GENERAL ANALYSIS AND COMPARATIVE COMPARISON OF PREPARATIONS CONTAINING FUROSEMIDE BY PHYSIC-CHEMICAL METHODS

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Annotation: *Repeated intraperitoneal administration of furosemide to rats (20 mg / kg per day) for 7 days revealed a decrease in the diuretic, natriuretic and kaliuretic effects of the drug due to a decrease in its renal excretion. It turned out that more than 85% of the daily sodium excretion is carried out in the first 6 hours after administration of furosemide against the background of a comparable amount of excretion of the latter. The release of water and potassium is distributed more evenly throughout the day.*

Keywords:*technological and pharmaceutical data, medicinal product, calculations*

It was found that during long-term use, there is a consistent decrease in furosemide excretion in the first 6 hours after administration and a gradual increase in this indicator over the next 18 hours. These changes in the dynamics of the daily excretion of the drug cause the development of a similar trend in relation to the daily excretion of water and electrolytes.

The substance in question is classified as highly soluble if the maximum single therapeutic dose (in accordance with the general characteristics of the reference medicinal product) is completely soluble in a buffer medium of 250 ml or in a smaller volume of medium in the pH range of 1.2 - 6.8 at a temperature of 37 ± 1 °C. In cases where the maximum single therapeutic dose does not meet this criterion, but the sample of the active substance corresponding to the highest dosage of the reference medicinal product is completely soluble under the above conditions, additional data should be provided in the registration dossier of the medicinal product to substantiate the BCS-based biowaver. It is necessary to experimentally establish the solubility of the active substance in the pH range of 1.2 - 6.8 at a temperature of 37 ± 1 °C. At least three pH values in this range should be studied, including buffer media with pH 1.2, 4.5 and 6.8. Additionally, the solubility of the active substance at the pH with the worst solubility should be studied if this pH value is within the specified range. These studies should confirm that the solubility of the active substance is maintained within a time frame corresponding to the expected duration of absorption of the active substance.

To confirm the obtained solubility value, at least 3 repeated determinations of solubility under each condition or pH are required using appropriate pharmacopoeial buffer media and a validated method for determining the active substance. In addition to the experimental data, the registration dossier of a medicinal product allows the presentation of scientific chemical, technological and pharmaceutical data in order to obtain evidence and substantiate the solubility values. It should be borne in mind that not all articles of scientific peer-reviewed journals (publications) contain research data necessary to assess the quality of these studies. It is necessary to confirm the sufficient stability of the active substance in the buffer medium of

solubility assessment. In cases where the active substance is unstable (its degradation is > 10% during the solubility assessment), it is impossible to correctly determine the solubility and BCS class of the active substance.

The analysis of the penetrating ability of the active substance is also carried out using validated and standardized in vitro research methods using the Caco-2 cell line (in accordance with the Procedure according to Appendix N. 1). The results of studying the penetrating ability of the active substance on the Caco-2 cell line should be analyzed taking into account the available data on the pharmacokinetics of the active substance in humans. If the conclusion about the good penetrating ability of the active substance is made on the basis of an in vitro study of the cellular system, it is necessary to prove the presence of the penetrating ability of the active substance, independent of its active transport, in accordance with Appendix No. 1 to these Requirements. If a good penetrating ability is not established, the active substance is recognized as having poor penetrating ability for its classification according to BCS.

It is necessary to ensure that the composition of the investigational medicinal product fully reproduces the composition of the reference medicinal product. If there are differences between the excipients of the studied and reference drugs, they should be evaluated in terms of the potential effect of such differences on the absorption of the active substance in vivo. Such an assessment includes an analysis of the properties of the active substance and the effect of excipients on its absorption. In order to use a BCS-based biowaver, the sponsor is required to justify why the proposed differences in the excipients of medicinal products will not affect the absorption profile of the active substance in question (its rate and degree of absorption) using physico-chemical studies and calculations, as well as a risk-based approach.

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