



Research Article

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Identification of glucosamine hydrochloride diclofenac sodium interaction products by chromatography-mass spectrometry

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ABSTRACT

Researches of chemical transformation products of diclofenac sodium and glucosamine hydrochloride at their joint presence have been carried out by means of the gas chromatography-mass spectrometry. Mechanical mixes of substances were investigated before and after technological operations of humidifying and drying. It has been proven that one medicinal substance influences another. The formation of several reaction products during the chemical interaction between diclofenac sodium and glucosamine hydrochloride has been shown.

Key words: diclofenac sodium, glucosamine hydrochloride, chemical transformation products, gas chromatography-mass spectrometry.

INTRODUCTION

Diclofenac sodium is in the first line of nonsteroidal anti-inflammatory drugs (NSAID) for the pain relief and reduction of an inflammatory process activity in most diseases of connective tissue and joints over decades. However, along with pronounced therapeutic effect the use of this NSAID is associated with several side effects, including lesions of the gastrointestinal tract and inhibition of the metabolism of articular cartilage [1, 2, 3, 4].

Creation of new combined drugs with NSAIDs and other medicinal substances is one of the major direction of NSAIDs pharmacological properties spectrum spread and reduce their toxicity [5, 6, 7, 8]. Thus, in the National University of Pharmacy at the Department of Clinical Pharmacology and Clinical Pharmacy under the supervision of prof. Zupanets I.A. it has been proved that the combined use of diclofenac sodium and glucosamine hydrochloride increases the anti-inflammatory properties of NSAID, reduces its gastro- and nephrotoxicity, also a composition of diclofenac sodium with glucosamine hydrochloride has chondroprotective properties [9]. Therefore, it is reasonable to create the new drug from the composition of these substances.

In developing the composition and technology of diclofenac sodium and glucosamine hydrochloride tablets it was found that the mechanical mixture of these medicinal substances gradually becomes darker in color. The emergence of a dark color is accelerated in wet conditions and high temperature in the process of tablets obtaining using the wet granulation.

The preliminary studies by the thermal and X-ray powder diffractometry analysis showed the formation of several reaction products during the chemical interaction between diclofenac sodium and glucosamine hydrochloride one of which is sodium chloride [10].

The aim of our research was to investigate the possible products of chemical interaction of diclofenac sodium and glucosamine hydrochloride in their mixture by the method of gas chromatography-mass spectrometry for selecting the excipients and technology of solid dosage form which stable during storage.

EXPERIMENTAL SECTION

A mixture of diclofenac sodium and glucosamine hydrochloride (1:1) were moistened by purified water and kept in an open glass in an thermostat at 60 °C for 2 h (sample # 1). The same mixture was under similar conditions in a sealed vial, then it was kept for 1 month at room temperature.

Purified water was added to formed dark-colored mixture. After the mixing the suspension was filtered to obtain a white crystalline powder, which was dried (sample # 2) and dark-colored filtrate, which was subjected to evaporation (sample # 3).

Samples preparation was carried out by chromatography-mass spectrometry standard methods for identification of chemical composition and determination of mass content of compounds in samples 1-3. The samples #1 and 2 were dissolved in various organic solvents (methanol, methylene chloride) for tests. Sample #3 was extracted by toluene in the Soxhlet apparatus and dissolved in acetonitrile after the toluene extract concentration in a rotary evaporator. The obtained solutions of samples 1-3 were chromatographed. Also acetonitrile solution was subjected to derivatization (silylation) followed by chromatography. N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) is used as silyl agent.

Distribution of components was carried out on a 30 m × 0.25mm × 0.25µm capillary column HP-5MS (with a 5% phenyl-methylsiloxane phase) under the following conditions: the carrier gas was helium, the carrier gas flow rate was 1 ml/min, evaporator temperature was 250 °C. Temperature conditions of thermostat: an initial temperature of 40 °C held 2 min and then ramped at 10 °C/min to 280 °C, with a final hold time of 10 min. Mass-selective detector characteristics: the ion source and interface line temperature was 280 °C, the solvent clipping was 2.7, the detection by ions was the scan mode over a range of m/z 40-450.

After separation and research on a chromatography-mass spectrometer spectral data were treated by a computer program, which included a library of data from the National Institute of Standards and Technology (NIST).

The content of the compounds was calculated by the ratio of their peaks square to the sum of all peaks areas in the chromatogram (method of normalization).

RESULTS AND DISCUSSION

The resulting chromatograms with compounds retention times and concentrations (%) are presented in Fig. 1-4. The major constituents were found to be 1-(2,6-dichlorophenyl) indoline-2-one (33.94%) and diclofenac sodium (64.19%) in the sample # 1; 1-(2,6-dichlorophenyl) indoline-2-one (46.38%) and 2-[(2,6-dichlorophenyl)amino] phenylacetic acid or diclofenac acid (53.19%) in the sample # 2. It indicated the possibility of conversion of diclofenac sodium in the presence of glucosamine hydrochloride in these products during storage.

The sample #3 contained 1-hexadecene (4.05 %), 1-docosene (7.38 %), 3-eicosene (8.55%), eicosane (2.56%), 17-pentatriacontene (7.00 %), heptaethylene glycol monododecyl ether (2.58%) and 1,4,7,10,13,16-hexaoxacyklooktadekan (4.09 %).

N-isopropyl-N'-phenyl-1,4-phenylenediamine (0.41 %, the possible transformation product of diclofenac sodium) and octaethylene glycol (3.89 %, the possible transformation product of glucosamine hydrochloride) were found additionally in sample #3 after silylation.

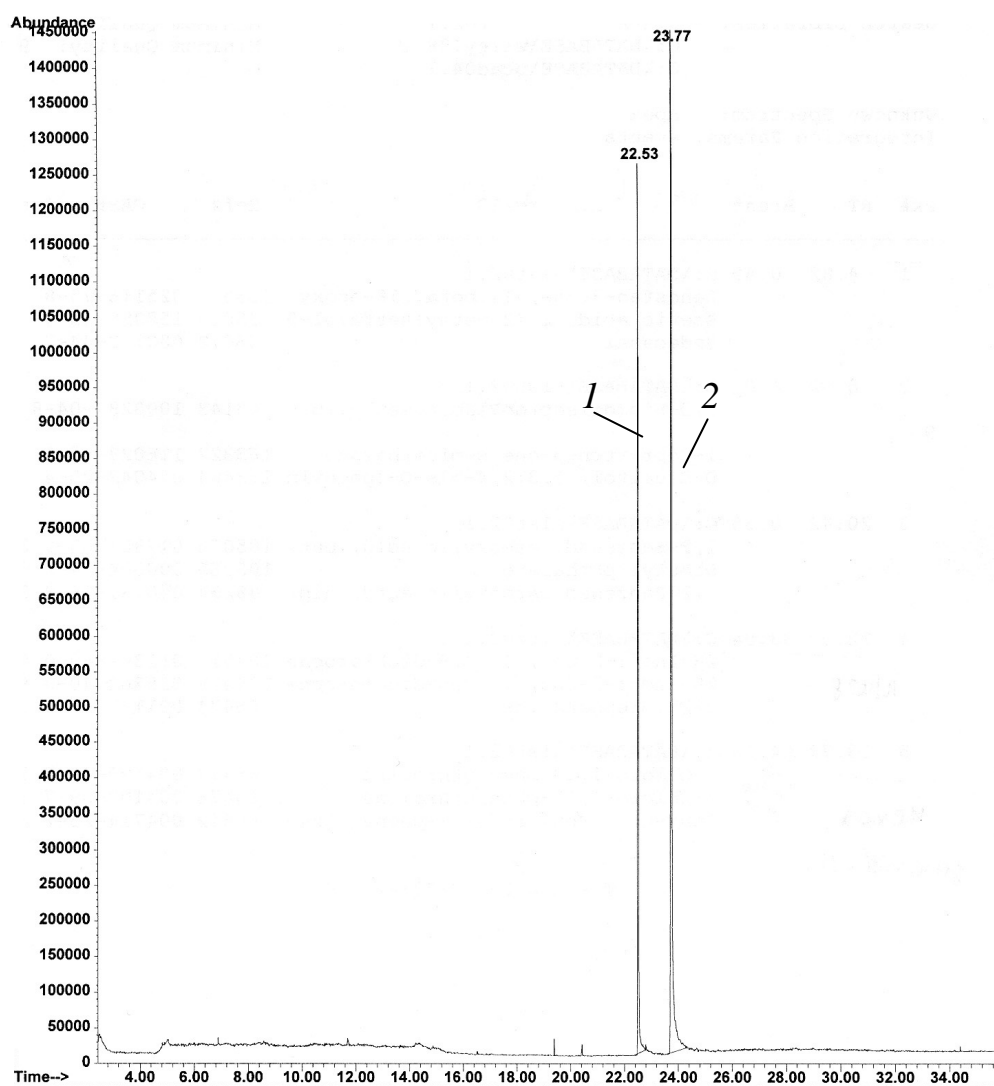


Fig. 1 The chromatogram of the sample # 1

1 – 1-(2,6-dichlorophenyl) indoline-2-one; 2 – diclofenac sodium

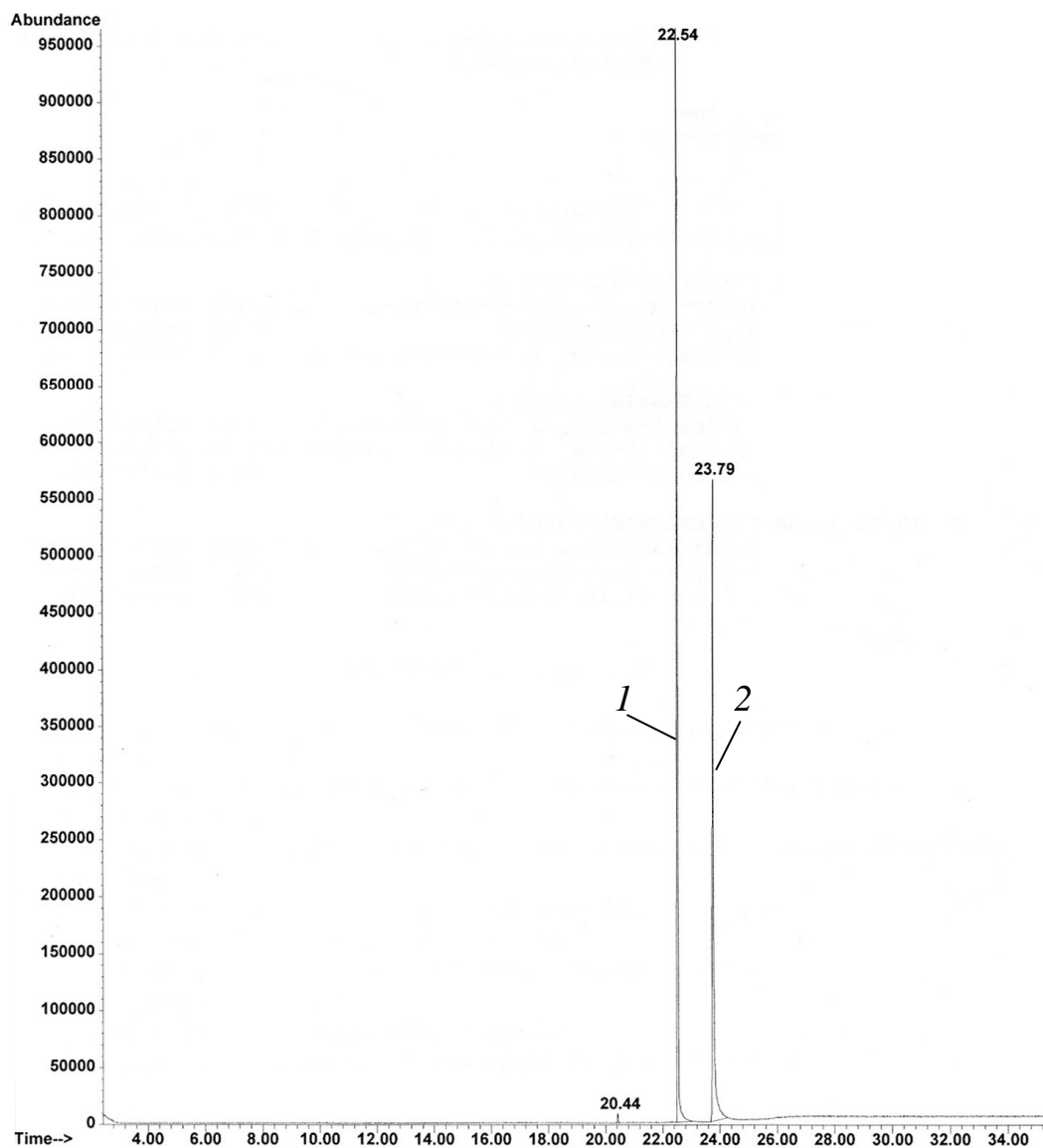


Fig. 2 The chromatogram of the sample # 2

1 – 1-(2,6-dichlorophenyl) indoline-2-one; 2 – 2-[(2,6-dichlorophenyl)amino] phenylacetic acid

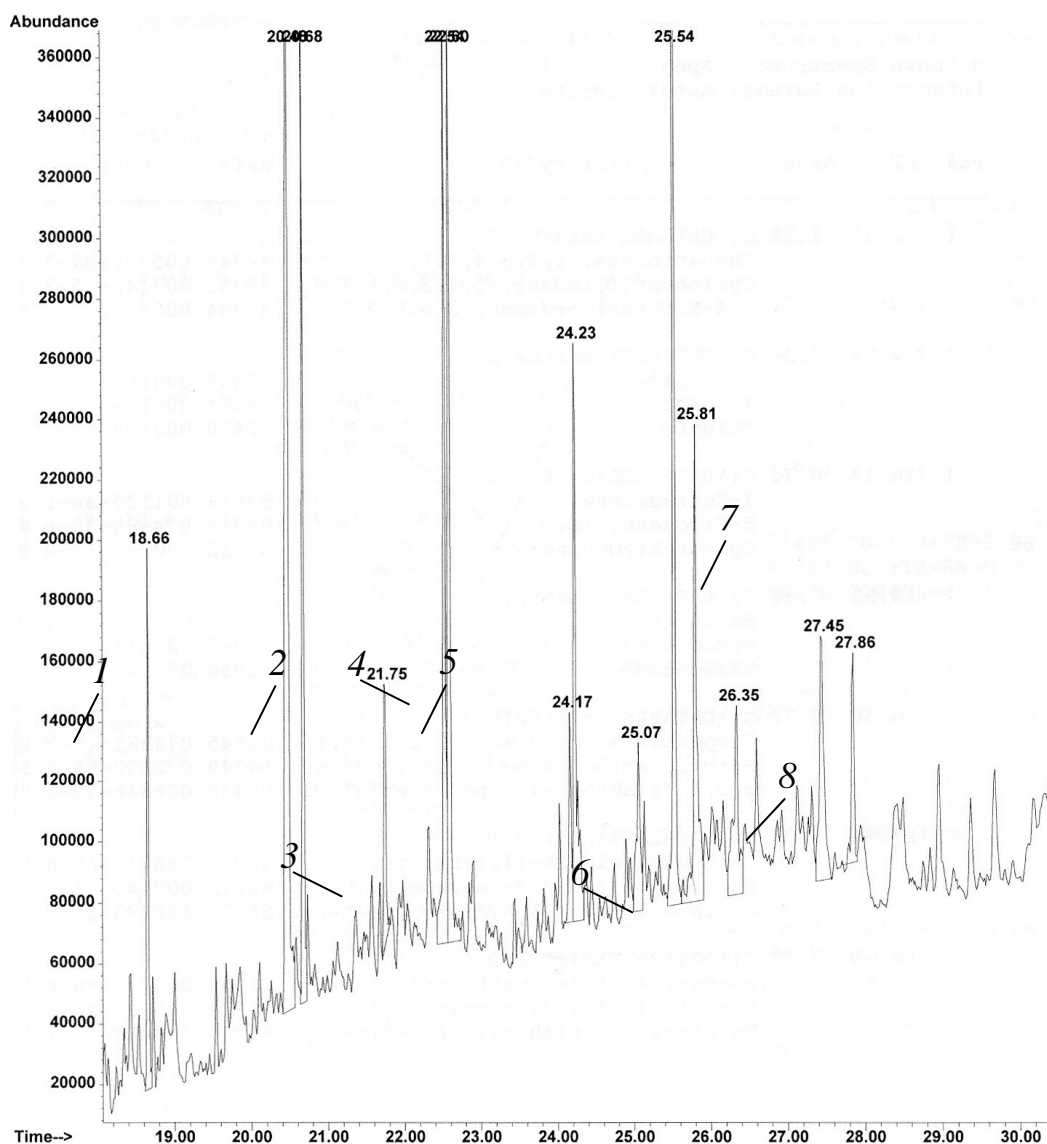


Fig. 3 The chromatogram of the sample # 3 before silylation

1 – 1-hexadecene; 2 – 1-docosene; 3 – heptaethylene glycol monododecyl ether; 4 – 3-eicosene; 5 – 1-(2,6-dichlorophenyl) indoline-2-one; 6 – eicosane; 7 – 17-pentatriacontene; 8 – 1,4,7,10,13,16-hexaoxacyklooktadekan

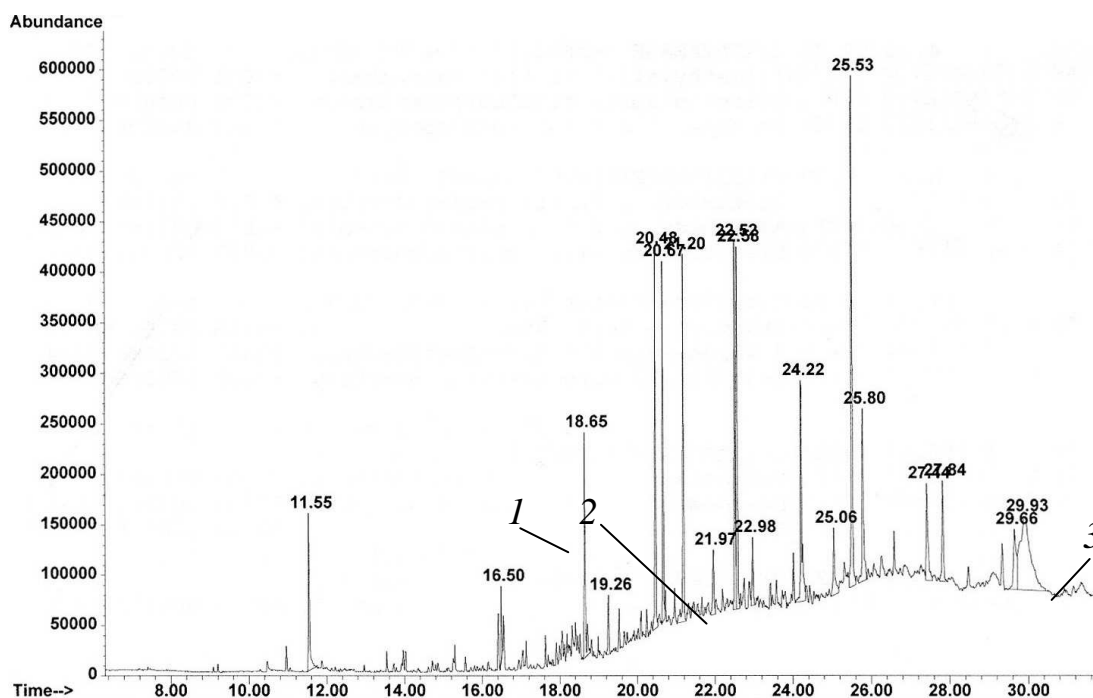


Fig. 4 The chromatogram of the sample # 3 after silylation

1 – 1-hexadecene; 2 – N-isopropyl-N'-phenyl-1,4-phenylenediamine; 3 - octaethylene glycol

Possible chemical transformations in the interaction of diclofenac sodium and glucosamine hydrochloride can be represented as follows (Fig. 5).

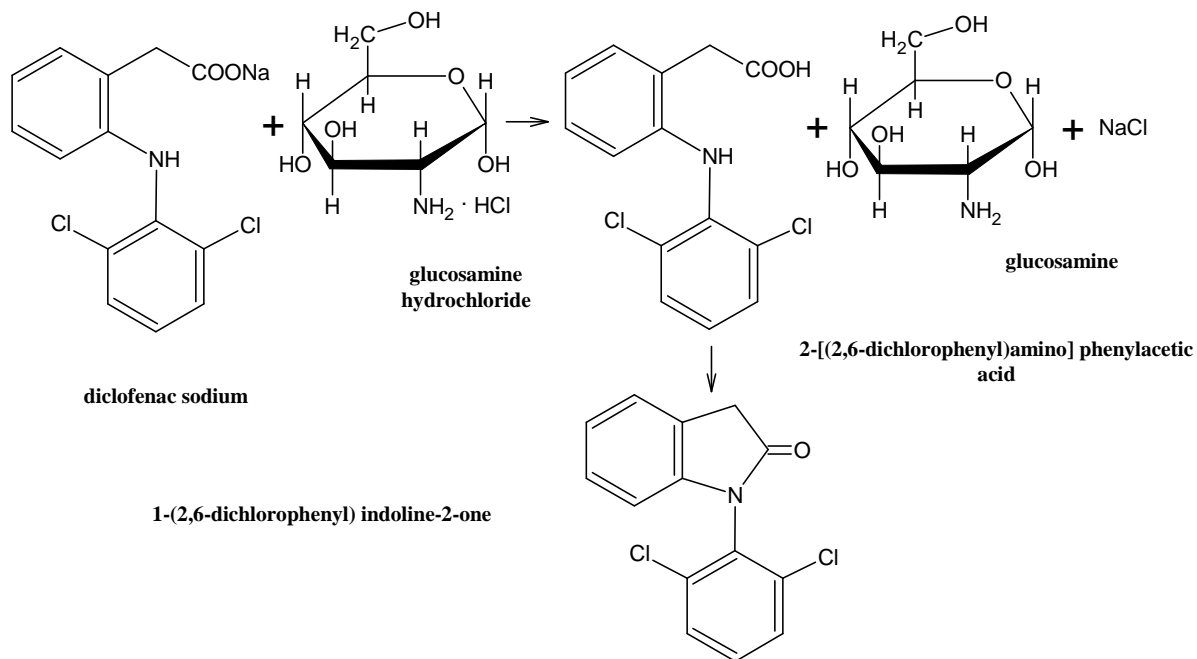


Fig.5 Possible chemical transformations in the interaction of diclofenac sodium and glucosamine hydrochloride

CONCLUSION

The qualitative and quantitative determinations of the products of chemical interaction between diclofenac sodium and glucosamine hydrochloride in a mixture of them have been carried out by chromatography-mass spectrometry. Possible chemical transformations in the interaction of diclofenac sodium and glucosamine hydrochloride after

moistening by water and exposure at 60 °C for 2 h have been proposed. The major constituents have been identified: 2-[(2,6-dichlorophenyl)amino] phenylacetic acid, 1-(2,6-dichlorophenyl) indoline-2-one, 1-docosene, 3-eicosene, 17-pentatriacontene.

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