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Kinetics and mechanism of solid state imidapril hydrochloride degradation and its degradation impurities identification

Research Article

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Abstract: A detailed stability testing of solid state imidapril hydrochloride (IMD) was performed and its degradation products were identified. The analysis was conducted according to ICH guidelines Q1A(R2). Pure IMD samples were exposed to stress conditions of elevated temperature and relative humidity (T = 363 K, RH = 76.4%) in order to accelerate degradation. The regular loss of IMD content with time, and the formation of two degradation impurities were observed. The appropriate reaction rate constants *k* (for IMD degradation and for the formation of product I and II) were calculated using Prout-Tompkins equation. The obtained degradation products were separated and identified by means of LC-MS technique. Based on the obtained *m/z* values, the masses and the structures of the formed degradation impurities were established. Also IMD degradation scheme was constructed. It was demonstrated that under the applied analytical conditions, IMD degradation follows an autocatalytic reaction model with the rate constant $k = (4.764 \pm 0.34) \times 10^{-6} s^{-1}$ and with the parallel formation of two degradation products: imidaprilat and the diketopiperazine derivative. The obtained experimental results are in agreement with IMD degradation pathways proposed theoretically.

Keywords: *Imidapril hydrochloride • Stability in solid state • LC-MS • Degradation impurities*

1. Introduction

Imidapril hydrochloride (IMD), chemically named as ((-)-(4S)-3-[2(S)-[N-[1(S)-(ethoxycarbonyl)-3-phenylpropyl]amino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid hydrochloride (Fig. 1), is a dipeptide-type, dicarboxylate-containing, non-sulfhydryl angiotensin converting enzyme inhibitor (ACE-I), which has been widely used as an antihypertensive agent in the treatment of essential hypertension, chronic congestive heart failure, and type 1 diabetic nephropathy [1,2]. After oral administration it is metabolized by ethyl ester bond hydrolysis to the active metabolite - imidaprilat [3]. At room temperature it occurs in a form of white crystalline powder, soluble in methanol and water, with the melting point about 203ºC [4]. Solid state IMD is chemically unstable under stress conditions. It undergoes a temperature- and humidity-dependent degradation according to an autocatalytic reaction model, meaning that the reaction product is also its catalyst [5]. The kinetic order of IMD degradation changes in the presence of magnesium stearate (MgS) which is a common lubricating substance used in the pharmaceutical industry as tablet excipient. The experimental data show that in the binary mixture MgS/IMD (1:1 w/w), its decomposition follows first-order kinetics yielding one major product verified as imidaprilat [6]. Another probable path of IMD decomposition is an intra-molecular cyclization between the two neighboring amino-acids with the formation of a diketopiperazine derivative (DKP), which has been recognized as a degradation pattern of other structurally-related dipeptide-

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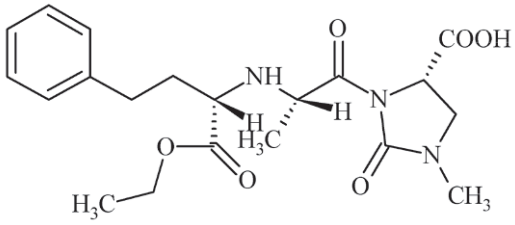

Figure 1. Molecular structure of imidapril hydrochloride (IMD).

type ACE-I, *i.e.*, moexipril hydrochloride [6,7], enalapril maleate [6,8] and quinapril hydrochloride [9]. There are, however, no studies analyzing main degradation pathways of pure IMD in solid state.

Identification of drug degradation impurities is a basic requirement for regulatory approval of any pharmaceutical intended for human use [10-12]. The recommended analytical approach involves the conduction of forced degradation or stress testing described in ICH Q1A(R2) guideline [13]. An important aspect of drug stability analysis is the selection of an appropriate analytical method that fulfills the established validity criteria, such as: selectivity, sensitivity, precision and linearity. There are several strategies for IMD determination described in the literature, including: gas chromatography-mass spectrometry (GC-MS) [14] and radioimmunoassay [15] for its pharmacokinetic studies, and single liquid chromatography-mass spectrometry (LC-MS) [4,6], reversed phase high performance liquid chromatography (RP-HPLC) and first derivative ultraviolet spectrophotometry (^{1}D-UV) for IMD stability analysis in pure, and in binary mixtures with MgS in solid state [5,6]. Thus, for the identification of solid-state IMD degradation products RP-HPLC and LC-MS were selected mainly because of their established applicability for IMD determination [5,6] and also due to their relatively low costs, simplicity, common accessibility and applicability for the analysis of a wide range of various drug products [5,6,16-19].

2. Experimental procedure

2.1. Chemicals

Imidapril hydrochloride was kindly provided by Jeleniogorskie Zaklady Farmaceutyczne (Jelenia Gora, Poland). Benzocaine was obtained from Novartis (Basel, Switzerland). Analytical grade potassium phosphate monobasic, natrium chloratum and *ortho*-phosphoric acid were purchased from POCh S.A. (Gliwice, Poland) and HPLC grade methanol and acetonitrile were supplied by Merck KGaA (Darmstadt, Germany). Freshly bidistilled water was used.

2.2. Apparatus

2.2.1. High-Pressure Liquid Chromatographic method

Shimadzu liquid chromatograph consisting of Rheodyne 7125, 100 µL fixed loop injector, UV-VIS SPO-6AV detector, LC-6A pump and C-RGA chromatopac integrator was used under the following operating conditions: stationary phase - LiChrospher 100 RP-18 (size 5 µm) 250×4 mm I.D column maintained at ambient temperature, and mobile phase - a mixture of acetonitrile and phosphate buffer (0.001 mol L^{-1} adjusted to pH 2.0 with *ortho*-phosphoric acid) (30:70 v/v). Chromatographic separation was achieved isocratically at a flow rate of 1.2 mL min^{-1}. The detector wavelength was set at 216 nm [5] and the injection volume was 25 µL. The mobile phase had been filtered through 0.22 µm filter and degassed by ultrasound prior to use. The technique employing an internal standard (a 0.020% methanolic solution of benzocaine; IS) was applied.

2.2.2. Liquid Chromatography/Electrospay Ionization-Mass Spectrometry System

The LC-MS system consisted of a Waters Alliance HPLC equipped with a Photodiode Array Detector Waters PDA 996 coupled to a Single Quadruple Mass Detector Waters Micromass ZQ 2000. The IMD degradation products were separated on a LiChrospher 100 RP-18 (size 10 µm, 250×4 mm) column at temperature 30°C. The mobile phase (methanol – water – formaldehyde (49:50:0.5 v/v/v)) had been filtered through 0.22 µm filter, degassed by ultrasound prior to use and pumped at a flow rate of 0.5 mL min^{-1}. The injection volume was 100 µL.

2.3. RP-HPLC mobile phase and IS optimization

Three concentrations of acetonitrile: 20, 30, 40%, mixed with phosphate buffer (0.001 mol L^{-1}), adjusted to pH 2.00 with 88% *ortho*-phosphoric acid, were used as mobile phase for chromatographic separation of IMD degradation products under the conditions described above. After the selection of the optimum mobile phase composition the flow rate was adjusted by the analysis of three different pump working modes: 1.0 mL min^{-1}, 1.2 mL min^{-1}, 1.5 mL min^{-1}.

The investigated samples were injected onto the chromatographic column manually. For this reason the technique employing an internal standard had to be used in order to avoid an error inherent during sample injection and eliminate random errors. The following internal standards were tested for their applicability: antazoline hydrochloride, naphazoline, oxymetazoline, teofiline and benzocaine.

2.4. Validation of RP-HPLC method

The RP-HPLC method was validated according to the International Conference on Harmonisation Guidelines [21].

2.4.1. Linearity

Stock solution was freshly prepared by dissolving 40.0 mg of IMD in 100.0 mL of methanol. Ten standard solutions (n=10) at the following concentrations: 0.002, 0.004, 0.008, 0.012, 0.016, 0.020, 0.028, 0.032, 0.036, 0.040% were obtained by diluting the stock solution with methanol. Each standard solution was mixed with 1.0 mL of IS (a methanolic solution benzocaine) at 1:1 (v/v) ratio and immediately injected onto the chromatographic column. Three measurements were performed for each concentration and for linearity assessment the mean value from triplicate analysis for each concentration was used. The obtained relative IMD peak areas (p_i/p_{IS}) were measured and plotted against corresponding IMD concentrations:

$$p_i/p_{IS} = f(c); \quad (1)$$

where: p_i is the area of IMD signal and p_{IS} is the area of IS signal. The appropriate regression equation was computed using least square method.

2.4.2. Precision and accuracy

The intra-day precision and accuracy were investigated by eight replicate analysis of IMD samples at the concentration of 0.0160% on the same analytical run. The inter-day precision and accuracy were assayed after repeated analysis of eight IMD samples at the concentration of 0.0200% performed on two different days over a period of a week. The inter- and intra-day coefficient of variation (CV) and an average recovery were calculated.

2.4.3. Limit of detection (LOD) and limit of quantitation (LOQ)

The LOD and LOQ were calculated on the basis of the regression equation (available in Table 2) using the following formulae:

$$LOD = 3.3Sy/a; \quad (2)$$

$$LOQ = 10Sy/a; \quad (3)$$

where: *Sy* is the standard deviation of the calibration curve and *a* is the slope of the calibration curve.

2.5. Kinetic studies

The study was conducted under the following stress conditions: temperature 363 K and relative humidity 76.4%. Pure IMD samples (0.0100 g) were weighed, placed into desiccators filled with saturated aqueous solution of sodium chloride (which maintained the desired humidity level throughout analysis) and heated for different periods of time in order to induce degradation. After heating the samples were cooled to room temperature, dissolved in bidistilled water, quantitatively transferred into volumetric flasks and made up to a total volume of 25.0 mL with methanol. The aliquots of 1.0 mL of the so obtained solutions (after filtration if necessary) were mixed with 1.0 mL of IS and chromatographed according to the validated RP-HPLC protocol. The measured relative peak areas (p_i/p_{IS}) were plotted *versus* time:

$$p_i/p_{IS} = f(t); \quad (4)$$

where: p_i is the area of IMD signal, p_{IS} is the area of IS signal and *t* is time.

2.6. Identification of IMD degradation products

The identification of IMD degradation products was performed by means of LC-MS method. The electrospray (ESI) ionization, which is known as a soft ionization technique, was applied. The mass spectrometer was run in positive (ES^+) and negative (ES^-) ionization modes in the mass range of *m/z* 100 - 1000. The molecular ions were identified and the corresponding mass-to-charge ratios (*m/z*) were compared to the theoretically-calculated molecular masses in order to confirm the presence of the predicted degradation impurities in the degraded IMD sample.

3. Results and discussion

3.1. Method development and validation

RP-HPLC is an established approach to stability testing of solid state IMD [5,6], however, the previously described mobile phase, consisting of acetonitrile – methanol – phosphate buffer (0.001 mol L^{-1}, adjusted to pH 2.0 by *ortho*-phosphoric acid) (60:10:30 v/v/v) [5], failed to provide an acceptable separation of IMD and its degradation products (Table 1, Fig. 2A). Therefore, an optimization of the analytical conditions was necessary and to that end the following factors were evaluated: concentration of an organic component in a mobile phase, the mobile phase flow rate and the internal

Table 1. Parameters of RP-HPLC separation efficiency.

Mobile phase flow rate 1.2 mL min^{-1}	acetonitrile – methanol – phosphate buffer pH 2.00 (60:10:30 v/v/v)	acetonitrile – phosphate buffer pH 2.00 (30:70 v/v)
Compound	Number of theoretical plates (n)	
Product I	2172	1064
Product II	2836	2015
IMD	4986	6382
IS	11364	4533
Resolution factor (R)	R_{I-II} = 0.59 R_{I-IMD} = 3.14 R_{II-IMD} = 2.36 R_{IMD-IS} = 1,48 R_{I-IS} = 3.73 R_{II-IS} = 3.54	R_{I-II} = 1.18 R_{I-IMD} = 4.28 R_{II-IMD} = 3.30 R_{IMD-IS} = 2.12 R_{I-IS} = 2.66 R_{II-IS} = 1.48

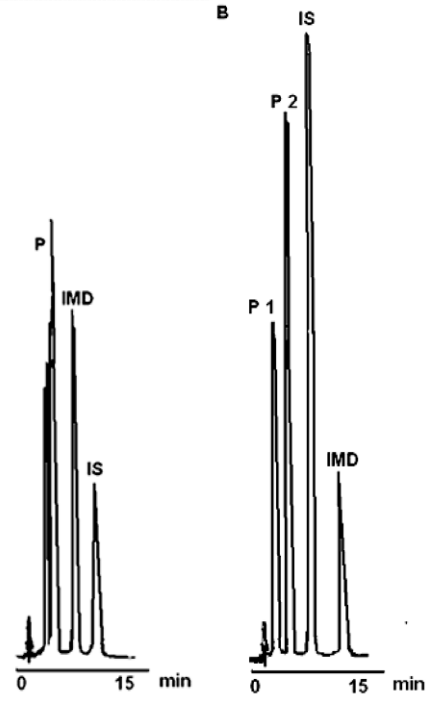

Figure 2. Comparison of quality of HPLC chromatograms obtained for the degraded IMD sample under various analytical conditions. (A) Mobile phase consisting of acetonitrile - methanol – phosphate buffer (0.001 mol L^{-1}, adjusted to pH 2.0 with ortho-phosphoric acid) (60:10:30), mobile phase flow rate: 1.0 mL min^{-1}; (B) Mobile phase consisting of acetonitrile – phosphate buffer (0.001 mol L^{-1}, adjusted to pH 2.0 with ortho-phosphoric acid) (30:70 v/v), mobile phase flow rate: 1.2 mL min^{-1}.

standard matching. The highest-quality chromatograms were achieved for a mixture of acetonitrile and phosphate buffer (30:70 v/v) at the flow rate of 1.2 mL min^{-1} with benzocaine as IS (t_R = 7 min) (Fig. 2B) and these parameters were accepted for further analysis. The efficiency of the developed analytical system was assayed and compared with the previously-described one. The results are shown in Table 1. The number of theoretical plates *(n)* and the resolution factor *(R)* for the optimized RP-HPLC method were within the acceptance criteria of >2000 and >1.5, respectively, confirming good column efficiency and optimum mobile phase composition [20]. The developed RP-HPLC protocol was subsequently validated and results are summarized in Table 2. A high value of correlation coefficient r = 0.999 indicated a strong linear relationship between the measured signal and the corresponding concentration. The average recovery obtained for intra-day and inter-day analysis was 99.37% and 100.5%, respectively and the coefficient of variation was less than 1.55% suggesting a good precision and accuracy of the method. The employed chromatographic system allowed a complete separation of IMD, its degradation products and IS, confirming method's good selectivity. Well-resolved, sharp peaks were observed at the following retention times: t_R = 12 min for IMD, t_R = 7 min for IS, t_R = 3 and 5 min for two degradation products (Fig. 2B).

3.2. Kinetics of IMD degradation in solid state

The kinetic order of solid-state IMD degradation was established by its content determination in the degraded samples stored under stress conditions over different time intervals. The relative peak areas p_i/p_{IS} (where p_i is IMD peak area and p_{IS} is IS peak area) were measured and plotted *versus* time to produce the sigmoid kinetic curve $p_i/p_{IS} = f(t)$ (Fig. 3A) characterized by induction, acceleration and termination period. This confirmed an autocatalytic character of the observed reaction and therefore the calculation of its kinetic parameters was performed by the use of Prout-Tompkins equation [22]:

$$\ln \{(p_i/p_{IS})_t/[(p_i/p_{IS})_0 - (p_i/p_{IS})_t]\} = C - k\,t; \quad (5)$$

where: $(p_i/p_{IS})_t$ *and* $(p_i/p_{IS})_0$ are relative IMD peak areas in time t and t_0 respectively, t is time, k is reaction rate constant and C is induction period (Fig. 3B). The results are demonstrated in Table 3.

Table 2. Validation report for the RP-HPLC method.

Linearity range	
Regression equation $y = ax + b$	
Slope a ± Δa	55.31 ± 1.87
Standard deviation of the slope	0.84
Intercept b ± Δb	0.036 ± 0.047
Standard deviation of the intercept	0.021
Correlation coefficient	0.998799207
n	10
S_y	0.035
LOD = 3.3 S_y/a	0.0021
LOQ = 10 S_y/a	0.0064
Statistical assessment of calibration curve y = ax + b	
Intercept *b* was evaluated by Student's- *t* test using $t = b/S_a$ equation. Experimental t =1.71 was less than the corresponding theoretical one $t_{\alpha 0.05}$ = 2.201 meaning that *b* is statistically insignificant and calibration line passes through zero according to the equation $y = ax$.	
Precision and accuracy	
Intra-day	
Nominal concentration (%)	0.0160
Assayed concentration (%)	0.0159 ± 1.01 10^{-4}
Average recovery (%)	99.37
Standard deviation	1.42 10^{-4}
Coefficient of variation (%)	0.890
Inter-day	
Nominal concentration (%)	0.0200
Assayed concentration (%)	0.0201 ± 2.22 10^{-4}
Average recovery (%)	100.5
Standard deviation	3.11 10^{-4}
Coefficient of variation (%)	1.55

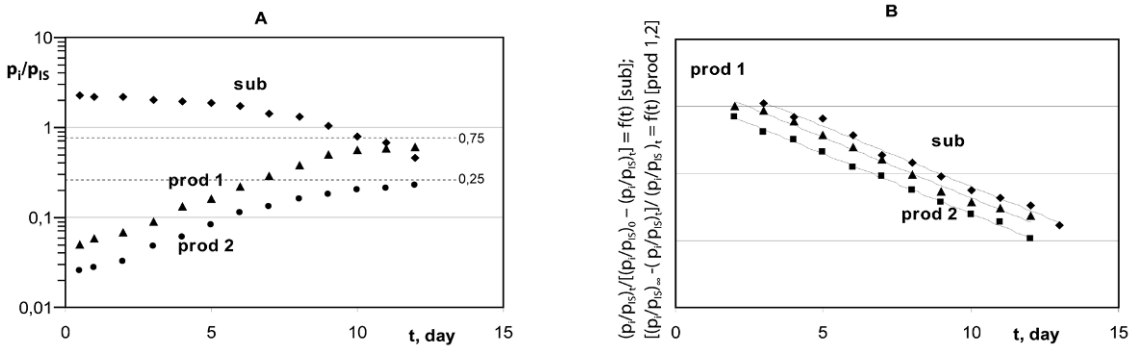

Figure 3.
(A) p_i/p_{IS} = f(t) plot for IMD degradation [sub] and for the formation of IMD degradation products [prod I, prod II] in solid state (T = 363 K, RH = 76.4%). (B) Semi-logarithmic plot of solid state IMD degradation $(p_i/p_{IS})_t/[(p_i/p_{IS})_0 - (p_i/p_{IS})_t]$ = f(t) [sub] and its degradation products formation $[(p_i/p_{IS})_\infty - (p_i/p_{IS})_t]/(p_i/p_{IS})_t$ = f(t) for products [prod I,II].

3.3. Kinetics of IMD degradation impurities formation in solid state

The kinetics of IMD degradation impurities formation was investigated by the determination of their contents in the degraded IMD samples using RP-HPLC. The appropriate plots for product I and product II were established:

$$p_i/p_{IS} = f(t) \quad (6)$$

where p_i is the peak area of product I or II and p_{IS} is the peak area of IS, t is time (Fig. 3A). In both cases autocatalysis was observed as indicated by sigmoid kinetic curves (Fig. 3B). The formation rate constants (k) for both products were calculated on the basis of Prout-Tompkins equation [22]:

$$ln\ \{[(p_i/p_{IS})_\infty - (p_i/p_{IS})_t]/(p_i/p_{IS})_t\} = -kt + C \quad (7)$$

where: p_i –peak area of product I or II, p_{IS} – peak area of IS, k –the formation rate constant of product I or II, t – time, C – induction period. The $(p_i/p_{IS})_\infty$ was assumed 0.75 for product I and 0.25 for product II since these are the points in which the appropriate kinetic curves achieve their *plateau* and therefore they can be considered as the concentrations in the infinite time

Table 3. Parameters of IMD degradation and its degradation products formation under T = 363 K and RH = 76.4%.

Compound	IMD	Product I	Product II
Slope of a straight line	-0.412 ± 0.03*	-0,411± 0,012**	-0.413 ±0.029**
Correlation coefficient	0.997	0.999	0.996
Relative deviation	0.139	0.195	0.136
Number of samples	11	11	11
Reaction rate constant (s^{-1})	(4.764 ± 0.34) 10^{-6}	(4.760 ±0.14) 10^{-6}	(4.785 ±0.33) 10^{-6}
	Statistical assessment		
$F_{0.05}$ (n_1-1; n_2-2) = 2.98		1.40	1.48
t (n_{1} + n_2 -2) = 2.086		0.052 10^{-6}	0.318 10^{-6}

*$ln\ \{(p/p_{IS})_t/[(p/p_{IS})_0 - (p/p_{IS})_t]\} = f(t)$
**$ln\ \{[(p/p_{IS})_\infty - (p/p_{IS})_t]/\ (p/p_{IS})_t\} = f(t)$

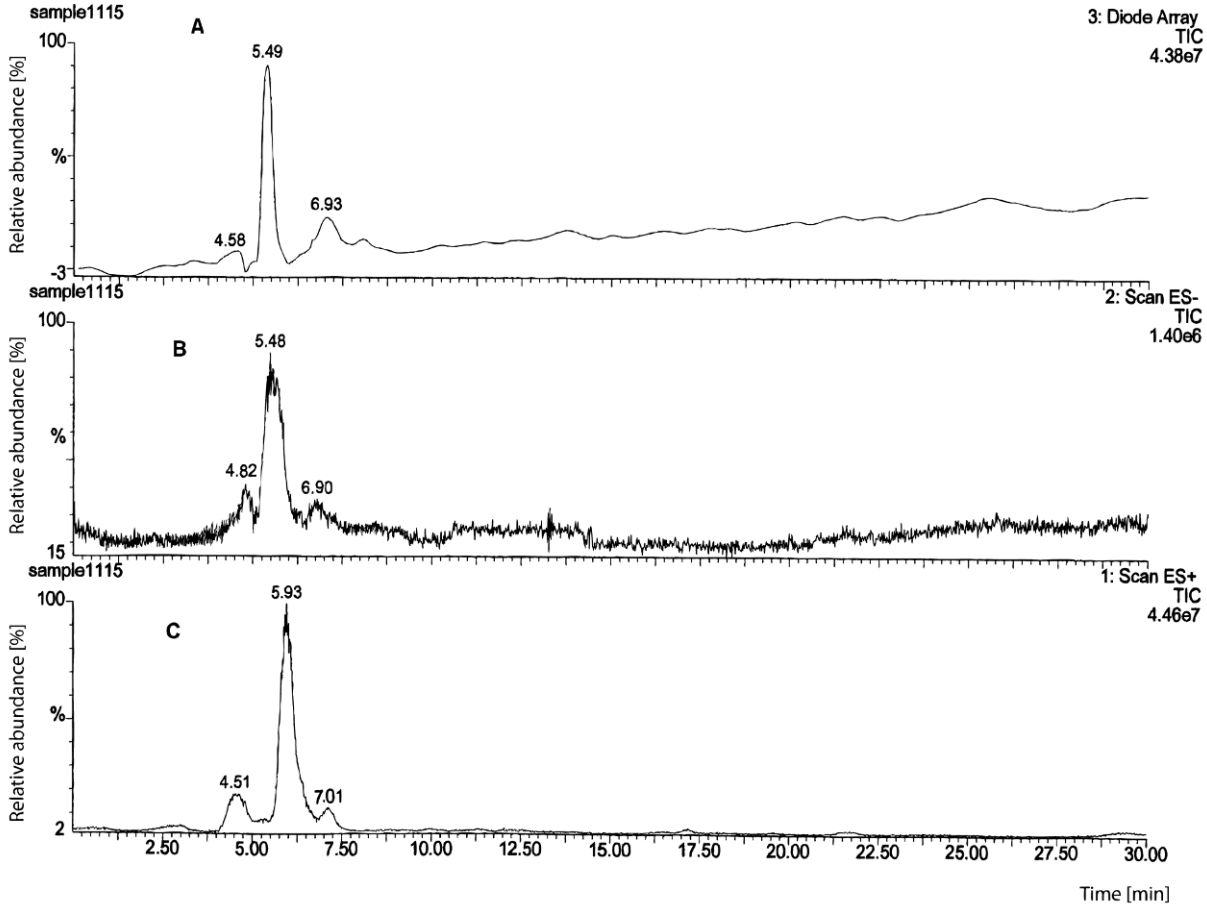

Figure 4. LC-MS chromatogram for IMD after 6 h of heating under T = 363 K and RH = 76.4% (A) detected by UV absorption using mass spectrometric total ion current (TIC); (B) acquired in negative ES- TIC mode; (C) acquired in positive ES+ TIC mode.

(Fig. 3A). The obtained *k* values were compared using *F*-Snedecor and Student's *t*-tests (Table 3) and since they were not statistically different it was concluded that both products were formed simultaneously according to parallel reaction kinetics.

3.4. Identification of IMD degradation products

The identification of IMD degradation products was performed by means of LC-MS method. The chromatogram obtained for an undegraded IMD demonstrated only one peak at t_R = 6.90 min, which

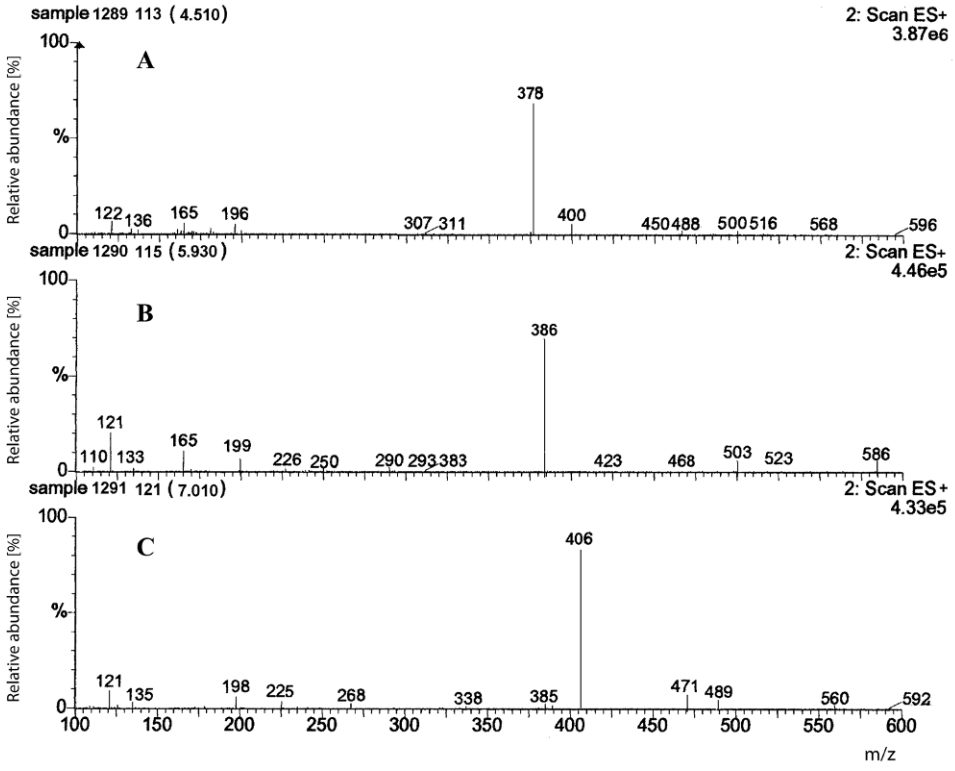

Figure 5. ES+ mass spectrum (A) for IMD degradation product I, (B) for IMD degradation product II and (C) for pure IMD.

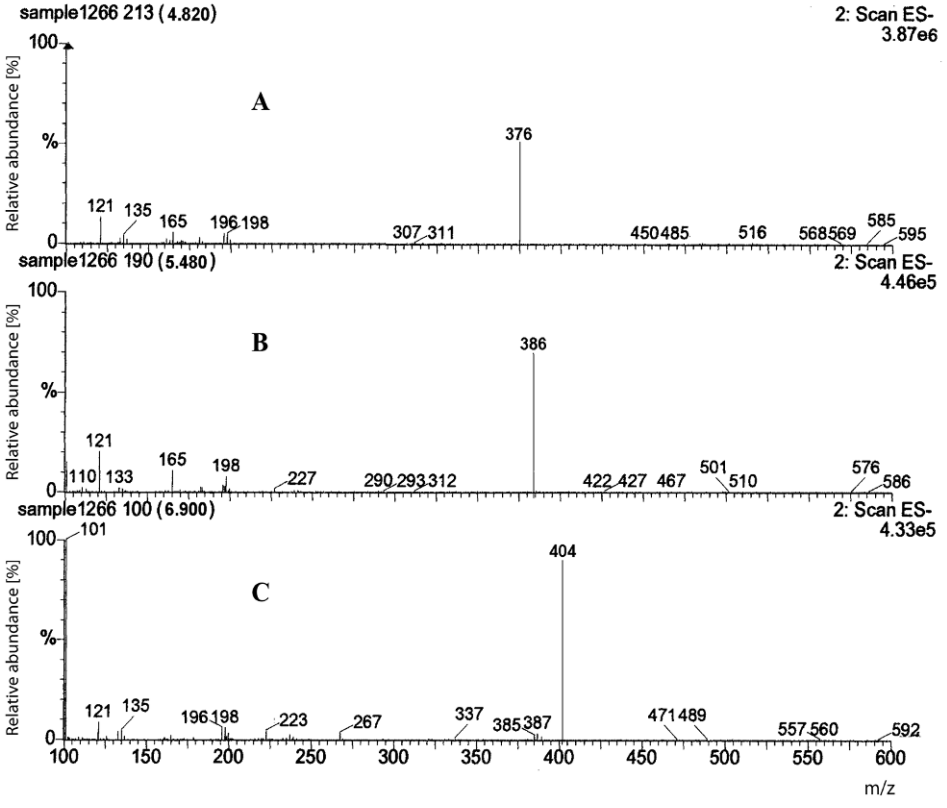

Figure 6. ES- mass spectrum (A) for IMD degradation product I, (B) for IMD degradation product II and (C) for pure IMD.

Table 4. The *m/z* values of $[M+H]^+$ and $[M-H]^-$ for IMD and its degradation impurities in solid state.

Compound	Chemical formula	Calculated molecular mass	Observed m/z value, ES+	Observed m/z value, ES-
IMD	$C_{20}H_{27}N_3O_6$	405	406	404
Product I (DKP)	$C_{20}H_{25}N_3O_5$	387	386	386
Product II (Imidaprilat)	$C_{18}H_{23}N_3O_6$	377	378	376

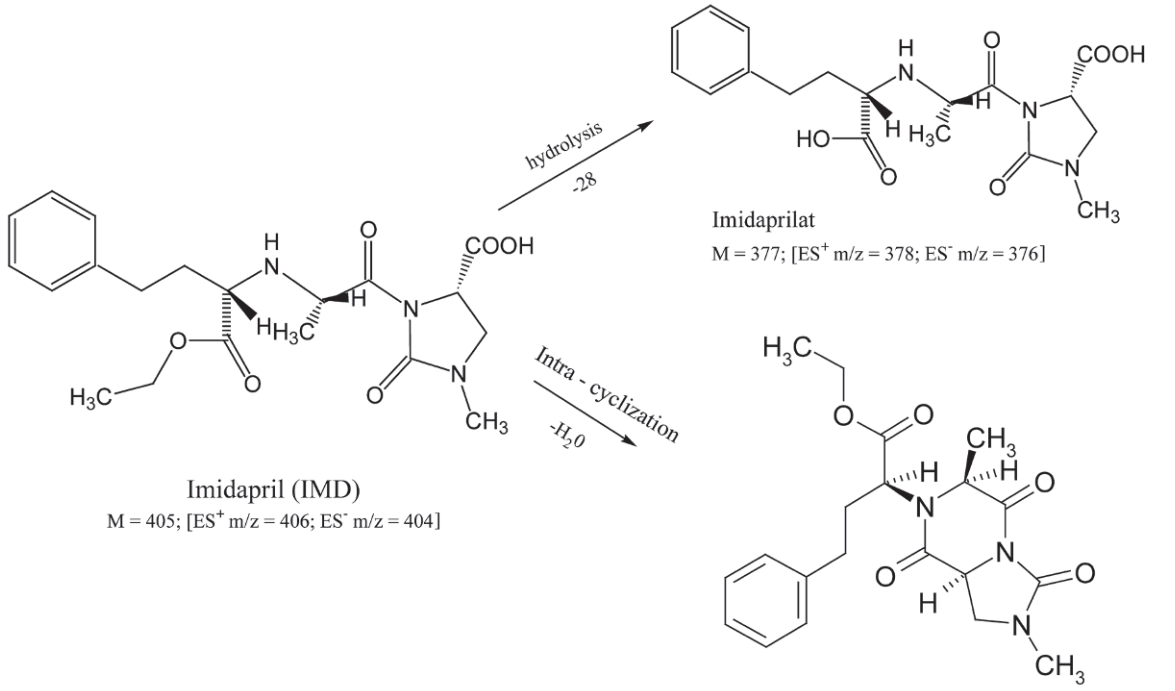

Figure 7. The proposed scheme for solid state IMD degradation under the conditions of T = 363 K, RH = 76.4%.

confirmed high purity of the analyzed sample. In the chromatograms achieved for IMD samples exposed to six-hour-stress conditions (T = 363 K, RH = 76.4%), two additional peaks appeared: at $t_R \approx 4.50$ min and at $t_R \approx 5.50$ min, and they were attributed to IMD degradation impurities (Figs. 4A, 4B, 4C).

The application of soft ionization technique in MS analysis enabled an unambiguous verification of the pseudo-molecular ions type $[M+H]^+$ or $[M-H]^-$ as the most abundant signals. Peaks at *m/z* = 404 $[M-H]^-$ and *m/z* = 406 $[M+H]^+$ matched with the molecular mass of pure IMD. Peaks at *m/z* = 386 $[M-H]^-$ were attributed to product I which was verified as DKP (molecular mass 387) formed by IMD intra-molecular cyclization. For product II the following *m/z* values were observed: 378 for protonated molecule $[M+H]^+$ and 376 for deprotonated molecule $[M-H]^-$ (Figs. 5,6), which corresponded to a diacidic derivative of IMD (molecular mass 377) formed by its ester bond hydrolysis. These results are listed in Table 4. The detailed fragmentation patterns of the investigated compounds were not analyzed due to a very limited fragmentation obtained under the applied analytical conditions. Based on the above findings the following paths of solid state IMD degradation could be proposed (Fig. 7).

4. Conclusion

The process of IMD degradation follows an autocatalytic reaction model with the rate constant *k* = (4.764 ± 0.34)×10^{-6} s^{-1} and with the formation of two major degradation impurities: imidaprilat, formed by IMD ethyl ester bond hydrolysis, and DKP formed by IMD intra-

molecular cyclization. The corresponding formation rate constants were: k = (4.785 ±0.33)×10^{-6} s^{-1}) for imidaprilat, and k = (4.760 ±0.14)×10^{-6} s^{-1}) for DKP. The difference between these values was statistically insignificant suggesting the simultaneous formation of these compounds. Imidaprilat and DKP are also considered to be present in the formulated drug stored under the conditions of ambient temperature and relative humidity 40-60%, which might have a negative clinical effect on drug's efficiency and safety. Imidaprilat is an active metabolite of IMD which is poorly absorbed after oral administration. Thus the hydrolysis of IMD to imidaprilat may impair drug's bioavailability. Moreover, there are no data on DKP pharmacological properties. For all these reasons the clinical importance of our findings needs to be further assessed in appropriate toxicological and pharmacokinetic studies.

The optimum HPLC resolution of IMD and its degradation products was influenced by the ratio of organic component in a mobile phase and by the flow rate of a mobile phase. The optimized and validated stability-indicating RP-HPLC assay method was able to separate IMD from its degradation impurities, and the degradation impurities from each other with satisfactory selectivity, precision, accuracy and linearity, which makes it appropriate for the kinetic analysis of IMD decomposition and its degradation products formation. Furthermore, the identification of IMD degradation impurities can be successfully performed by means of LC-MS method with ESI ionization, which, provides an unambiguous molecular weight information.

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