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Thermoanalytical Study and Purity Determination of Azelastine Hydrochloride and Emedastine Difumarate

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Abstract

The thermal behavior of antihistaminic drugs, azelastine hydrochloride, and emedastine difumarate in their drug substances were investigated using different thermal techniques. The thermogravimetry was used to study the thermal degradation and kinetic parameters; activation energy (E_a), frequency factor (A), and reaction order (n) of both drugs. The data revealed that the cited drugs followed first order kinetic behavior. The fragmentation pathway of azelastine hydrochloride with mass spectrometry was taken as example; to correlate the thermal decomposition with the resulted MS-EI. The melting point and purity were determined using DSC and Van't Hoff equation for the studied drugs. The results were in agreement with the recommended pharmacopoeias.

Keywords: Thermal analysis; Azelastine hydrochloride; Emedastine difumarate; Kinetic studies; MS-EI; Purity determination

Introduction

Azelastine-HCl, is 4-(4-chlorobenzyl)-2-[(4RS)-1- methylhexahydro-1H-azepin-4-yl] phthalazin-1(2H)-one hydrochloride [1]. It is an intranasal antihistamine indicated for use in patients with seasonal allergic rhinitis (SAR) and non-allergic vasomotor rhinitis (VMR). It is also used topically in the symptomatic relief of allergic conditions including rhinitis and conjunctivitis [2,3]. Emedastine difumarate, is 1H-benzimidazole, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1, 4- diazepin-1-yl), (E)-2-butenedioate (1:2) [4]. It is a second generation antihistamine used in eye drops to treat allergic conjunctivitis [5].

The available methods for analysis of azelastine-HCl in pharmaceutical dosage forms and biological fluids are volumetric [6] like UV spectrophotometry [7], colorimetry [7], TLC [8], HPLC [9-11], and capillary electrophoresis [12]. Few methods were reported for analysis of emedastine difumarate including only HPLC with tandem MS [13,14] or radioreceptor assay [15].

Thermal analysis techniques cover all methods in which a physical property is monitored as a function of temperature or time, whilst the sample is being heated or cooled under controlled conditions. Thermogravimetry (TG) and differential scanning calorimetry (DSC) are useful techniques that have been successfully applied in the pharmaceutical industry to reveal important information regarding, the physicochemical properties of drug and excipient molecules such as polymorphism, stability, purity, formulation compatibility among others, and assessing the drug degradation kinetics. There are definitive advantages to employing multiple thermal analysis methods to attain varying views of the physicochemical properties of pharmaceuticals. The determination of the key physical and chemical properties of a new material is essential [16-23].

Therefore, the aim of this study was to evaluate the thermal characterization of azelastine hydrochloride and emedastine difumarate using a variety of techniques including TGA/DTG, DTA and DSC. The search of thermal degradation and kinetics, were carried out to help understanding the solid-state characterization, evaluate the quality control and stability for these important active pharmaceutical ingredients.

Experimental

Materials

Azelastine HCl was kindly supplied from European Egyptian Pharm Co., Egypt with 99.0% purity. Zalastine nasal spray, BN 7579001(European Pharm Co., Egypt) labeled to contain 1 mg azelastine HCl per 1 mL and Azelast eye drops, BN 86872, (El-Kahira Pharm and Chem Ind Co., for EPCI, Cairo, Egypt) labeled to contain 0.5 mg azelastine HCl per 1 mL. Emedastine difumarate was kindly supplied from Chem., Swiss, SIGMA, Co., Egypt, with 99.0% purity. Emedastine 0.05% Ophthalmic Solution, BN 190409-F_1, (SIGMA, Co., Cairo, Egypt) was labeled to contain 0.5 mg emedastine difumarate per 1 mL.

Instrumentation and methods

TGA/DTG and DTA: Their curves of drug substances were recorded using Simultaneous Shimadzu Thermogravimetric Analyzer TGA-60 H with TA 60 software in dry nitrogen atmosphere at a flow rate of 30 mL/min in platinum crucible with an empty platinum crucible as a reference. The experiments were performed from ambient temperature up to 1000°C with a heating rate of 8°C/min and 10°C/min for azelastine HCl and emedastine difumarate respectively. The sample mass was about 5 mg of the drug without any further treatment. The kinetic parameters of decomposition such as, activation energy (E_a), frequency factor (A) and reaction order(n) were calculated from TG/DTG curves. The mathematical models of Horowitz, Metzger [24] and Coats, Redfern [22] were used for kinetic parameters determination.

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DSC: The curves of azelastine hydrochloride and emedastine difumarate were recorded using Shimadzu-DSC 50, in dynamic nitrogen atmosphere with a constant flow of 30 mL/min, and heating rate of 2°C/minute, up to temperature 300°C. The sample with a mass of about 2 mg was packed in platinum pan. DSC equipment was preliminarily calibrated with standard reference of indium (99.9%). The purity determination was performed using heating rate of 2°C/minute in the temperature range from 25 to 300°C in nitrogen atmosphere.

Mass spectrometry electron impact (MS-EI): Mass spectra of azelastine hydrochloride was recorded using Shimadzu-GC-MS-QP 1000 EX quadruple mass spectrometer with Electron Impact detector equipped with GC-MS data system.

Melting point: Opti Melt Automated Melting Point System, SRS Stanford Research System.

Results and Discussion

Thermal characterization of the investigated compounds

The TGA/DTG curves of azelastine hydrochloride presented in Figure 1 revealed two thermal decomposition stages and thermal stability up to 294.51°C. The first step showed a mass loss (Δm=79.6%) in the interval of 294 – 345°C, suggesting the release of $C_{17}H_{16}Cl_2N_2O$ (79.9%, calc). The second decomposition step showed a mass loss (Δm=20.89%) in the temperature range 345 – 572.1°C, suggesting the hydrolysis of $C_5H_{13}N$ (20.79%, calc). The suggested thermal decomposition pathway of azelastine is summarized in Scheme 1.

The DTA curve (Figure 1) exhibits endothermic and exothermic peaks. The first endothermic peak at 225.96°C is due to the melting of the compound (official mp 225-229°C) [25]. The endothermic peak at 311.30°C is attributed to the first decomposition corresponding to the first mass loss observed in TG/DTG thermogram curves as shown in Figure 1. The sharp exothermic peaks at 544.77°C are due to the pyrolysis of the compound. As shown in the suggested thermal decomposition pathway of azelastine hydrochloride in Scheme 1.

The TG/DTG and DTA curves of emedastine difumarate are shown in Figure 2. The TG/DTG curves show that emedastine difumarate is thermally stable up to 218.32°C. TG/DTG curves show three thermal decomposition steps. The first step shows mass losses 64.80% in temperature range (218.32 – 298.10°C) suggesting the release of difumarate and 1-methyl-[1,4] diazepane (64.60%, calc.). The second step shows mass loss 13.20% in temperature range (299-396°C), is due to the release of ethoxy ethane (13.80%, calc.). The third step shows mass loss 22.70% corresponding to pyrolysis of 1 H Benzoimidazole (22.10% calc.) in temperature range (396-660°C). The suggested thermal decomposition pathway of emedastine difumarate is summarized in Scheme 2.

The DTA curve presented in Figure 2 exhibits endothermic and exothermic peaks. The fist sharp endothermic peak at 153.39°C is due to melting of compound (official mp 148 - 151°C). The endothermic peak at 441.97°C is attributed to the first decomposition corresponding to the first mass loss observed in TG/DTG curves. The broad exothermic peak at 587.74°C is due to the pyrolysis of the compound.

Kinetic analysis

The kinetic studies of the main thermal decomposition (degradation) steps of azelastine-HCl, and emedastine difumarate were investigated by mathematical models (1 and 2) of Horowitz and Metzger (HM), [24] and Coats-Redfern (CR), [22] respectively. For azelastine-HCl the kinetic parameters obtained for the first step was activation energy (E_a), value 141 kJ mol^{-1} (HM), and 132.88 KJ mol^{-1} (CR), and frequency factor 7.66 x 10^{10} Sec^{-1} (CR), which evidenced a first order kinetic behavior. Also the calculated E_a value 129.13 kJ mol^{-1} (HM), and 114.26 KJ mol^{-1} (CR), and frequency factor 3.12 × 10^{10} Sec^{-1} for emedastine difumarate proved a first order kinetic behavior (Table 1).

$$\log.[\log\frac{W_f}{W_f - W}] = \frac{\theta.E^*}{2.303RT_s^2} - \log 2.303 \quad (1)$$

Where W is the mass loss at time t and W_f after total decomposition, R is the gas constant, T_s is the DTG peak temperature and θ = T-T_s. A plot of *log [log W_f / (W_f - W)] vs* θ will give a straight line and E_a was then calculated from the slope (Table 1).

$$\log\left(\frac{\log\left[W_f / W_f - W\right]}{T^2}\right) = \log\left[\frac{AR}{\varphi E^*}\left(1 - \frac{2RT}{E^*}\right)\right] - \frac{E^*}{2.303RT} \quad (2)$$

φ is the heating rate (°C/min). Since 1- 2RT / E^*≅1, the plot of the left-hand side of equation (2) *vs* 1000/T will give a straight line. Where E_a was then calculated from the slope and the frequency factor (A) was obtained from the intercept (Table 1).

Correlation between the mass spectra and thermal behavior of azelastine hydrochloride

The mass spectra of azelastine hydrochloride are presented graphically. In mass spectrometry the compound is ionized and fragmented using the electron spray ionization technique. While for

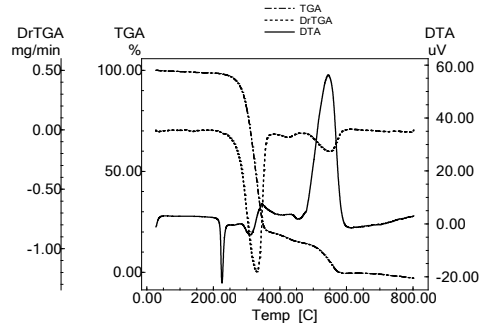
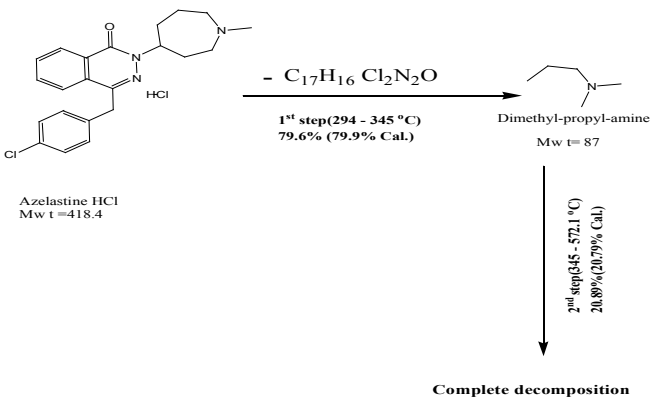


Figure 1: Thermal decomposition of azelastine HCl (TG/DTG and DTA).



Scheme 1: The suggested thermal degradation of azelastine HCl.

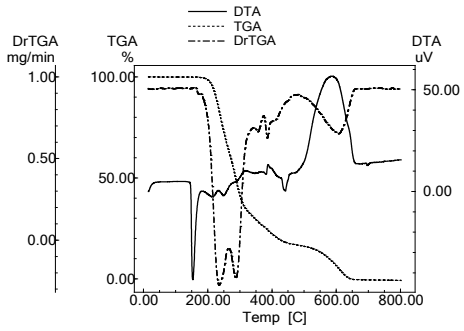
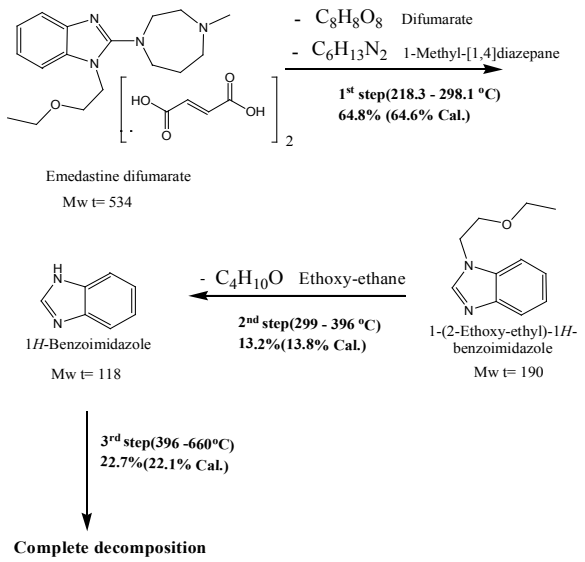


Figure 2: Thermal decomposition of emedastine difumarate (TG/DTG and DTA).



Scheme 2: The suggested thermal degradation of emedastine difumarate.

Drugs	Temperature range °C		E_a/kJ mol^{-1}		n		A. Sec^{-1}
			HM	CR	HM	CR	CR
Azelastine	294.51	345.6	141	132.88	1	1	7.66 ×10^{10}
Emedastine	218.32	298.07	123.75	114.26	1	1	3.12 ×10^{10}

Table 1: Kinetic parameters obtained by the methods of Horowitz, Metzger (HM) and Coats Redfern (CR) for azelastine HCl and emedastine difumarate.

thermal analysis the term decomposition signifies the breakdown of one or more constituents of the substance into simpler atomic grouping. The electron ionization mass spectrum of the fragmented azelastine shows an abundance with m/z=298 (RI=1.89%), 4-(4-Chloro-benzyl)-2-ethyl-2H-phthalazin-1-one and dimethyl-propyl-amine with m/z=87 (RI=10.6%), suggesting that these are the major parts of the decomposition lost in thermal reaction. The correlation was presented in Scheme 3. The other suggestion mass spectra decomposition give two main fragments, 2-(1-Methyl-azepan-4-yl)-2H-phthalazin-1-one with m/z=256 (RI= 2.41%) and the second 1-chloro-4-methyl-benzene with m/z=126 (RI=20.3%). Fragments at m/z=381 (RI=100%) represent the base peak of azelastine.

Application of differential scanning calorimetry for purity determination

The melting transitions of a pure 100% crystalline material should be infinitely sharp, but impurities or defects in the crystal structure will broaden the melting range and lower the final melting point to a temperature lower than T_o [23]. Purity determination is officially listed in Merk index [25]. The effect of impurities on T_o azelastine hydrochloride and emedastine difumarate was determined by DSC method based on Van't Hoff equation (3).

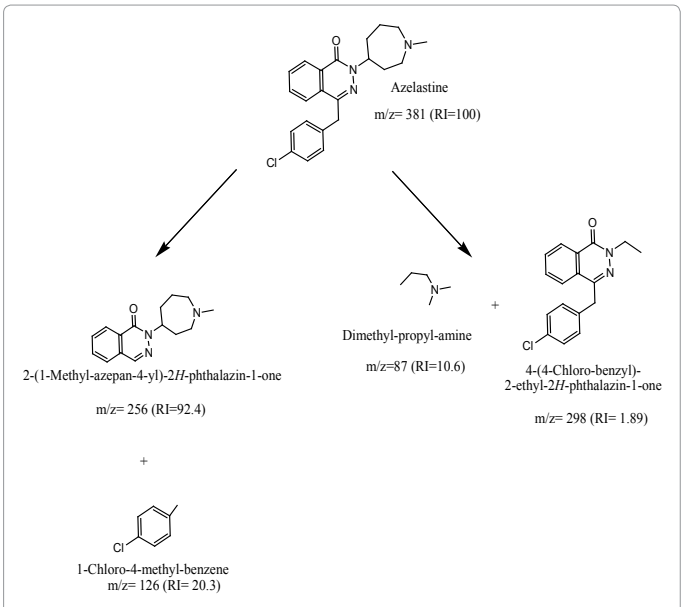
$$T_s = T_o - RT^2_o X_2 . 1/ \Delta H_f . F \quad (3)$$

Where, T_s is the sample peak at temperature (K), T_o is the melting point of pure component (K), R is the gas constant, X is the concentration of impurity (grams fraction), ΔH_f = Heat of fusion of pure component (J mg^{-1}), and F is the fraction of sample melted at T_s.

The melting points obtained from DSC curves (Figure 3) were in accordance with those of officially reported (Table 2), justifying the use of DSC as a routine technique for identification of drugs through the melting point.

Conclusions

The thermal stability of azelastine hydrochloride and emedastine difumarate showed thermal stability up to 294.5°C and 218.32°C, and melting point at 146.99°C and 147°C respectively. Assessing the degradation kinetic of both drugs, the molecules showed first order. Good correlation between mass spectra and thermal behavior of azelastine-HCl was obtained. Using the Van't Hoff equation, a



Scheme 3: The mass spectral fragmentation pathway of azelastine HCl.

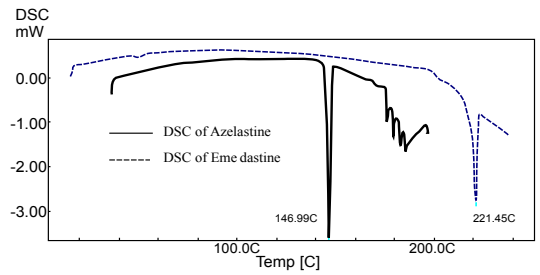


Figure 3: DSC profile of azelastine hydrochloride and emedastine difumarate.

Drugs	Degree of purity%		Melting point °C		
	DSC	Pharmacopoeial	DSC	mp Apparatus	Merk index
Azelastine	99.97	99.00 -101.00*	222	223	225-229
Emedastine	98.97	98.50-101·00**	147	149	148-151

* Official BP 2011.
** Official USP 2011.

Table 2: Degree of purity and melting point of azelastine HCl and emedastine difumarate in drug substances by DSC, melting point apparatus, and pharmacopoeial.

peak purity of 99.97% and 98.97% for azelastine hydrochloride and emedastine difumarate was obtained which is in agreement with the official pharmacopoeias. The simplicity, speed and low operational costs of thermal analysis of pharmaceuticals, justify its application in quality control of both drugs.

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