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Monitoring of fosinopril sodium impurities by liquid chromatography–mass spectrometry including the neural networks in method evaluation

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Abstract

In this paper, the mass spectrometry (MS) detection has been applied for screening of fosinopril sodium impurities which arise during forced stress study. Before MS analysis, liquid chromatographic method with suitable mobile phase composition was developed. The separation was done on SunFire 100 mm × 4.6 mm 3.5 μm particle size column. The mobile phases which consisted of methanol–ammonium acetate buffer–acetic acid, in different ratios, were used in a preliminary study. Flow rate was 0.3 mL min^{-1}. Under these conditions, percent of methanol, concentration of ammonium acetate buffer and acetic acid content were tested simultaneously applying central composite design (CCD) and artificial neural network (ANN). The combinations of experimental design (ED) and ANN present powerful technique in method optimization. Input and output variables from CCD were used for network training, verification and testing. Multiple layer perceptron (MLP) with back propagation (BP) algorithm was chosen for network training. When the optimal neural topology was selected, network was trained by adjusting strength of connections between neurons in order to adapt the outputs of whole network to be closer to the desired outputs, or to minimize the sum of the squared errors. From the method optimization the following mobile phase composition was selected as appropriate: methanol–10 mM ammonium acetate buffer–acidic acid (80:19.5:0.5 v/v/v). This mobile phase was used as inlet for MS. According to molecular structure and literature data, electrospray positive ion mode was applied for analysis of fosinopril sodium and its impurities. The proposed method could be used for screening of fosinopril sodium impurities in bulk and pharmaceuticals, as well as for tracking the degradation under stress conditions.

Keywords: Fosinopril sodium; Impurity profiling; Artificial neural networks; MS detection; Forced degradation studies

1. Introduction

In order to assemble complete information of some active pharmaceutical ingredient, it is indispensable to do detection with mass spectrometer. It is very well known that mass spectrometry (MS) detection offers more data than classical methods. For liquid chromatographic (LC) method, which precedes MS detection, certain requirements must be fulfilled (mobile phase with volatile buffers, low flow rate, etc. . .). A useful tool, as a support in method development, is combining experimental design (ED) and artificial neural network (ANN). Combination of appropriate experimental design and neural networks was used in method optimization [1–6]. The advantages of such way of optimization, as well as mathematical methods to be used are given in the review paper [7]. Generally, ANNs are applicable in many areas of pharmaceutical studies. It can be used in the optimization of formulation parameters [8–11] or to define the quantitative structure–retention relationship (QSRR) [12,13], etc. . . In this paper, combination of central composite design (CCD) and ANNs is applied in optimization of mobile phase composition for MS analysis. Fosinopril sodium and its degradation product/active metabolite fosinoprilat were observed in this stage of optimization.

In literature, papers dealing with fosinopril sodium analysis can be found. Fosinopril sodium in mixture with hydrochlorothiazide in tablets was determined by spectrophotometric [14–16] and RP–HPLC [17,18] methods. Capillary electrophoresis (CE) was used for quantitative analysis of fosinopril sodium [19] or optimization of several angiotensin converting enzyme (ACE) inhibitors separation [20–22]. By capillary gas chromatography with nitrogen–phosphorus detection after a two-step derivatization SQ 27519 impurity was determined in human serum [23]. For the analysis of fosinopril sodium and its active form, fosinoprilat, in human serum, LC–MS–MS method was applied

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[24–26]. In our previous paper, fosinoprilat in human plasma was detected using the microemulsion as eluent [27]. For the determination of palladium in fosinopril sodium atmospheric pressure ionization –mass spectrometry (API–MS) method was proposed [28]. Determination of fosinopril sodium and fosinoprilat in tablets can also be found in the literature [29–31].

The aim of this study was analysis of potential degradation products of fosinopril sodium, under stress conditions, using MS detection. From obtained results some useful data about fosinopril sodium were obtained.

2. Experimental

2.1. Chemicals

All reagents used were of an analytical grade. Methanol – gradient grade (*Lab Scan*, Ireland), water – HPLC grade, ammonium acetate (*Merck*, Germany), glacial acetic acid (*Zorka Pharma*, Serbia) were used to prepare a mobile phase. Sodium hydroxide (*J.T. Backer*, The Netherlands), hydrochloric acid (*Zorka Pharma*, Serbia) and hydrogen peroxide (*Zorka Pharma*, Serbia) were used for preparing solution during stress study. The reference standards of fosinopril sodium and fosinoprilat were obtained from *Bristol–Myers Squibb*.

2.2. Chromatographic conditions

Optimization was done on the chromatographic system *Waters* Breeze consisted of *Waters* 1525 Binary HPLC Pump, *Waters* 2487 UV/Vis detector and Breeze Software, Windows XP, for data collection. All experiments were done on SunFire RP C_{18}, 3.5 μm, 4.6 × 100 mm, with flow rate 0.3 mL min^{-1} and room temperature. Detection was at 220 nm. The mobile phase was filtered through a 0.45 μm membrane filter *Alltech* (Belgium). Mobile phases for method optimization were prepared according to CCD for three factors. Mobile phases were prepared on next way: in appropriate volume of methanol acetic acid was added and then ammonium acetate buffer to final 100%. Matrix for experiment is presented in Table 1.

Final mobile phase compatible with MS detector was methanol–10 mM ammonium acetate buffer– glacial acetic acid (80:19.5:0.5 v/v/v).

2.3. Mass spectrometric conditions

The mass spectrometer was operated in the electrospray ion (ESI) positive mode. Capillary voltage was set at 3.90 kV and cone voltage 32.00 V. Temperature of source was 115 °C and desolvation temperature was 350 °C. Flow of cone gas was 50 L h^{-1} and desolvation gas 653 L h^{-1}. Nitrogen was used as the cone gas and the desolvation gas.

Investigation was done on HPLC *Waters* Alliance, with 2695 separation module pumps and with detector triple quadruple mass spectrometer Quattro Micro (*Micromass*, UK).

2.4. Solutions for method optimization

Stock solutions were prepared by dissolving the respective amount of the working standards in mobile phase to obtain the concentration of 5 μg mL^{-1} for fosinopril sodium and 5 μg mL^{-1} for fosinoprilat.

2.5. Sample solution

Ten tablets (contained 10 mg of fosinopril sodium) were accurately weighted and finally powdered. The quantity of

Table 1
Matrix of experiment, experimentally obtained data, date predicted by ANN and case errors

	Factors			Predicted data		Experimental data		Errors	
	x_1	x_2	x_3						
Full factorial design	82	0.7	15	0.864	4.584	2.149	7.425	−1.285	−2.841
	78	0.7	15	1.739	8.926	2.750	9.244	−1.011	−0.318
	82	0.1	15	0.853	4.300	1.017	3.505	−0.164	0.795
	78	0.1	15	2.113	9.602	1.880	8.232	0.233	1.370
	82	0.7	5	2.211	4.481	2.959	3.920	−0.748	0.561
	78	0.7	5	2.981	8.824	2.650	8.050	0.331	0.774
	82	0.1	5	2.302	4.550	2.899	5.056	−0.597	−0.506
	78	0.1	5	3.639	10.082	4.580	11.160	−0.941	−1.780
Star design	82	0.5	10	1.539	4.384	1.151	3.745	0.388	0.639
	78	0.5	10	2.544	9.134	2.821	9.657	−0.277	−0.523
	80	0.7	10	1.972	6.581	2.300	6.367	−0.328	0.214
	80	0.1	10	2.211	6.952	2.163	5.896	0.048	1.056
	80	0.5	15	1.312	6.592	1.858	5.640	−0.546	0.952
	80	0.5	5	2.700	6.688	4.184	7.140	−1.484	−0.452
Replications	80	0.5	10	2.031	6.629	2.230	7.20	−0.199	−0.571
	80	0.5	10	2.031	6.629	2.219	7.219	−0.188	−0.590
	80	0.5	10	2.031	6.629	2.230	7.233	−0.199	−0.604
	80	0.5	10	2.031	6.629	2.249	7.246	−0.218	−0.617

x_1 – Methanol content (%); x_2 – glacial acetic acid content (%); x_3 – concentration of ammonium acetate buffer (mM).

powdered tablets, containing 40 mg of fosinopril sodium was transferred to the volumetric flask of 100 mL. After that 40 mL of methanol–water (80:20 v/v) mixture was added and the solution was dissolved into the ultrasonic bath for 15 min. The volumetric flask was filled to the mark with a same mixture and the final solution was filtered. From that stock solution the final concentration 5 μg mL^{-1} of fosinopril sodium was prepaired.

2.6. Forced degradation studies

Stock solution of fosinopril sodium with concentration of 1 mg mL^{-1} prepared in mixture methanol–water (20:80 v/v) was used in all degradation studies. Solutions for use in forced degradation studies were prepared by diluting of stock solution with sodium hydroxide, hydrochloric acid and hydrogen peroxide to achieve concentration of 100 μg mL^{-1} of fosinopril sodium. Prior MS final concentration of 10 μg mL^{-1} of fosinopril sodium was prepared.

3. Results and discussion

API–MS analysis implies some tuning of classical LC methods because there are certain restrictions in order to achieve optimal API–MS sensitivity. In general, API techniques require the use of volatile solvent additives like acetic acid, formic acid, ammonium acetate buffer instead of non volatile phosphate, sulphate or borate buffer. Also, some limitations of flow rate also exist and recommendation is to use low flow rates in order to have the best sensitivity. When LC method for analyzed substance already exist some adaptations and adjustments for API–MS analysis must be done. In our previous paper, fosinopril sodium and its degradation product fosinoprilat were analyzed using mixture of methanol–water at low pH adjusted with orthophosphoric acid and flow rate 1 mL min^{-1} on C_{18} column [30]. Some important conclusions from that work were helpful for setting initial analysis conditions. For example, column with C_{18} packing material (SunFire RP C_{18}, 3.5 μm, 4.6 mm × 100 mm) was chosen for this study. Then, high content of organic solvent (methanol, higher then 75%, v/v) in mobile phase and low pH controlled by ammonium acetate buffer and glacial acetic acid were used as a starting point in eluent optimization. Flow rate was set at 0.3 mL min^{-1}.

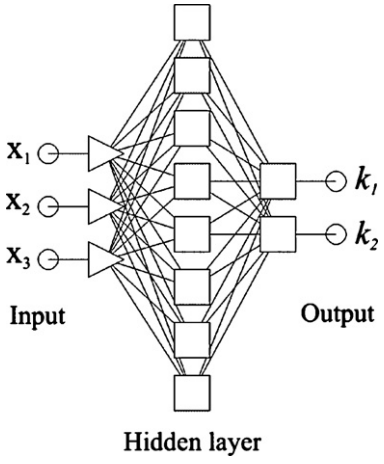

Fig. 1. Illustration of network topology.

Table 2
Regression analysis for training, verification and testing sets of data

	Fosinoprilat			Fosinopril sodium		
	Tr.	Vr.	Te.	Tr.	Vr.	Te.
Data mean	2.550	2.09	2.206	6.871	7.299	6.571
Data SD	0.979	0.297	0.061	2.296	1.319	0.954
Error mean	−0.607	−0.021	−0.419	−0.024	0.135	0.439
Error SD	0.871	0.0517	0.259	1.465	0.310	1.201
Abs. E mean	0.674	0.036	0.419	1.204	0.219	0.849
SD ratio	0.890	0.174	4.263	0.638	0.235	1.258
Correlation	0.456	1.000	1.000	0.822	1.000	−1.000

Tr. – training set; Vr. – verification set; Te. – testing set.

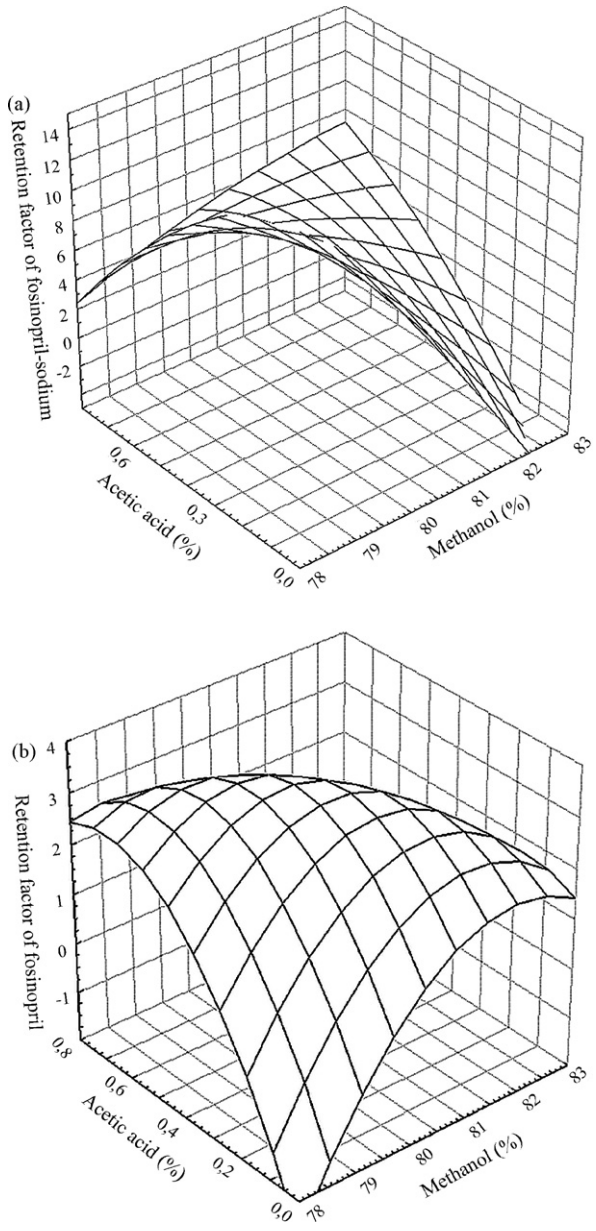

Fig. 2. 3D graph: (a) k (fosinopril sodium) = f (%MeOH, %acetic acid) and (b) k (fosinoprilat) = f (%MeOH, %acetic acid).

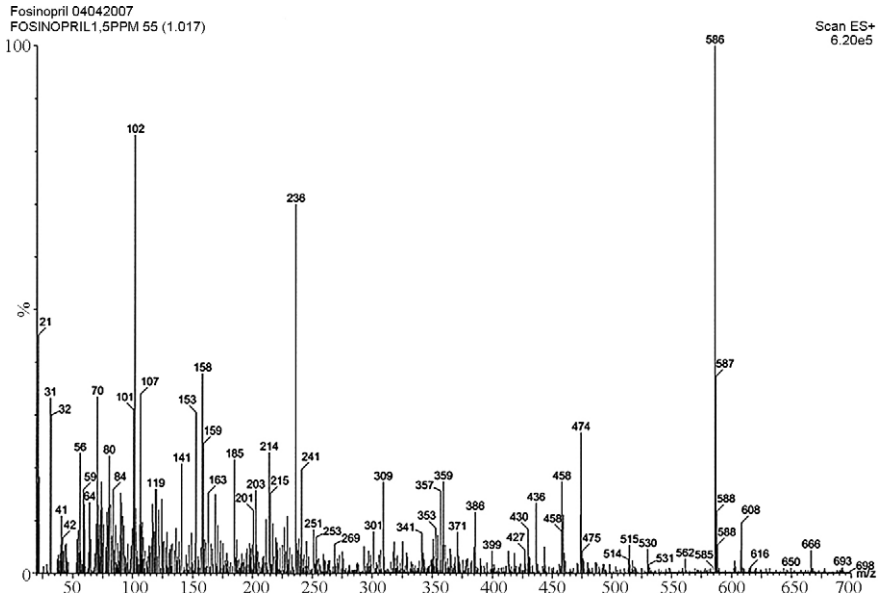

Fig. 3. Full scan spectra of fosinopril sodium $[M + Na]^+ = 586$ obtained using positive-ionization LC–MS.

Next step was setting the optimal chromatographic conditions for fosinopril sodium and fosinoprilat separation, compatible with MS detection. For method optimization coupling of ED and ANN was chosen. The ED–ANN is based on a suitable design of experiments and then the optimal separation conditions were predicted with an artificial intelligence method using input and output data of ED experiments [2]. Various types of ED were investigated, however, utmost data could be obtained from CCD. CCD can be used for systematic optimization and it offers an efficient route for rapid optimization of resolution with multiple interacting parameters [7]. The CCD is build up of a full factorial 2^k design to which a star design is added. The CCD is completed by addition of a center point. The total number N of experiments with k factors is:

$$N = 2^k + 2k + c \quad (1)$$

The first term is related to the full factorial design, the second to the star points and the third to the center point. From the repetition of the center point, the experimental variance at the center of the domain can be estimated. For three factors to be considered at least $8 + 6 + 1 = 15$ experiments are necessary but some extra replications need to be done [32]. In this study, authors built CCD design and appropriate matrix of experiment is presented in Section 2. As input variables methanol content, concentration of ammonium acetate buffer and content of glacial acetic acid were used. Regions of input variables were defined during the

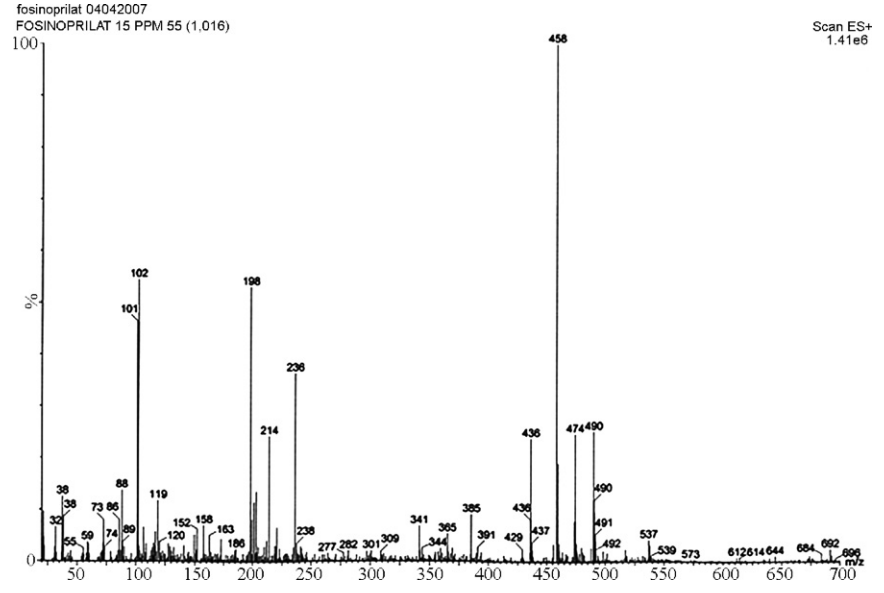

Fig. 4. Full scan spectra of fosinoprilat $[M + H]^+ = 436$ and $[M + Na]^+ = 458$ obtained using positive-ionization LC–MS.

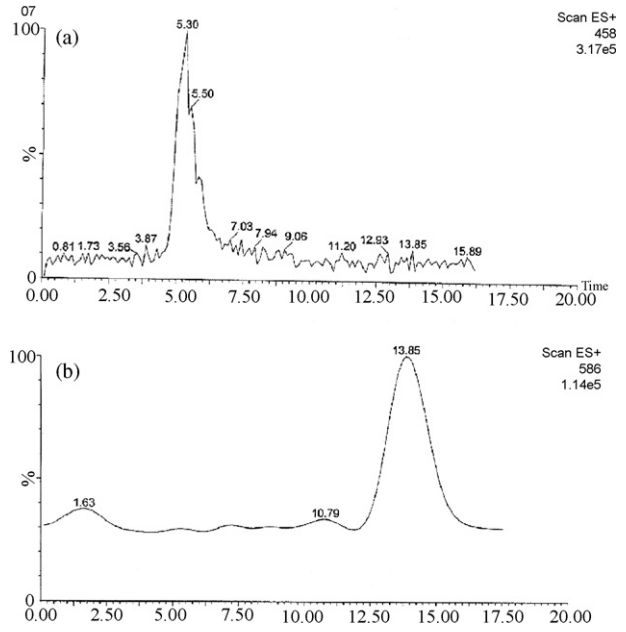

Fig. 5. Selected ion recording (SIR) spectra of (a) fosinoprilat and (b) fosinopril sodium.

preliminary study, namely small variations in methanol content gave remarkable changes in substances retention so it was chosen to test this variable in narrow range (from 78% to 82%, v/v). Concentration of ammonium acetate buffer was varied in routine range (from 5 to 15 mM). Higher concentrations than 15 mM are not recommendable when MS detector is used. For acetic acid, influence of various concentrations was tested and acceptable were same and lower than 0.7%. Other factors such as temperature, column packing and flow rate were kept on the constant level during the method optimization. Retention factors of fosinopril sodium and fosinoprilat were defined as output variables.

Experimental data (inputs) and results from experiments (outputs) were used to train of ANN with aim to define correlation among variables. Out of 18 experiments, 14 were used for network training, set of two experiments for verification as well as two experiments for network testing. Multilayer perceptron (MLP) networks architecture was applied. Back propagation (BP) algorithm was used for network training. The network with best performance was obtained in 100th epoch. At that moment the values for root mean square (RMS) were the smallest for training, verification and testing sets. Optimal network had eight hidden neurons, so the obtained topology was 3–8–2 (Fig. 1).

Values predicted by obtained neural network, as well as experimentally obtained data and corresponding case errors are presented in Table 1.

The experimentally obtained results for retention factors of fosinopril sodium and fosinoprilat were compared with data predicted by ANN. Obtained correlation for fosinopril sodium is $y = 1.2752 + 0.8008x$ ($S_b = 0.35$; $t_b = 1.655$) and for fosinoprilat $y = 0.535 + 0.426x$ ($S_b = 0.307$; $t_b = 1.748$). Corresponding correlation coefficients 0.8729 and 0.7958 for fosinopril sodium and fosinoprilat, respectively, and t_b values for both lower than t_{tab} (2.235 for $p = 0.02$) confirmed the obtained ANN adequacy to give the investigated system precise representation.

During the network training weights were adjusted in order to get the lowest error values. Weights present coefficients of mathematical input and output connection. For the obtained network weight distribution was from −1.25 to +1.25.

Results for regression analysis for trening, verification and testing set of data are given in Table 2.

On the basis of values predicted by ANN 3D-graphs were constructed as $k = f$ (%MeOH, %glacial acetic acid). Ammonium acetate buffer concentration had the lowest influence on the retention factor, so it could be kept on constant level. Constructed 3D-graphs are presented in Fig. 2a and b for fosinopril sodium and fosinoprilat, respectively.

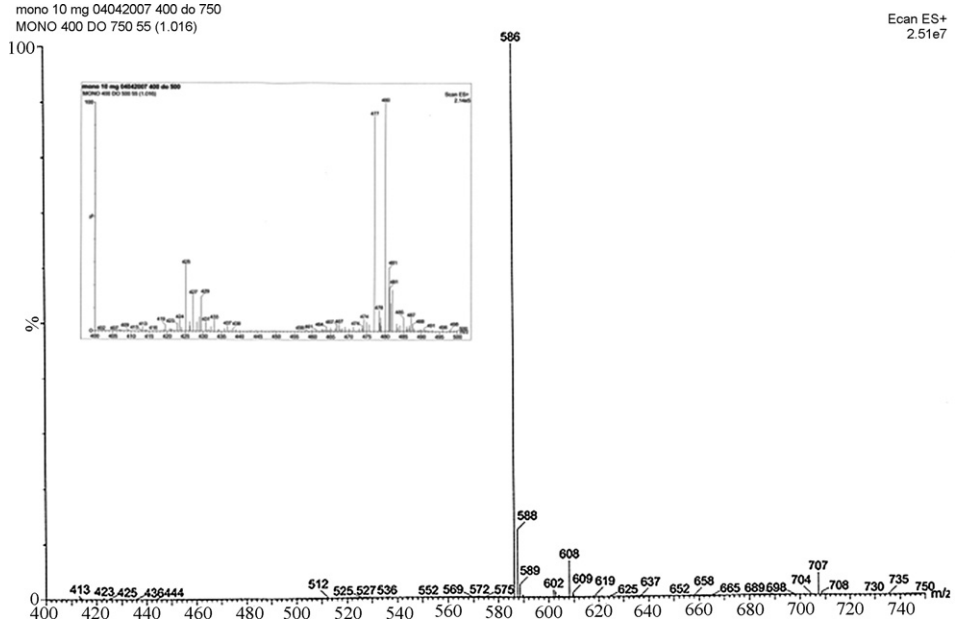

Fig. 6. MS spectra of tablets for masses from 400 to 750 *m/z* with inset for masses from 400 to 500.

The 3D-graphs are the most appropriate way to visualize chromatographic behavior of analytes in defined experimental domain of investigated factors. Closer investigation enabled definition of optimal separation conditions. The most appropriate mobile phase composition was: methanol–10 mM ammonium acetate buffer– acetic acid (80:19.5:0.5 v/v/v).

Next step in investigation was definition of MS parameters to get the highest sensitivity. According to fosinopril sodium and fosinoprilat structure both positive and negative mode could be applied. Both structures posses carboxylic and amide functional group which could give proton in process of ionization. Unlike fosinopril, where phosphinate group is esterificated, fosinoprilat has free phosphinate group which could be deprotonated. On the other hand, both molecules could be protonated. Finally, they could be determinate in both positive ESI mode and negative ESI mode. According to preliminary investigations as well as literature data [24–26] ESI in positive mode was chosen. MS parameters were defined (Section 2) and full scan spectra of fosinopril sodium and fosinoprilat were recorded using direct infusion in MS (Fig. 3 for fosinopril sodium and Fig. 4 for fosinoprilat).

Under defined chromatographic conditions and settled MS parameters MS scan was done after elution of laboratory mixture from column and obtained spectra are presented in Fig. 5.

Full scan spectra was recorded for sample solution obtained from tablets (one tablet contains 10 mg of fosinopril sodium) and presented in Fig. 6.

In Fig. 6 authors present MS spectra for masses from 400 to 750 because *m/z* masses of investigated substances are in that range. Besides, as better presentation of fosinoprilat masses, in Fig. 8 inset is given highlighting MS spectra for masses from 400 to 500.

Under the given conditions full scan spectra for active substance, subjected to stress conditions, were recorded. During the investigation of stress conditions, influence of acid, alkali and oxidation was performed [33]. Presence of ester group in the structure of fosinopril sodium causes fast and complete degradation in alkaline solutions. Chromatographic analysis applying optimal conditions proved the complete degradation within 10 min in 0.01 M, 0.05 M and 0.1 M sodium hydroxide solutions at room temperature. The major product of alkaline hydrolysis was fosinoprilate. Because of total hydrolytic degradation under these initial conditions, further increase of alkali strength and temperature would be totally useless and unnecessary.

Acid forced degradation studies were done in 0.1 M HCl solution. Chromatographic analysis had shown that the significant structural changes would not happen before 12 h at room temperature. After that some degradations occur, but for significant cleavage at least 24 h at room temperature was needed. So the full scan spectra were recorded for solutions obtained after 24 h treatment with 0.1 M HCl. Obtained spectra are presented in Fig. 7.

According to structure of fosinopril sodium and obtained spectra some of the degradation pathways can be foreseen (Fig. 8).

As expected acid forced degradation caused amide bond hydrolysis and the resulting products are present in spectra as

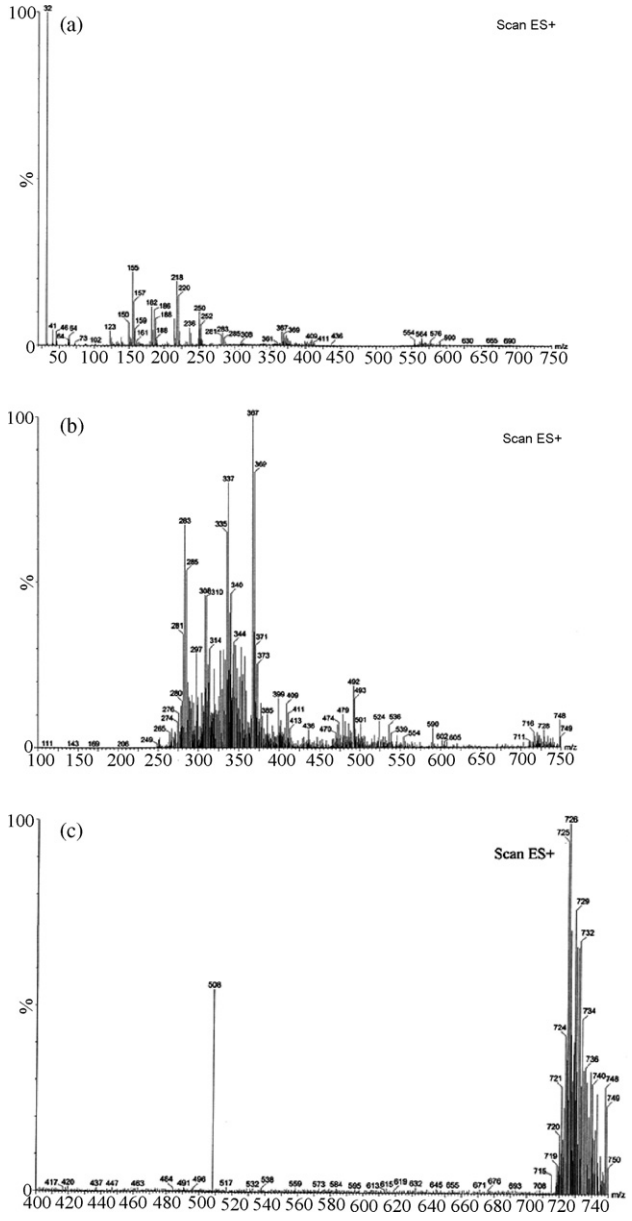

Fig. 7. MS spectra of fosinopril sodium in 0.1 M HCl: (a) masses from 0 to 750 *m/z*; (b) masses from 100 to 750 *m/z* and (c) masses from 400 to 750 *m/z*.

m/z 220 and *m/z* 385. However, intermediate product of *m/z* 385 with *m/z* 367 is also present. Mass *m/z* 508 arose from the degradation of ester with propyonic acid. In Fig. 9A masses corresponding positive forms of fosinopril and fosinoprilat can be found (*m/z* 564 and *m/z* 436, respectively). It can be concluded that the degradation was not complete and that a certain amount of fosinoprilat can also ensue in acid forced degradation. As it is very well known in acidic solutions transesterification can occur and for that reason some other intermediate products can be seen in spectra. However, these are not as important as the products of amide bond and ester hydrolysis.

For the test for oxidation, it is suggested to use hydrogen peroxide in the concentration range of 3–30% [33]. Chromatographic analysis within 24 h shows important processes occuring using 3% and 15% of hydrogen peroxide, so further increas-

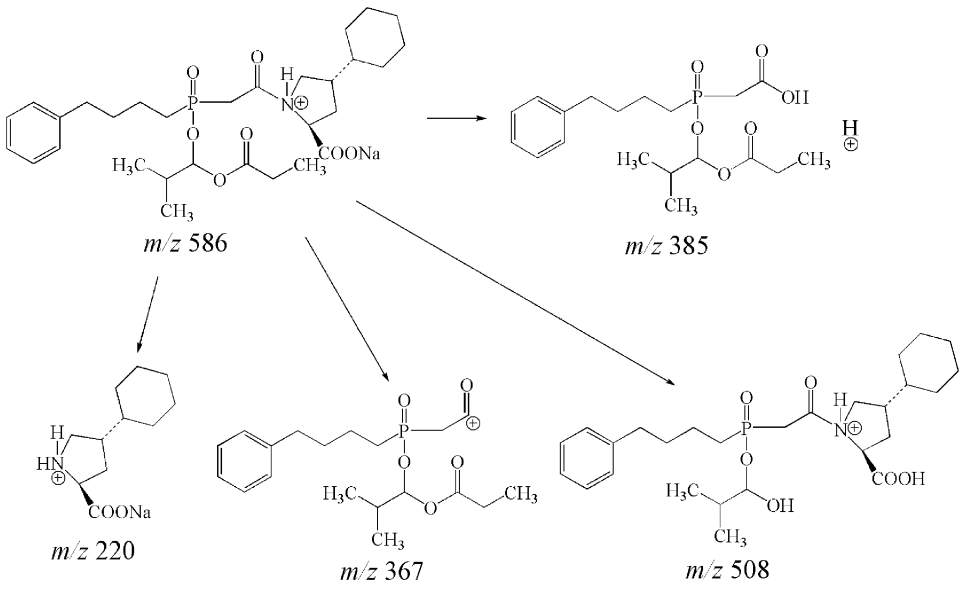

Fig. 8. Some of the degradation pathways of fosinopril sodium in acid solution.

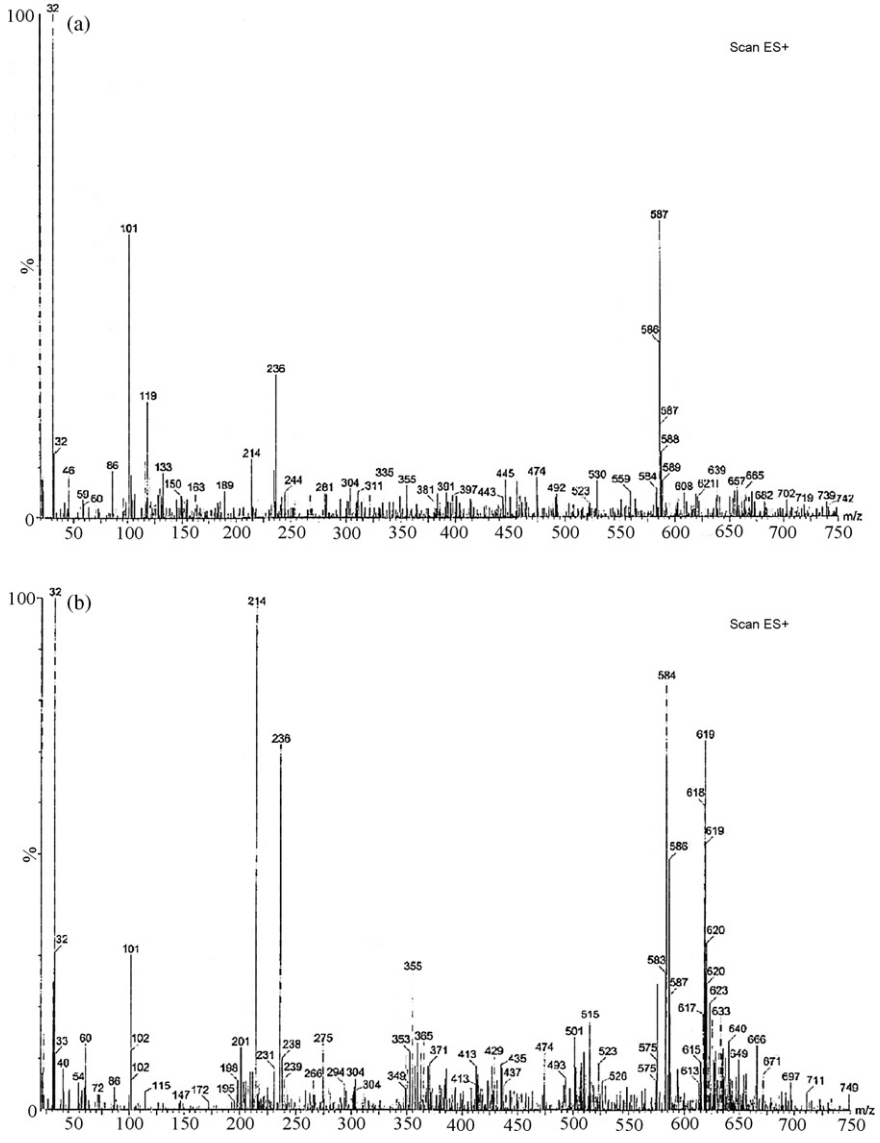

Fig. 9. MS spectra of fosinopril sodium in: (a) 3% hydrogen peroxide solution and (b) 15% hydrogen peroxide solution.

ing of oxidative agent concentration is useless. For that reason MS spectra were recorded for the solutions of fosinopril sodium treated with 3% and 15% hydrogen peroxide within 24 h at room temperature. Obtained MS spectra are presented in Fig. 9 (Fig. 9a and b for 3% and 15% hydrogen peroxide, respectively).

According to obtained *m*/*z* masses and structure of investigated substances under oxidative forced degradation various types of oxidation had happened. Reaction of dehydrogenation corresponds mass of 584 *m*/*z* which appeared in both spectra but as expected 15% of hydrogen peroxide promoted this reaction in higher degree. Mass of 618 *m*/*z* (Fig. 9 B) conforms oxidation of two carbon atoms and such kind of oxidation required higher concentration of oxidative agent. The same oxidation conditions would lead to peroxide formation (*m*/*z* 620). However, presence of both 3% and 15% resulted in amide bond cleavage and oxidation of formed proline derivate (*m*/*z* 236).

4. Conclusion

For full and complete active compound impurity qualification, application of MS detection proved to be the most appropriate. Hyphenation of LC method with MS detection requires some modification of existing LC method. Therefore, some previous deductions become the basis for setting new chromatographic conditions. In order to get the most appropriate conditions as quick as possible, combination of CCD and ANN was employed in method optimization. Input variables (methanol content, ammonium acetate buffer concentration and acetic acid content) and output variables (retention factor) defined by CCD were used for ANN train. MLP with BP algorithm was used for network training. Optimal network topology was 3–8–2 and the lowest RMS error was obtained in 100th epoch. Good correlation obtained *vs.* predicted data (coefficients correlations were 0.8729 and 0.7958 for fosinopril sodium and fosinoprilat, respectively) confirmed good capability of network. In that way, optimal conditions were set and used in stress study and as inlet in MS. Forced stress study proved that fosinopril sodium completely degraded after alkaline hydrolysis subjection. MS spectra confirmed amide bond and ester group hydrolysis in acid solution. In the presence of hydrogen peroxide fosinopril sodium partially degraded and several products of oxidation were formed. Proposed approach enabled efficient chromatographic method modification and adaptation to MS detection leading to definition of suitable stability-indicating method for fosinopril sodium.

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References

[1] A.B. Hameda, S. Elosta, J. Havel, J. Chromatogr. A 1084 (2005) 7.
[2] K. Novotna, J. Havliš, J. Havel, J. Chromatogr A 1096 (2005) 50.
[3] E. Marengo, V. Gianotti, S. Angioi, M.C. Gennaro, J. Chromatogr. A 1029 (2004) 57.
[4] A.T.K. Tran, R.V. Hyne, F. Pablo, W.R. Day, P. Doble, Talanta 71 (2006) 1268.
[5] J. Havel, J.E. Madden, P.R. Haddad, Chromatographia 49 (1999) 481.
[6] H. Wang, W. Liu, J. Sep. Sci. 27 (2004) 1189.
[7] A.M. Siouffi, R. Phan-Tan-Luu, J. Chromatogr. A 892 (2000) 75.
[8] N. Arulsudar, N. Subramanian, R.S.R. Murthy, J. Pharm. Sci. 8 (2005) 243.
[9] B.D. Glass, S. Agatonovic-Kustrin, M.H. Wisch, Curr. Drug Discov. Technol. 2 (2005) 195.
[10] K. Takayama, M. Fujikawa, T. Nagai, Pharm. Res. 16 (1999) 1.
[11] M. Gašperlin, L. Tušar, M. Tušar, J. Kristl, J. Šmid-Korbar, Int. J. Pharm. 168 (1998) 243.
[12] S.Z. Tham, S. Agatonovic-Kustrin, J. Pharm. Biomed. Anal. 28 (2002) 581.
[13] F. Ruggieri, A.A. D'Archivio, G. Carlucci, P. Mazzeo, J. Chromatogr. A 1076 (2005) 163.
[14] A.L. Magri, F. Balestrieri, A.D. Magri, D. Marini, Talanta 42 (1995) 1719.
[15] S. Saglik, O. Sagirli, S. Atmaca, L. Ersoy, Anal. Chim. Acta 427 (2000) 253.
[16] N. Erk, J. Pharm. Biomed. Anal. 27 (2002) 901.
[17] S.A. Ozkan, C. Akay, S. Cevheroglu, Z. Saenurk, J. Liq. Chromatogr. 24 (2001) 983.
[18] R. Lozano, F.V. Warren, S. Perlman, J.M. Joseph, J. Pharm. Biomed. Anal. 13 (1995) 139.
[19] S. Hillaert, Y. Vander Heyden, W. Van den Bossche, J. Chromatogr. A 978 (2002) 231.
[20] S. Hillaert, W. Van den Bossche, J. Chromatogr. A 895 (2000) 33.
[21] S. Hillaert, K. De Grauwe, W. Van den Bossche, J. Chromatogr. A 924 (2001) 325.
[22] S. Hillaert, W. Van den Bossche, J. Pharm. Biomed. Anal. 25 (2001) 775.
[23] M. Jemal, E. Ivashkiv, M. Ribick, A.I. Cohen, J. Chromatogr. 345 (1985) 299.
[24] M. Jemal, D.E. Mulvanab, J. Chromatogr. B 739 (2000) 255.
[25] M. Jemal, M. Huang, Y. Mao, D. Whiga, A. Schuster, Rapid Commun. Mass. Spectrom. 14 (2000) 1023.
[26] C. Shuangjin, F. Fang, M. Ming, L. Han, C. Yun, J. Chromatogr. B 854 (2007) 143.
[27] B. Jancic, D. Ivanovic, M. Medenica, A. Malenovic, N. Dimkovic, J. Chromatogr. A 1008 (2005) 187.
[28] N. Lewen, M. Schenkenberger, T. Larkin, S. Conder, H.G. Brittain, J. Pharm. Biomed. Anal. 13 (1995) 879.
[29] B. Jancic, D. Ivanovic, M. Medenica, A. Malenovic, Acta Chim. Slov. 50 (2003) 327.
[30] D. Ivanovic, M. Medenica, B. Jancic, A. Malenovic, S. Markovic, Chromatographia 60 (2004) S87.
[31] B. Jancic, M. Medenica, D. Ivanovic, A. Malenovic, S. Markovic, Anal. Bioanal. Chem. 383 (2005) 687.
[32] T. Lundstedt, E. Seifert, L. Abramo, B. Thelin, A. Nyström, J. Pettersen, R. Bergman, Chemom. Intell. Lab. Syst. 42 (1998) 3.
[33] M. Bakshi, S. Singh, J. Pharm. Biomed. Anal. 28 (2002) 1011.