1 Introduction and Objectives

In the past decade, with the advancement of various physicochemical methods, pharmaceutical analysis has shown a trend toward using automation for analytical assays carried out in appropriate control laboratories. At the same time, during its twenty-nine years of existence, the flow injection analysis (FIA) technique became a versatile tool that contributed substantially to the development of automation in pharmaceutical analysis. This results from the many advantages of FIA such as simplicity of instrumentation, high throughput capacity, reliable and inexpensive determinations, and the possibility of gathering a large body of analytical information [1].

The FIA of pharmaceuticals specifically requires determining analytes in complex matrices and at trace level. Thus, one of the problems that restrict the application of FIA to pharmaceutical analysis is the need to selectively determine of substances with high sensitivity. Various approaches were used for improving the selectivity and sensitivity of flow injection such as the application of highly selective detectors, derivatization of analytes, and the use of traditional analytical technologies for the extraction and preconcentration of analytes.

Although derivatization is the main chemical approach to expand the analytical possibilities of FIA of pharmaceuticals, the use of the extraction and preconcentration technologies for the enhancement of selectivity and sensitivity of pharmaceuticals play an important role. These technologies result in the isolation and enrichment of components of interest from a sample matrix. Extraction can vary in degree of selectivity, speed, and convenience, and depends not only on the approach and conditions used but also on the geometric configurations of the extraction phase. Liquid-

liquid extraction is one of the most widely used methods of sample preparation in the analysis of natural samples, foodstuffs, and other biological samples. The liquid-liquid solvent extraction is realized through three separate steps. First, two immiscible liquid phases must be dispersed with a constant volume ratio, then the two phases have to remain in close contact with each other to attain effective mass transfer, and finally a physical separation of both of the phases has to be implemented. Conventional techniques of liquid-liquid extraction require a significant amount of organic solvents, thus themselves creating environmental and occupational hazards, can be hardly automated and often provide very little selectivity.

Increased interest in sample preparation research has been generated by the introduction of nontraditional extraction technologies. These technologies address the need for reduction of solvent use, automation, and miniaturization, and ultimately lead to on site in situ and in vivo implementation. These extraction approaches are frequently easier to operate but provide optimization challenges. More fundamental knowledge is required from an analytical chemist, not only about equilibrium conditions but, more importantly, also about the kinetics of mass transfer in the extraction systems. Optimization of this extraction process enhances overall analysis. The general tendency toward the instrumentation and automation of chemical analysis has inspired analysts' increasing interest in membrane separation. The above tendency has manifested itself in a steadily growing number of publications on the use of membrane separation in chemical analysis.

In recent years, the widest prospects for the use of membranes in chemical analysis have opened up in developing of flow method of analysis. The history of flow analysis methods, the known methods for

determining different substances, and the main flow separation and preconcentration methods, including membrane ones, have been already published in several monographs and reviews [2-6]. Interest in analytical flow methods combined with membrane methods of substance separation arises from the simplicity of automating extraction procedures in designing continuous flow control systems. Membrane methods fulfill two functions in flow injection sample preparation. The first function is the extraction of substances in the state of aggregation most convenient for their subsequent determination with flow detectors. The second function is the purposeful variation of the composition of the test medium, for example, solution acidity, and the creation of the optimum conditions for the formation of analytical species.

Nevertheless, the lack of principally new ideas and of selectively permeable membrane development, and, correspondingly, the lack of new methods for the continuous selective extraction of substances all called for new solutions that could fill the sustainability in the development of continuous separation methods. From this standpoint, a promising technique is chromatomembrane cell (CMC) liquid extraction [7], by which the three steps of extraction procedures are combined in one small device that allows the omission of organic solvents and makes automation possible.

An automated extraction and enrichment system coupled to flow injection analysis would be an ideal tool for speedy and efficient analysis of pharmaceuticals. The principle of the chromatomembrane mass transfer has been used in flow injection analysis mainly for determining inorganic and organic substances in environmental samples and coupled with several detection systems such as photometry, voltammetry, inductively coupled plasma-atomic emission spectroscopy, gas chromatography, ion

chromatography, and high performance liquid chromatography to yield acceptable results. The application of this method in pharmaceutical analysis, however, has not yet been introduced. These facts highlight the possibility of using the chromatomembrane method as a sample preparation step for continuous liquid chromatographic and spectrophotometric determinations of organic and inorganic compounds involved in pharmaceutical preparations.

Thus, the topic of this work will be the possibilities for applying chromatomembrane cell liquid extraction to the automation flow analysis of substances in pharmaceutical preparations. The main experiments in this work were divided into two parts. First, CMC was applied as an extraction and preconcentration manifold for automation flow analysis of organic substances in pharmaceutical preparations. Ethinylestradiol (ETE) and levonorgestrel (LEV) were used as model substances and will be determined by HPLC method. All parameters that influence the selectivity, precision, accuracy, and sensitivity of the analysis will be optimized. The proposed method will be then applied in determining those substances in pharmaceutical preparations which in form of tablet. The results are then compared with those results obtained by existing standard method (US Pharmacopeia).

Second, CMC was applied as an extraction and preconcentration manifold for automation flow analysis of inorganic substances in pharmaceutical preparations. Zn(II) and Cu(II) were used as model substances and will be determined by spectrometric method as a complex substance with 1-(2-pyridilazo-2-naphtol)(PAN) as a complexing agent. All parameters that influence the selectivity, precision, accuracy, and sensitivity of the analysis will be optimized. The proposed method will then be applied in determining

those substances in pharmaceutical preparations, which take the forms of tablets, liquids, and ointments.