

University of Medicine and Pharmacy, Târgu Mures
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RESEARCH ON THE OPTIMIZATION OF SOME IN VITRO DISSOLUTION TEST
PARAMETERS IN MEDICINAL SUBSTANCES AND IN VITRO - IN VIVO
CORRELATIONS

PHD THESIS - ABSTRACT

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The importance of active substance release from pharmaceutical forms for attaining absorption and pharmacological effects is well known. The main purpose of this research was the study of active substance release from solid pharmaceutical forms under conditions that are as close as possible to the physiological conditions and the scientific background of the standardization of *in vitro* dissolution techniques especially for poorly soluble drug substances. Hence dissolution techniques were developed for the investigated medicinal substances. Based on *in vitro* dissolution tests obtained by the aid of the researched medicinal substances I decided to include the solid pharmaceutical form of Indapamide with modified active substance release. I performed preformulation, formulation and technology optimization studies and finally I investigated *in vitro* release profiles in the developed pharmaceutical form in biorelevant media. Finally I performed *in vitro-in vivo* correlation studies with developed formula.

The thesis comprises 2 main parts. The general part is a compilation of information about the current state of science. The experimental part comprises the description of the personal study as follows:

1. The development of some dissolution techniques

During the development of a dissolution technique, *in vitro* and chromatographic analysis were selected for the **dissolution of extended-release tablets containing Indapamide (base)**. The type of dissolution apparatus, composition of the dissolution medium, and the number of rotations per minute was determined, respectively for the dosage of the dissolved drug substance, chromatographic conditions were selected. **In case of Simvastatin tablets (base) a dissolution technique was developed.** During development the dissolution conditions were optimized. A spectrophotometric method was used in order to determine the dissolved Simvastatin. **In order to study the *in vitro* release rate of Loratadine (base) tablets** a dissolution technique was developed and for the quantitative determination of the released drug substance the CLP method was used.

After studying the *in vitro* release of some drug substances that are poorly soluble in water or insoluble, I chose to study **Desloratadine** (salt), an active substance which is highly soluble in water. After optimizing the dissolution rate a spectrophotometric method was developed to determine the released drug substance.

II. Based on the performed experiments on the four medicinal substances I decided to conduct further research on Indapamide, a water-insoluble drug substance whose inclusion in a solid pharmaceutical form with prolonged release and appropriate bioavailability proved to be a technological challenge. In order to perform formulation and optimization studies on the drug substance of the tablets a Contract Laboratory Program (CLP), method of quantitative determinations was developed, aimed to determine impurities in the tablets. The discriminatory character of the dissolution method was tested and the method itself validated.

III. In the framework of a preformulation study the properties of the drug substance and excipients were investigated. During formulation I monitored the followings: appropriate selection of agent to create a hydrophilic matrix, hypromellose, determining the appropriate amount of hypromellose per tablet, appropriate selection of the other excipients, optimization of the used technology to develop manufacturing technology. In the prolonged release tablets, developed with the previously described technology, the in vitro dissolution profile in different pH dissolution media respectively in dissolution media simulating similar conditions to the intestine was tested, and at the same time a stability study was also performed.

IV. A level A *in vitro/ in vivo* correlation was performed between the in vitro and in vivo release data. Subsequently to correlation the following conclusion could be drawn: the developed in vitro test conditions can be considered biorelevant for the developed prolonged-release tablets.

In conclusion, the developed dissolution methods can be used successfully in the development and manufacturing of some drugs containing Indapamide, Simvastatin, Loratadine and Desloratadine. The developed prolonged-release tablets containing Indapamide as drug substance are stable, have similar dissolution profiles to the selected reference product and the developed dissolution technique, based on level A in vitro - in vivo correlation, is biorelevant. The described technology corroborated with the developed analytical methods allows both implementation and patenting.

Key words: dissolution test, CLP, spectrophotometry, Indapamide, preformulation, formulation, optimization, stability study, *in vitro- in vivo* correlation.