

New Technologies in Manufacture of Original Medical Preparations

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Abstract

The progressive, ecologically pure technologies of isolation of sesquiterpene γ -lactones of plant origin were examined in this article. The original phytopreparations were developed on their basis. The pharmaco-economic characteristics of the obtaining of substances of phytopreparations with application of supercritical CO₂-extraction and method of preparative centrifugal partition chromatography in comparison with the classical methods of extraction and column chromatography were presented.

Introduction

At present, a question of competitiveness of domestic medical drugs and the pharmaceutical enterprises has the special urgency and becomes the priority task for the domestic pharmaceutical enterprises. Methods of increase of the competitiveness pharmaceutical production for the domestic enterprise are: maintenance of quality of domestic medical drugs on the basis of cardinal updating of technological base of branch and introduction of standard GMP, increases of profitability of manufacture on the basis of introduction of innovative technologies, realization of marketing strategies for maintenance of steady market niches for domestic medical drugs in the retail market, the organization of cluster groups for the obtaining of benefits from the external cluster effects.

Thus, the method of the supercritical fluid extraction of plant raw material with the subsequent separation and purification of the obtained CO₂-extract by a method of the high-speed centrifugation in a combination with high-performance preparative chromatography was introduced into the Karaganda pharmaceutical complex.

Experimental

The using of these innovative technologies in manufacture of substance and the finished medicinal forms of some original phytopreparations permitted to introduce the advanced methodological approach in development of new medical preparations on the basis of the pharmacological active plant substances.

The introduced methodological scheme (Fig.1) consists of a complex of technological actions. It includes 4 stages. Each stage comes to the end with the obtaining of the intermediate product providing statement of tasks for each subsequent stage.

The final stage of the introduces methodological approach is a choice of perspective medicinal forms with output of pilot lots, introduction in manufacture of technological regulation and the state registration of new medical preparation.

One of the perspective groups of biologically active natural compounds is sesquiterpene γ -lactones of plant origin. At present, the antivermicular, cardiotoxic, antiulcer and antimalarial preparations (Santonin, Tauremisin, Alanton, Artemisinin and others) were developed on basis of these lactones.

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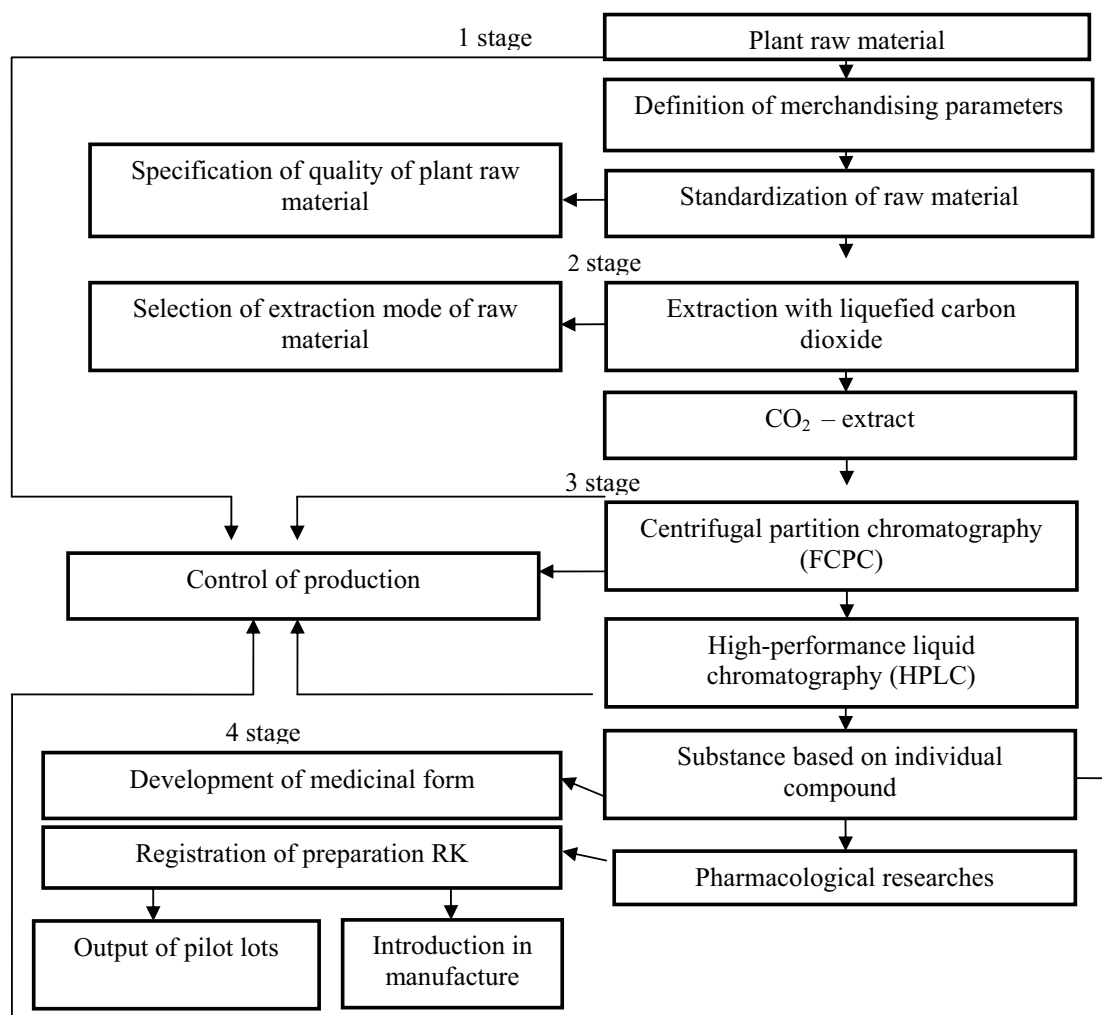


Fig. 1. The methodological scheme of the obtaining of original phytopreparations

The analysis of technology of the obtaining of medical drugs on the basis of natural sesquiterpene lactones has shown that their basis was consisted of the plant raw material with the various organic solvents. After that the subsequent chemical and chromatographic purification of the isolated sum of substances was carried out [1-9].

The above-stated technologies of medical drugs' manufacture on the basis of sesquiterpene lactones from the plant raw material were characterized with the multistage, the use of expensive, highly inflammable, toxic and organic solvents (chloroform, benzene, petroleum-ether, hexane, acetone, etc.).

The indicated features of the production cycles of the obtaining of these preparations were reflected finally in the cost price of production and give rise

in price. On the other hand, the application of toxic solvents at the separate stages of the industrial order was not permitted to the standards GMP. Thus, it reduced the competitiveness of the pharmaceutical production and prohibited the output in the foreign market.

The works on introduction of method of the extraction of the medicinal raw material with the liquid carbon dioxide (CO₂) and purification of the obtained sum of the extractive substances by a method of the centrifugal partition chromatography in combination with the high-performance preparative liquid chromatography were carried out by the International Research and Production Holding "Phytochemistry" together with the Karaganda Pharmaceutical Complex.

Thus, the technological orders of the obtaining

of the new preparations of “Arglabin” and “Aterolid” were introduced in the pharmaceutical manufacture. There was used CO₂ – extraction of the plant raw material and the preparative high-performance liquid chromatography. It permitted to exclude the application of toxic organic solvents (chloroform, benzene, etc.) in the manufacture and provided the output of the Kazakhstan preparations in the foreign market [10-12]. So, the original antitumor preparation “Arglabin” was registered. At present, preparation “Arglabin” is realized in Russia, Uzbekistan, Georgia, Tajikistan and

Kyrgyzstan.

The major factor for introduction of these stages in the technology of manufacture of “Arglabin” and “Aterolid” is an increase of profitability and decrease in the cost price of the obtained production.

Two technologies of the obtaining of substances of the original medical drugs were compared on an example of preparation “Aterolid”. The active substance of preparation “Aterolid” is sesquiterpene lactone leucomisin (Fig. 2).

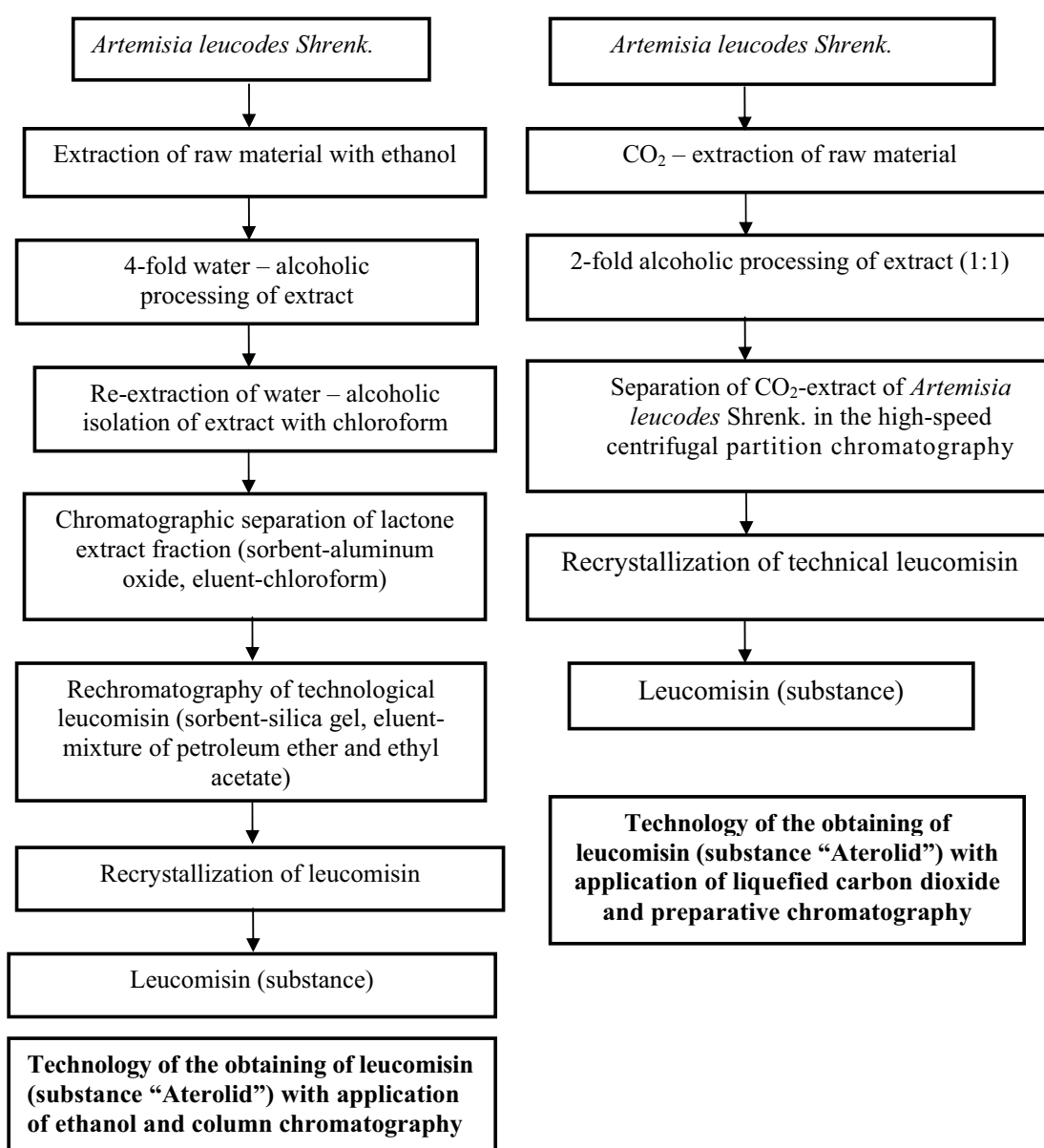


Fig. 2. The comparative schemes of the manufacture technology of substance of preparation “Aterolid”

Results and Discussion

As follows from the comparative analysis of the technologies, the decrease in the cost price of production was observed at CO₂ - extraction of raw material of *Artemisia leucodes* Schrenk. and separation of the obtained extract on the high-speed centrifugal partition chromatograph. So, it permits to exclude the expensive stages in the production of the obtaining of leucomisin.

Results of the analysis of material balance of the technological order during the application of CO₂-extraction for raw material of *Artemisia leucodes* Schrenk. with separation and purification of an extract into the high-speed centrifugal preparative chromatography. So, it reduces in 3,4 times the cost price of the obtained production. The cost of 1g of substance leucomisin is 1201 tenges.

The cost price of 1 g of substance leucomisin, obtained at extraction of raw material by ethanol with purification of extract on the aluminum oxide column and eluting with chloroform, makes 3985.62 tenges.

The decrease in the cost price of production was observed at CO₂ – extraction of raw material of *Artemisia glabella* Kar. et Kir. with the separation of an extract in the high-speed centrifugal partition chromatography in a combination with the preparative high-performance liquid chromatography. Some stages, characteristic for extraction of plant raw material by chloroform with chromatographic purification of extract on silica gel with application of toxic solvent of benzene, were reduced.

The cost price of 1 g of substance arglabin, obtained during the application of extraction of raw material of *Artemisia glabella* Kar. et Kir. with liquefied carbon dioxide and during the purification and separation of an extract in the high-speed centrifugal preparative chromatography, makes 2488,86 tenges. Extraction of raw material with chloroform and chromatographic purification of the sum of substances on silica gel column and eluting benzene makes 8335,78 tenges.

Thus, the cost price of one vial of the finished medicinal form “Arglabin lyophilized, 0,04 g”, obtained on technology of CO₂ - extraction, makes 621 tenges. The finished medicinal form, obtained on technology of chloroformic extraction, makes 855 tenges.

Thus, introduction of new technology in manufacture of an original preparation “Arglabin” allowed to lower the cost price of the finished

medicinal form in 1,4 times. The competitiveness of the Kazakhstan preparation was raised in the foreign pharmaceutical market. Preparation “Arglabin” was registered as antitumor and realized in five foreign countries.

Conclusions

As a result the innovative technologies, such as extraction of medicinal raw material with liquefied carbon dioxide and purification of active component from extract with application of the modern centrifugal preparative chromatography, allow to reduce the use of organic solvents in 10 times in the phytochemical manufacture. Thus, productivity was raised in 10 times. The production costs decrease in 5-10 times with the corresponding decrease in the cost price of the finished pharmaceutical production in 1,5–3,5 times.

The application of ecologically pure technology and exception of technological orders of the toxic organic solvents provide the introduction of the international standards in the domestic pharmaceutical manufacture. It raises the competitiveness of the Kazakhstan preparations in the pharmaceutical market.

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