Thermal Stability of Desipramine and Imipramine

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In this paper we present a preliminary study regarding the solid-state characterization of two tricyclic antidepressants of the dibenzazepine group mainly used in attention deficit hyperactivity disorder, major depression, enuresis and panic disorder. The study revealed the impossibility of separation the contribution of degradative steps in the breakdown of molecular skeleton of studied compounds. It is surprisingly to notice that in this case, the elimination of hydrochloric acid from the imipramine and desipramine salts is not an individualized, well-defined process, occurring simultaneously with the degradation of the functionalized 10,11-Dihydro-5H-dibenzo[b,f]azepin heterocycle.

Kwywords: tricyclic antidepressant, desipramine, imipramine, thermal stability, FTIR

Tricyclic antidepressants (TCA) are widely used in therapy nowadays not only for their antidepressant properties, but also because of their sedative, anxiolytic and anticholinergic effects. They represent a good choice for the treatment of various psychological disorders such as endogenous depression syndrome, Parkinson's disease, as a co-analgesic for acute pains unresponsive to conventional medication and for nocturnal enuresis in children [1-3].

The chemical structure of tricyclic antidepressants contains a common core of two benzene rings fused with an azepine ring, a seven-atom unsaturated ring with one nitrogen atom replacing a carbon atom. In vivo, TCA suffer a series of metabolic transformations in the liver that lead to the formation of various metabolites, some of them with active properties, after which they are eliminated mainly through urine [2].

TCA's effects were related with their ability to block the reuptake of chemical mediators such as norepinephrine, dopamine, serotonin, histamine and acetylcholine in the central system nerve endings, which in turn leads to an increase in their availability [2,4,5].

Imipramine is a dibenzazepine derivative that was synthesized for the first time in 1951 by Franz Hofliger and Walter Schinder and received FDA approval for clinical use in 1959 [6]. White, microcrystalline, odorless powder with a melting point of 174-175°C, imipramine is soluble in water and alcohol but is basically insoluble in ether. It is also sensitive to light [7].

Imipramine (IMI) has a quick oral and intramuscular absorption and it reaches maximal serum concentration after 30 min . However, in order to obtain a visible effect in the treatment of depression syndrome, a chronic administration of 10-21 days is required. During this time, imipramine suffers a series of transformations that lead to its active metabolite, desipramine [5].

Desipramine (DES), also a dibenzazepine representative, was included as a therapeutic choice for the treatment of clinical depression in 1964 after being discovered and synthesized in 1962. Water soluble crystals with a melting point of 214-218 °C, desipramine is mostly used as hydrochloride [8].

Being the active metabolite of imipramine, desipramine needs a shorter period of administration, about 2 to 5 days, for the therapeutic effect to occur. Due to its chemical structure and its similarities to imipramine, desipramine is used to reduce anxiety and to treat major depressive disorders, [9] to manage chronic peripheral neuropathic pain and some eating disorders, as a possible therapeutic alternative in the treatment of attention deficit hyperactivity disorder and for the treatment of nocturnal enuresis in children [10].

In regard to desipramine side effects and toxicity there are a number of symptoms with high prevalence such as sedation, anticholinergic effects (dry mouth, urine retention and blurred vision), cardiotoxicity (hypotension or tachycardia), impaired memory and sometimes delirium [8].

In order to obtain the desired pharmaceutical effects, a specific therapeutic range is required. This lies between 115 and 250 ng/mL [4]. If the concentration does not reach the desired level, sub-optimal effects or even the lack thereof can occur [1]. However, even at therapeutic concentration adverse reactions may appear, such as: hallucinations, delusions, convulsions and anticholinergic effects [4]. Over a certain limit (500 ng/mL), considered being the toxic dose, severe reactions like myocardial

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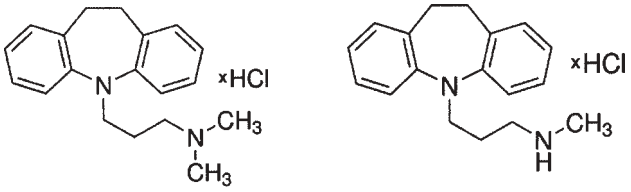
damage with tachycardia or arrhythmias, respiratory depression and coma can arise.

Therefore, in order to minimize the risk of toxicity and to assure the optimal quality of the pharmaceutical forms containing the before mentioned active substances, a thorough analysis is of the utter most importance [1].

The structures of the two tricyclic antidepressants (TCA) – imipramine (IMI) and desipramine (DES) – are presented in figure 1.



a) IMI b) DES

Fig. 1. Structural formulas of IMI and DES

This paper deals with the preliminary study of solid-state stability of IMI and DES, since to our knowledge, the physico-chemical characterization in the field of TCA are poorly investigated up to the date. The employment of several investigational physico-chemical methods was previously reported by our research group [11-14], showing the direct application mainly in pharmaceutical technology, in the field of preformulation study and the appropriate selection of excipients.

Experimental part

Materials and methods

Bioactive compounds

The bioactive compounds were commercial products: imipramine hydrochloride (abbreviated IMI, CAS Number 113-52-0, Molecular mass 316.87 g/mol, BioXtra, purity ≥ 99%, Sigma I0899) and desipramine hydrochloride (abbreviated DES, CAS Number 58-28-6, Molecular mass 302.84 g/mol, purity ≥ 98%, Sigma D3900) and used as received, without preliminary purification.

Infrared spectroscopic analysis

The FTIR spectra of the two TCA (imipramine hydrochloride and desipramine hydrochloride) were drawn on a Perkin Elmer SPECTRUM 100 device. The data was collected directly on solid samples in the spectral domain 4000-600 cm^{-1} on an UATR device. Samples weren't recovered. Spectra were built up after a number of 16 co-added acquisitions, with a spectral resolution of 4 cm^{-1}.

Thermal analysis TG-DTG-HF

Thermoanalytical data (TG/DTG/HF) were collected on Perkin-Elmer DIAMOND thermo-balance, the samples (~6 mg) were heated (heating rate $\beta = 5^{o}C\ min^{-1}$) in open crucibles (aluminum) in air atmosphere (dynamic flow of 100 $mL \cdot min^{-1}$) in the temperature interval of 35-500 °C. The associated thermal effects were recorded as HF (Heat Flow) data (in mW), after converting the DTA data (in μV). Two determinations were carried out for each sample and the thermograms were practically identical.

Results and discussions

Spectroscopic analysis

The UATR-FTIR spectra of the two TCA are presented in figure 2. A similarity of the spectra is observed for IMI and DES, including in the fingerprint region and it was expected, since the molecular structure of both compounds is similar, the only difference being that in the case of IMI the aliphatic chain is a N,N-dimethylpropan-1-amine moiety, while in the case of DES, a N-methylpropan-1-amine moiety is present.

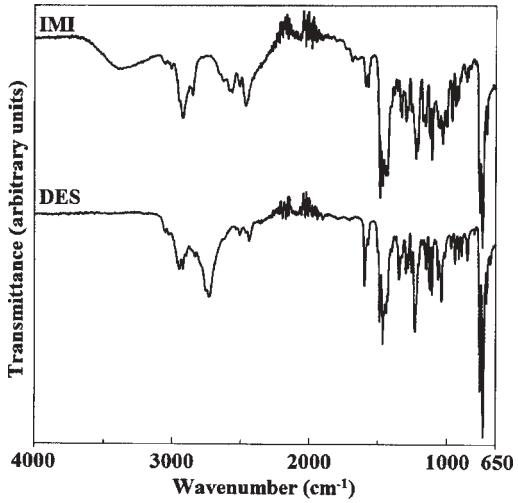


Fig. 2. ATR-FTIR spectra of IMI and DES recorded on the spectral domain 4000-650 cm^{-1}

Several IR bands appear in both spectra, at the same wavenumber or shifted with ±2 cm^{-1}. These bands are associated with identical bonds or moieties appearing in both compounds. Here it worth mentioning the bands at 3027, 1572, 1485, 1467, 1447, 1430, 1297, 1260, 1125, 1110, 1066, 919, 762, 741 and 714 cm^{-1}. In the case of IMI spectrum, the presence of the second methyl group grafted on the aminic nitrogen is revealed by some new bands in the spectral region 1300-1000 cm^{-1} (at 1212 and 1171 cm^{-1}).

The formation of protonated amines due to the crystallization of compounds with hydrochloric acid is proved by appearance of some intense large combination bands in the spectral range 3000-2700 cm^{-1}, as well some medium-intense bands in the 2700-2250 cm^{-1} and 1600-1575 cm^{-1} spectral ranges. The bands appearing in the fingerprint region are mainly associated with skeleton vibrations and deformations of the 10,11-dihydro-5*H*-dibenzo[*b,f*]azepin structure.

The UATR-FTIR bands appearing in the spectrum of IMI and DES are presented in table 1.

Compound	Wavenumber (cm^{-1})
IMI	3060, 3027, 3011, 2953(sh), 2927, 2854, 2631, 2567, 2511, 2466, 1592, 1572, 1485, 1467, 1446, 1430, 1384, 1359, 1340, 1330, 1297, 1260, 1226, 1212, 1171, 1156, 1125, 1110, 1066, 1056, 1032, 1002, 965, 939, 919, 847, 770, 762, 743, 714.
DES	3052, 3027, 2950, 2924, 2899, 2835, 2756, 2731, 2508, 2439, 1597, 1571,1488, 1466, 1447, 1439, 1430, 1400, 1375, 1347, 1297, 1282, 1258, 1231, 1151, 1126, 1110, 1066, 1051, 1040, 1015, 969, 942, 916, 895, 854, 763, 740, 714, 686.

Table 1
READINGS OF THE UATR-FTIR SPECTRA OF IMI AND DES

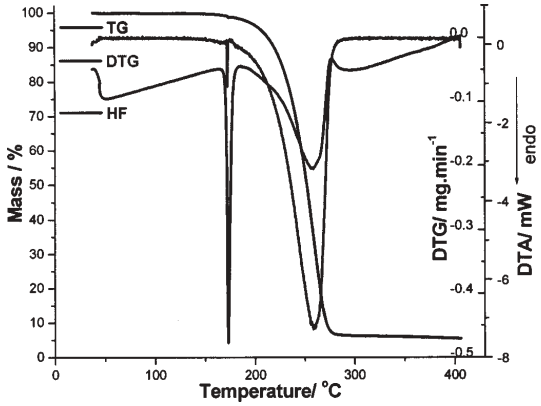


Fig. 3. Thermoanalytical curves determined for IMI

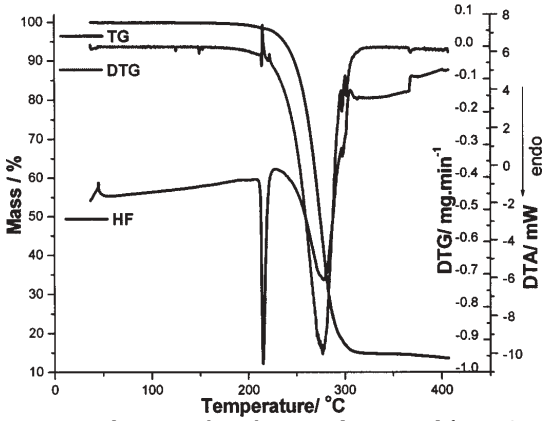


Fig. 4. Thermoanalytical curves determined for DES

Thermal study

The thermoanalytical curves determined for IMI and DES are presented in figures 3 and 4.

Thermal stability of the analyzed substances under air was determined by thermogravimetry and derivative thermogravimetry, while the melting temperature and the nature of the processes were determined using the HF technique. These results indicate that both compounds have an excellent thermal stability until 173ºC (for DES) and 151ºC (for IMI) respectively. However, IMI showed a lower stability in comparison to DES and this can be explained by the dimethylation of the aminic nitrogen – a different solid packaging is expected, with less H-bonding type interactions.

The HF curves of IMI and DES show similar processes. An endothermic peak due to melting was observed at 173 ºC for IMI, lower than this of DES observed at 217ºC, values which are in accord with the literature [7,8]. The difference between the melting points can be attributed to the difference in the strengths of hydrogen-bonds present in IMI and DES molecules (primary and secondary amines have higher melting and boiling points comparative with tertiary amines because they can engage in intermolecular hydrogen bonding, as previously mentioned.

An interesting sharp peak is observed on the DTG curve during melting of the samples, which can be assumed to the starting of the decomposition process (the mass loss begins), or by the sensitivity of the thermobalance to the variation of physical properties of the sample during melting, i.e. the intensive molar properties.

The decomposition temperatures of IMI and DES have maximum at 260 and 278ºC, respectively, the shapes of the TG and DTG curve being similar for the two substances. Another notable difference between thermogravimetrical curves is the residual masses. The experimental values are $\Delta m = 5.4$ % for IMI decomposition and $\Delta m = 13.6$ % for DES degradation.

However, it is not possible to separate the different degradation processes of studied TCA because the degradative mechanism is complex and overlapping of events are noticed in the temperature range of decomposition. It is surprisingly to notice that in this case, the elimination of hydrochloric acid is not recognized as a well-defined and separated process, like in the case of other salts [15].

Conclusions

Important information regarding thermal behavior of two TCA (imipramine and desipramine) was obtained by analyzing of their thermoanalytical TG-DTG-HF curve, as well as their FT-IR spectra. Differences between onset temperature and peak temperature for the melting point (HF curves) and the degradation temperature (TG and DTG curves) allow establish the correct processing parameters for avoid the thermal degradation.

For IMI and DES, the breakdown of the crystalline lattice due to the presence of chlorohydrate takes place simultaneously to the degradation of the functionalized 10,11-Dihydro-5*H*-dibenzo[*b,f*]azepin heterocycle.

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