CLOUD POINT EXTRACTION OF IBUPROFEN AND DEXKETOPROFEN BY PHASES OF NON-IONIC SURFACTANT FOR HPLC-UV DETERMINATION

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The control of residues of active pharmaceutical ingredients (API) on the surface of the technical equipment at the end of the manufacturing cycle is one of the most important tasks that always appear in the manufacture of drugs. During mass production of the nomenclature of drugs by the manufacturer the control prevents contamination. The residual concentration of API on the surface of technical equipment after the end of the production cycle is determined by physicochemical and toxicological properties of API, dosage and pharmacological strength of the drug, batch size, surface area of equipment, etc. and is to be found in the range of nano and pico levels of API. The maximum allowable carryover (MACO) is one of the criteria for the acceptability of equipment cleaning. There are two suggested methods for it to be calculated. According to the first method, the maximum daily dose of the drug may contain no more than 0.1% of the average therapeutic dose of any drug produced before it. According to the second method, when there is no information about the toxicity of API, no more than 10 ppm of any product can be transferred into the next product. Therefore, there is ananalytical problem of determining the nanoquantities of API in flushing fluids, which in turn requires the use of highly sensitive methods of determination.

The solution to this problem is found in the use of chromatographic methods with tandem mass spectrometric detection or hybrid methods of pre-concentration of API with the definition of less sensitive UV detectors. The first option provides sufficient sensitivity, but requires the use of expensive, and therefore uncommon in real production equipment. On the other hand, HPLC-UV systems are widely available in routine pharmaceutical analysis. From our point of view, an efficient solution to the low sensitivity of HPLC-UV systems is the use of pre-concentration by cloud point extraction (CPE) of the API with nonionic surfactants during sample preparation. Conceptually, under such conditions these surfactants solutions can be used to wash the analyte from the controlled surfaces due to solubilization processes and at the same time serve as a medium for absolute concentration.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the world's leading producers, the level of which is further increasing in the context of the COVID-19 pandemic. Therefore, the aim of the work was to develop HPLC-UV conditions for the determination of ibuprofen (Ibp) and dexketoprofen (Dkp) in flushing fluids with prior cloud extraction concentration.

The distribution coefficient between water - *n*-octanol (log P) is a common and universal criterion for the hydrophobicity of substances, which determines the efficiency of their cloud point extraction. Thus, the values of log P for the molecular forms of Ibp and Dkp are 3.20 and 3.61. This indicates the high hydrophobicity of the drugs and the feasibility of using cloud point extraction into surfactant-rich phases for their preconcentration.

Firstly, the conditions of HPLC-UV determination of Ibp and Dkp were developed in the presence of the main component of the receiving surfactant-rich phase - nonionic

surfactant Triton X-114. It was found that while using a chromatographic column Perfect BOND ODS HD (150x4.6 mm, 5 μm) in complete gradient elution with mobile phases of 0.1% H_3PO_4 and acetonitrile, the complete and efficient separation of the chromatographic peaks Ibp, Dkp and Triton X-114 can be observed (Figure 1). Detection of Ibp was performed at 220 nm, Dkp at 256 nm. Thus, the selectivity of HPLC-UV determination is sufficient to control the content of Ibp and Dkp in micellar concentrates.

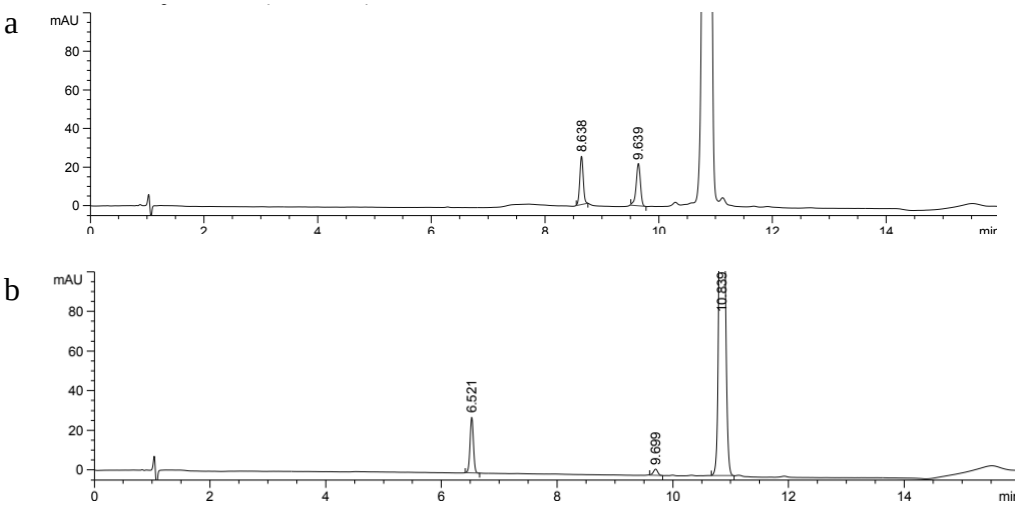

Figure 1. HPLC chromatograms of 10μg/ml Ibp (a) and Dkp (b) in presence of Triton X-114

It was found that Ibp and Dkp are efficiently extracted in the surfactant-rich phase from acidic solutions under the conditions of their molecular hydrophobic forms. Thus, complete extraction of Ibp and Dkp is observed in the pH ranges 1.3-4.6 and 2.8-5.0, respectively. The dependences of the extraction degree of Ibp and Dkp on the concentration of Triton X-114 have the form of saturation curves with a plateau at a concentration of Triton X-114 0.3% and 0.8%, respectively and in a wide concentration range according to the analyte 0.01 - 1.0 μg/ml. The influence of the main experimental factors (equilibrium cloud point extraction temperature, centrifugation time, peculiarities of surfactant-rich phase dilution, etc.) on the efficiency of cloud point extraction of substrates is also investigated.

Finally, the conditions for the extraction of Ibp and Dkp from steel plates with an area of 100 cm^2 using the swab-taking method with lint-free wipes usage were optimized in the paper. The main experimental factors determining the solubilization of the extracted drugs with solutions of Triton X-114 extractant were found. It was found that the removal of Ibp and Dkp from the surfaces in the micellar solution constitutes about 75%. Based on the obtained data, the method of HPLC-UV determination of Ibp and Dkp with preliminary cloud point extraction preconcentration is proposed.