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THE USE OF INNOVATIVE MECHANISMS OF IMPROVEMENT OF QUALITY OF MATERIOLOGICAL EXPERT PRODUCTION

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One of the ways to improve the efficiency of conducting forensic expertise is considered to be the use of validation mechanisms of methodological materials, including procedures such as sampling and sample preparation. In the Physical and Technical Examinations and Chemical Expertises Department of the National Bureau of Expertises of the Republic of Armenia (hereinafter referred to as the Bureau), when conducting expert studies, it becomes necessary to determine the belonging of the object submitted for expertise to narcotic or psychotropic, highly active or toxic substances. Considering the importance and practical nature of this issue, as well as the obligation of conducting the mentioned expertise in accordance with the requirements of the international standard ISO / IEC 17025:2017, over the past three years validated methods of quantitative calculation and assessment of measurement uncertainty based on the active ingredient for drugs from the current list of the most popular drugs of high demand in Armenia have been developed in the Bureau and implemented in forensic practice.

In this case, the algorithm for calculating the assessment of the measurement uncertainty was based on quantitative determinations prepared by the fractional addition of methanol to pre-concentrated standard solutions of active components of narcotic and psychotropic substances in concentrations from 0.5 to 8 mg in 1 ml of methanol. Using the retention time obtained in the course of experimental studies, processing of the constructed calibration dependences and the calculated values of the peak areas, the values of the coefficients "k" and "s" were calculated, which were subsequently used to determine the values of the measurement uncertainty for delta-9-tetrahydrocannabinol, codeine, methamphine, diazepam, lorazepam, buprenorphine, methadone and tramadol. We should also note that validation of the developed methods was carried out in accordance with the following parameters: "Specificity", "Linearity", "Accuracy", "Repeatability" and "Intermediate precision".

Thus, at present in the Bureau quantitative calculations for the determination of the abovementioned active components in the composition of the examined narcotic objects submitted for expertise are carried out on the basis of validated methods, which provide more trustworthy and reliable results when conducting materiological and gas chromatographic analyzes.

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BIOPHARMACEUTICAL ANALYSIS OF THE DOXORUBICIN-LOADED PLGA NANOPARTICLES WITH DIFFERENT RELEASE PROFILES OF DOXORUBICIN

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Ddevelopment of the drug delivery systems based on biodegradable PLGA nanoparticles (NPs) is a promising area of pharmaceutical technology. At the same time, the influence of the physicochemical parameters of PLGA NPs for IV administration on the *in vitro* release profile and *in vivo* PK has not been thoroughly elucidated. In accordance with the FDA recommendations, the pharmacokinetic study (PK) of the drug products that contain nanomaterials requires determination of not only the total drug concentration in plasma (free and bound to the carrier), but also the concentration of these fractions separately.

The objective of the present study was to perform a pharmacokinetic study of doxorubicin-loaded PLGA NPs (Dox-PLGA NPs) modified with poloxamer 188 (P 188) with different drug release rates in comparison with the drug substance.

The PLGA-Dox NPs were obtained using a double emulsion technique. A 1% solution of polyvinyl alcohol in phosphate buffer at pH 7.4 (PLGA-Dox/7.4) or 6.4 (PLGA-Dox/6.4) was used as the external aqueous phase. The kinetics of doxorubicin release from the NPs ***in vitro*** was determined by ultracentrifugation in a 1% solution of P 188. Doxorubicin formulations were injected IV to healthy Wistar rats at a dose of 5 mg/kg. The main PK parameters were calculated for both free and total doxorubicin using the non-compartment model.
Compared to the PLGA-Dox/7.4 NPs (average size 114 nm), the PLGA-Dox/6.4 NPs (average size 142 nm) were characterized by a lower encapsulation efficiency (79% and 92%, respectively) and a higher ***in vitro*** doxorubicin release rate. Binding of doxorubicin to the NPs significantly increased the concentration of total doxorubicin in plasma during the first minutes after administration and prolonged the drug circulation time, reduced the drug stationary distribution volume and clearance (Cl_{total}) and increased the AUC. The influence of the drug release rate on the plasma concentration profiles as well as the PK parameters was observed during the first hour post injection.
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OPTIMIZATION OF THE METHOD FOR EVALUATION OF DOXORUBICIN RELEASE FROM PLGA NANOPARTICLES INTO MODEL MEDIA AND BLOOD PLASMA

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Establishment of the correlations between the kinetics of the drug release ***in vitro*** and its pharmacokinetics (PK) ***in vivo*** (IVIVC) for the drug-loaded nanoparticles is a complex problem that requires employment of the adequate methods for evaluation of the ***in vitro*** drug release from the nanoparticles. In this study, kinetics of the doxorubicin release from the doxorubicin-loaded nanoparticles based on copolymers of lactic and glycolic acids (Dox-PLGA) into model media and blood plasma was studied after the nanoparticles separation using the FDA-approved techniques such as ultracentrifugation and dialysis. Moreover, the approaches to the mathematical description of the release profiles were considered.
The Dox-PLGA nanoparticles were prepared by a double emulsion technique using Resomer® 502H (Evonik, Germany). 1% solutions of polyvinyl alcohol in phosphate buffer (PBS) at pH 7.4 (Dox-PLGA/7.4) or 6.4 (Dox-PLGA/6.4) were used as the external aqueous phase. Optimization of the ultracentrifugation method was carried out by varying the following parameters: receiving medium (water, 0.9% sodium chloride, PBS, HEPES buffer, 1% poloxamer 188, 1% polysorbate 80, blood plasma), dilution (1:5; 1:25), incubation temperature (+25 °C; +37 °C) and centrifugation mode (15000×g; 48254×g). The content of free doxorubicin in the plasma after separation of the nanoparticles was determined by HPLC, in other media – by UV spectrophotometry. Mathematical description and comparison of the release profiles of doxorubicin in different media was carried out using the different mathematical models (zero and first order, Higuchi, Hickson-Crowell, and Korsmeyer-Peppas models).
The average hydrodynamic size measured by dynamic light scattering of PLGA-Dox/7.4 and PLGA-Dox/6.4 nanoparticles were 114 nm (ζ-potential -9.5 mV) and 142 nm (ζ-potential -4.8 mV), respectively. The average size determined using transmission electron microscopy was 50±16 nm. It appeared that the Dox-PLGA nanoparticles obtained at different pH had distinct doxorubicin release profiles. Among the tested methods, the method using ultracentrifugation (48254×g, +4 °C) for the nanoparticles separation was best suited when using 1% poloxamer 188 as a receiving medium.
We suggest that thus optimized method for evaluation of the ***in vitro*** release profile is suitable for the establishment of IVIVC for the Dox-PLGA nanoparticles.
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