IDENTIFICATION OF DEGRADATION PRODUCTS OF FENSIPIRIDE HYDRICHLORIDE IN STRESS DEGRADATION MEDIA

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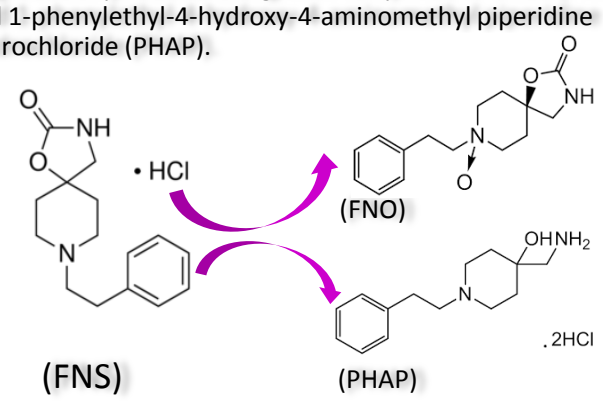
INTRODUCTION AND OBJECTIVE

Fenspiride hydrochloride is used on chronic inflammatory diseases. Most used formulations are liquid oral solutions. Fenspiride hydrochloride (FNS) enables a series of degradation products along with fenspiride N-oxide (FNO) and 1-phenylethyl-4-hydroxy-4-aminomethyl piperidine hydrochloride (PHAP).



The aim of the study was development and validation of a chromatographic method suitable for pharmaceutical field which has the suitable specificity to identify the main degradation products in the presence of other compounds from the liquid preparation.

MATERIAL AND METHODS

The chromatographic method was developed on the Thermo Ultimate 3000 system with quaternary pump 600 barr, online degasser, autosampler, column thermostat and diode array detector produced by Thermo Waltham, USA

ANALYTICAL COLUMN	Thermo Hypersil Gold Aq C18 with 250 X4.6 MM. 5 UM
FLOW RATE	1,5 ml/min
CHROMATOGRAPHY RUN	20 MIN
COLUMN TEMPERATURE	25 °C
DETECTION, UV	210 NM
INJECTION VOLUME	20 µL

ELUTION

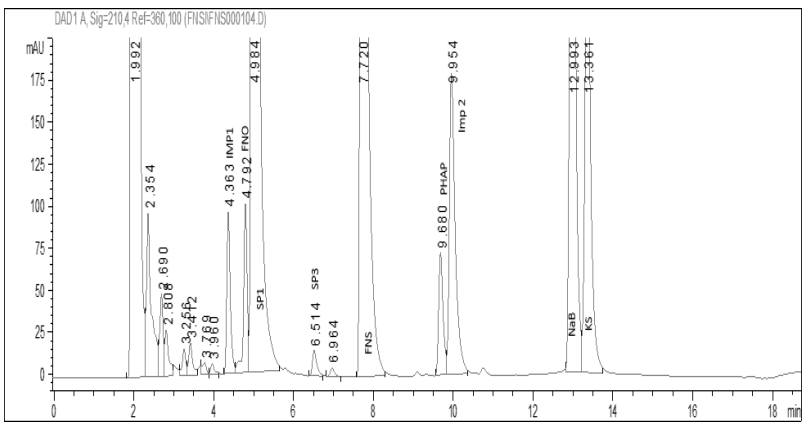
Solution S1 (sodium phosphate monobasic 0.05 M pH 4.5), acetonitrile, methanol and solution S2 (sodium phosphate monobasic 0.05 M pH 2.9)

Time (min)	Solution S1	Acetonitrile	Methanol	Solution S2
0	90	-	10	-
10	-	15	10	75
15	-	15	10	75
16	90	-	10	-
18	90	-	10	-

METHOD DEVELOPEMENT AND VALIDATION

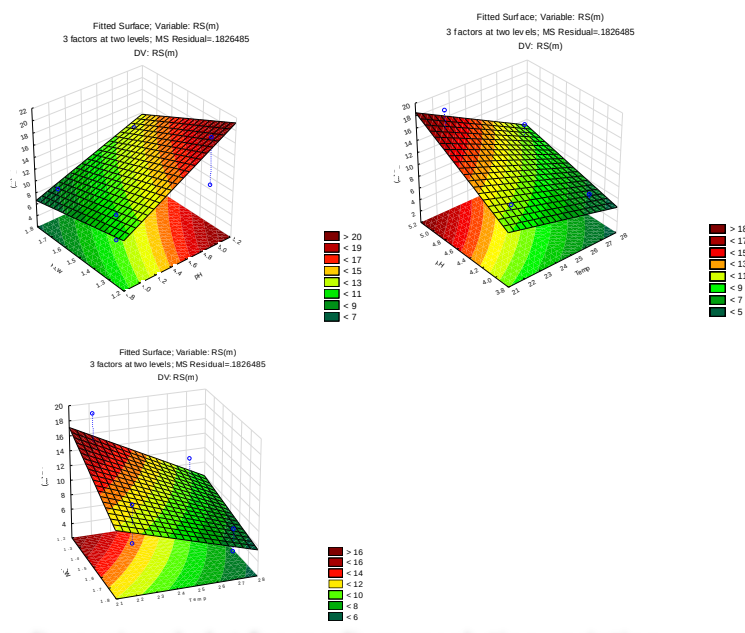
A full factorial design was used for the optimization of model. Previous mentioned parameters were considered as started conditions. The design had a number of 2 factors, 4 runs and 1 block. The factors were coded as -1 and +1. First factor was associated with the variation of pH. We have used pH 4.5 (-1) and the gradient of pH as slope (β=0.66) from 4.5 to 2.9 (+1). The second factor was acetonitrile gradient (ACN) in the mobile phase. As pH, acetonitrile modification produced a important modification in terms of resolution and separation efficiency. Factor code (-1) was associated with the isocratic percentage of 10% for acetonitrile for the mobile phase and (+1) was associated with the gradient from 0% to 15 % during 10 minutes and maintaining to 15% for more 5 minutes.

METHOD DEVELOPEMENT



In this case the equation had the following distribution.

$$Y = 71.17 + 31.36pH + 32.44ACN + 13.15pH * ACN$$



Three dimensional plot for medium resolution variation between FNO, FNS and PHAP at modification with ±10% of pH (4.5), temperature (25 °C), and flowrate (1.5 ml/min)

METHOD VALIDATION

Parameter		FNO	FNS	PHAP
Repeatability	Retention time, RSD%	0.31	0.13	0.99
	Area, RSD%	0.85	0.99	0.68
Within day Precision (area), RSD%		2.38	1.46	0.69
Intra day precision (area), RSD%		3.05	4.08	2.65
Rezolution		15.05	8.92	11.7
Theretical plates		10189	25801	33457
Peak purity		0.997	0.996	0.997
Liniarity	Error of slope			0.7930
	Correlation coefficient	0.998	0.995	0.996
Accuracy	Average recovery	103.18	100.47	100.46
	Skewness O_x%	0.8587	0.3164	0.4222
Limit of qualification, µg mL^{-1}		0.190	0.195	0.332
Confidence level of slope, 95%		21.49 – 26.33	22.45 – 26.45	26.396 – 31.443

RESULTS AND DISCUSSION

Most important parameters which may affect method specificity are pH and temperature. The method is suitable for pharmaceutical field which require HPLC determinations. The method is applicable to determination for active subtances but also for determinations from pharmaceutical products

References:

- Arnone, A., Metrangolo, P., Novo, B., & Resnati, G. (1998). Selectivities in the oxidation of tertiary amines and pyridine derivatives by perfluoro cis-2,3-dialkyloxaziridines. Tetrahedron, 54, 7831–7842.
- Council of Europe (2014a). Acyclovir. In European pharmacopoeia (8th ed.) (pp. 1482–1484). Strasbourg.
- Gamst, G., Meyers, L. S., & Guarino, A. J. (2008). Table of critical f values. In A conceptual and computational approach with SPSS and SAS (1st ed.) (pp. 551–555). Cambridge: Cambridge University Press.
- Hale, G. M., & Querry, M. R. (1973). Optical constants of water in the 200-nm to 200-µm wavelength region. Applied. Optics, 12, 555–563.
- Pidpruzhnykov, Y. V., Sabko, V. E., Iurchenko, V. V., & Zupanets, I. A. (2013). UPLC-MS/MS quantification of fenspiride in human plasma. Journal of Bioequivalence and Availability, 5, 185–190
- Sweetman, S. (2009). Martindale: The complete drug reference (36th ed.).Shanghai: Pharmaceutical Press.