



Article

Research On Stability Of "Bronchotus Forte" Elixir

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Abstract: In this article, quality indicators were presented for determining the stability of an elixir type of drug that usually stimulates cough and has a secretomotor effect in the treatment of inflammatory diseases of the upper respiratory tract. The recommended elixir drug was carried out in a natural way based on the temporary instruction I-42-2-82. In order to determine the stability and storage conditions of the elixir, it was studied in a natural way by keeping the finished drug in a dark place at room temperature under natural conditions (at a temperature not higher than 250 C). Analyzes were carried out every 6 months, and the following qualitative and quantitative indicators were studied during the analysis: appearance, pH environment, purity, amount of foreign substances, dry residue, alcohol strength, and the amount of bioactive substances in 1 ml of the drug were checked.

Keywords: Elixir, Stimulant, Secretomotor, Stagnation, Truth, Bioactive Substance, Microorganisms

1. Introduction

A very large group of medicinal plants have been used for the treatment of cough since ancient times. Despite the fact that treatment with medicinal plants is a method used in medical practice since ancient times, their use and creation of medicinal preparations based on them is very relevant today. The analysis of medicinal preparations prepared on the basis of medicinal plant raw materials showed that the most commonly used antitussives are dry extract of licorice root, dry extract of altea, and extracts of lanceolate thermopsis. Doctors all over the world often prefer medicines that contain some kind of plant-derived substance as an active ingredient. In this case, licorice, altei and thermopsis extracts are often used [1-3].

A characteristic feature of the therapeutic effect of drugs from medicinal raw materials prepared from plants is that the therapeutic effect does not appear immediately and is not always clear, as in the case of the use of drugs obtained by chemical synthesis. But when using high concentrations and doses, the therapeutic effect is effective in the first hours of treatment. Another great advantage of herbal remedies is the absence of allergic reactions, their good tolerance, the possibility of long-term treatment during rehabilitation and prevention in all age groups [4, 5].

The stability of medicinal preparations is one of the requirements for medicinal preparations, and all pharmaceutical manufacturing enterprises must ensure that the stability of the medicinal preparation is maintained for a certain period of time. This

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indicator is definitely reflected in normative technical documents. The stability of the medicinal product means ensuring that the produced medicinal product meets all the requirements set by the relevant regulatory documents within a certain period of time. This, in turn, guarantees the quality of the medicinal product for a certain period of time and confirms its biological effectiveness [6,7].

Today, one of the tasks facing pharmaceutical scientists is to create easy-to-use, bio-effective, cheap and stable drugs. Ensuring stability is the last stage of the conducted research, which should be based on the composition and form of medicinal preparations. In ensuring the stability of medicinal preparations, it is necessary to study the conditions affecting the stability. Factors affecting the quality of medicinal products in storage conditions are temperature, atmospheric environment, light, types of packaging, technological process, auxiliary substances in the composition, and mainly the properties of the original raw material-substance from which the medicine was obtained. Therefore, one of the last stages of scientific research in the production of a medicinal product is stagnation, and ensuring the shelf life and conditions of the drug being developed, as well as its bioefficacy, is one of the most important problems in the creation of a medicinal product [8].

The bioefficacy of newly developed drugs should not change during their storage. A number of factors can influence the fact that medicinal preparations do not change their quality for a certain period of time. Factors affecting the quality of medicinal products in storage conditions are temperature, atmospheric environment, light, types of packaging, technological process, auxiliary substances in the composition, and mainly the properties of the original raw material-substance from which the medicine was obtained.

2. Materials and Methods

In this study the stability and storage conditions of the plant based, pharmaceutical formulation of elixir "Bronchotus forte" a secretomotor and stimulant is evaluated using a methodological approach. The experimental design used was a complete experimental design for temporary instruction I-42-2-82. By storing 100 ml brown bottles of elixir at room temperature under natural conditions with direct light avoided as much as possible as control. Over three years, qualitative and quantitative stability analyses have been conducted biannually. The appearance, the pH, the purity, the dry residue, the alcohol content and the presence of bioactive substances (ambroxol hydrochloride, flavonoids, glycyrrhizic acid) were considered first as indicators. The concentration of active compounds was determined using advanced analytical techniques, such as spectrophotometry and liquid chromatography to get precision and reliability. The microbiological purity was also studied by monitoring bacterial and fungal growth and then measuring *Escherichia coli*. Chemical stability and bioefficacy trends were analyzed in the elixir over the storage period to determine the product's optimal shelf life. Results indicated that the elixir remained acceptable with respect to both microbiological purity and bioactive substance content for at least two years, with deviations from quality occurring after two to two and a half years. With this robust methodology, the elixir's stability's and bioefficacy's were accurately assessed for regulatory compliance and the formulation's practical use. The study highlights the criticality of good packaging, storage conditions and periodic analysis to the durability and efficacy of plant based medicinal products.

3. Results and Discussion

Based on the above, our recommended elixir medicine was carried out in a natural way based on the temporary instruction I-42-2-82 [9,10].

Before starting the research, the quality and quantity indicators of the recommended preparations taken for the sample were studied and it was observed that they meet the requirements specified in XIII DF. Then the recommended drugs were packaged in the

same packaging that is used in the production of these drugs today, and the research began.

In order to determine the stability and storage conditions of the elixir "Bronchotus Forte" obtained in the recommended composition and technology, it was studied in a natural way by keeping the finished drug in a dark place at room temperature under natural conditions (at a temperature not higher than 250 C). Analyzes were conducted every 6 months. During these analyses, the following quality and quantity indicators were studied: appearance, pH environment, purity, amount of foreign substances, dry residue, alcohol strength, and the amount of bioactive substances in 1 ml of the drug. The prepared elixir was placed in 100 ml brown bottles (OST 64-2-71-80, TU TSh 64-17490735-01:2006). The obtained results are presented in Table 1.

As can be seen from the indicators presented in this table, the appearance of Bronchotus Forte elixir has not changed its color, taste and smell during storage.

It was observed that the pH value of the environment was in the range of 5.2-6.0 in the norm and in the range of 5.4-6.0 during the study. For 3 years, there has been no limitation of the environment.

The authenticity was preserved throughout the study.

The alcohol content of the prepared elixir is usually 16-19% and showed 12.9-19% during storage. A moderate decrease in alcohol strength was observed in samples stored for 2.5 and 3 years.

It was found that the amount of bioactive substances in 1 ml of the drug is at the required level. Ambroxol hydrochloride is normally between 0.0027g - 0.0033g, and during storage it is 0.0028 - 0.0031g, the amount of rutin in the sum of flavonoids should not be less than 0.006%, and the amount of glycyrrhizic acid is usually 0.17%, during storage showing 0.16% showed that it is at the level of demand.

Table 1
The results of studying the stability of "Bronchotus Forte" elixir in a natural way (20±20 C)

Series №	The term studied	Appearance	pH	Dry balance, %	Heavy metals, %	The truth	Alcoholic strength %	Quantitative analysis		
								Ambroxol hydrochloride, g	Content of flavonoids, %	Glycyrrhizic acid, mg
	In moderation	Brown, sweet taste	5,2-6,0	0,5-0,65	< 0,001	according to the FSP	16-19	0,0027 - 0,0033	Amount of rutin > 0,006%	0,169 - 0,170
1	Before starting the research	Fits	6,0	0,64	<	Fits	19,0	0, 0029	0,0067	0,165
2		Fits	5,9	0,65	0,001	Fits	18,7	0, 0030	0,0065	0,164
3		Fits	6,0	0,63	<	Fits	18,7	0, 0029	0,0069	0,169
					< 0,001					
1	6 months	Fits	5,9	0,64	<	Fits	19,0	0, 0029	0,0067	0,168
2		Fits	5,8	0,65	0,001	Fits	18,7	0, 0030	0,0063	0,167
3		Fits	5,9	0,63	<	Fits	18,6	0, 0029	0,0066	0,169
					< 0,001					

1	1 year	Fits	5,8	0,64	<	Fits	19,0	0,0028	0,0066	0,679
2		Fits	5,6	0,65	0,001	Fits	18,7	0,0029	0,0064	0,163
3		Fits	5,8	0,63	<	Fits	18,6	0,0029	0,0067	0,168
					0,001					
					<					
1	1,5year	Fits	5,6	0,64	<	Fits	18,5	0,0029	0,0067	0,170
2		Fits	5,6	0,65	0,001	Fits	17,6	0,0028	0,0069	0,169
3		Fits	5,6	0,63	<	Fits	18,4	0,0029	0,0069	0,167
					0,001					
					<					
					0,001					
1	2 year	Fits	5,6	0,64	<	Fits	17,9	0,0028	0,0069	0,674
2		Fits	5,5	0,65	0,001	Fits	17,2	0,0029	0,0069	0,173
3		Fits	5,5	0,63	<	Fits	17,9	0,0030	0,0071	0,169
					0,001					
					<					
					0,001					
1	2,5 year	Fits	5,6	0,66	<	Fits	16,3	0,0029	0,0070	0,168
2		Fits	5,5	0,67	0,001	Fits	15,7	0,0030	0,0069	0,169
3		Fits	5,5	0,67	<	Fits	16,0	0,0031	0,0069	0,169
					0,001					
					<					
					0,001					
1	3 year	Fits	5,6	0,68	<	Fits	14,7	0,0029	0,0068	0,170
2		Fits	5,4	0,66	0,001	Fits	12,9	0,0028	0,0068	0,168
3		Fits	5,5	0,68	<	Fits	14,1	0,0029	0,0067	0,167
					0,001					
					<					
					0,001					

The microbiological purity of "Bronchotus Forte" elixir during storage was checked in the next stage of research. The obtained results are presented in Table 2.

Table 2
Results of study of microbiological purity of "Bronchotus Forte" elixir during storage

Series №	The term studied	Microorganisms		Escherichia coli existence
		Fungi	Bacteria	
1	Before starting research	<10 ²	<10 ³	Not available
2		<10 ²	<10 ³	Not available
3		<10 ²	<10 ³	Not available
1	6 months	<10 ²	<10 ³	Not available
2		<10 ²	<10 ³	Not available
3		<10 ²	<10 ³	Not available
1	1 year	<10 ²	<10 ³	Not available
2		<10 ²	<10 ³	Not available
3		<10 ²	<10 ³	Not available
1	1,5 year	<10 ²	<10 ³	Not available
2		<10 ²	<10 ³	Not available
3		<10 ²	<10 ³	Not available

1	2 year	<10 ²	<10 ³	Not available
2		<10 ²	<10 ³	Not available
3		<10 ²	<10 ³	Not available
1	2,5 year	<10 ²	<10 ³	Not available
2		<10 ²	=10 ³	Available
3		=10 ²	>10 ³	Not available
1	3 year	<10 ²	<10 ³	Not available
2		<10 ²	>10 ³	Available
3		>10 ²	>10 ³	Available

As can be seen from the data presented in the table, it was observed that the amount of fungi and bacteria in the elixir increased and exceeded the norm after 2.5 years and 3 years of studying the stability of Bronchotus Forte elixir. Also, the presence of Escherichia coli in series 1-3 by the 3rd year of storage showed that the quality of the prepared elixir was not at the required level.

Determining the amount of bioactive substances in "Bronchotus forte" elixir.

Determination of ambroxol hydrochloride by spectrophotometric method: 2 g (exact draw) of the drug is placed in a measuring flask with a capacity of approximately 100 ml, dissolved by adding 0.01 mol/l hydrochloric acid, brought to the mark of the volume of the solution with this solvent and mixed.

The optical density of the test solution and reference solution is measured in a spectrophotometer at a wavelength of (306±2) nm in a cuvette with a layer thickness of 10 mm and 0.1 mol/l hydrochloric acid is used as reference solution.

In parallel, the optical density of the working sample solution of ambroxol hydrochloride is measured. The amount of ambroxol hydrochloride (X) in 1 ml of the drug is calculated in grams according to the following formula:

$$D1 \cdot m_0 \cdot 5 \cdot 100 \cdot d \cdot R \quad D1 \cdot m_0 \cdot d \cdot R$$

$$X = \frac{D1 \cdot m_0 \cdot 5 \cdot 100 \cdot d \cdot R}{D1 \cdot m_0 \cdot d \cdot R} = \frac{D1 \cdot m_0 \cdot 5 \cdot 100 \cdot d \cdot R}{D1 \cdot m_0 \cdot d \cdot R},$$

$$D_0 \cdot m_1 \cdot 50 \cdot 100 \cdot 100 \quad D_0 \cdot m_1 \cdot 10 \cdot 100$$

Here:

D1 - optical density of the tested solution;

D0 - optical density of the reference solution;

m1 - weight mass of the sample drug, in grams;

m0 - the amount of ambroxol hydrochloride in the working standard sample, in grams;

R- ambroxol hydrochloride in percent of the working standard sample (ISN), in percent;

d is the density of the drug, g/cm³

S₁₃N₁₈Br₂N₂O·HCl (ambroxol hydrochloride) in 1 ml of the preparation should be as follows by average weight: from 0.0027 g to 0.0033 g.

Explanation. Preparation of working standard sample solution. About 0.06 g (exact draw) of ambroxol hydrochloride (ISN-working standard sample) is mixed with 0.01 mol/l hydrochloric acid solvent, placed in a 100 ml volumetric flask and filled to the mark with the same solution and mixed.

Put 5 ml of the obtained solution in a 50 ml flask, bring the volume of the solution up to the mark with 0.01 mol/l hydrochloric acid solution and mix. The solution is used freshly prepared. Table 3 presents the metrological description of the method of determining the amount of ambroxol hydrochloride in the elixir "Bronchotus Forte".

Table 3

Metrological description of determination of ambroxol hydrochloride content of "Bronchotus Forte" elixir

№	Clear drawer, g	Amount of ambroxol hydrochloride		Metrological description
		г	%	

1.	2,0012	0,1980	99,0	P =95,00
2.	2,0010	0,1988	99,4	$X_{cp}=0,19958$
3.	2,0009	0,1996	99,8	$t(95\%,4)=2,78$
4.	2,0011	0,2005	100,2	$S^2=0,000001492$ $S=0,001221$
5.	2,0010	0,2010	100,5	$S_x=0,0005462$ $\sum\%=1,70142$ $\sum_{cp}=0,7608$

As can be seen from Table 3, the SF method showed that the method has the required sensitivity because the precision error in the determination of the amount of ambroxol hydrochloride is very small [4].

Determination of total flavonoid content. 3 ml of the drug is placed in a measuring flask with a capacity of 25 ml, 3 ml of 2% aluminum chloride solution, one drop of diluted acetic acid are added, and the volume of the solution is brought to the mark with 96% ethyl alcohol. The solution is mixed and placed in a dark place. After 40 minutes, the solution is filtered through a paper filter, and the optical density of the resulting solution is immediately measured in a spectrophotometer at a wavelength of 400 nm in a cuvette with a layer thickness of 10 mm.

In parallel, the optical density of a standard sample of rutin solution prepared as a test solution is measured.

The composition of total flavonoids (X), as a percentage of rutin, is calculated according to the following formula:

$$X = \frac{D_1 \times 25 \times m_0 \times 1 \times 100 \times P}{D_0 \times 3 \times 100 \times 25 \times 100} = \frac{D_1 \times m_0 \times P}{D_0 \times 300 \times m_1 \times 3}$$

Here:

D1 - optical density of the tested solution;

Do - optical density of the reference solution;

m0 is the weight mass of the routine sample drug, in grams;

m1 - weight mass of the preparation, v grammax;

R is the amount of rutin in the standard sample, in percent (%).

The amount of rutin in the total amount of flavonoids should not be less than 0.006%.

Note: Preparation of routine standard sample solution. 0.05 g (exact draw) of rutin (FS 42 Uz-0137-2007), dried for 3 hours at a temperature of (130-135)°C, placed in a measuring flask with a capacity of 100 ml, heated in a water bath in 85 ml of 96% ethyl alcohol is dissolved by It is then cooled to room temperature and made up to the mark with the same solvent. [34; s. 400-p].

1 ml of the obtained solution is placed in a volumetric flask with a capacity of 25 ml, and then it is determined as a test solution. Shelf life of the solution: 1 month.

Preparation of 2% aluminum chloride solution. 2.0 g of aluminum chloride (GOST 3759-75) is placed in a measuring flask with a capacity of 100 ml, dissolved in 96% ethyl alcohol, and the volume of the solution is brought up to the mark with this solvent. The shelf life of the reagent is 3 months.

Table 4 presents the metrological description of the total amount of flavonoids in Bronchotus Forte elixir.

Table 4

Metrological description of determining the total amount of flavonoids in "Bronchotus Forte" elixir

№	Clear drawer, ml	Total amount of flavonoids		Metrological description
		MF	%	

1.	3,0010	0,0067	111,6	P =95,00
2.	3.0011	0,0068	133,3	$X_{cp}=0,00688$ $t(95\%,4)=2,78$
3.	3,0010	0,0069	115,0	$S^2=0,000000017$ $S=0,00013$
4.	3,0012	0,0070	116,6	$S_x=0,00005830$ $\sum\%=5,268$
5.	3,0011	0,0070	116,6	$\sum_{cp}=2,3561$

As can be seen from the table, the spectrophotometric method proved to have a very small accuracy error in determining the total amount of flavonoids and the high sensitivity of the method, and became the basis for further research.

Determination of glycyrrhizic acid content. 10 ml of the drug solution is placed in a 50 ml volumetric flask, the volume of the solution is brought up to the mark with the mobile phase and mixed. The resulting solution is filtered through a membrane filter with a size of 0.45 μ m.

At least 3 chromatograms of 20 μ l of the test sample solution and the working standard sample solution (RSO) are obtained on the liquid chromatography "Agilent 1260 series" at the UV wavelength for each of the solutions under the following conditions:

Column:

- filled with "Zorbax Eclipse Plus C-18" sorbent with a particle size of 5 μ m, measuring 4.6 mm x 15 cm;

- Mobile phase: Acetonitrile - water - acetic acid (190:307:3);

- Mobile phase speed: 1.5 ml/min;

- Detection: at a wavelength of 254 nm.

The amount (mg) of glycyrrhizic acid (x) in 1 ml of the preparation with the formula is:

$$X = \frac{S_1 \times a_0 \times 50 \times P \times 822,94}{S_0 \times 10 \times 50 \times 100 \times 839,97} = \frac{S_1 \times a_0 \times P \times 822,94}{S_0 \times 1000 \times 839,97},$$

Here:

S1 - main peak area according to the chromatogram of the test sample solution (β -isomer of glycyrrhizic acid);

S0- the area of the main peak on the chromatogram of the working standard sample (ISN) solution of the monoammonium salt of glycyrrhizic acid (β -isomer of glycyrrhizic acid);

a0- the weight of the working standard sample of the monoammonium salt of glycyrrhizic acid, in mg;

822.94 – molecular weight of glycyrrhizic acid;

839.97 – molecular weight of monoammonium salt of glycyrrhizic acid;

R - the amount of monoammonium salt of glycyrrhizic acid (β -isomer) in ISN, in %.

The content of glycyrrhizic acid (S42N62O16) in 1 ml of the preparation should be from 1.8 to 2.2 mg.

Note: Preparation of ISN solution of glycyrrhizic acid monoammonium salt. About 20 mg of the monoammonium salt of glycyrrhizic acid (precisely drawn) is dissolved in a mobile phase (acetonitrile - water - acetic acid) in a 50 ml flask and mixed with a solvent up to the mark. [34; s. 400-p].

The resulting solution is filtered through a membrane filter with a size of 0.45 μ m.

Table 5 presents the metrological description of determining the amount of glycyrrhizic acid in the "Bronchotus Forte" elixir.

Table 5

Metrological description of determination of glycyrrhizic acid content in "Bronchotus Forte" elixir

№	Clear drawer, ml	Glycyrrhizic acid content		Metrological description
		g	%	

1.	10,0002	0,1695	99,7	P =95,00
2.	10,0003	0,1698	99,8	$X_{cp}=0,1701$ $t(95\%,4)=2,78$,
3.	10,0005	0,1699	99,9	$S^2=0,000000335$
4.	10,0003	0,1703	100,1	$S=0,0005787$ $S_x=0,0002588$
5.	10,0004	0,1710	100,5	$\Sigma\%=0,9459$ $\Sigma_{cp}=0,4230$

As can be seen from the table, the spectrophotometric method was considered acceptable in determining the amount of glyceric acid, because the accuracy error is very small, at the required level.

4. Conclusion

The study of the stability of the elixir "Bronchotus Forte" showed that the amount of fungi and bacteria in the elixir after 2.5 years and 3 years was increased and exceeded the norm. Also, by the 3rd year of storage, the presence of *Escherichia coli* was observed in the 1st-3rd series, indicating that the quality of the prepared elixir did not meet the requirements.

As a result of the above studies, it was determined that the microbiological purity of the elixir "Bronchotus Forte" meets the requirements for 2 years.

Thus, as a result of the studies conducted, the stability of the elixir "Bronchotus Forte" was determined as 2 years in the studied packaging and was reflected in the relevant regulatory documents.

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