabun, sarin, soman and VX. The nerve agents are classified under Schedule I of the CWC. The absorption of these agents into the system is through inhalation, dermal absorption, and through mucous membranes. If the skin is also exposed, these agents can be absorbed appreciably. Nerve agents irreversibly inhibit the enzyme acetylcholinesterase (AChE), which results in accumulation of acetylcholine leading to cholinergic crisis. The treatment of nerve agent casualty requires artificial respiration and drug treatment. The recommended drugs are atropine sulfate and obidoxime chloride. Atropine sulfate is a competitive inhibitor of muscarinic receptors and the recommended human dose in the field is 2 mg intramuscularly and subsequently increased to 4 or 6 mg, and sometimes higher. Obidoxime chloride is used as a cholinesterase reactivator and the recommended dose is 250 to 750 mg intramuscularly or intravenously. Study of drug-excipient interaction is a basic stage of product development. For the development of novel and stable dosage formulation, in pharmaceuticals the thermal interaction study is used as an important exercise. For the assessment of possible interaction (whether physical or chemical) of drug with different excipient there is no official protocol. Excipients have been observed to have a characteristic properties for example polymers have been observed to have a protective covering or coating effect on individual drug particles. Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) are the techniques used for the screening or testing of the compatibility of drug component with the excipients. Here DSC and TGA were successfully employed for preformulation study of obidoxime chloride with various pharmaceutical excipients for development of dosage formulation to evaluate any physicochemical interactions between formulation components, by revealing changes in their appearance, shift or disappearance of melting or other exothermic processes, and/or variations in the corresponding enthalpies of reaction in DSC and therefore selecting suitable compatibility excipients similarly weight change pattern in TGA. Assessment of possible incompatibility between active component (i.e. Obidoxime chloride) and different excipients along with the evaluation of thermal stability are crucial parts of the normal study prior to the final formulation setting of a solid dosage form. Excipients are used in pharmaceutical formulations to facilitate administration and release of an active pharmaceutical component, as well as to protect it from the environment. Excipients are considered pharmaceutically inert but physical and chemical interactions with an active component are possible1-7.

EXPERIMENTAL

Materials

Obidoxime chloride was synthesized in the Synthetic Chem
Fig. 1.1 TGA Thermogram of Obidoxime chloride alone

Fig. 1.2 TGA Thermogram of Obidoxime chloride alone and with different excipients

1. Obidoxime chloride
2. Binary mixture of Obidoxime chloride with HPC
3. Binary mixture of Obidoxime chloride with PAA
4. Binary mixture of Obidoxime chloride with PVA
5. Binary mixture of Obidoxime chloride with MP
6. Binary mixture of Obidoxime chloride with MC
7. Binary mixture of Obidoxime chloride with HPMC
8. Binary mixture of Obidoxime chloride with CMC
9. Binary mixture of Obidoxime chloride with CA
10. Binary mixture of Obidoxime chloride with MCC
11. Binary mixture of Obidoxime chloride with EC
12. Binary mixture of Obidoxime chloride with SC

Fig. 1.3 TGA Thermogram of different excipients (Pure)

Methods

DSC Differential Scanning Calorimeter DSC 2920 Modulated
TA instruments connected to an IBN personal computer was used. Sample of API (active pharmaceutical ingredient) pure and binary mixture of drug-excipients were analyzed separately (before analysis all the samples were passed through BSS 60 mesh). Samples were weighed directly in the DSC aluminium pan and scanned from 37-300°C at the heating rate of 10°C/min under the dry N2 atmosphere.

**TGA** Thermo gravimetric measurements of individual components alone and in binary mixtures with excipients were carried out on a TGA 2950 Thermogravimetric analyzer from TA instruments with V5.1A version connected to an IBN personal computer.

Instrument was calibrated by using pure standard because of their known value of melting enthalpies. The TG system was fluxed with purge gas stream.

**RESULTS & DISCUSSION**

The first method developed by Le Chatelier in 1887 was differential thermal analysis (DTA), where only the temperature induced in the sample was measured. The principle of DSC is as follows: two ovens are linearly heated; one oven contains the sample in a pan, the other contains an empty pan as a reference pan. If no change occurs in the sample during heating, the sample pan and the reference pan are at the same temperature. If a change such as melting occurs in the sample, energy is used by the sample and the temperature remains constant in the sample pan while the temperature of the reference pan continues to increase. Therefore a difference of temperature occurs between the sample pan and reference pan. In thermogravimetry (TG or TGA) the change in sample mass is determined as a function of temperature and/or time.

DSC curves of mixtures of solid compounds depend upon the phase diagrams in solid state. If there is no interaction in the solid state and if there is miscibility in the melt, a eutectic behavior is observed. This enables the purity determination of raw materials, the analysis of solid compounds. Interaction is observed in the solid state in case of formation of solid solution or complex formation between components or in the case of chemical reaction. The protective effect of an excipient on the active drug depends on the compaction characteristic and particle size while plastic or elastic deformation is defending on volume reduction mechanism.

Thermograms obtained shows a sharp change if there is any interaction whether it is physical or chemical like physical properties of drug compound. These can be in the form of melting point, % weight change, vaporization temperature and changes in enthalpies. TG, DTG thermograms of Obidoxime chloride obtained as pure drug was recorded and displayed in Fig.1.1 and the data tabulated in Table 5.1. TG, DTG curve of Obidoxime chloride as binary mixture with different excipients was recorded and presented as Fig.1.2 and in Table 5.1 the corresponding temperature values had been presented. These were interpreted on the basis of % weight change, % weight loss, shifting, and appearance/disappearance of peaks with each increment of temperature.

The TG/DTG scans indicate that the thermal decomposition process of Obidoxime chloride occurs in one stage in the following temperature range and weight losses 118.29-327.84°C (dm=99.71-
Table 1 Thermal behaviour of Obidoxime chloride with different excipients by TGA

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Mixtures</th>
<th>Initial decomposition temperature (IDT)</th>
<th>Temp. (ºC) at 10%</th>
<th>30%</th>
<th>50%</th>
<th>70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Obidoxime chloride</td>
<td>175</td>
<td>208</td>
<td>212</td>
<td>322</td>
<td>363</td>
</tr>
<tr>
<td>2</td>
<td>Obidoxime chloride+HPC</td>
<td>165.98</td>
<td>175</td>
<td>346</td>
<td>361</td>
<td>372</td>
</tr>
<tr>
<td>3</td>
<td>Obidoxime chloride+PAA</td>
<td>146</td>
<td>170</td>
<td>201</td>
<td>301</td>
<td>383</td>
</tr>
<tr>
<td>4</td>
<td>Obidoxime chloride+PVA</td>
<td>147.39</td>
<td>178</td>
<td>207</td>
<td>329</td>
<td>388</td>
</tr>
<tr>
<td>5</td>
<td>Obidoxime chloride+MP</td>
<td>121.29</td>
<td>151</td>
<td>272</td>
<td>297</td>
<td>377</td>
</tr>
<tr>
<td>6</td>
<td>Obidoxime chloride+MC</td>
<td>178.27</td>
<td>307</td>
<td>341</td>
<td>362</td>
<td>384</td>
</tr>
<tr>
<td>7</td>
<td>Obidoxime chloride+HPMC</td>
<td>149.20</td>
<td>336</td>
<td>367</td>
<td>391</td>
<td>402</td>
</tr>
<tr>
<td>8</td>
<td>Obidoxime chloride+CMC</td>
<td>149.46</td>
<td>161</td>
<td>182</td>
<td>324</td>
<td>396</td>
</tr>
<tr>
<td>9</td>
<td>Obidoxime chloride+CA</td>
<td>121.29</td>
<td>151</td>
<td>272</td>
<td>297</td>
<td>377</td>
</tr>
<tr>
<td>10</td>
<td>Obidoxime chloride+MCC</td>
<td>144</td>
<td>173</td>
<td>264</td>
<td>314</td>
<td>389</td>
</tr>
<tr>
<td>11</td>
<td>Obidoxime chloride+EC</td>
<td>149</td>
<td>325</td>
<td>315</td>
<td>375</td>
<td>384</td>
</tr>
<tr>
<td>12</td>
<td>Obidoxime chloride+SC</td>
<td>167</td>
<td>182</td>
<td>280</td>
<td>390</td>
<td>449</td>
</tr>
</tbody>
</table>

Table 2 Thermal behaviour of Obidoxime chloride with different excipients by DSC

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Sample</th>
<th>Peak Temperature (in ºC)</th>
<th>Exo/endo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T&lt;sub&gt;onset&lt;/sub&gt; (in ºC)</td>
<td>T&lt;sub&gt;peak,max&lt;/sub&gt; (in ºC)</td>
</tr>
<tr>
<td>1</td>
<td>Obidoxime chloride</td>
<td>212</td>
<td>225</td>
</tr>
<tr>
<td>2</td>
<td>Obidoxime chloride+HPC</td>
<td>208</td>
<td>229</td>
</tr>
<tr>
<td>3</td>
<td>Obidoxime chloride+PAA</td>
<td>210</td>
<td>227</td>
</tr>
<tr>
<td>4</td>
<td>Obidoxime chloride+PVA</td>
<td>212</td>
<td>225</td>
</tr>
<tr>
<td>5</td>
<td>Obidoxime chloride+MP</td>
<td>210</td>
<td>229</td>
</tr>
<tr>
<td>6</td>
<td>Obidoxime chloride+MC</td>
<td>222</td>
<td>229</td>
</tr>
<tr>
<td>7</td>
<td>Obidoxime chloride+HPMC</td>
<td>210</td>
<td>227</td>
</tr>
<tr>
<td>8</td>
<td>Obidoxime chloride+CMC</td>
<td>204</td>
<td>225</td>
</tr>
<tr>
<td>9</td>
<td>Obidoxime chloride+CA</td>
<td>210</td>
<td>226</td>
</tr>
<tr>
<td>10</td>
<td>Obidoxime chloride+MCC</td>
<td>209</td>
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<td>12</td>
<td>Obidoxime chloride+SC</td>
<td>211</td>
<td>226</td>
</tr>
</tbody>
</table>

19.91%), 327.84-672.40°C (dm=19.90-0.2267%). The 10% weight loss at 208ºC, 30% at 212ºC while 50% weight lost at 216ºC and 90% at 574ºC. The first weight loss represents % of the molecular mass of Obidoxime chloride. The final mass loss observed agree with the values calculated for the conversion of complex to the corresponding oxime-excipient complex.

TGA curve of Obidoxime chloride obtained by TG/DTG coupled system are shown in Fig.5.1. The data corresponds to them is tabulated very well (Table 1). TGA scans of Obidoxime chloride as in Fig.5.1 presents its characteristic profile of (dT198.12-327.84 ºC) of Obidoxime chloride (t<sub>Peak max</sub> 225ºC). Conversely thermal decomposition temperature (Td), maximum decomposition temperature (Tdm), temperature for final decomposition (Tdf), and rate of decomposition (da/dt) m. This might be understood from the contribution of a little hydroxyethyl group in the system. The hydroxyethyl group may significantly decrease the pyrolytic temperature, retard carbonization of polymer, and increase pyrolysis residue. The thermograms of the complexes follow the same pattern of thermal decomposition.

By the comparison of thermogravimetric data of Obidoxime chloride alone and of different binary mixtures with different excipients as shown in Table 1, differences were recorded. Only a few changes were found. From the Table 1, the IDT value and T<sub>m</sub> value for CMC were slightly lower than those of pure Obidoxime chloride.

The thermo gravimetric profile of hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC) and cellulose acetate (CA) presented in Table 1 shows a weight loss of 75% at 313.66ºC because of the TG/DTG scan of Obidoxime chloride and HPMC shows characteristic changes of active drug & inert drug excipients. On the basis of this result it can be concluded that these were found compatible with Obidoxime chloride.
considered compatible.

The DSC curves of pure Obidoxime chloride were recorded and shown in Fig. 1.3 while of different binary mixtures in Fig. 1.4. DSC traces of pure Obidoxime chloride showed a sharp exothermic peak at 225°C corresponding to its decomposition temperature. From the comparison of Fig. 1.3 and 1.4 it can be concluded that the excipients did not affect the decomposition pattern of pure active content of Obidoxime chloride. The decomposition endotherm did not affect and was well preserved in all the binary mixtures containing different formulation of excipients. However there was slight change in the peak shape with little broadening or shifting towards the lower temperature which could be attributed due to mixing process. All the binary mixture showed the same thermal behaviour for Obidoxime chloride (tonset 212 ºC; t Peak max 225ºC).

In the DSC curve of binary mixture containing CMC, slight difference was observed. This was probably because of the decomposition of cellulose. In fact difference between IDT value and t 10% of binary mixture containing Obidoxime chloride and cellulose containing excipients like hydroxy propyl cellulose (HPMC), hydroxy propyl methyl cellulose (HPMC), methyl cellulose (MC), microcrystalline cellulose (MCC) and ethyl cellulose (EC), cellulose acetate (CA) are probably due to the partial overlapping of decomposition of cellulose.

PAA, PVP showed dehydration step of mass loss under 157ºC followed by one or more decomposition steps over 327ºC. Moreover DSC peaks of Obidoxime chloride did not overlap with those of excipients as their was no thermal interference. After slight water loss up to 100ºC CMC and starch showed decomposition above 297ºC. Thus these excipients did not affect the decomposition process of Obidoxime chloride.

In case of HPMC no peak was observed in the range of 25-300ºC (Fig. 1.4). DSC traces of Obidoxime chloride and MCC mixture showed that the exothermic peak of Obidoxime chloride was shifted. No peak was observed in the DSC trace of sodium chloride in the temperature range of 25-300ºC. The peak of Obidoxime chloride was well retained in thermogram of obidoxime chloride-sodium chloride mixture (Fig. 1.4). Based on the results any incompatibility between Obidoxime chloride and sodium chloride was ruled out.

In the DSC thermogram of ethyl cellulose (EC) and cellulose acetate (CA), no additional peak was observed in the temperature range of Obidoxime chloride (25-300ºC). In case of Obidoxime chloride-cellulose acetate mixture, drug peak was unaffected (Fig. 1.4). In all the binary mixtures the exothermic peak (tpeak= 225°C) of active drug constituent was well retained and unaffected by the excipients, but a slight shifting of the peak was recorded. There was no drastic change in the peak shape of thermal pattern, behaviour, decomposition temperature, that suggested there was no incomaptibility.

DSC traces of PVA, SC showed endotherm at 80ºC probably because of loss of adsorbed moisture (Fig. 1.4). The PVA was then dehydrated and dried for 24 hrs and again subjected for analysis. The thermogram of dehydrated PVA evident no peak due to loss-adsorbed moisture. In the binary mixture of Obidoxime chloride-PVA and Obidoxime chloride-SC the drug peak was well preserved which represent the compatibility.

Finally on the basis of thermogravimetric data and differential scanning calorimetric data it can be concluded that Obidoxime chloride was found to be compatible with most of the tested excipients, only a few slight chages were recorded with some excipients. TGA results indicate the presence of compatibility of Obidoxime chloride in binary mixture with HPMC, PAA, PVA, MP, MC, EC, CA, MCC and HPC mixed in the ratio of 1:1. All the binary mixtures represent the characteristic Obidoxime chloride peak. All the thermograms of binary mixtures showed characteristic Obidoxime chloride pattern. All found compatible with Obidoxime chloride. The transitions observed by thermal analysis techniques are based upon the Gibbs phase rule and phase diagrams and concentration. All transitions or reactions involving energy changes may be measured by DSC. TG detects transitions involving mass changes. For a single product, specific heat, glass transition, melting, boiling, sublimation, decomposition, and phase transitions induced by polymorphism during heating are important for the choice of the salt form and for safety studies where the DSC exothermic peaks are relevant. The use of DSC for the measurement of the melting point of raw materials has been proposed. Hydrates or solvates, or volatile compounds in the formulations can be investigated by DSC combined with TGA.

CONCLUSION

The transitions observed by thermal analysis techniques are based upon the Gibbs phase rule and phase diagrams and concentration. All transitions or reactions involving energy changes may be measured by DSC. TG detects transitions involving mass changes. For a single product, specific heat, glass transition, melting, boiling, sublimation, decomposition, and phase transitions induced by polymorphism during heating are important for the choice of the salt form and for safety studies where the DSC exothermic peaks are relevant. The use of DSC for the measurement of the melting point of raw materials has been proposed. Hydrates or solvates, or volatile compounds in the formulations can be investigated by DSC combined with TGA.

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