A NEW APPLICATION OF CLOUD POINT EXTRACTION FOR THE DETERMINATION OF IBUPROFEN RESIDUES ON STAINLESS STEEL SURFACE OF PHARMACEUTICAL MANUFACTURING EQUIPMENT

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Cleaning manufacturing equipment to prevent cross contamination of pharmaceutical products is a fundamental aspect of GMPs. Development and validation of cleaning processes for equipment used in the manufacture of pharmaceutical dosage forms is critical to the assurance of efficacy, safety, and quality of the final product. The purpose of a cleaning method is to minimize cross-contamination from previously manufactured product when the subsequent product is to be manufactured on cleaned equipment.

Consequently, the control of residues of active pharmaceutical ingredients (API) on the stainless steel surface of pharmaceutical manufacturing equipment at the end of the manufacturing cycle is one of the important tasks in drugs manufacturing that need constant solution. In terms of analytics, there is a problem of determining the nanoquantities of API in flushing solutions, which in turn requires the use of highly sensitive methods of analytes determination. The solution to this problem lies in the use of chromatographic methods with tandem mass spectrometric detection or hybrid methods of pre-concentration of API with the determination by less sensitive UV detectors.

Despite its incredibly high sensitivity tandem mass spectrometric detection is an uncommonly used method due to its high cost. In opposite, HPLC-UV systems are commonly accessible in routine pharmaceutical analysis. From our point of view, the use of cloud-point extraction (CPE) of API into surfactant-rich phases at the stage of sample preparation is a rational solution to the low sensitivity of HPLC-UV systems.

Considering the unique properties of nonionic surfactants namely solubilization ability and the presence of a cloud point, it is claimed that such a solution can be used to wash API residues from the surface and at a subsequent time as a medium for cloud point extraction. The prospectiveness of cloud point extraction is that it's easily combined with the majority of physico-chemical methods of determination, including HPLC-UV. Moreover, CPE provides the achievement of high absolute concentration coefficients when used for analysis of small sample volumes.

In order to evaluate cleaning method, it is necessary to sample the product contact surfaces of the equipment and establish the level of residuals present. The choice of sampling and analytical methods will depend upon the nature of the residue and manufacturing equipment. Frequently used methods of sampling are the swabbing and the rinse sampling. Swabbing is a widely used sampling technique. Swabs may be saturated with solvent (e.g., water, alcohol), aiding the solubilization and physical removal of surface residues, or used dry. Rinse samples (using the normal cleaning solution) can be evaluated at intervals during the cleaning and at the completion of the cleaning process.

Ibuprofen – (RS) -2- (4-isobutylphenyl) – propionic acid belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs) and is widely used in medical practice for acute

and chronic pain treatment, fever, osteoarthritis, rheumatoid arthritis and other diseases. World demand for ibuprofen in particular has increased due to the SARS-CoV-2 coronavirus pandemic worldwide, which has led to a significant increase in ibuprofen-based production. This trend poses a necessity for constant monitoring of ibuprofen content on pharmaceutical manufacturing equipment.

Therefore, this work based on study of cloud point extraction for the determination of ibuprofen residues on stainless steel surface. Triton X-114 was chosen as non-ionic surfactant due to its main advantages: low CPT (23 °C), low UV absorbance and high density, which facilitates the phase separation by centrifugation. Chromatography was conducted on Perfect BOND ODS HD column (150 x 4.6mm, 5μm) at the flow rate 2 mL min^{-1} at 35°C. Acetonitrile (B) and 0.1% H_3PO_4 (v/v) in water (A) were used as the mobile phases. Elution was performed in a linear gradient mode. The UV detection was carried out at 220 nm. For optimal cloud point extraction of ibuprofen in the surfactant-rich phase was selected solution of Triton X-114 with concentration 0.3% (w/v) with pH=3.0, at which the analyte is in hydrophobic form. An equilibrium temperature for formation of surfactant-rich phase was chosen 45 °C. Such phase is centrifuged at 3500 rpm for 10 minutes. To determine ibuprofen when cleaning the equipment, swabbing is performed with a wipe soaked in solution of 0.001 M sodium carbonate, which is then stirred for 30 minutes in 0.3% (w/v) Triton X-114 solution with pH=10 and cloud point extraction is carried out. The method was validated over a concentration range of 10 - 100 ng mL^{-1}. The LOD and LOQ for ibuprofen were found to be 14 and 46 ng mL^{-1}, respectively.

A smear test study demonstrated the accuracy, precise and linear of the method, and more than 90% of ibuprofen was removed from stainless steel plates. Therefore, the developed technique can be used as part of a program to test the purification in the pharmaceutical production of drugs based on ibuprofen.