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Choice and justification of the method of bacterial purification of hormonal substances at production of medicinal preparations in suspension form for injections in rheumatology

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ABSTRACT

The aim of our research is to choose and justify the method of bacterial purification of hormonal substances of active ingredients of betamethasone dipropionate and hydrocortisoni acetas at developing of the most acceptable ways of receiving sterile prepared parenteral suspensions of «Hydrocortisoni Acetas + Lidocaine Hydrochloride» and «Betamethasone» is conducted. We developed two technological methods for obtaining these medicinal preparations which are characterized by identical final quality. They correspond the requirements of the State pharmacopoeia of Ukraine and the European regulatory requirements concerning the choice of a method of bacterial purification of the ready-made dosage forms.

Introduction

Considering continuous development of the pharmaceutical market, development of new original and generic medicinal preparations have gained the increasing popularity and is necessary for improvement of life quality, specifically for improvement of possibility of realization of the human right for available, effective and qualitative drugs.

Obviously, not each pharmaceutical company can afford development of new original drugs therefore the production of generics remains the direction of current interest financially and in terms of scientific resources for many pharmaceutical companies. A main objective of development of generic drug is its future price availability to patients in comparison with original drug keeping the same requirements to quality, safety and efficiency that were also applied to the reference drug.

So far topical question is rheumatic disease treatment that is considered around the world as one of the most widespread pathologies and as one of the most significant medical and social and economic problems of modern times [1].

Rheumatoid arthritis takes the greatest part among rheumatic diseases, one of the most disabling and widespread diseases of connecting tissue. Intrasynovial insertion of glucocorticosteroids (GC) is expedient at a joint form of rheumatoid arthritis with primary lesion of large joints [2].

GC deposit formulation provides long therapeutic action after insertion in the parenteral route and rather widespread now. One

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of the directions of prolongation of therapeutic effect of the drugs is usage of suspension injection in rheumatology [3].

The range of the combined drugs of domestic production of specific appointment for topical treatment of rheumatoid arthritis, osteoarthritis and various monoarthroses is limited, and the available drugs are presented generally by medicines of foreign producers and their quantity doesn't solve a problem of medicamental provision of patients with qualitative and available drugs.

Thus, pharmaceutical development of new medicinal preparations for usage in rheumatology which will be characterized by combination of several active ingredients, financially low-cost technology (for ensuring low prime cost and availability of the developed drug to most of the patients) remains the up-to-date direction now.

Aim of the Research

The choice and scientific justification of the method of bacterial purification of hormonal substances of active ingredients of betamethasone dipropionate and hydrocortisoni acetas at developing of the most acceptable ways of receiving sterile prepared parenteral suspensions of "Hydrocortisoni Acetas + Lidocaine Hydrochloride" and "Betamethasone" suspensions with use of substances of hydrocortisoni acetas, lidocaine hydrochloride, betamethasone dipropionate and betamethasone of sodium phosphate.

Materials and Methods

The pharmacopoeial method of thermal bacterial purification of substances and drug products with usage of the steam autoclave was used for realization of research objective (The European Pharmacopoeia / State Pharmacopoeia of Ukraine (SPU) 5.1.1 and 5.1.5) [4–6].

Control of model solutions of semi-products and prepared dosage forms on quality indicators such as "Quantitative contents", "The accompanying impurity" and "Sterility" were carried out with usage of the validated analytical techniques (the HELC method, State Pharmacopoeia of Ukraine / The European Pharmacopoeia 2.6.1) for medicinal preparations "Hydrocortisoni Acetas + Lidocaine Hydrochloride" and "Betamethasone" in the form of parenteral suspensions.

Control of drug products of «Particle size» and «Form of crystals» was carried out on quality indicators with usage of methods of laser diffraction (State pharmacopoeia of Ukraine / The European pharmacopeia 2.9.31) and method of optical microscopy (State Pharmacopoeia of Ukraine / The European Pharmacopeia 2.9.37) [4–6].

Substances of active ingredients (hydrocortisoni acetas, lidocaine hydrochloride, betamethasone dipropionate and betamethasone of sodium phosphate) and excipients which met the requirements of the European Pharmacopeia of the existing edition were used for researches.

Results and Discussions

During pharmaceutical development of generic medicinal preparation it is necessary to provide implementation of the main regulatory requirement — the developed drug must have the same qualitative and quantitative composition of active ingredients, to be one dosage form and to be bioequivalent. Two medicinal preparations are bioequivalent if they are pharmaceutically equivalent and close to their bioavailability after insertion in the same molar dose so that their efficiency and safety are completely identical. So, at a stage of pharmaceutical development of generic drug the main objective is development of medicinal preparation, pharmaceutically equivalent to the original.

Suspension the liquid dosage form containing one or several morselized powdery substances distributed in liquid variance medium as a disperse phase.

According to the existing pharmacopoeial requirements to quality of finished pharmaceutical products medicinal preparations for parenteral use must be controlled on such main indicators as the description; transparence; chromaticity; pH; quantitative contents; accompanying impurity; bacterial purification; bacterial endotoxins; heavy metals; osmolality; volume; that can be taken; particulate matter: visible and invisible particles, and other indicators in appropriate cases.

Considering impossibility of final thermal bacterial purification of ready-mixed solution of suspension in primary packing, for providing requirements on quality indicator "bacterial purification" production of injection suspensions demands aseptic conditions and special requirement to processing equipment by production of this dosage form.

So far as concerns the future generic medicinal preparations in the form of suspensions for injections, considering the prolonged therapeutic effect of this dosage form, the size and a form of crystals of active agents will influence on bioequivalence in relation to original drug. Existence of various forms of active ingredients will also influence on prolongation of therapeutic effect and, of course, bioequivalence of generic medicinal preparation original (like firm ready dosage forms).

Technological process of production of the majority of parenteral suspensions consists of two main stages: receiving unsterilized solution of excipients with usage of filtration via sterilizing filter with a size of pores of 0.2 μm and association in aseptic conditions of this solution with the sterile micronized substance of active agent. An alternative way of receiving a sterile

drug product was offered considering economic efficiency and high prospects of usage of the unsterilized micronized substances of active ingredients, cheaper in comparison with sterile ones, within pharmaceutical development of hormonal suspensions for parenteral usage on the basis of combination of substances of betamethasone dipropionate with betamethasone of sodium phosphate and hydrocortisoni acetas with lidocaine hydrochloride.

From references it is known that substances of hormonal substances can be sterilized thermally by Pharmacopoeial method of steam sterilization (121°C within 15 min, State Pharmacopoeia of Ukraine / The European pharmacopoeia 5.1.1 and 5.1.5) providing moistening them with minimum quantity of the water for injections (water for injections has to be only in the quantity sufficient for substance moistening) saturated with sodium chloride. As sodium chloride at dissolution is ionized and its ions need water for hydration, in saturated solution of sodium chloridum when heated there is very few water (or doesn't remain in general). Such saturated solution protects water-insoluble substance at the increased temperatures and excludes possibility of change of the sizes and a form of crystals after cooling. It is allowed to add surfactants [7, 8] to solution for improvement of moistening with water insoluble substances.

Surfactant "Polysorbate 80" was added into solution of substances of betamethasone dipropionate and hydrocortisoni acetas for improvement of moistening. The minimum quantity of water for injections sufficient for moistening of betamethasone dipropionate and hydrocortisoni acetas was selected for the purpose of prevention of admixtures increase in drug products at thermal bacterial purification of these substances. This quantity was 4–7% of the general size of series of finished suspension. The process of steam bacterial purification was carried out at continuous slow hashing for the purpose of elimination of sedimentation of the moistened particles of betamethasone dipropionate and hydrocortisoni acetas and also their homogeneous distribution.

The received concentrated suspensions were analyzed on the following indicators of quality: "Quantitative contents", "The accompanying impurity" and "Bacterial purification" (Table 1, 2).

At the following stage aggregate stability of suspensions, the size and a particle shape of substances of betamethasone dipropionate and hydrocortisoni acetas in finished suspensions were investigated at usage of this method of thermal bacterial purification of substances of active ingredients during technological process in comparison with the finished suspensions received when using of the sterile micronized substances of these active agents.

The size and form of crystals were investigated by means of the following methods and devices:

1. The 3000 Mastersizer laser diffraction particle size analyzer by Malvern.

2. The microscopic examination by means of the Motic optical microscope.

Table 1

Research on the choice of a method of bacterial purification of concentrate of hydrocortisoni acetas suspension

Quality indicators	Before bacterial purification	After bacterial purification (121°C, 15 min)
The quantitative maintenance of hydrocortisoni acetas, mg/ml (in concentrate)	625.7	625.2
The accompanying impurity, %:		
any identified impurity	0.21; 0.09	0.22; 0.11
any unidentified impurity	0.11	0.12
Bacterial purification	—	Sterile

Table 2

Research on the choice of a method of bacterial purification of concentrate of betamethasone dipropionate

Quality indicators	Before bacterial purification	After bacterial purification (121°C, 15 min)
The quantitative maintenance of betamethasone dipropionate, mg/ml (in concentrate)	128.7	128.6
The accompanying impurity, %:		
betamethasone (base)	0.17	0.18
any identified or unidentified impurity	0.12	0.12
Bacterial purification	—	Sterile

Figure 1 and 2 show results of control of particle size in the final suspension of "Hydrocortisoni Acetas + Lidocaine Hydrochloride" received by means of two technological methods (with usage of sterile substance of hydrocortisoni acetas and the unsterile substance of hydrocortisoni acetas sterilized during technological process).

Figure 3 and 4 present results of control of particle size in the final betamethasone suspension received by means of two technological methods (with usage of sterile substance of betamethasone dipropionate and unsterile substance of betamethasone dipropionate sterilized during technological process).

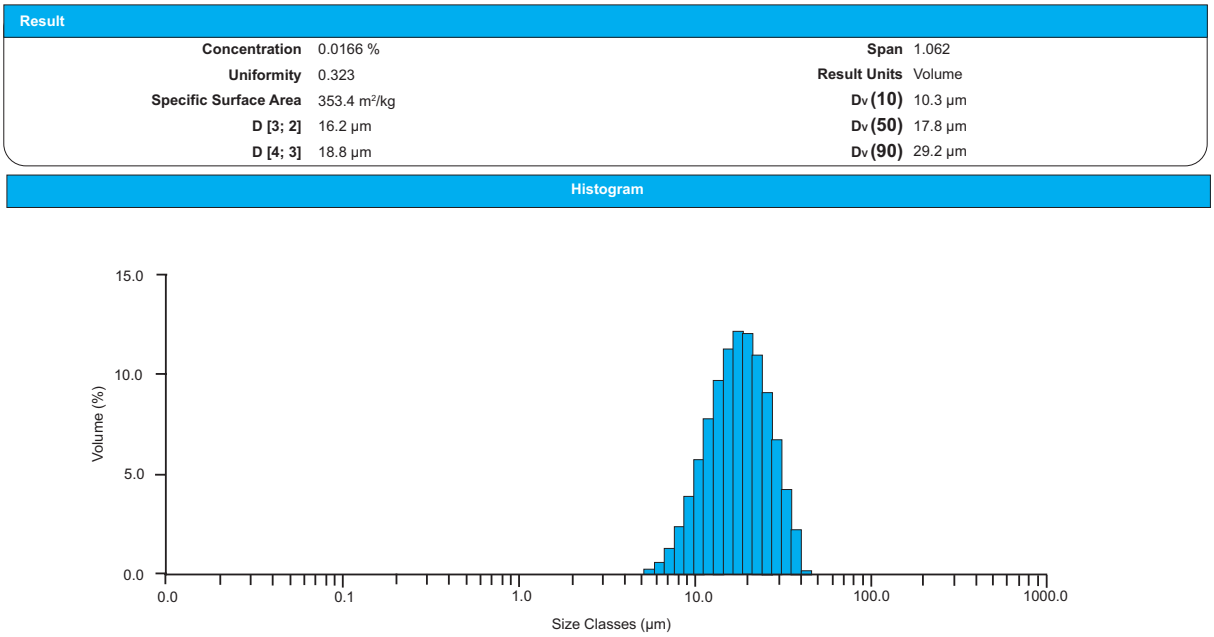

Figure 1. Results of control of particle size in final suspension of "Hydrocortisoni Acetas + Lidocaine Hydrochloride" received with usage of sterile substance of hydrocortisoni acetas at technological process

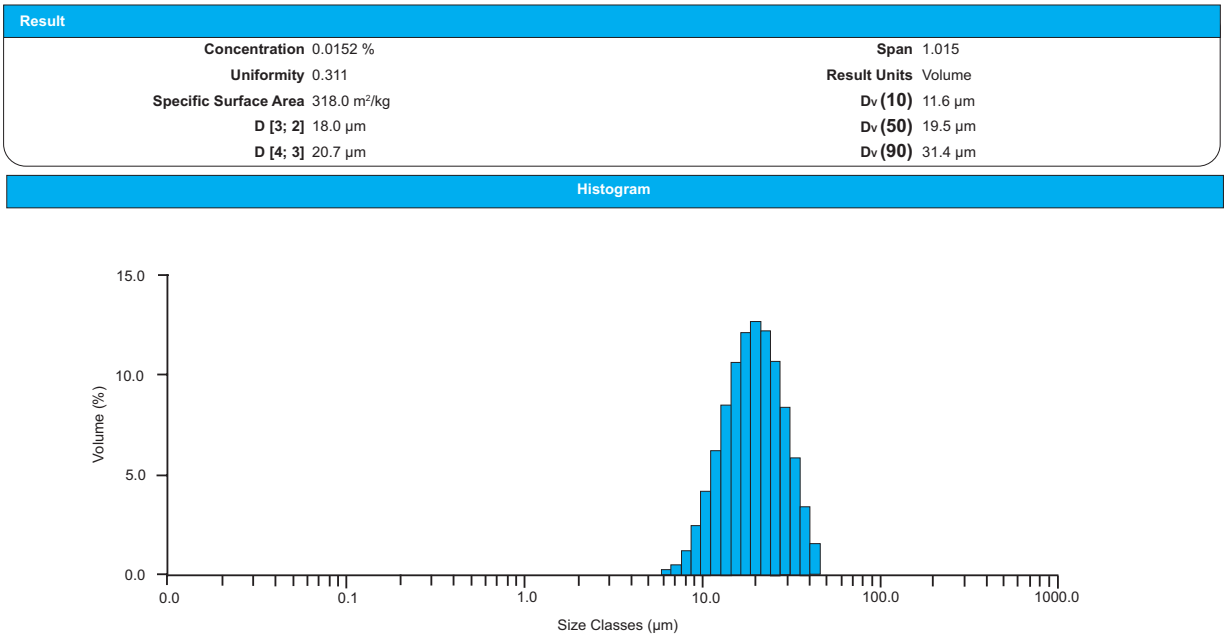

Figure 2. Results of control of particle size in the final suspension of "Hydrocortisoni Acetas + Lidocaine Hydrochloride" received with usage of the unsterile substance of hydrocortisoni acetas sterilized during technological process

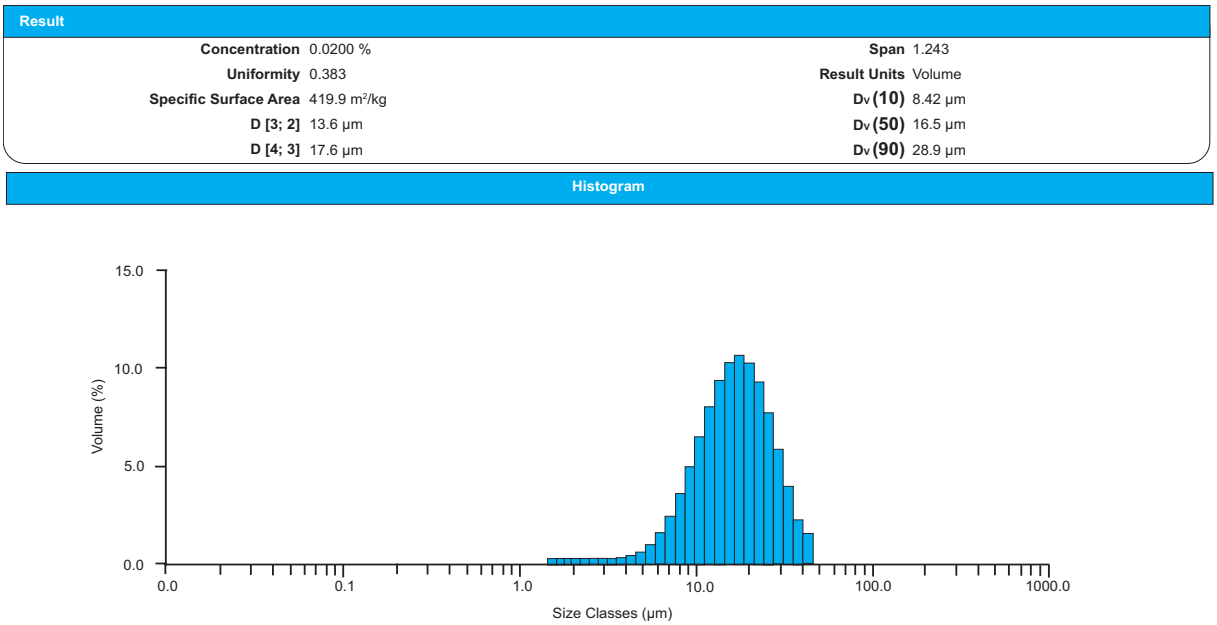

Figure 3. Results of control of particle size in the final betamethasone suspension received with usage of sterile substance of betamethasone dipropionate at technological process

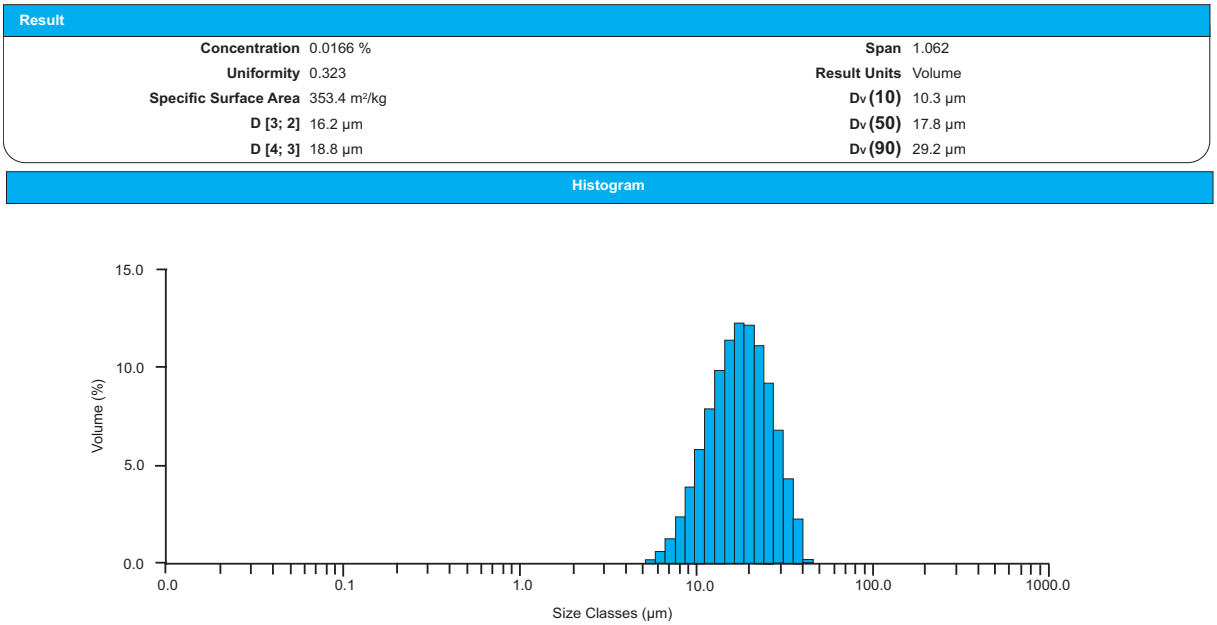

Figure 4. Results of control of particle size in the final betamethasone suspension received with usage of the unsterile substance of betamethasone dipropionate sterilized during technological process

Results of researches concerning crystals form of substance of hydrocortisoni acetas in the final suspension received by means of two technological methods of production of final drug products (with usage of sterile substance of hydrocortisoni acetas and the unsterile substance of hydrocortisoni acetas sterilized during technological process) are presented in Figure 5.

Results of researches of crystals form of substance of betamethasone dipropionate in the final suspension received by means of technological methods of production of final drug products (with usage of sterile substance of betamethasone dipropionate and unsterile substance of betamethasone dipropionate sterilized during technological process) are provided in Figure 6.

The received results (see Table 1, 2 and Figure 1–6) testify to lack of degradation of active ingredients of betamethasone dipropionate and hydrocortisoni acetas at the developed method of their sterilization and confirm similarity in a form and the size (considering

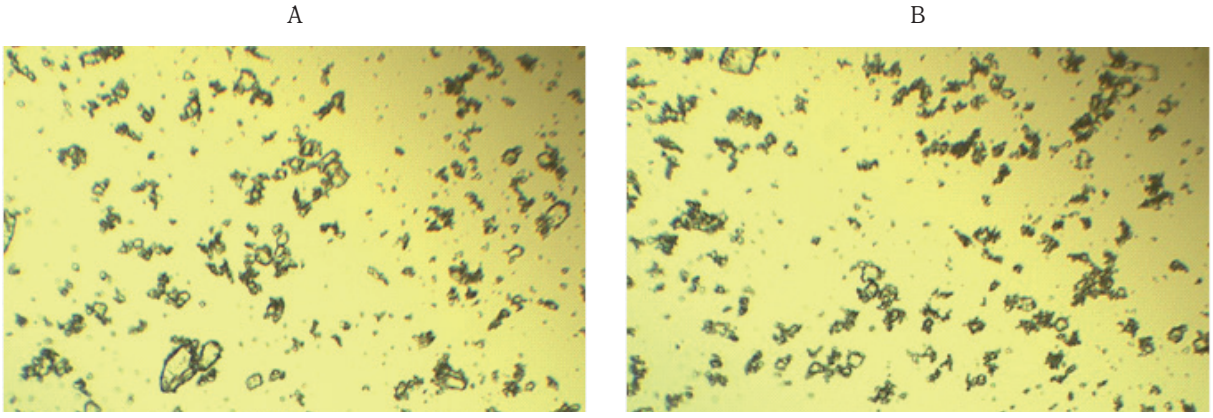

Figure 5. Microscopy of the drug "Hydrocortisoni Acetas + Lidocaine Hydrochloride" received with hydrocortisoni acetas substance usage:
A — sterile; B — unsterile, sterilized during technological process

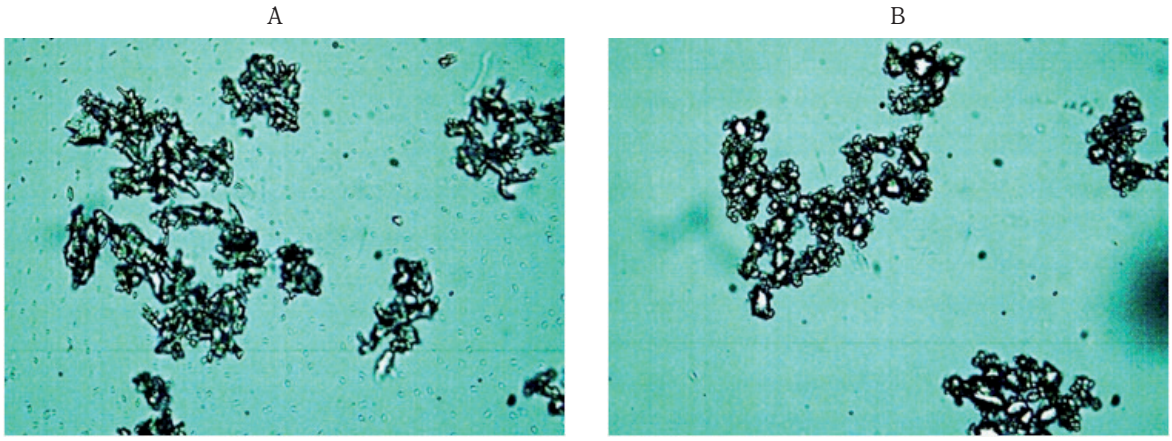

Figure 6. Microscopy of «Betamethasone» drug received with betamethasone dipropionate substance usage:
A — sterile; B — unsterile, sterilized during technological process

D_{10}, D_{50}, D_{90} values) crystals of these substances in final drug products in the form of parenteral suspensions at using two technological methods of receiving drugs (with usage of sterile substances of hydrocortisoni acetas and betamethasone dipropionate and unsterile substances of these active ingredients sterilized during technological process of receiving final drug products).

Conclusion

Two technological methods of receiving parenteral suspensions "Hydrocortisoni Acetas + Betamethasone Dipropionate" and "Betamethasone", sterile and ready for use, characterized by identical final quality of medicinal preparations, that conforms to requirements of State Pharmacopoeia of Ukraine and the european regulatory requirements concerning choice of method of sterilization of final drug products [9] were developed on the basis of the performed researches.

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