UNIVERSITY OF MEDICINE AND PHARMACY OF TÎRGU MUREŞ
DOCTORAL SCHOOL
PhD Thesis

Transdermic absorption. Possibilities of modulating the pharmacokinetic properties in specific therapeutic systems

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Abstract

The physico-chemical properties of a drug substance are determined for crossing the cutaneous barrier, to this adding the barrier properties which are naturally manifested by the skin for external factors. Modulation of the pharmacokinetic properties of the drug ingredient from the pharmaceutical form, by means of physical or physico-chemical methods, constitutes a modality of favoring cutaneous permeation.

Administration of drug substances under the form of transdermal therapeutic systems (TTS) has become in the last years an attractive form of therapeutic approach due to the advantages which it confers and due to the patient's high compliance, being a viable treatment alternative especially in chronic diseases (rheumatoid polyarthritis).

The general part of the PhD thesis represents the current stage of knowledge and it represents an informative basis for the subsequent studies. Recent data were presented concerning the skin as a biological coating, TTS bioadhesive matrix type as forms of drug administration and nonsteroidal anti-inflammatory (NSAID) as active substances for the TTS formulation.

The purpose of the thesis consisted in conceiving and formulating a product with transdermic release, polymeric matrix type with an NSAIDs content. In order to reach the proposed goal, the PhD thesis approaches five studies of personal research.

The realization of a pre-formulation study for an appropriate selection of the polymers which form the matrices was necessary. The biggest challenges in the development of such a system are: optimization of the release profile of the drug substance and compatibility of the active substance with the polymer. Stability and bioavailability of the active substance are affected by interactions with excipients, reason why, in a first research stage, we proceeded to screen the compatibility of components, using thermal analysis by means of differential scanning calorimetry (DSC) and infrared spectrometry (IR).

The second study included the formulation and preparation of TTS with NSAIDs content (meloxicam, tenoxicam, indomethacin) under the form of a bioadhesive polymeric film using the solvent evaporation technique and characterization through their DSC analysis.

The formulations selected based on the results of the first two studies were then submitted to an analysis of the mechanical properties of the pharmaceutical form with drug content. Two types of tests were taken into consideration for this purpose, one of them allowing the evaluation of viscoelastic properties in the mass of the polymeric matrix, and the others allowed evaluation of the TTS texture and of the surface properties.

In order to be able to make a pertinent analysis of the drug content of the proposed formulations, and, subsequently, of the release and permeation capacity of NSAIDs from the TTS polymeric matrix type, the development and validation of certain analytical methods for the dosing of the selected active substances was necessary. Two methods have been validated for the quantitative determination of the NSAIDs from TTS: high performance liquid chromatography (HPLC) and near infrared spectroscopy (NIR).

In the last study stage of the thesis we performed the evaluation of the release capacity of NSAIDs from TTS polymeric matrix type. For this purpose we used the method with the Franz difuzometric cell, availability of the active ingredient being evaluated by means of three types of membranes: nylon synthetic membrane, biological pig skin membrane, and biological human skin membrane, respectively. For the studies carried out on the biological membrane made of human skin we sampled the skin flaps

from male patients, after abdominal area surgical interventions carried out in Tîrgu Mureş Emergency County Clinic Hospital with the patients' informed consent. The study was approved by the Ethics Committee of Tîrgu Mureş Emergency County Clinic Hospital (No. 1276/16.02.2016) and by the Ethics Committee of Scientific research from the University of Medicine and Pharmacy, Tîrgu Mureş (No. 46/21.03.2016).

In order to obtain the comparative results between formulations, we used two types of experimental data which involved calculations of "% released NSAID from the TTS dose", and "μg/cm^2 released from the TTS dose", respectively. The analysis of the experimental results was carried out using graphic methods, as well as mathematical and statistical methods concerning the analysis of variation, of differences and, implicitly, of similarity of the yield curves. For evaluation of the release kinetics of NSAIDs from TTSs proposed in the study, we applied analysis through model-independent methods and analysis through model-dependent methods. The software used was: *GraphPad Prism* (GraphPad Software Inc); *DDSolver:* An Add-In Program.

The original contribution of the PhD thesis refers firstly to the development of certain new TTS formulations obtained through the solvent evaporation technique, having at their base a polymeric matrix with an NSAID content which is suitable for cutaneous administration.

The development and validation of a NIR spectroscopic method for the quantitative determination of the active ingredients from TTS also represents an innovative contribution, no study being reported in the specialized literature, which can approach such an analytical method for TTS. The results of the study have shown a good similarity compared to the ones obtained through other conventional methods (HPLC).

The manner of approach and processing of the experimental data also has a personal contribution. The obtained results categorically highlight the potential of the pharmaceutical TTS - type forms for transepidermal administration of the studied NSAIDs.

Keywords: transdermal therapeutic system, matrix type, non-steroid anti-inflammatory, HPLC, NIR spectroscopy, permeation