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THE DENSITOMETRIC DETERMINATION OF PURITY OF SODIUM METAMIZOL INJECTIONS AND TABLETS

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Abstract: Densitometry has been used to examine the purity of sodium metamizol preparations. The hydrolyzate of the active substance was determined in injections and tablets. The percentage of the impurity that was characterized by R_f=0.75 was determined from the stain of sodium metamizol having R_f=0.25 (by using a suitably diluted solution). Readings were taken from the calibration curve ascertained within the range of concentrations from 0.25 to 2.75 mg ml^{-1}. The dilution ratio was established for injection–grade solutions and for extracts from tables, corresponding to minumum values of the coefficient of variation. Sodium metamizol was hydrolyzed to help reidentify the stains due to the decomposition product having R_f=0.75. Sodium metamizol was found to undergo acid hydrolysis only, and the decomposition observed is believed to be a zero–order reaction.

Sodium metamizol [sodium N–(1–phenyl–2,3–dimethyl–5–oxo–3–pyrazolin–4–yl)–N–methylaminomethanesulfonate, MS] has been used as an analgesic to smooth strong pains of various origins. It also has antipyretic and spasmolytic properties. In medical practice it is used in the form of simple and compound preparations. Prolonged application can result in functional changes of the kidney, liver, and gastric mucosa; intravenous administration can produce a shock. Dangerous myelic lesions can occur (1–3): therefore, when possible, MS should be replaced by other drugs. In each EU country, the use of sodium metamizol has been restricted; in some countries like Austria, Denmark, Ireland and Norway, MS has been entirely abandoned in medical therapy (3). These facts render a more thorough examination of the preparations containing MS as the major component desirable.

A method most frequently used to determine sodium metamizol in pharmaceutical preparations is iodometry. Titration of MS (4) allows to determine the sum of sodium metamizol and its decomposition products. The combination of TLC with spectrophotometric detection has afforded lower values than those obtained by iodomerty or by direct spectrophotometry. TLC has been recommended by DAB 10 as the method for purity control of the MS substance, whereas a HPLC method has been developed to determine individual impurities of sodium metamizol used in injections (5). The impurities were subdivided to include the following five compounds: 4–methylaminophenazone (MAF), 4–aminophenazone, 4–methylformylaminophenazone, 4–oxyphenazone, and phenazone. 4–Methylaminophenazone has been established to be the major hydrolyzate occurring in amounts of 5 to 10%: 4–methylformylaminophenazone was only 0.02 to 0.3% and an unindenitified impurity was about 0.04–0.4%. The model solutions stored for 30 min have been found to contain the hydrolyzate in an amount of about 3% of the MS content.

The purpose of the present work is to develop a densitometric method for examining the purity of sodium metamizol (MS) preparations, to determine quantitatively 4–methylaminophenazone (MAF) and to fully validate the method developed.

EXPERIMENTAL

Material for investigation

Sodium metamizol (Sigma), Pyralgin ampules 1g/2ml (Polpharma), Pyralginum tablets 0.5 g (Polpharma)

Apparatus

A Shimadzu CS–9000 densitometer equipped with a deuterium lamp.

Quantitative and qualitative determination of 4–methylaminophenazone

Chromatographic system

The active substance was separated from impurities by using TLC technique and GF_{254} (Merck's 20/20 cm) silica gel plates as the stationary phase (60:25:14:1) chloroform–metha-

nol–ethyl acetate–10% ammonia as the mobile phase.

Calibration curve

Six solutions of a MS standard substance were prepared to cover the concentration range of 0.25 to 2.80 mg ml^{-1} (0.27, 0.80, 1.08, 1.60, 2.15, 2.71 mg ml^{-1}.). Each solution, 5 µl, was placed onto a chromatographic plate.

Preparation of samples

To determine the impurities present in the injections, a 50% sodium metamizol solution, 0.5 ml, was diluted with methanol to the volume of 10 ml (Solution A). To determine sodium metamizol, Solution A was diluted with methanol, *viz.*, 0.1 ml and 2.5 ml to the volumes of 10 ml and 100 ml, respectively. The resulting solution, 5 µl, was applied onto a chromatographic plate.

To determine the content of impurities in tables, the tablets were thoroughly powdered and 1.8 g powder (corresponding to about 1.5 g MS) was weighed in 25 ml volumetric flask and the contents was made up to the mark with methanol. The contents was shaked, allowed to stand for 15 min in an ultrasonic bath and filtered through a 0.2 µm filter (Solution B). To determine MS in tablets, Solution B was diluted with methanol to prepare the following dilutions: 1.5 ml to 50 ml; 0.5 ml to 25 ml; 0.5 ml to 50 ml. Each of the resulting solutions, 5 µl, was applied onto a chromatographic plate.

Prior to the densitometric determination, the analytical wavelenght was established by plotting the spectra for the impurity stain of R_f=0.75 (MAF) and for the sodium metamizol stain of R_f=0.25. The maxima for 4–methylaminophenazone and sodium metamizol were found to be closely related (Fig. 1). The wavelenght 275 nm was selected as the one at which to carry out the analytical determination. A calibration curve was plotted (Fig. 2) to cover the concentration range from 1 to 10% MAF in MS in a 25 mg ml^{-1} MS sample (y = 133.5x–1857; correlation coefficient, 0.9996). The concentration 0.5% was found to be the detectability limit for MAF.

In the same series of injection–grade solutions, 4–methylaminophenazone was determined densitometrically and MS was determined iodometrically by the FP V method. Then a Pyralgin ampule was left open in a dark place with free access of air. In 4 days, MAF and MS were redetermined by densitometry and iodometry, respectively.

To confirm the identity of the R_f=0.75 stain corresponding to 4–methylaminophenazone, obtained after the chromatographic separation, sodium metamizol was submitted to acid hydrolysis. To a 25 mg ml^{-1} solution (Solution I), 3 ml, a 1 mol dm^{-3} hydrochloric acid was added in the following amounts: 0.05 ml (Solution II), 0.10 ml (Solution III), and 0.15 ml (Solution IV) (Figs. 3 and 4). At the same time analogous solutions were prepared by using a 1 mol dm^{-3} sodium hydroxide. Then each solution, 5 µl was applied onto a chromatographic plate. With Solutions III and IV, deter-

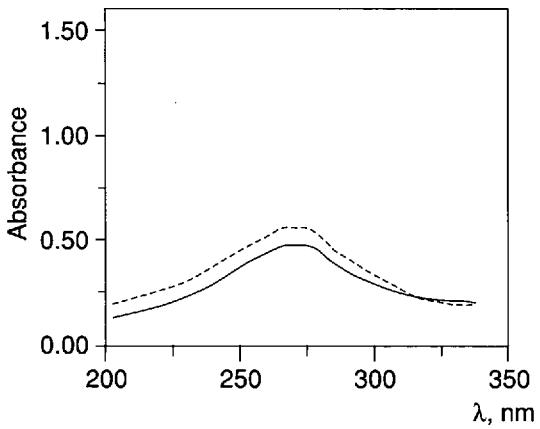

Figure 1. UV spectra of methanolic sodium metamizol solutions (dashed line) and 4–methylaminophenazone (MS hydrolyzate) (continuous line) after chromagraphic separation.

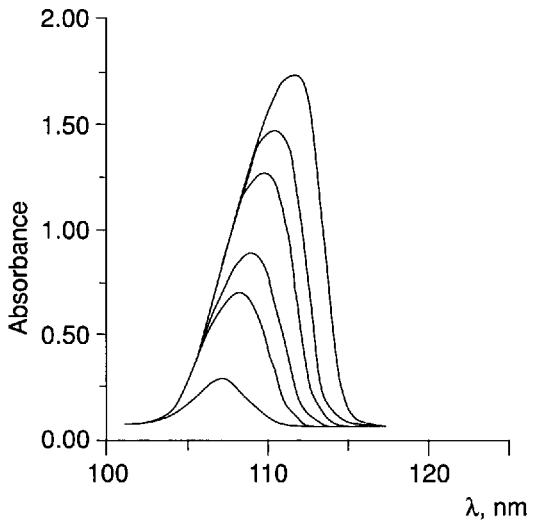

Figure 2. Densitograms of methanolic sodium metamizol solutions at concentrations of 0.25, 0.80, 1.08, 1.60, 2.15 and 2.71 mg ml^{-1}. The volume of the solution applied onto a chromatographic plate was 5 µl.

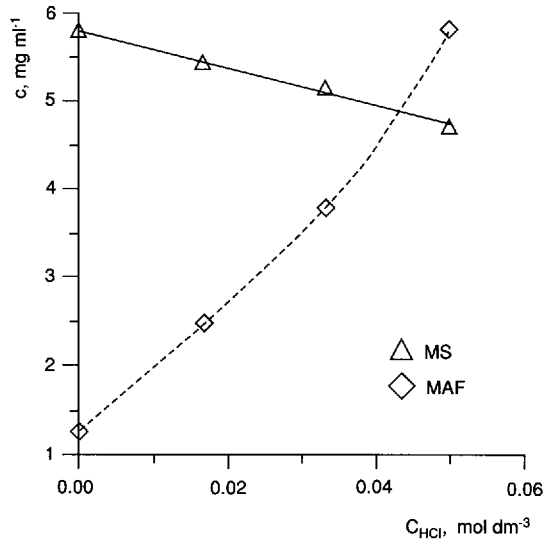

Figure 3. The concentrations of sodium metamizol and its hydrolyzate, MAF, in methanolic MS solutions in relation to hydrochloric acid concentration.

minations were made after 7–day storage. For Solution I, densitometric determinations were carried out after 7 and 14 days (Fig. 4).

DISCUSSION, RESULTS AND CONCLUSIONS

The determinations carried out for injection–grade MS solutions in 4 days after the ampule had been opened, confirmed that 4–methylaminophenazone is not the only product of the decomposition of sodium metamizol. In 4 days the solution acquired a yellowish discoloration and iodometric method gave a result exceeding the theoretical MS content by about 20%. The peak areas corresponding to 4–methylaminophenazone determined densitometrically in the samples stored for 1 and 4 days were close to each other. Therefore, the densitometric method can be used to determine MS and its hydrolyzate: on the other hand, no other decomposition products could be found.

Densitometry allows 4–methylaminophenazone to be quantitatively determined in the presence of sodium metamizol. Table 1 lists the statistical evaluation data for the densitometric determination of the hydrolyzate of MS. The coefficients of variation are 1.31% and 1.30% for the MS and the MAF stains, respectively. Table 2 gives the statistical evaluation for the determination procedure developed. This evaluation shows the results obtained by this method to be burdened with the least error (maximum precision of the method) when, in the solutions examined, MS is used at the following concentrations: for ampules: 25 mg ml^{-1}, to determine the decomposition products, and 1.25 mg ml^{-1} to determine the active substance; for tablets, the respective values are 60 and 1.2 mg ml^{-1}. These values are justified by the lowest values of the coefficients of variation.

The higher RSD–values obtained for the solutions with higher MS concentrations are associated with the error committed in applying the solution onto the plate, and for the solutions with the lower MS concentrations with the error committed in dilution operations and also with read–out of the surface area of the peak which was less compact.

Methanolic MS solutions were studied over a period of time of 1 to 14 days. MS and MAF concentrations determined were plotted in relation to time (Fig. 4). Results showed the methanolic solutions to be stable and at the same time demonstrated the necessity to apply correct dilution ratios of sample solutions to produce correct MS stains in the densitometric determinations. The method developed was used to determine MS and MAF in acid and in alkaline solutions. The sodium metamizol solutions were found to undergo acid hydrolysis only. The MS concentration was found to vary

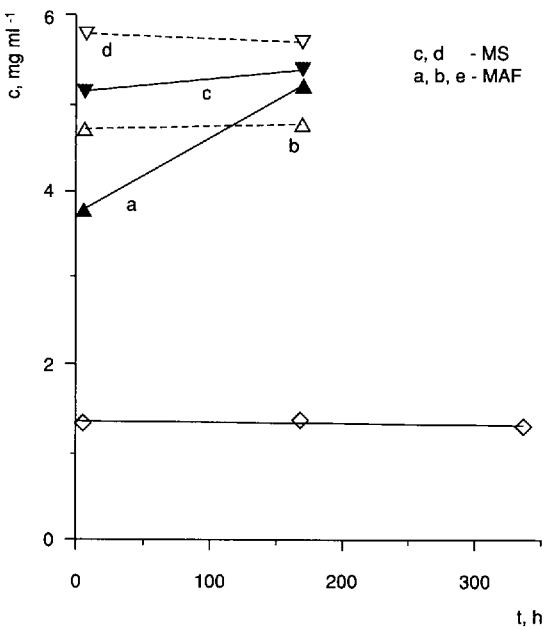

Figure 4. The concentrations of MS (c,d) and MAF (a,b,e) in methanolic sodium metamizol solutions in relation to storage time. The methanolic solutions were 50 mg ml^{-1} MS and contained a 3.22 (a,c) or a 4.99 mol dm^{-3} HCl (b,d).

Table 1. Statistical evaluation data for peak area-based densitometric determination of sodium metamizol hydrolyzate

Material	No. of samples	s	$x \pm tS_x$, p = 0.95	RSD %
Sodium metamizol solution 1.25 mg ml^{-1}	6	1706.53	149768.04 ± 1791.18	1.14
Ampules Pyralgin 1g $2ml^{-1}$ s. 1021997	10	1390.91	10742.24 ± 994.93	1.30
Ampules Pyralgin 1g $2ml^{-1}$ s. 1021997	10	2599.38	197748.26 ± 1859.35	1.31

Table 2. Statistical evaluation data for the procedure of densitometric determination of sodium metamizol hydrolyzate

Material	Dilution ratio	No. of samples	s	$x \pm tS_x$, p = 0.95 %	RSD
Ampules	1:10	10	0.30	6.33 ± 0.21	4.57
Pyralgin 1g $2ml^{-1}$	0.5:10	10	0.15	6.20 ± 0.11	2.47
s. 1010198	2.5:100	10	0.56	6.63 ± 0.40	9.30
Tablets	1.5:50	6	0.14	2.31 ± 0.14	5.01
Pyralginum 05 mg	0.5:25	6	0.07	2.02 ± 0.14	5.01
s. 990998	0.5:50	6	0.10	177 ± 0.10	5.41

directly with the concentration of hydrogen ions, whereby the reaction is belived to be a zero–order reaction; on the other hand, the course of the increasing MAF concentrations was indicative of a higher–order reaction (Fig. 3). Thus, the injection–grade solutions to be analyzed should have a pH close to neutral to allow a minimum of decomposition products to be formed.

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