New Technologies in Manufacture of Original Medical Preparations

Ye.G. Tolokonnikov

JSC “International research and production holding “Phytochemistry”,
str. M. Gazaliev, 4, 100009, Karaganda, Republic of Kazakhstan

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 pharmacoeconomic 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, cardiotonic, antiulcer and antimalarial preparations (Santonin, Tauremisin, Alanton, Artemisinin and others) were developed on basis of these lactones.
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

---

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

| 1 stage | Plant raw material |
|---------|--------------------|
|         | Definition of merchandising parameters |
|         | Standardization of raw material |

| 2 stage | Extraction with liquefied carbon dioxide |
|---------|-----------------------------------------|
|         | CO₂ – extract |

| 3 stage | Centrifugal partition chromatography (FCPC) |
|---------|-------------------------------------------|
|         | High-performance liquid chromatography (HPLC) |

| 4 stage | Development of medicinal form |
|---------|------------------------------|
|         | Registration of preparation RK |
|         | Output of pilot lots |
|         | Introduction in manufacture |
|         | Substance based on individual compound |
|         | Pharmacological researches |

---

Eurasian ChemTech Journal 12 (2010) 63-67
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 Kazakhstani 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.

References

1. Pharmaceutical preparations containing sesquiterpene lactones: claim 2124486 Great Britain, MKI A 61 K 31/365, A 61 K 35/78/ E.S. Johnson, P.J. Hylands, D.M. Hylands.
2. Maiotis, L.S. Chemistry and technology of chemically pharmaceutical preparations. Issue: M.-1964.-P.438-444.
3. Patent USSR № 202468, MPK A 61K Method of the obtaining of tauremisin / K.S.Rybalko, A.I.Bankovsky, R.I.Evstratova, V.A.Gorely. - № 836516/31-16; claim 13.05.1963; publication 14.09.1967.
4. Patent USSR № 577034, MK1 A61 K35/78. The method of the obtaining of sesquiterpene lactones / P.P. Hvorost, N.F. Komissarenko, G.V. Obolencova, A.I. Vidukova, Ya.I. Hadzhai, M.M. Luchkova, V.P. Georgievsky, L.D. Degtyarev, V.V. Zinchenko. - №235593/13; claim 15.04.1976; publication 25.10.1977.
5. Patent SU №1710062 A1 from 07.02.2009. The method of the obtaining of sesquiterpene lactones. Babaev N.F., Serkerov S.V.
6. Belyakov, K.V., Popov, D.M. The obtaining of
alantolactone of the standard sample // Pharmacy. №1- 2004.-P.37-38.
7. Patent US 2003/0185914 A1 A61K 035/78 Process for isolating artemisinin from Artemisia annua / Kumar Sushil, Gupta, Shiv Kumar, Singh, Digvijay, Gupta, Madan Mohan; Jain, Dharam Chand, Kahol, Atul Prakash, Khanuja, Suman Preet Singh, Ram, Govind October 2, 2003.
8. Patent US 1999/005955084A A61K 35/78 Process for the simultaneous production of artemisin and essential oil from plant Artemisia annua / Dharam Chand Jain, Sudeep tendon, Rajendra Singh, Mohammed Shafigu.
9. Luo, X., Shen, C.-C. The Chemistry, Pharmacology and Clinical Applications of Qinghaosu (Artemisinine) and Its Derivatives // Medicinal Research Reviews – 1987.-V. 7.-P. 29-52.
10. PCT/KZ/00006 from 20.12.97 Adekenov, S.M. The method of the obtaining of hydrochloride 1β, 10 β-epoxy-13-dimethylamino-gaia-3(4)-en-6,12-olid – antitumor preparation “Arglabin lyophilized” and device for its obtaining.
11. Adekenov, S.M. Patent USA 6242 617; China CN1095845C; European Patent 0 946 565; Eurasian patent № 009712.
12. Conclusion on issuance of the innovative patent RK from 24.05.2010 by claim №2009/0601.1 from 29.04.2009. S.M. Adekenov “The method of the obtaining of antiatherosclerotic and hypolipidemic drug “Aterolid” from Artemisia leucodes Schrenk.

Received 15 May 2009.