ON MANUFACTURE OF PLATYPHYLLINE HYDROTARTRATE FROM THE AERIAL PARTS OF *SENECIO PLATYPHYLLUS*

R.A.Botirov[a], D.K.Mutalova[a], Z.Ch.Abraeva[a], A.Z.Sadykov[a],
Sh.Sh.Sagdullaev[a], Haji Akber Aisa[b]

a) Acad.S.Yu.Yunusov Institute of the Chemistry of Plant Substances, AS RUz, 100170, Tashkent, Uzbekistan, e-mail:botiroovr@mail.ru
b) Xingiang Technical Institute for Physics and Chemistry, AS PRC, Xingiang, China

Resume. An industrial technological line for the production of drug substances from alkaloids by the method of water-alcohol extraction of plant raw materials is developed at the Institute of the Chemistry of Plant Substances the Academy of Sciences of the Republic of Uzbekistan [1].

Keywords: alkaloids, extraction, technology, optimization process, Box-Wilson method, platyphylline, extract, *Senecio platyphyllus*

Introduction. A serial production of the substance of allapinin (antiarrhythmic drug) [2] from the aerial part of *Aconitum leucostomum* or from the rhizomes with roots of *Aconitum septentrionale* and *Aconitum leucostomum*, aklezine (antiarrhythmic drug) [3] from the aerial part of *Aconitum leucostomum*, aksaritmine (antiarrhythmic drug) [4] from the rhizomes with the roots of *Aconitum septentrionale* and *Aconitum leucostomum*, galanthamine hydrobromide (anticholinesterase agent) [5] from the aerial part of *Ungernia victoris*, lycorine hydrochloride (expectorant) [6] from the aerial part of *Ungernia severtsovii*, protopine hydrochloride (cholagogue) [7] from the aerial part of the *Fumaria Vaillantii,* cytisine (analeptic respiration) [8] from the aerial part of *Thermopsis alterniflora*, deoxypeganine hydrochloride (anticholinesterase) [9] from the aerial part of *Peganum harmala*, etc. is organized. The production of the abovementioned preparations fully covers the need of our country and the export. Thus, the method of water-alcohol extraction of alkaloids from plant raw materials with the subsequent production of the basic substance allows produce alkaloids of different chemical structure from the plant raw materials of the above-mentioned technological line with a small modification in industrial conditions [1].

This work is devoted to the development of an industrial technology for the production of platyphylline hydrotartrate drug substance. Platyphylline hydrotartrate is used in medical practice for reducing spasms of smooth muscles of abdominal organs, peptic ulcer of stomach and duodenum, bronchial asthma, hypertension, angina, spasms of blood vessels, and in

ophthalmology for pupil dilatation [10]. The source of platyphylline is the aerial parts of *Senecio platyphyllus* growing on Georgia and the People's Republic of China with the content of the target alkaloid platyphylline not less than 0.1-0.2% of the air-dry mass of the raw material.

The technology developed using the method of water-alcohol extraction of plant raw materials and further purification with reference to the existing industrial line operating at the Experimental Manufacture of the Institute of the Chemistry of Plant Substances, Academy of Sciences of Uzbekistan.

The processes of alkaloids extraction, reduction of platyphylline N-oxide form, isolation of alkaloids from the extract, production of technical platyphylline hydrotartrate and its purification are considered.

The main factors affecting the extraction of alkaloids from raw materials were established, namely degree of grinding of raw materials-X1, temperature of the process-X2, density of the feedstock-X3, extraction time-X4. To determine the influence of these factors on the extraction process and optimal conditions for its implementation the process was optimized by mathematical planning of the Box-Wilson experiment [11].

As an optimization parameter (Y), the output of technical platyphylline-base from the content in the raw material at the first phase contact was selected. 1/4 replica of the total factor experiment of type $Y = 2^4$ was used with the following generating relations: $X_4 = X_1 \cdot X_2 \cdot X_3$. Factor levels and their variation intervals (X_1-10 ± 5mm, X_2 - 50 ± 25°C, X_3 - 1.0 ± 0.2g/cm^3, X_4 - 6 ± 2h) has been chosen. After carrying out the experiment of $Y = 2^{4-1}$ type, we obtained a mathematical model of the process:

$$Y = 31.04\text{-}0.91X_1 + 4.16X_2 + 044X_3 + 5.18X_4$$

From the regression coefficients of the equation, after calculating the confidence interval (bi = 1.99), it was established that the main factors affecting the process are the extraction process temperature and extraction time. Statistical analysis (F_{calc}= 2.4 < F_{tab} = 4.5) of the obtained data showed that the mathematical model adequately describes the linear approximation to the optimum.

After a steep ascent, it was revealed that the optimum conditions for the process are extraction of ground (0.5-15 mm) raw materials at room temperature with a 75-85% solution of ethyl alcohol for at least 8 hours, with the product yield at the first phase contact being 42% of the content in raw materials.

In order to determine the amount of discharges necessary for maximum depletion of raw materials, the kinetics of the extraction process has been studied. The results showed that the equilibrium between the phases at the second contact of the phases appears in 6 hours, at the

third - 5h, the fourth, the fifth, and the sixth - 3h. At a sixfold extraction, at least 90% of the technical platyphylline is recovered from the content in the feedstock.

The resulting water-alcohol extracts were concentrated on a vacuum evaporator until the alcohol was completely removed (water residue). As is known, chlorophyll and other resinous substances float to the surface and may be released by filtration or decanting the extract. The N-oxide forms of the alkaloids in the extract were recovered in the presence of zinc dust with stirring for 10-12 hours in sulfuric acid (8-10%). After filtration from the excess of zinc dust, chloroform was used to isolate the alkaloids from extract. The alkaloids extracted exhaustively at 4-5 multiple contacts of the phases and pH 10-12 (alkalinization with aqueous ammonia). From the chloroform solution the alkaloids were extracted with a solution of 10% sulfuric acid. The sulfate solution of the alkaloids is cooled to a temperature of 2-4°C and the alkaloids are precipitated with a solution of ammonia (pH 10-12). The sediment contained a mixture of alkaloids platyphylline and seneciphylline. Their separation was carried out using different solubility in ethyl alcohol. By a known technique the platyphylline hydrotartrate was recrystallized from 90% ethanol solution. The yield of platyphylline hydrotartrate was 60-80% of the content in plant raw materials.

The yield of the final product is strongly depend on the presence of such concomitant alkaloids as seneciphylline and saracine in the alkaloid sum; in the absence of saracine the final product can be obtained with the maximum yield. Saracine can be separated from the sum of alkaloids only by column chromatography using alumina of the first degree Brockman activity as a sorbent.

Thus, it is possible to produce the substance of platyphylline hydrotartrate by water-alcohol extraction of plant raw materials and organize its serial production with a yield of 60-80% of the content in plant raw materials on the industrial line for the production of drug substances from alkaloids of the Experimental Manufacture of the Institute of the Chemistry of Plant Substance.

Experimental part

Platyphylline obtaining. 10 kg of the aerial part of the flat - topped ragwort after grinding (platyphylline content in the air - dry mass of the raw material was 0.2%) was loaded into the extractor, filled with an 80% solution of ethyl alcohol in a ratio of 1: 3 and insisted 8 hours, then 16 liters of alcohol extract of alkaloids was poured out. The second time 16 liters of 80% alcohol solution was poured. The following four extractions were carried out similarly. The extracts were concentrated in a vacuum evaporator to a residue of 8.0-11.0% of the original

volume. The resinous substances were separated, and the N-oxide forms of the alkaloids were reduced in the presence of zinc dust in the sulfuric acid medium (10% sulfuric acid). After removing the excess of zinc dust, the obtained filtered extract (9.0 L) was basified with ammonia to pH 10-12 and the alkaloids were extracted four times with 2.5 L of chloroform. Alkaloids were extracted from the chloroform extract (5 times) by 2 L of 10% sulfuric acid solution. The sulfate solution of the alkaloids was cooled to 2-4°C, and the alkaloids precipitated with ammonia. The precipitate was separated and dried. The dry residue was treated with ethyl alcohol (96%) and heated to a boil. After boiling for 10 minutes, the insoluble majority of the seneciphylline was separated. The solution was added with the calculated amount of wine acid to produce the platyphylline hydrotartrate. Recrystallization of the final product was carried out from a 90% solution of ethyl alcohol.

References

1. Sadykov A.Z. *Avtoreferat of Doctoral thesis…technical sciences*. Tashkent: 2015.

2. Sadykov A.Z., Shakirov T.T. *Chem. Nat. Compd.,* Volume 224, Issue 1, 1988, 79-81.

3. Sadykov A.Z., Sagdullaev Sh.Sh., Dzhakhangirov F.N., Shakirov T.T. *Chem. Nat. Compd.,* special issue 1999, 134

4. Sadykov A.Z., Sagdullaev Sh.Sh., N.V.Valiev. *Pharmaceutical Journal,* 2016, 79-82.

5. Sadykov A.Z., Sagdullaev Sh.Sh*., Chem. Nat. Compd.,* special issue 2005, 190.

6. Sadykov A.Z., Sagdullaev Sh.Sh., Shakirov T.T. *Chem. Nat. Compd.,* special issue 1999, 115.

7. Sadykov A.Z., Shakirov T.T., Israilov I. *Method for obtaining of protopine hydrochloride*. Uzbek patent No. *1755, 1994.*

8. Mamatkhanov A.U., Vinogradova V.I., Yakubova M.R., Sotimov G.B., Khalilov R.M., Mamatkhanova M.A., Nigmatullaev A., Pulatov A.A., Nuritdinov Kh. *Method for obtaining of cytisine.* Uzbek patent No. *04187, 2010.*

9. Aripov Kh.N. *Doctoral thesis…technical sciences*, Tashkent,1979.

10. Mashkovski M.D. *Medicinal preparations. Abu Ali ibn Sino Publishers*, Tashkent, 1998, 543.

11. Adler Yu.P., Markova E.V., Grinovski V.V. *Experiment planning in the optimal condotions searching. Moscow*, 1971, 286.

О ПРОИЗВОДСТВЕ СУБСТАНЦИИ ЛЕКАРСТВЕННОГО ПРЕПАРАТА ПЛАТИФИЛЛИНА ГИДРОТАРТРАТА ИЗ НАДЗЕМНОЙ ЧАСТИ КРЕСТОВНИКА ПЛОСКОЛИСТНОГО (*SENECIO PLATYPHYLLUS*)

Р.А.Ботиров[а], Д.К.Муталова[а], З.Ч.Абраева[а], А.З.Садиков[а], Ш.Ш.Сагдуллаев[а], Хожиакбар Айша[б]

а) Институт химии растительных веществ им. акад. С.Ю.Юнусова АН РУз.
б) Синцзянский технический университет физики и химии АН КНР

На базе ОП ИХРВ АН РУз функционирует промышленная технологическая линия по производству субстанции лекарственных препаратов на основе алкалоидов методом водно-спиртовый экстракции растительного сырья.

ЯССИ БОШЛИ САРИҚБОШ (*SENECIO PLATYPHYLLUS*) ЎСИМЛИГИ ЕР УСТКИ ҚИСМИДАН ПЛАТИФИЛЛИН ГИДРОТАРТРАТ ДОРИ ВОСИТАСИ СУБСТАНЦИЯСИНИ ИШЛАБ ЧИҚАРИШ ҲАҚИДА

Р.А.Ботиров[а], Д.К.Муталова[а], З.Ч.Абраева[а], А.З.Садиков[а], Ш.Ш.Сагдуллаев[а], Хожиакбар Айша[б]

а) ЎзР ФА акад. С.Ю.Юнусов номидаги Ўсимлик моддалари кимёси институти.
б) ХХР ФА Синцзян физика ва кимё техник институти

ЎзР ФА ЎМКИ ТИЧК базасида алкалоидлар асосидаги дори воситалари субстанцияларини ўсимлик хом ашёсидан сув-спирт экстракцияси усулида ишлаб чиқаришнинг саноат технологик тизими йўлга қўйилган.