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The Peculiarities of Studies on the Stability of Ambronat

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ABSTRACT: In this article, the quality indicators for determining the persistence of a cough–stimulating and secretomotor type of drug commonly used in the treatment of inflammatory diseases of the upper respiratory tract were investigated. “Ambronate” qiyami did not change its color, taste and smell during the years of its stability in terms of its appearance. The indicator of pN environment is normally in the range of 5.0–7.5 and during the study it was in the range of 6.3–7.8. The results for the 3 years of the study were presented. In the 2.5–3rd year of storage, the amount of fungi and bacteria in the kiyama increased, and the results of the study in 2.5 years of storage were presented. In the quantitative analysis, the amount of ambroxol hydrochloride was determined by the spectrophotometric method, the obtained results were reflected in the regulatory documents.

KEYWORDS: ambronat, syrup, stimulant, secretomotor, truth, bioactive substance, microorganisms, stagnation, inflammatory diseases, stability.

INTRODUCTIONS

Today, one of the challenges facing pharmaceutical scientists is the creation of easy–to–use, bio effective, cheap and stable drugs. Ensuring stability is the last stage of research, which should be based on the composition and form of the drugs. When ensuring the stability of drugs, it is necessary to study the conditions affecting stability. Factors affecting the quality of medicinal products under storage conditions are temperature, atmospheric environment, light, types of packaging, technological process, excipients in the composition and mainly the properties of the starting raw material from which the medicinal product is obtained. Therefore, one of the last stages of scientific research in the production of a drug is stagnation, and ensuring the shelf life and conditions of the drug being developed, as well as its bio effectiveness, is one of the most important problems in creating a drug [1–3]. The stability of “Ambronate”, obtained using the technology recommended by us, was studied over a certain period of time when stored in a dark place at room temperature (under natural conditions (at a temperature not exceeding 250 C). Quality indicators were measured every 6 days and months.

MATERIALS AND METHODS.

In the studies, the following qualitative and quantitative indicators were determined: appearance, pH of the medium, purity, density, amount of foreign substances and the amount of biologically active substances in 1 ml of the drug. The solution prepared for this purpose was placed in 100 ml brown bottles (OST 64–2–71–80, TU TSh 64–17490735-01:2006).

RESULTS AND DISCUSSIONS

The results obtained are presented in Table 1. As can be seen from the indicators presented in Table 1, the Ambronat cues have not changed their color, taste and smell over the years of stability of their appearance. The pH of the environment is normally in the range of 5.0–7.5, and during the study it was in the range of 6.3–7.8. The limit from the norm corresponded to 3 years of the study.

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Table 1. The authenticity was maintained throughout the study

№	The term studied	Appearance	pH	Truth	density, g/cm^3	Foreign substances	The amount of bioactive substances in 1 ml of the drug	
	On average	Dark brown and smells like an aromatizer	5,0–7,5	Belongs to FSP	1,200–1,240	< 0,5 %	Ambroxol hydrochloride –0,0027g–0,0033g	Sodium benzoate–0,0047g–0,0053g
1	Before starting research	Fits	6,3	Fits	1228	0,38	0,0029	0,0050
2		Fits	6,4	Fits	1230	0,38	0,0029	0,0051
3		Fits	6,3	Fits	1230	0,37	0,0029	0,0048
1	6 months	Fits	6,5	Fits	1228	0,38	0,0029	0,0051
2		Fits	6,4	Fits	1230	0,40	0,0028	0,0049
3		Fits	6,6	Fits	1230	0,35	0,0029	0,0050
1	1 year	Fits	6,4	Fits	1229	0,39	0,0029	0,0052
2		Fits	6,8	Fits	1233	0,41	0,0030	0,0050
3		Fits	6,5	Fits	1232	0,36	0,0029	0,0049
1	1,5 year	Fits	6,5	Fits	1230	0,40	0,0029	0,0047
2		Fits	6,4	Fits	1233	0,42	0,0030	0,0047
3		Fits	6,6	Fits	1235	0,39	0,0031	0,0049
1	2 year	Fits	6,7	Fits	1232	0,41	0,0030	0,0049
2		Fits	7,0	Fits	1235	0,40	0,0029	0,0050
3		Fits	6,8	Fits	1233	0,40	0,0030	0,0050
1	2,5 year	Fits	7,4	Fits	1230	0,42	0,0028	0,0052
2		Fits	7,5	Fits	1232	0,41	0,0030	0,0051
3		Fits	7,3	Fits	1235	0,44	0,0032	0,0052
1	3 year	Fits	7,8	Fits	1233	0,42	0,0030	0,0050
2		Fits	7,8	Fits	1234	0,42	0,0029	0,0051
3		Fits	7,7	Fits	1235	0,44	0,0029	0,0048

Table 2. The results of study of microbiological purity during storage of "Ambronat" paste

№	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

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

It can be seen that the density of the solution is 1200–1240 g/cm3 during storage and 1228–1235 g/cm3. In studies, foreign substances have been observed to be normal at <0.5% and remain positive at 0.35–0.41% with diet.

It was noted that the amount of biologically active substances in 1 ml of the drug is at the required level.

Ambroxol hydrochloride is usually in the range of 0.0027g–0.0033g and during storage–0.0028–0.0032g, and the amount of sodium benzoate is in the range 0.0047g–0.0053g and during storage–0.0047–0.0052 at the demand level, showing indicators.

The above indicators, in turn, determine the quality of the recommended syrup in a certain period of time.

The next stage of research was devoted to checking the microbiological purity of the Ambronat paste, obtained in the recommended composition, during storage. According to the literature, it is believed that the microbiological purity of alcohol–containing preparations in liquid content is maintained for a long time.

The results obtained are presented in Table 2. From the data presented in this table, it is clear that the microbiological purity of the Ambronat paste during 2–year storage is at the required level in all studied series. In the 2.5–3rd year of storage, the number of fungi and bacteria in the mixture increased, and the presence of E. coli in the 1st series in the 2.5th year of storage and in the 2nd and 3rd series in the 3rd year storage observed. This, in turn, means that the quality of Ambronate in the years under study (2.5 and 3 years) is not at the required level. As a result of the above studies, it was established that the microbiological purity of the Ambronat paste, obtained according to the recommended composition and technology, meets the requirements for 2 years. Thus, as a result of the studies, the stability of the drug “Ambronate” was determined as 2 years in the studied packaging and is reflected in the relevant regulatory documents [4,5].

The assessment of quality indicators “Ambronat”. The quality of Syrup obtained in the recommended content and technology was examined in accordance with the requirements for syrup using the methods listed in XIII DF. Quality indicators such as appearance, purity, density, pH of the medium, foreign impurities in the paste, microbiological purity and quantitative analysis were studied. The amount of recommended syrup poured into packaging containers was also studied [6–9].

The next stage of research was devoted to studying the organoleptic properties of the prepared syrup. The assessment was carried out using a 100–point system.

The results obtained are presented in Table 3.

Table 3. The organoleptic properties of “Ambronat” consistency learning outcomes

Appearance	Grade	Color	Grade	Taste and smell	Grade	Total score
Clear, viscous liquid	100	White clear	100	Sweet, delicious, orange smell	100	100

As can be seen from the obtained indicators, the Ambronat composition, obtained according to the recommended composition and technology, is at the required level in terms of organoleptic indicators.

Further studies examined the appearance, purity, density, pH of the medium, foreign substances in the composition, microbiological purity and quantitative analysis of the recommended syrup using the methods presented in Chapter II.

The results of the study of quality indicators of the recommended Ambronat foundation are presented in Table 4. The fact that the standard and results obtained in Table 4 are at the required level indicates that the content and technology we recommend are chosen correctly [10,11].

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Table 4. Evaluation of the quality indicators of "Ambronat"

Learned indicators	Specification (Normally)	The results obtained
Appearance	Sweet delicious, orange–scented, clear, viscous liquid.	Fits
The truth	1. In the chromatogram of the test solution, the main spot should be the same as the ambroxol hydrochloride with the standard solution; 2. Specific reaction to chlorides; 3. Reaction specific to primary amines; 4. The main peak of propylene glycol in the test solution chromatogram should coincide with the working solution and hold for 5 minutes; 5. Specific reaction of benzoate ion; 6. Specific reaction to ethyl alcohol.	Fits; Fits; A yellow spot has formed; 4.5 minutes; Pink–yellow; A precipitate formed; A precipitate formed with light yellow.
Density	1,200 to 1,240 g/cm3	1228 g/cm3
pH environment	5,0–7,5	6,3
Foreign substances	In addition to the main spot, up to two more spots are allowed in the chromatogram of the test solution. But they should not be larger than the stain of the standard solution of Ambronate hydrochloride (each foreign substance should not be larger than 0.5%). Also, it is allowed to have only one spot on the starting line, but they should not be larger than the spot of the standard solution of ambroxol hydrochloride (each foreign substance should not be larger than 1%).	0,38% 0,89%
The volume filled in the package	50 ml, 90 ml and 100 ml of solution can be deviated from ±3%, and ±1.5% for 200 ml.	OST 64–492-85.
Microbiological cleanliness	Category 3A	At the level of demand
Quantitative analysis: –Ambroxol hydrochloride –Sodium benzoate	From 0.0027 to 0.0033 g in 1 ml of the drug	0, 0029g 0,0050g

Determination of the amount of biologically active substances in Ambronat paste:

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

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

The amount of ambroxol hydrochloride (X) in 1 ml of the drug is calculated in grams using the following formula:

$$X = \frac{D_1 \cdot m_o \cdot 5 \cdot 100 \cdot d \cdot P}{D_o \cdot m_1 \cdot 50 \cdot 100 \cdot 100} = \frac{D_1 \cdot m_o \cdot d \cdot P}{D_o \cdot m_1 \cdot 10 \cdot 100},$$

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Here:

D1–optical density of the test solution;

Do–is the optical density of the reference solution;

m1–is the mass of the drug sample, in grams;

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

R–ambroxol hydrochloride as a percentage of the working standard sample (WRS), as a percentage;

d–density of the drug, g/cm3.

$C_{13}H_{18}Br_2N_2O \cdot HCl$ (ambroxol hydrochloride) in 1 ml of the drug should be from 0.0027 g to 0.0033g based on the average weight in 1 ml of the drug.

Note: The preparation of a working standard sample solution. About 0.06 g (exact set) of ambroxol hydrochloride (ISN working standard sample) was mixed with a 0.01 mol/L hydrochloric acid solvent, placed in a 100 ml volumetric flask, filled to the mark with the same solution and mixed. Place 5 ml of the resulting solution in a 50 ml flask, bring the volume of the solution to the mark with 0.01 mol/l hydrochloric acid solution and mix. The solution is used freshly prepared.

Note: Reagents, titration solutions, nutrient media in the quality control methods of these drugs correspond to what is written in the sections of the European Pharmacopoeia [12, 13]. The metrological classification for determining the amount of ambroxol hydrochloride in Ambronate paste is given in Table 5.

Table 5. Metrological classification of the amount of ambroxol hydrochloride in "Ambronat" syrup (n=7)

№	Clear drawer, g	Amount of ambroxol hydrochloride found		Metrological characteristics
		g	%	
1.	2,0001	0,2905	96,8	P=95,00, X_{cp}=0,2965,
2.	2,0003	0,2955	98,5	t(95%,4)=2,78,
3.	2,0001	0,2977	99,2	S^2 =0,00001381, S=0,003716,
4.	2,0002	0,2994	99,8	S_x=0,001662,
5.	2,0004	0,2994	99,8	∑%=3,4849, $\sum_{cp}$=1,5585

II. Determination of the amount of sodium benzoate. 2.0 g (exact dosage) of the drug is placed in a 25 ml flask, adjusted to the mark with water and mixed. Take 20 ml of the resulting solution and 20 ml of a working standard solution of sodium benzoate and conduct at least 5 chromatograms of each solution with a UV detector in a liquid chromatogram under the following conditions:

– Column size (125x4.6) mm SorbentEclipseXDBC$_8$, a 5 µm packed column was used;

– Mobile phase: 20.0 g/mol concentrated phosphoric acid–acetonitrile solution (9:1) ammonium hydrogen phosphate to pH 7.0;

– Mobile phase speed 1.0 ml/min;

– Detectable at a wavelength of 240 nm;

– Chromatograph with 20 µl of standard solution (B).

The applicability of the chromatographic system is determined by the following conditions:

– The coefficient separating the two peaks should not be less than 2.0;

– The relative standard deviation of the two main peak surfaces should not exceed 1%;

Chromatograph 20 µl of the test solution and the reference solution (B) [176;].

The amount of sodium benzoate in 1 ml of the drug (X) in grams is found using the following formula:

$$X = \frac{S_1 \cdot m_o \cdot 5 \cdot 25 \cdot P \cdot \rho}{S_o \cdot m_1 \cdot 100 \cdot 25 \cdot 100} = \frac{S_1 \cdot m_o \cdot P \cdot \rho}{S_o \cdot m_1 \cdot 2000},$$

Here:

S_1–indicator of the peak area of sodium benzoate in the test solution;

So–the indicator of the peak area of sodium benzoate, calculated from the chromatogram of the reference solution (B);

m_1- is the mass of the medicine box, in grams;

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m_{0-} is the mass of a standard box of sodium benzoate, in grams;

p–is the density of the drug, g/cm3;

P–is the amount of sodium benzoate in the standard sodium benzoate solution specified in the certificate, percentage;

The amount of $C_7N_5O_2Na$ (sodium benzoate) in 1 ml of the drug should be from 0.0047 to 0.0053 g.

Note: 1. The preparation of a standard solution of sodium benzoate. 0.2 g (exact dosage) of sodium benzoate is placed in a 100 ml flask and dissolved in 50 ml of water. The volume of the solution is filled with water to the level of the flask and mixed.

The preparation of a working standard solution of sodium benzoate. 5 ml of standard solution (A) is placed in a 25 ml flask, diluted to the mark with water and mixed well [176, – p. 11].

The metrological classification for determining the amount of sodium benzoate in Ambronate paste is given in Table 6.

Table 6. The metrological classification of determining the amount of sodium benzoate in "Ambronat" syrup (n=7)

№	Anik torma, g	Sodium benzoate quantity		Metrological characteristics
		g	%	
1.	2,0001	0,4855	97,1	P=95,00, X_{cp}=0,4932,
2.	2,0003	0,4888	97,7	t(95%,4)=2,78,
3.	2,0001	0,4954	99,0	S^2 =0,000034, S=0,005835,
4.	2,0002	0,4977	99,5	S_x=0,0026, ∑%=3,2888
5.	2,0004	0,4989	99,7	$\sum_{cp}$=1,47

Thus, based on the chosen scientific and methodological approach, the specific composition and technology of the Ambronat base was chosen.

CONCLUSIONS

From the results obtained, it is clear that the Ambronat cue has not changed its color, taste and smell over the years of stability in its appearance. The pH of the environment is normally in the range of 5.0-7.5, and during the study it was in the range of 6.3–7.8. The limit from the norm corresponded to 3 years of the study.

In the 2.5–3rd year of storage, the number of fungi and bacteria in the mixture increased, and the presence of E. coli in the 1st series in the 2.5th year of storage and in the 2nd and 3rd series in the 3rd year storage observed. This, in turn, means that the quality of Ambronate in the years under study (2.5 and 3 years) is not at the required level. It has been established that the microbiological purity of the resulting Ambronat paste meets the requirements for 2 years. Thus, as a result of the research, the shelf life of "Ambronate" in the packaging under study was determined to be 2 years and is reflected in the relevant regulatory documents.

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