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Content analysis of medicines based on glycyrrhizinic acid of the pharmaceutical market of the Republic of Uzbekistan

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Abstract

The article presents a review of the literature, comparative analysis of indicators of the quality of some medicines based on licorice and the results of the content analysis of the nomenclature of drugs (DP) containing glycyrrhizinic acid. Studied the following parameters of drugs: composition, quality indicators, method of production, therapeutic class and country of origin and manufacturer.

Keywords: Standardization, liquorice, glycyrrhizinic acid, pharmacopoeia article, content analysis, register, nomenclature, quality indicators.

INTRODUCTION

Licorice Naked (Licorice)is popular in modern folk and scientific medicine and has great potential in the pharmaceutical industry, and is also a commodity exported abroad [1]. The main active ingredient of licorice is glycyrrhizinic acid, which contains up to 23.6% of the plant's roots .

In eastern medicine, licorice was considered a panacea for many diseases, it has been used for 5 thousand years. A bundle of licorice roots was found among the treasures in the tomb of Tutankhamun. The Egyptians, Greeks and Romans recommended licorice as a means to help combat physical exertion and overwork [2]. Avicenna noted that licorice increases potency. In the army of Alexander the Great, the dried roots of licorice were included in the soldiers rations: they were prescribed to chew to suppress thirst and increase stamina [2, 5].

Aim of the study is to compare the standardized quality indicators of drugs based on bare licorice registered in the Republic of Uzbekistan, review literature data and conduct a content analysis of the range of drugs.

MATERIAL AND RESEARCH METHODS

One of the main methods for obtaining comprehensive information about the object under study is content analysis. In this regard, to achieve this goal, this analytical method was used in combination with methods of comparison and grouping.

Studies on the content analysis of drugs were carried out in the following areas: trade name, composition, standardization methods, dosage form and pharmacological group. The information source was the quality standards of medicines, the State Pharmacopoeias of various countries and the State Register of Medicines and Medical Products of the Republic of Uzbekistan No. 23, 2019.

The analysis took into account all drugs, substances containing glycyrrhizinic acid, registered by various domestic and foreign manufacturers. The ratio of the shares of non-combined and combined drugs was distributed as follows: the total number of non-combined drugs containing glycyrrhizinic acid is 32 trade names, which corresponds to 40.50% of the total number of all analyzed items, and combined drugs are represented by 47 names for which accounting for 59.49%.

Of the 8883 trade names of drugs registered in the Republic of Uzbekistan [4], we attributed 79 drugs to

glycyrrhizinic acid-containing drugs, i.e. 0.899% of the total number of registered drug names (Table 1).

The distribution by country of origin is as follows: non-CIS countries - 35 trade names (0.398%); neighboring countries (CIS) - 6 items (0.06%); Republic of Uzbekistan - 38 items (0.432%), respectively.

Table 1: The Distribution of drugs (in the form of dosage forms)by country of origin

№	Dosageform	Uzbekistan	CIS	Foreigncountries	Total
1	Granules	-	-	7	**7**
2	Fluid	2	-	-	**2**
3	Capsules	3	2	2	**7**
4	Medicinalplantmaterial	11	-	-	**11**
5	Pastille	-	-	6	**6**
6	Powderfororaladministration	-	-	1	**1**
7	Infusionsolution		-	1	**1**
8	Injection	2	-	2	**4**
9	Syrup	12	-	13	**25**
10	Spray for outdoor and vaginal use	-	-	1	**1**
11	Substance (dryextract)	6	-	-	**6**
12	Tabs	2	2	2	**6**
13	Elixir	-	2	-	**2**
Total		**38**	**6**	**35**	**79**

Among foreign countries, the most widely represented dosage forms from countries such as India - 15 trade names, Pakistan – 12, China - 4, Japan and Spain, 2 of the CIS countries are as follows: Russia - 5 and the Republic of Belarus - 1.

There are highly purified drugs based on locally produced glycyrrhizinic acid, such as Lipero, Novopharma Plus JV LLC, Hepaglitz, O'zkimyo farm and a foreign-made injection solution: Stronger Neo-Minofagen S (Minophagen Pharmaceutical Co. Ltd), Japan, Heporal (North China Pharmaceutical Co., Ltd) China, also an infusion solution, Ammonium Glycerate (Shijiazhuang Siao Co. Ltd) China. Table 2 presents the results of the analysis of the assortment that passed registration by year in Uzbekistan, the CIS, and foreign countries.

Table 2: Distribution by country of origin

Years	Uzbekistan	CIS	Foreign countries	Total
2012	2	-	5	7
2013	4	3	5	12
2014	4	1	7	12
2015	12	2	6	20
2016	5	-	9	14
2017-19	11	-	3	14
Total	38	6	35	**79**

The distribution of drugs based on glycyrrhizinic acidby pharmacotherapeutic groups. Licorice-based preparations are natural compounds with a wide spectrum of biological activity. In nature, there are about 12 species of licorice plant, but only three of them - naked licorice, Ural licorice and Korzhinsky licorice - have medicinal value and are widely used in the pharmaceutical and cosmetic industries [3]. The compos-

tion of licorice in%: glycyrrhizinic acid 7.3-23.6; starch up to 34; glucose 0.6-15.2; sucrose 0.3-11.0; fiber 9.7-28.2; organic acids 11-31.2; flavonoids (liquiquirithin, isoliquirithin, liquiquiritoside) 3.0-4.0; steroids (β-sitosterol) 1.5-2.0; protein substances 6.18-10.13.

Of great interest from triterpene compounds are glycyrrhizinic acidin the form of a mixture of ammonium, potassium and calcium salts and glycyrrhetic acid, which is similar to the structure of glucocorticoid hormones. Roots and rhizomes of licorice are the main raw materials, from which glycyrrhizinic acidbegan to be obtained in 1843, and glycyrrhetic acid since 1907.

All 79 drugs (4 drugs are registered) registered by domestic and foreign manufacturers, are represented by 11 pharmacotherapeutic groups (biogenic stimulant, hepatoprotector, immunomodulating (immunostimulating) drug, cardiotonic, non-steroidal anti-inflammatory drug, expectorant, local anti-inflammatory drug sedative, a means for the treatment of diseases of the ENT organs, a means to eliminate the symptoms of acute respiratory infections.

The composition of the dry extract of “Sharq-tabibi” includes glycyrrhizinic acidand is used as a substance for the preparation of “Sharq-tabibi” tablets, it acts as a biogenic stimulant. The Japanese drug Stronger Neo-Minofagen C is successfully used as an intravenous infusion for the treatment of chronic viral hepatitis B, C and cirrhosis, as well as our local original drug Hepaglitz manufactured by O’zkimyofarm JSC.

The Spanish drugs Viusid and Epigen Intimate have no analogues in the pharmacotherapeutic groups in our market, they contain the ammonium salt of glycyrrhizinic acid (ammonium glycyrrhizinate). “Viusid” is used as an immunostimulating agent, “Epigen Intimate” for intimate hygiene is available in the form of a spray used for the prevention and treatment of genital herpes.

Table 3: Comparison of quality indicators of substances of glycyrrhizinic acid

№	Indicators	European Pharmacopoeia 8.0, 2014 (01/2008: 1772)	LLC Navkar Servis FSP 42 Uz-18307420-2556-2014	Iboh AN RUz VFS 42 Uz-2369-2013	UzKFITI named after A. Sultanov FS 42 Uz- 0979-2012
1	Nameofdrug	**Ammonium Glycyrrhizate**	**Glycyram**	**Glyceram**	**Glycyrrhizinic acid**
2	Description	White or yellowish white, sugary sweet taste hygroscopic powder.	White or yellowish white, sugary sweet taste hygroscopic powder.	Fine-crystalline powder from dark yellow to cream color, with a sugary sweet taste, with a specific smell.	Amorphous powder, light cream color, with a sweet taste, odorless.
3	Authenticity	1) IR spectrophotometry versus ammonium glycyrrhizinate CRS.	1. The UV spectrum of a 0.004% solution of the drug in 50% ethyl alcohol in the region from 220 nm to 300 nm has an absorption maximum at a wavelength of (252 ± 2) nm.	1. Staininginorange (triterpenoids).	1. When mixed with chloroform, acetic anhydride and concentrated sulfuric acid, the lower liquid layer turns orange (triterpenoids).
		2) 0.5% alkaline solution of the drug gives a characteristic reaction to alkali on litmus paper.	2. 0.1 g of the drug is dissolved in 10 ml of a 0.25% ammonia solution and shaken vigorously, a stable foam (saponins) is formed.	2. The UV spectrum in the range from 240 to 260 nm has a maximum absorption at (251 ± 2) nm (glycyrrhizinic acid and its salt)	2. The UV spectrum of a 0.002% solution of the drug in 50% ethyl alcohol in the region from 230 to 300 nm has a maximum absorption at a wavelength of (251 ± 3) nm.
			3. 0.2% aqueous solution of the drug gives a characteristic reaction to ammonium (GF XI, issue 1, p. 167, method II).		

Table 3 Cont'd

4	Solubility	Slightly soluble in water, slightly soluble in boiling water (the solution becomes cold when cooled), very slightly soluble in ethanol, practically insoluble in acetone, ether and chloroform. Soluble in dilute alkali solutions.	Slightly soluble in water, slightly soluble in boiling water (the solution becomes cold when cooled), very slightly soluble in ethanol, practically insoluble in acetone, ether and chloroform. Soluble in dilute alkali solutions.	Slowly soluble in water with the formation of a viscous solution, easily soluble in boiling water, practically insoluble in chloroform, ethyl ether, acetone and 96% ethanol.	It is soluble in 96% alcohol, slightly soluble in acetone, very slightly soluble in water, insoluble in ether, chloroform (GF XI, issue 1, p. 175).
5	Meltingtemperature	Noindicator.	Noindicator.	Not lower than 200^0C (with decomposition)	Not lower than 195^0C (with decomposition)
6	Specificrotation	Polarimetric. From $+49^0$ to $+54^0$ (1% (anhydrous substance) solution in a 50% (v / v) ethanol solution)	Polarimetric. From $+49^0$ to $+54^0$ (1% (anhydrous substance) solution in a 50% (v / v) ethanol solution)	Polarimetric. From $+54^0$ to $+68^0$ (0.5% solution of the drug in 0.25% ammonia solution)	From + 54^0 to + 65^0 (5% solution in methanol, GF XI, issue 1, p. 30).
7	Solutiontransparency	Noindicator.	The resulting solution should be transparent (GF XI, issue 1, p. 198).	Noindicator.	A solution of 0.1 g of the drug in 10 ml of 96% alcohol should be transparent (GF XI, issue 1, p. 198).
8	The color of the solution	The color intensity of the solution prepared for determining transparency should be no more than the BY7 standard (2.2.2, method 1).	The color intensity of the solution prepared for determining transparency should be no more than the BY7 standard (Heb. F 6.0, 2.2.2, method 1).	Noindicator.	A solution of 0.1 g of the drug in 10 ml of 96% alcohol should not exceed reference 46 (GF XI, issue 1, p. 194).
9	Masslossondrying	nomorethan 6.0%	There should be no more than 6.0% (GF XI, issue 1, p. 176).	Not more than 10% (GF XI, issue 1, p.176).	Not more than 8% (GF XI, issue 1, p. 176).
10	Chlorides	Noindicator.	Noindicator.	no more than 0.01% (GF XI, issue 1, p. 166)	Noindicator.
11	Sulphates	Noindicator.	no more than 0.2% (GF XI, issue 1, p. 166)	no more than 0.2% (GF XI, issue 1, p. 166)	Noindicator.
12	SulphatedAsh	shouldnotexceed 0.2%	should not exceed 0.2% (GF XI, issue 2, p.25)	should not exceed 0.35% (GF XI, issue 2, p.24)	should not exceed 1.0% (GF XI, issue 2, p.24)
13	Heavymetals	nomorethan 20 ppm	not more than 0.002% (GF XI, issue 1, p. 165)	no more than 0.001% (GF XI, issue 1, p. 165)	no more than 0.001% (GF XI, issue 1, p. 165)
14	pH	Noindicator.	Potentiometric. Must be between 4.0 and 4.5.	Potentiometric. From 4.0 to 5.0 (1% r-r water)	Potentiometric. 2.5 to 4.5 (0.5% solution in 50% alcohol)
15	Residualorganicsolvents	Noindicator.	Noindicator.	GC method. The drug should not contain residual alcohol	GLC method. The drug should not contain residual alcohol

Table 3 Cont'd

16	RelatedCompounds	The content of 18 b-glycyrrhizinic acid is not more than 10.0%; The content of related compound A is not more than 5.0%; The content of individual impurities is not more than 2.0%; The content of the amount of unidentified impurities is not more than 7.0%. **Method - HPLC**	The content of 18 b-glycyrrhizinic acid is not more than 10.0%. The content of related compound A is not more than 5.0%. The content of individual impurities is not more than 2.0%; The content of the amount of unidentified impurities is not more than 7.0%. **Method - HPLC**	Noindicator.	HPLC method. the sum of the areas of all additional peaks should not exceed the area of the main peak (not more than 10%).
17	Microbiological purity	Noindicator.	GF XI, issue 2, p.193 and Amendment No. 2 dated October 12, 2005, category 1.2.	GF XI, issue 2, p.193 and Amendment No. 2 dated 10/12/2005, category 3.2.	GF XI, issue 2, p.193 and Amendment No. 2 dated 10/12/2005, category 3.2.
18	Quantitation	The content of the basic substance shall be not less than 98.0% and not more than 102%, in terms of dry matter (2.2.20). **Method - non-aqueoustitration.**	The glycyram content should be at least 98.0% and not more than 102%, calculated on the dry matter. **Method - spectrophotomerism**	From 80% to 82% MASHK and the accompanying 18-a-H isomer, partially hydrolyzed derivatives of 18-a and 18-p glycyrrhizinic acid and glycyrrhetic acid. **Method - HPLC**	The content of glycyrrhizinic acid should be at least 85%. **Method - HPLC**
19	Packaging	Noindicator.	0.5 kg, 1.0 kg, 2.0 kg (cans)	0.25 kg, 0.5 kg, 1.0 kg (cans)	100 g (vials)
20	Shelflife	Noindicator.	3 years	2 years	2 years

HPLC - high performance liquid chromatography.

According to the table 3, the standardized indicators for the substance shows that the manufacturer LLC "NavkarServis" began harmonization according to the requirements of the European Pharmacopoeia of the 8th edition [6, 7, 8, 9, 10, 11, 12]..

CONCLUSIONS

1. A review of the literature data, a comparative analysis of the standardized quality indicators of some drugs based on licorice naked, and the results of a content analysis of the nomenclature of drugs containing glycyrrhizinic acidwere obtained.
2. All local manufacturers of the substance of glycyrrhizinic acidand its derivatives gradually (upon expiration of the registration certificate or when amendments are made to ND) harmonize the quality in accordance with the requirements of the European Pharmacopoeia.
3. The analysis of data from the State Register of Medicines and Medical Devices and Literature showed an increase in interest in glycyrrhizinic acid. The structure of each group of the studied nomenclature of drugs was studied by quality indicators, composition, release forms, pharmacotherapeutic group, origin and manufacturers.

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