

A new approach for controlling the quality of pharmaceutical production

Usually the content of the active components in pharmaceutical preparations is estimated by the high-performance liquid chromatography method (HPLC) by using the corresponding standard samples for the ascertainment of the respective authenticity and quality. This approach requires a lot of time for gauging and analysis. The productivity of quality control is rather low and the cost is rather high in view of the time spent on the particular drug analysis along with the necessity of the analysis conditions (column, eluent, etc.) that are typical for each drug (along with sample preparation). In view of that fact, the development of quick and universal methods to authenticate medical agents and to estimate their quality without applying the standard samples of the drug active component would enable the fulfilment of expeditious screening for falsifications.

We have offered and developed a new method to solve this problem. It is based on the rapid revealing during the pharmaceutical preparation of the elements, which comprise the active molecule of the drug but not the filling agent molecules, and the determination of the active component content based on these data. The accuracy of such a determination is higher than the commonly used methods because there is no need to extract the active component and to subsequently gauge it in accordance with the standard. It is only required to weigh a small sample of the grinded solid drug (or solution) and to convert the active substance into the corresponding element compounds. The data received after the application of element analysers (determination of N, F, Cl, Br, P, and S) and a gas chromatography device with an atomic-emissive detector showed that the offered approach provides an accurate determination of the active component content in the pills without using the standard active component samples. Our experiments also showed that this approach was suitable for the determination of the active component contained in the pharmaceutical substances.

The advantages of the offered approach are: there is no need to extract or have the standard samples of each active component in order to determine and gauge it; the conditions

of the determination with the application of the element analyser are universal for all the matter to be determined irrespective of their individual structure; high analysis productivity (one determination time - 3-7 min. depending on the elements); the product quantity that is required for the analysis of 1 mg and less, which is important for all expensive pharmaceuticals and substances; the possibility of the expeditious revealing of the most common false drugs, in which the active component content does not correspond to the specified actual content.

In spite of the advantages and possibility of element analysis that can be used for controlling the active component content in pharmaceuticals, in the literature there are no publications that reference the rapid and accurate determination of active components as well as quick and secure confirmation of its presence during pharmaceutical preparations.

The quality of the medical agents (therapeutic effectiveness, presence of side effects) is determined not only by the active component content but also by the admixtures number as well as their nature and content. It is well known that the therapeutic activity of the original medical agents that are produced according to patented technology are rather often much higher than the therapeutic

effectiveness of generics.

The difference in the side effects for original preparations and generics is higher.

Even at the approximate equal therapeutic effectiveness and bioequivalence of the original medical agents and generics, in a number of cases a significant number of side effects is observed in generics, unlike in original pharmaceuticals.

It can be supposed that this occurs because of the difference in the admixture composition and their respective content.

The usual approach to the comparison of the original pharmaceutical preparations and the corresponding generics is based on the determination of bioequivalence (seldom) and therapeutic effectiveness (very seldom).

The comparison of the profiles of the admixtures (medium-volatile and non-volatile) for both products is not executed because it is not required. Only the specified admixtures are determined by such methods as high-performance liquid (HPLC) and thin-layer (HPTLC) chromatography and much rarer – high-performance liquid chromatography-mass spectrometry (HPLC/MS). Gas chromatography (GC) is seldomly used and only for the determination of the specified volatile solvent. There is no test-method for the rapid comparison of the physiological activity of original pharmaceuticals, the corresponding generics, or pharmaceutical substances.

It is rather important to clear up the quality question for generics, both for pharmaceutical companies producing the original medical agents and the corresponding generics and doctors, patients, and state controlled organisations in Russia and abroad. Furthermore, it is important to determine the quality of the corresponding pharmaceutical substances that are produced by many different companies and that are used for the production of the corresponding medical agents.

To solve the problem of an accurate comparison of the quality of the original pharmaceuticals, the corresponding generics, and the pharmaceutical substances, we have developed a new control methodology, which is based on admixtures extraction from the solid matrix by the supercritical fluid extraction (SFE) method without applying solvent or by the liquid extraction method with the further extraction of the admixtures from the extract by the chromo-distillation method and in the presence of sorbent and at the transfer of all the admixtures concentrate to the analytic unit. The registration of the admixtures contained in the concentrate is fulfilled by using chromatography-mass spectrometry (GC/MS) with the electronic, chemical ionisation (EI and CI), and photo- and photochemical ionization under atmospheric pressure (APPhI and APPhCI, accordingly). In the latter cases, the most reliable information about the co-eluted components and their molecular weights is guaranteed, because the mass-spectrums of the individual

components comprise molecular (M^+) or quasi-molecular (MH^+) ions only. The main feature of the registrable admixture is its retention time, mass-spectrum of electronic ionisation and molecular weight, and estimation of the content.

By using a gas chromatography device with an atomic emission detector (GC/AED) the additional characteristics involve information about the elements that are present in the admixture molecules, and the ration of the corresponding element signals. Thus, because of the whole concentrate analysis with the application of the complex of the considered analytical methods the receipt of the multivariate profile of the medium-volatile admixtures that are contained in the corresponding products and substances, at the same time a more accurate determination of the admixture number (in 5 – 25 and more times more accurate determination compared to the standard methods) and their identification are guaranteed.

The registration of non-volatile admixtures is executed with the application of high-effective liquid chromatography, high-effective thin-layer chromatography, and their combination (off-line) with mass-spectrometry with ionisation by electro-spraying (ESI), chemical ionisation at atmospheric pressure, photochemical ionisation via atmospheric pressure methods, and by the MALDI method.

Along with this, the analysis of excreted fractions corresponding to the registered admixtures is executed by the method of the element analysis of F, Cl, Br, P, and S as developed by us, and the method of reacting chromatography-mass spectrometry (electronic and chemical ionisation), in which because of that the accuracy of non-volatile admixture identification has increased compared to the existing methods.

Furthermore...

For this day, in the Russian Federation, there are not many scientific magazines that specialise in the cellular technology sphere. The magazine “Cellular transplantology and tissue engineering” that is by the publishing house of the Institute of the Human Stem Cells publishes unique articles on the clinical use, research, legislative control, as well as news on cellular technologies in our country and abroad. The chairman of the magazine’s editorial board, M. I. Davydov, is also the president of PAMH (Russian Academy of Medical Sciences), which includes famous specialists in cellular technologies. The magazine is distributed by subscription and retail. The subscription for 2007 has already started. It is possible to subscribe via the Rospechat catalogues (index No. 20092), “Pressa Rossii” (index No. 42083), or through the magazine’s editor. It is also possible to obtain the magazine’s archive numbers from the editor.

Moreover, the determination of the summarised content of all the admixtures (medium-volatile and non-volatile), containing F, Cl, Br, P, and S via the method that we developed is executed, which enables the evaluation of the pollution rate of the observable products by such admixtures (without their excretion).

For the expeditious comparison of the (physical activity effects) of the original pharmaceuticals, corresponding generics, and pharmaceutical substations as well as the estimation of their hazards, we researched these preparations’ influences on the state of the blood cell membrane structure (erythrocytes, thrombocytes, and lymphocytes). It is known that any change made to the structural state of the cell membrane in turn leads to a change in the structure and dynamic properties that are incompatible with the correct functioning of the membrane protein components.

Therefore, the new method that we offer ensures the possibility for the expeditious revealing of false pharmaceutical preparations and a comparison of the quality of the original medical agents, generics, and corresponding pharmaceutical substances.