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

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Annotation: The relevance of the topic. Currently, it has been established that the pharmacokinetics of drugs are significantly influenced by many factors: concomitant diseases, food intake, gender, age, physical activity of patients. However, the effect of antiorthostatic hypokinesia on the pharmacokinetics and bioavailability of most drugs has not been sufficiently studied. The purpose of the study. To study the pharmacokinetics of furosemide after a single dose oral administration of Furosemide and Furesis compositum drugs under normal human conditions and in patients with antiorthostatic hypokinesia (AHH). Materials and methods.
Keywords: pharmacokinetic parameters, fundamental factor, antibiotic
The study included 10 practically healthy individuals (men aged 24 to 50 years), who were divided into two groups. One group of healthy volunteers (6 people) took Furosemide tablets at a dose of 40 mg, and the other (6 people) took Furesis compositum tablets containing 40 mg of furosemide and 50 mg of triamterene. The pharmacokinetics of two drugs were studied in two volunteers: and Furosemide and Furesis compositum. The volunteers took the drugs once in the morning on an empty stomach. Blood was taken for analysis before and after 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours after taking the drug. The volunteers received a standard breakfast 4 hours after taking the drug. A repeat study - under the conditions of ANOG - was conducted after 4 days according to an identical scheme. The concentration of furosemide in the blood plasma of the volunteers was determined by HPLC with spectrophotometric detection. The data obtained was analyzed using a model-independent method using the M-IND program. Results. It was found that the pharmacokinetic parameters of Furosemide in normal terrestrial conditions and in ANOG conditions did not significantly differ, and statistically significant differences were found for Furesis compositum: in ANOG conditions, the concentrations were lower by 22.8 D%, AUCo-ae-by 24.3 D%. All volunteers under ANOG conditions also showed a tendency to increase Cl (from 62±10 to 95±24 l/h) and a shortening of 1t (from 0.3±0.1 h to 0.1+0.02 h). These differences are statistically unreliable, apparently due to the fact that the group of subjects is small. The relative bioavailability of furosemide after taking Furesis compositum in ANOG conditions compared to normal terrestrial conditions is 74.4±8.6%, and the ratio of maximum concentrations is 75.3+11.8%, i.e. the relative bioavailability of Furesis compositum is statistically significantly lower in ANOG conditions. A comparative analysis of the pharmacokinetic parameters of Furosemide and Furesis compositum showed that Cmax, AUCo, MRT, and Ct were statistically significantly lower, and Clt was higher for Furesis compositum both in normal human activity and in ANOG conditions. The relative bioavailability of furosemide when taken concomitantly with trnamterene decreases statistically significantly and averages 42.7% in normal terrestrial conditions, and 28.9% in ANOG conditions. The ratio of the maximum concentrations of Furesis compositum and Furosemide in normal terrestrial conditions averages 44.4%, and in ANOG conditions - 39.0%.

The assessment of the stability of medicinal products (LP) is a pivotal direction in the quality assurance system, since it is this parameter that determines the reliability of pharmacotherapy, the duration of storage and the safety of use. The loss of the initial properties of a medicinal substance can be accompanied not only by a decrease in its clinical efficacy, but also by the formation of potentially dangerous decomposition products, which becomes especially important with long shelf life and in the logistics process [2]. In the context of the expansion of

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international pharmaceutical trade, the task of harmonizing approaches to stability control is becoming more urgent, since in different countries, including EAEU members, there remains a heterogeneity of regulatory requirements, test protocols and principles of interpretation of results [4]. The purpose of this study is a comprehensive analysis of the factors affecting the stability of medicinal products, as well as the systematization of applied control methods in the context of regulatory requirements. The objectives of the study include: classification of destabilizing factors, review of analytical techniques and identification of areas for harmonization of requirements. The initial hypothesis is that the use of validated analysis methods and the identification of universal degradation factors will increase the reproducibility of results and simplify the cross-border circulation of medicines [1]. The formation of a regulatory framework for stability assessment began with WHO initiatives in the 1970s, and at the present stage, the International Council for Harmonization (ICH) is a fundamental factor. The ICH Q1A(R2) Guideline defines the algorithms for accelerated and long-term testing, as well as the principles of interpretation of the results, which are the basis for the requirements of the EMA and the FDA [2].

The formation of stable drug characteristics is a complex process that depends on a number of factors, primarily on the specifics of chemical transformations. The predisposition to destruction is already laid at the level of the molecular structure, where the reactivity of functional groups determines the potential directions of degradation. Among the most typical mechanisms of loss of initial properties are hydrolysis, oxidation, exposure to light (photolysis) and isomerization. The processes significantly modify the chemical nature of the active compound, reducing its pharmacological activity and causing risks of toxic effects.

Another significant mechanism of destabilization is oxidation, which is accompanied by the loss of electrons and the formation of free radicals. Compounds containing phenolic, aldehyde, and aminofunctional groups are most often subjected to this process. Thus, ascorbic acid is easily oxidized by atmospheric oxygen., turning into dehydroascorbate, which has significantly lower biological activity [4]. Oxidation can be accelerated in the presence of heavy metal ions, light, and high temperature, which requires the use of antioxidants and sealed packaging to slow down such processes. Photolysis, or light destruction, is one of the key causes of the instability of medicinal substances with chromophore groups capable of absorbing light energy. Under the influence of ultraviolet or visible radiation, bonds break in such molecules, leading to the formation of products with altered physico-chemical and pharmacological properties.

Special attention in ensuring the stability of drugs is given to the choice of packaging as a barrier element that protects the drug from external destabilizing factors. The effectiveness of such solutions directly depends on the physico-chemical properties of the active substance. UV-impermeable dark glass vials provide protection against photo destruction, aluminum blisters reduce contact with oxygen, and moisture-absorbing capsules with sorbent (for example, lycogel in the lid) effectively prevent hydrolysis. An additional level of protection is formed due to the inclusion of auxiliary substances in the composition of dosage forms — antioxidants, chelating agents (for example, EDTA), buffer systems and photo stabilizers such as benzo-phenones, capable of inhibiting key chemical degradation pathways [3]. The effectiveness of the solutions was confirmed by the results of accelerated and stress tests, which demonstrated a reduction in the rate of degradation with the correct selection of both packaging material and stabilizing components. The deliberate use of protective mechanisms allows not only to extend the shelf life, but also to create sustainable pharmaceutical forms adapted to various climatic and logistical conditions.

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At the same time, by the fifth month, a decrease in the solubility of tablets was noted, presumably due to a violation of the structure of the excipients. The changes are confirmed by thermogravimetric data — the temperature of the onset of thermal decomposition decreased by 5 ° C, which indirectly indicates increased sensitivity to humidity. Omeprazole proved to be the most stable in the study group: over the entire period, losses amounted to less than 5%, and the appearance of the capsules did not change. The high stability is explained by the protective properties of the packaging — a PET bottle with a desiccant and the presence of an acid-resistant shell. Similarly, loratadine retained almost the full concentration of the active substance, despite minor signs of external destruction of the shell (stickiness, loss of gloss) associated with the influence of humidity.

The results of the study confirmed the complex relationship between the stability of drugs and external storage conditions, packaging features and the molecular nature of the active ingredients. The experimental data obtained demonstrated that even when using validated stability assessment methods, variables such as humidity, temperature fluctuations, and light radiation have a significant impact. It is through the prism of these factors that it is worth considering the dynamics of degradation of pharmaceutical substances, as the models constructed in the framework of this work have clearly shown. Ascorbic acid in solution exhibits a pronounced tendency to destruction: its residual concentration decreases exponentially already in the first months of storage. It indicates a high sensitivity to oxidative conditions and confirms previously formulated hypotheses about the instability of water-soluble vitamins in the presence of light and oxygen. Transparent packaging, unable to block photochemical processes, enhances this effect, which emphasizes the need to replace it with light-proof materials. A similar effect was described in the studies of Kuznetsova and Ivanova, but the present study allowed us to quantify the contribution of packaging to the degradation process [2]. The relative stability of omeprazole and loratadine demonstrates that pharmacologically active substances with a high degree of lipophilicity, subject to the correct choice of auxiliary components and protective shells, are able to maintain their properties even under unfavorable storage conditions. The protective mechanisms provided by desiccants and sealed packaging have proven to be key elements in the stability strategy. The results echo the conclusions of Lebedev and Smirnova [8], however, in this work it was possible to clarify that the combination of barrier packaging and acid-resistant coating can slow down the decomposition of active substances to minimal loss values (<5%). Amoxicillin, as a beta-lactam antibiotic, has confirmed its tendency to hydrolysis: by the fifth month of storage, changes were observed affecting not only the concentration, but also the physico-chemical properties of the tablet. This circumstance is important to consider at the stage of formulation development, where the choice of excipients can have a significant impact on the stability of the finished product. The presented data suggest that when designing forms of antibiotics, it is necessary to pay attention to moisture control not only inside the package, but also at all stages of the logistics chain.

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