ABSTRACT

Thermal analysis (TGA, DTG and DTA) and differential scanning calorimetry (DSC) have been used to study the thermal behavior of alfuzosin HCl as a raw material and in tablets. Thermogravimetric analysis (TGA/DTG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) were used to determine the thermal behavior and purity of the used drug. Thermodynamic parameters such as activation energy ($E^*$), enthalpy ($\Delta H^*$), entropy ($\Delta S^*$) and Gibbs free energy change of the decomposition ($\Delta G^*$) were calculated using different kinetic models. The purity value for the drug was found to be 99.99%. Thermal analysis technique gave satisfactory results to obtain quality control parameters such as melting point, water content and ash content in comparison to what were obtained using official methods. Thermal analysis justifies its application in quality control of pharmaceutical compounds due to its simplicity, sensitivity and low operational costs. DSC data indicated that the degree of purity of alfuzosin HCl is similar to that found by official methods.

Keywords: Alfuzosin HCl, TGA, DTG, DTA, DSC, Xatral tablet, Quality control

INTRODUCTION

Alfuzosin HCl (Fig. 1) is a quinazoline derivative that reduces the tone of the contractions of the prostate, bladder base and proximal urethral smooth muscle, acting as a selective and competitive antagonist of α1-adrenoceptors. It is regarded as first line therapy for symptomatic treatment of non-complicated mild to moderate benign prostatic hyperplasia, because it provides rapid and sustained symptom relief irrespective of prostate size. Recent studies indicate that alfuzosin is also a drug of choice for urinary bladder dysfunction in patients with nephro-tuberculosis.

Alfuzosin HCl, raw material and Xatral tablets were provided from Amriya for Pharmaceutical Industries, Alexandria, Egypt.

MATERIALS AND METHODS

Materials

Alfuzosin HCl raw material and Xatral tablets were provided from Amriya for Pharmaceutical Industries, Alexandria, Egypt.

Methods

Thermal analysis studies were made by using simultaneous TGA-DTA thermal analyzer apparatus (Shimadzu DTG-60H). The experiments were performed between ambient and 800 °C. The temperature program had a heating rate 10 °C/min. Dry nitrogen at a flow rate of 30 ml/min was used as the purge gas. α-Al2O3 was used as the reference material.

RESULTS AND DISCUSSION

Thermodynamic parameters such as activation energy ($E^*$), enthalpy ($\Delta H^*$), entropy ($\Delta S^*$) and Gibbs free energy change of the decomposition ($\Delta G^*$) were obtained using the Horowitz-Metzger and Coats-Redfern relations. DSC curves were measured on Shimadzu DSC-50 cell. Approximately 2 mg of samples were mass out and placed in a sealed aluminum pan. An empty aluminum pan was used as a reference. The purity determination was performed using heating rate of 10 °C/min in the temperature range from 25 to 400 °C in nitrogen atmosphere with flow rate of 30 ml/min. DSC equipment was preliminary calibrated with standard of indium.

The determination of purity using DSC method is based on the assumption that the impurities will lower the melting point of a pure substance. The melting transition of a pure, 100% crystalline substance. The melting point, water content and ash content in comparison to what were obtained using official methods. Thermal analysis justifies its application in quality control of pharmaceutical compounds due to its simplicity, sensitivity and low operational costs. DSC data indicated that the degree of purity of alfuzosin HCl is similar to that found by official methods.
A substance should be infinitely sharp, but impurities or defects in the crystal structure will broaden the melting range and lower the melting point. In a system which contains impurities, Van’t Hoff equation approximately holds and allows the purity value to be calculated as follow:

\[ T_f = T_0 - \left[ \frac{R T_0^2 X}{\Delta H_f} \right] \]

Where \( T_f \) is the melting temperature of the sample, \( T_0 \) is the melting point of pure substance in Kelvin (K), \( R \) is the gas constant, \( \Delta H_f \) is the heat of fusion, \( F \) is the fraction melted and \( X \) is mole fraction of impurities.

The DSC curve of Alfuzosin HCl in Fig. 3 shows an endothermic reaction with a very sharp peak at 235 °C due to melting of the drug and another weak exothermic peak at 320 °C. The sample seems to be suitable for purity determination by the DSC method. The drug was found to be very pure 99.99%, the purity of the drug was compared with that obtained by using the official method 99.70% confirming low impurities content. The results were listed in Table 2.

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**Table 1: Thermodynamic parameters of the thermal decomposition of Alfuzosin HCl**

<table>
<thead>
<tr>
<th>Temperature range (°C)</th>
<th>( E^\ast ) (kJ/mol)</th>
<th>( A ) (S(^{-1}))</th>
<th>( \Delta S^\ast ) (kJ/mol.K)</th>
<th>( \Delta H^\ast ) (kJ/mol)</th>
<th>( \Delta G^\ast ) (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>190-286</td>
<td>97.63</td>
<td>2.92 X10^9</td>
<td>-68.32</td>
<td>93.31</td>
<td>128.27</td>
</tr>
<tr>
<td></td>
<td>(94.98)</td>
<td>(2.25X10^9)</td>
<td>(-89.63)</td>
<td>(90.67)</td>
<td>(137.18)</td>
</tr>
<tr>
<td>286-475</td>
<td>76.07</td>
<td>1.04X10^9</td>
<td>-135.60</td>
<td>71.08</td>
<td>152.57</td>
</tr>
<tr>
<td></td>
<td>(67.27)</td>
<td>(4.12X10^9)</td>
<td>(-162.41)</td>
<td>(62.27)</td>
<td>(159.89)</td>
</tr>
<tr>
<td>475-800</td>
<td>61.25</td>
<td>8.18X10^9</td>
<td>-197.65</td>
<td>54.39</td>
<td>217.45</td>
</tr>
<tr>
<td></td>
<td>(55.85)</td>
<td>(1.61X10^9)</td>
<td>(-211.16)</td>
<td>(48.99)</td>
<td>(223.20)</td>
</tr>
</tbody>
</table>

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Table 2: Melting point and degree of purity of Alfuzosin HCl

<table>
<thead>
<tr>
<th>Melting point (°C)</th>
<th>DTA method</th>
<th>Melting point apparatus</th>
<th>DSC Method</th>
<th>Literature</th>
<th>DSC Method</th>
<th>Official Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>237</td>
<td>233</td>
<td>235</td>
<td>235</td>
<td>99.99%</td>
<td>99.70%</td>
<td></td>
</tr>
</tbody>
</table>

Application of thermal analysis to quality control of Alfuzosin HCl

Thermal analysis is used as an alternative technique for the determination of different quality parameters such as water content and ash content. No significant difference was observed between the obtained results when compared with reported method as shown in Table 3.

Application of thermal analysis on Xatral tablets

Figure 4 shows the TGA, DTG and DTA curves of Xatral tablets. The DTA curves of Alfuzosin HCl and its tablets were showed in Fig. 5, where, the onset and the end set temperatures were shifted to lower temperature. The DTA curve of Xatral tablets indicates that the melting point of Alfuzosin HCl is 186 °C. It was observed that the drug melting event occurs with mass loss, suggesting an interaction but not necessary corresponding to incompatibility. In fact a similar effect was observed for other drug excipients mixtures and was attributed to drug dissolution in the melted excipients.27

The excipients can produce a different environment in which the behavior of the drug is modified but they are still compatible with the drug. Based on the results of DTA, majority of the excipients (Mg stearate, povidone, microcrystalline cellulose) were found to be compatible with the drug. See Figures 6 and 7.

Table 3: Quality control parameters obtained from the thermal analysis of Alfuzosin HCl compared with reported method

<table>
<thead>
<tr>
<th>Water content (%)</th>
<th>Ash content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal analysis method</td>
<td>Reported method</td>
</tr>
<tr>
<td>0.025 (Max. 0.5%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Fig. 4: TGA, DTG and DTA curves of Xatral tablets

Fig. 5: DTA curves of Alfuzosin HCl (a) and Xatral tablets (b)
The DSC curve of Xatral tablets (Fig. 8) shows very sharp endothermic peak at 182.18 °C corresponding to melting point of Alfuzosin HCl. By comparing the melting point values for Alfuzosin HCl in tablets with those values obtained for the pure drug showed in Table 2, we found that the melting point values of the pure drug are higher than those in tablets which may be attributed to the presence of excipients.

Fig. 6: Excipients microcrystalline cellulose (a), Magnesium stearate (b) and povidone (c)

Fig. 7: DTA curves of Xatral tablets (a), microcrystalline cellulose (b), magnesium stearate (c) and povidone (d)

Fig. 8: DSC curve of Xatral tablet
CONCLUSION
Thermal analysis and differential scanning calorimetry (DSC) are the techniques used for the screening or testing of the compatibility of drug component with the excipients. Comparison of the data obtained in this work reveals the importance of the thermal analysis and DSC techniques for the quality control of bioactive drugs. The melting points obtained by DSC reveal the precision of the technique in yielding this thermal parameter. This justifies the use of DSC as a routine technique for the identification of compounds destined for pharmaceutical use through the melting point. The uses of clean, fast and simple techniques of the analytical methods applied to obtain the results are the reasons behind the even growing importance of thermal analysis in the quality control of active ingredients for medications.

REFERENCES