Stability Research of “Biomayrin” Capsules

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Abstract

Research objective is to study the stability and shelf life of Biomayrin capsules, which were obtained by chemical modification of high-molecular weight compounds by incorporation into polymers.

Materials and Method: “Biomayrin” capsules weighing 600±6 mg containing isoniazid, rifampicin, ethambutol, polygalacturonic acid and calcium stearate, obtained by disk dosing into capsules No.0. The shelf life was set by the method of “accelerated aging” when the samples were stored in PVCA1 blister packs (20 capsules each) at the temperature of 60^0C in the thermostat TV-80-1. The tests “Decomposability” of capsules and “Average mass and homogeneity by mass” were conducted in accordance with the requirements of the State Pharmacopoeia of the XIV edition. Experiments were conducted in at least three repetitions. Decompressibility of capsules was determined on PJ-3 Tablet Four-usage Tester (China). Isoniazid, rifampicin and ethambutol were quantitatively determined in solution by spectrophotometry (SF). The analysis was performed on SHIMADZU UV-1601, UV-VISIBLE spectrophotometer in 1 cm cuvette against the background of the solvent. The pH value was controlled with the EV-74 universal ionometer. Mathematical processing of the results was carried out according to General monograph. 1.1.0013.15 “Statistical processing of chemical experiment results” using standard computer programs MsExcel.

Results: The results on properties of capsules at storage of 60^0C and 25^0C are shown, after dissolution the content of active substances (isoniazid, rifampicin and ethambutol) in preparations was within the limits of regulated norms (60-120 mg), at 60^0C it is for isoniazid 101, 7-106.7 mg, at 25^0C 100.1-106.0 mg for rifampicin the regulated norm was 72-132 mg and at 60^0C it was 94.2-92.2 mg, and at 25^0C it was 94.7-91.2 mg, as well as ethambutol hydrochloride content was 60-120 mg and at 60^0C it was 62.5-60.5 mg, and at 25^0C it was 62.0-60.2 mg.

Conclusion: “Biomainrin” capsules with different expiration dates were investigated, and also the change of their quality according to the indicators “Active substance content” and “Dissolution” was found. It was shown that after the expiration of the shelf life there is a gradual decrease in the active ingredient content.

Keywords: *Anti-tuberculosis drug, biomayrin, isoniazid, rifampicin, ethambutol hydrochloride, spectrophotometry, shelf life, stability study, dissolution, capsules.*

Introduction

During the production of solid formulations[1] the corresponding required indicators of finished product quality should be provided[2], including appearance, decomposition[3], average mass and homogeneity by mass, dissolution, foreign impurities and stability during storage[4].

Nowadays, in medical practice, the problem of treatment of lung tuberculosis patients occupies an important place in the structure of phthisiologicalpathology[5]. Lung tuberculosis is an infectious disease which occupies the second place among infectious diseases by mortality. Approximately 9 million people in the world get TB every year and about 2 million die from it[6]. This figure is increasing due to unfavorable living conditions, frequent stressful situations, contact with tuberculosis patients, poor and unhealthy diets, and the presence of diseases and bad habits that weaken immunity[7]. Low-molecular synthetic drugs currently used for tuberculosis treatment are highly toxic and have no ability to penetrate selectively into phagocytes (eaters of cells) containing the tuberculosis pathogen[8]; in addition, they are rapidly excreted from the body without providing a prolonged action, since they only have an effect on extracellular tuberculosis[10] pathogens [9]. WHO has recommended a tuberculosis control strategy known as the Directly Observed Treatment Short course[11]. An integral part of the program is the creation of a reliable system for supplying high quality, effective TB medicines to health care institutions[12]. First of all, it is relevant for standard "first-line" medicines used for treatment of common (sensitive) tuberculosis[13]. Poor quality of one of the medicines taken by patients at this stage violates the whole system and may lead to transition of easily treatable sensitive form of the disease to multidrug-resistant tuberculosis[14]. Improving the efficacy as well as reducing the side effects of anti-TB drugs remains a topical issue [15].

The combined anti-tuberculosis drug "Biomayrin" was developed at the Institute of Bioorganic Chemistry in the Academy of Sciences of the Republic of Uzbekistan by chemical binding of isonicotinic acid hydrazide with modified dialdehyde of polygalacturonic acid, with subsequent inclusion of ethambutol and rifampicin in the macromolecule by means of ionic bond [16].

The combination of isoniazid, ethambutol, and rifampicin along the chain of modified polysaccharides allowed creating a drug[17], which not only combines the properties of these drugs, but also manifests new properties due to its macromolecular nature[18] - prolonged action, membranotropicity, change of activity, possible synergetic action, and others[19]. Creation of combined drug of macromolecular nature "Biomayrin" due to activity increase (at lower content of individual drugs in macromolecule) and latitude of pharmacological action leads to significant reduction of side effects[20].

The research purpose is to develop method of standardization, study stability and establishment of shelf life of "Biomayrin" 600 mg capsules.

This article presents the results of the study of stability of the capsule form of the anti-tuberculosis drug "Biomayrin".

Subject of Research: The subject of research is capsules "Biomayrin" with the mass of 600±6 mg containing isoniazid, rifampicin, ethambutol, polygalacturonic acid and calcium stearate obtained by disk dosing into capsules No.0.

Materials and Method

The research on development of standardization method, stability studies and determination of shelf life for "Biomayrin" capsules was carried out using materials and equipment on the basis of the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan[16]. Besides, we considered it expedient to study the dissolution profiles of "Biomayrin" capsules, since their change in time provides additional information when studying the stability of drugs and to justify the shelf life.

Shelf life time of capsule "Biomayrin" was set by the method of "accelerated aging" at storage of samples in PVCA1 blister packages (20 capsules each) at 60^0C in the thermostat TV-80-1.

Testing "Decompossibility" of capsules and "Average mass and homogeneity by mass" were conducted in accordance with the requirements of the State Pharmacopoeia of the XIII edition. The experiments were conducted in at least three repetitions. Decompressibility of capsules was determined on PJ-3 Tablet Four-usageTester (China). Isoniazid, rifampicin and ethambutol were quantitatively determined in solution by spectrophotometry (SF). The analysis was performed on SHIMADZU UV-1601, UV-VISIBLE spectrophotometer in 1 cm cuvette against the background of the solvent. The pH value was controlled with the EV-74 universal ionometer. OFS.1.1.0013.15 "Statistical processing of chemical experiment results" using standard computer programs MsExcel. The "Dissolution" of the combined drug was investigated according to [20] using the RCZ-6C3 device of the "Rotating Basket" type. At the first stage, purified water (pH 7.0) in the volume of 900 ml at a temperature of 36.5±0.50 C was used as a medium for dissolution at a basket rotation speed of 150 rpm and the duration of

the analysis was 60 min. At the second and third stage, when determining the dissolution profile of the capsules, two dilution media similar to pH of human stomach (pH 1.2) and pH of duodenum (pH 8.0) were consistently used. Sampling for analysis was carried out every 15 min during 1 h. Release of isoniazid, rifampicin and ethambutol as one of the main groups of biologically active substance of the combined drug was determined by direct spectrophotometry on the device "UV-7504" in a cuvette with thickness of 1 cm at wavelength 262±2; 336±2 and 450±2 nm.

Results and Discussion

To determine the quantitative content of isoniazid, the content of 10 capsules was thoroughly stirred and selected 100 mg (precise attachment) of powder, placed in a measuring flask of 100 ml, 50 ml 0 was added, 1 M of hydrochloric acid solution dissolved in an ultrasonic bath for 15 minutes, brought the volume of the solution with the same solvent to the mark, 5 ml of the resulting solution was placed in a measuring flask with a capacity of 100 ml and brought the volume of the solution to the mark 0.1 M with hydrochloric acid solution. The obtained solution was filtered through a "White Ribbon" filter, discarding the first 10-15 ml of filtrate, optical density was measured at 262 nm wavelength. At the same time the optical density ofisoniazid solution was measured.

Calculation of isoniazide (mg) content in Biomayrin capsule was performed by the formula:

$$\frac{D \times 100 \times 100 \times m_{st} \times 1 \times m_{caps}}{D_0 \times 5 \times m_{test} \times 100 \times 100},$$

Where: D1 – optical density of the test solution.

D0 – optical density of SSS (Solution standard samples) isoniazid solution.

m_{caps}– average mass of content of one capsule, in mg.

m_{test}– precise hinge of the test specimen, in mg.

m_{st}- precise attachment of standard sample, in mg.

The quantitative content of rifampicin was determined using the above method and optical density was measured at a wavelength of 472 nm. The optical density of rifampicin SS solution was measured in parallel. The calculation of rifampicin (mg) content in Biomayrin capsule was carried out by the formula:

$$\frac{D \times 25 \times 100 \times 2 \times m_{st} \times m_{caps}}{D_0 \times 5 \times m_{test} \times 100 \times 100},$$

Where: D_1 – optical density of the test solution.

D_0 – optical density of SS rifampicin solution.

m_{caps}– average mass of content of one capsule, mg.

m_{test}– precise hinge of the test sample, in mg.

m_{st}- accurate attachment of standard sample, in mg.

Determination of the quantitative content of ethambutol by the above method, with a difference after filtration to 10 ml of leachate was applied 1 ml solution of iron ammonium alum, thoroughly stirred and left for 5 minutes. Then 0.2 ml of solution of mercury rhodiumized was added and stirred again. In parallel, a similar treatment with 10 ml of SS solution of ethambutol dihydrochloride was performed. After 10 min the optical density of the analyzed solutions was measured at a wavelength of 457 nm.

The calculation of the content of ethambutol (mg) in the Biomayrin capsule is done by the formula:

$$\frac{D \times 100 \times m_{st} \times m_{caps}}{D_0 \times m_{test} \times 100}$$

Where: D_1 – optical density of the test solution.

D_0 – optical density of ethambutol SS solution.

$m_{капс}$– average mass of one capsule content, mg.

$M_{исп}$– precise hinge of the test sample, in mg.

$m_{ст}$- accurate attachment of standard sample, in mg.

According to SF (State Pharmacopoeia) XIV, a formula based on the Vant-Goff law is used to determine whether the experimental storage period at elevated temperature (C) corresponds to the storage period (C) at 25^0C:

$$SP=K*P_{ex},$$

Where the coefficient of conformity $K=A(t_e–t_{xp})/10$, the temperature coefficient of chemical reaction speed (A) is 2.5. At a temperature difference $t_e–t_{xp=}60\text{-}25=35^0$C the conformance coefficient K=9.0. Calculated terms of experimental storage at 60^0C are given in Table 1, the results of studies are shown in Table 2.

Table 1: Consistency of experimental storage terms at 60^0C and 25^0C

At 60^0C	At 25^0C
6 days	3 months
12 days	6 months
18 days	9 months
24 days	12 months
36 days	18 months
48 days	24 months

Table 2 Properties of experimental capsules during storage at 60^0C

Term of experimental storage at 60^0C, a day.	Decompossibility, no more than 20 min	Average weight and homogeneity in weight, deviations ±10%.	Dissolution, at least 75%.		
			Isoniazid from 60.0 to 120.0 mg	Rifampicin from 72.0 to 132.0 mg	Etambutol from 60.0 to 120.0 mg
0 days (Start)	15 min	587,92mg. +8,17% -5,94%	93,6 %		
			106,7 mg	94,2 mg	64,5 mg
6 days	15 min	585,62mg. +6,70% -3,14%	91,1%		
			105,6 mg	94,7 mg	64,2 mg
12 days	15 min	580,45mg. +4,17% -3,25%	95,6 %		
			104,7 mg	94,2 mg	62,7 mg
18 days	16 min	583, 22mg. +5,45% -2,67%	92,4%		
			106,0 mg	93,6 mg	62,1 mg
24 days	16 min	586,34mg. +7,23% -4,34%	94,6 %		
			105,7 mg	92,9 mg	62,0mg
36 days	16 min	585,56mg. +6,79% -3,35%	90,2 %		
			106,2 mg	91, 7 mg	61,6 mg
48 days	16 min	584,18mg. +6,20% -4,62%	89,5%		
			101,7 mg	92,2 mg	60,5 mg

Table 3: Properties of experimental capsules during storage at25 ^{0}C

Term of experimental storage at 60^0C, a day.	Decompossibility, no more than 20 min	Average weight and homogeneity in weight, deviations ±10%.	Dissolution, at least 75%.		
			Isoniazid from 60.0 to 120.0 mg	Rifampicin from 72.0 to 132.0 mg	Etambutol from 60.0 to 120.0 mg
Start	15 min	585,0 mg.+6,6%-3,54%	93,1%		
			106,0 mg	94,7 mg	62,5 mg
3 months	15 min	585,62 mg.+6,70%-3,14%	91,0%		
			105,0 mg	93,2 mg	62,2 mg
6 months	16 min	580,40 mg.+4,17%-3,25%	95,6 %		
			104,7 mg	93,0 mg	61,7 mg
9 months	16 min	583, 22 mg.+5,45%-2,67%	92,4%		
			106,0mg	92,6 mg	60,1 mg

Term of experimental storage at 60^{0}C, a day.	Decompossibility, no more than 20 min	Average weight and homogeneity in weight, deviations ±10%.	Dissolution, at least 75%.		
			Isoniazid from 60.0 to 120.0 mg	Rifampicin from 72.0 to 132.0 mg	Etambutol from 60.0 to 120.0 mg
1 year	16 min	586,27 mg.+7,23%-4,34%	94,6 %		
			105,5 mg	92,0 mg	60,1 mg
18 months	16 min	585,56 mg.+6,79%-3,35%	90,2 %		
			104,2 mg	91,7 mg	61,1 mg
2 years	16 min	584,18 mg.+6,20%-4,62%	89,5%		
			100,1 mg	91,2 mg	60,2 mg

The results of determining the content of active substances in dissolution in the studied preparation are presented in Tables 2 and 3.

As follows from the above data on the properties of the capsules during storage of 60^{0}C and 25^{0}C, after dissolution the content of active substances (isoniazid, rifampicin and ethambutol) in preparations with the shelf life up to 2018. is within the limits of regulated norms (60-120 mg) at 60^{0}C is for isoniazid 101.7-106.7 mg, at 25^{0}C 100.1-106.0 mg for rifampicin the regulated norm should be 72-132 mg and at 600C is 94, 2-92.2 mg, and at 25^{0}C 94.7-91.2 mg, and also the content of ethambutol hydrochloride should be 60-120 mg and at 60^{0}C of storage its content was 62.5-60.5 mg, at 25^{0}C 62.0-60.2 mg. In the study of samples with expired shelf life (2018) a moderate decrease in the level of active substances was noted.

In order to obtain the most complete picture of Biomayrin quality changes during storage, we considered it expedient to study its release from the investigated samples along with the tests of "Active substance content" [22].

The results of the experiments to study the release of the active ingredients of the combined preparation from the capsules in the device "Rotating basket" are presented in Fig. 1 - 3.

The graphs show that the amount of substances transferred to different solvents in 60 min varies within the limits for:

- Isoniazid in water purified from 74.0 to 92.0%; in acidic medium from 56.0 to 84.6%, and in buffer solution from 65.5 to 83.0%;
- Rifampicin in the first medium from 58.3 to 84.0%; in the second medium from 44.0 to 77.0%; in the third medium from 62.0 to 85.0%;
- Ethambutol on Wednesday from 65.0% to 85.0%; on Wednesday 2 from 67.0% to 85.0%; on Wednesday 3 from 64.0% to 77.0%.

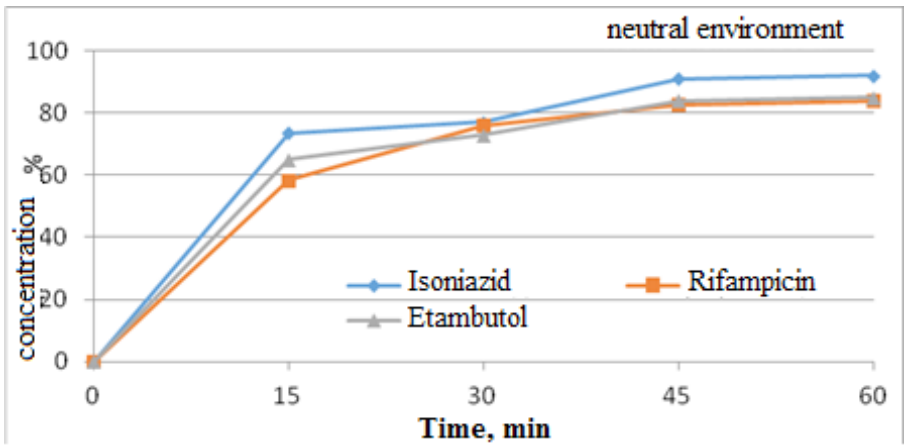

Figure 1: Kinetic release profile of DS (drug substance) from capsule at 36.5±0.5^{0}C and V = 900 ml, pH = 7.0 (dissolution test method)

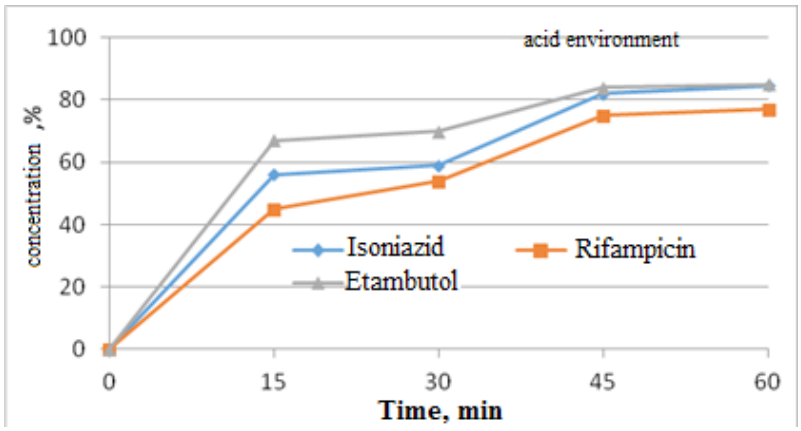

Figure 2: Kinetic release profile of DS (drug substance) from capsule at 36.5±0.5^{0}C and V = 900 ml, pH = 1.2, 0.1 m hydrochloric acid (dissolution test method)

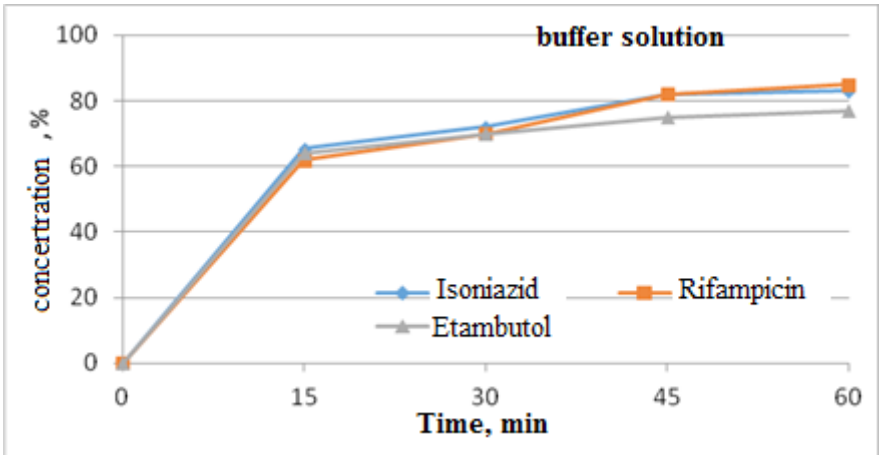

Figure 3: Kinetic release profile of DS (drug substance) from capsule at 36.5±0.5^{0}C and V = 900 ml, pH = 8.0 (buffer solution) (dissolution test method)

Based on the results of the first set of experiments in the dissolution test, we can conclude that isoniazid, rifampicin and ethambutol dissolve well within 60 minutes in all the solutions we used.

Based on the above studies, a table was made on the results of the accelerated stability test for Biomayrin capsules. The results are given in Table 4.

Table 4: Results of the accelerated stability test of "Biomayrin" capsules

Test	Specifications	0 Days (Start)	6 Days (3 Months)	12 Days (6 Months)	18 Days (9 Months)	24 Days (12 Months)	36 Days (18 Months)	48 Days (24 Months)
Description	Hard gelatin capsules No.0, light green, containing brown powder with a slight peculiar smell	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Originality	Spectrum of approx. 233 nm, 262 nm, 269 nm, 336 nm and 473 nm	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
	Add 10 ml of water to the powder of Biomairin capsule contents shake for 10 minutes and filter. To the resulting filtrate add 0.2 ml of copper (II) sulfate solution and 0.5 ml of diluted sodium hydroxide solution; blue staining appears.	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate

Test	**Specifications**		**0 Days (Start)**	**6 Days (3 Months)**	**12 Days (6 Months)**	**18 Days (9 Months)**	**24 Days (12 Months)**	**36 Days (18 Months)**	**48 Days (24 Months)**
Average mass and homogeneity by mass	From 553.0 mg to 636.0 mg Deviations from average weight ±10%.		587,92 mg. +8,17% -5,94%	585,62 mg. +6,70% -3,14%	580,45 mg. +4,17% -3,25%	583, 22 mg. +5,45% -2,67%	586,34 mg. +7,23% -4,34%	585,56 mg. +6,79% -3,35%	584,18 mg. +6,20% -4,62%
Decompressibility	Not more than 20 min		15 min	15 min	16 min	16 min	16 min	16 min	16 min
Dissolution	Minimum 75%		93,6 %	91,1 %	95,6 %	92,4 %	94,6 %	90,2 %	89,5 %
Quantitative content	Isoniazid	From 60,0 to 120,0 mg	106,7 mg	105,6 mg	104,7 mg	106,0 mg	105,7 mg	106,2 mg	101,7 mg
	Rifampicin	From 72,0 to 132,0 mg	94,2 mg	94,7 mg	94,2 mg	93,6 mg	92,9 mg	91,7 mg	92,2 mg
	Etambutol	From 60,0 to 120,0 mg	62,5 mg	62,0 mg	61,7 mg	62,1 mg	62,6 mg	61,6 mg	60,5 mg

Conclusion

In the research of samples with expired shelf life (2018) was found out that capsules “Biomayrin” at storage of 60^0C and 25^0C, after dissolution the content of active substances (isoniazid, rifampicin and ethambutol) in preparations is within the limits of regulated norms (60-120 mg) at 60^0C is for isoniazid 101, 7-106.7 mg, at 25^0C 100.1-106.0 mg, for rifampicin the regulated norm 60^0C was 94.2-92.2 mg, and at 25^0C 94.7-91.2 mg, and also the content of ethambutol hydrochloride at 60^0C was 62.5-60.5 mg, at 25^0C 62.0-60.2 mg. This indicates that, when stored at different temperatures the content of active substances is within the limits of regulatory standards, as well as a moderate decrease in the level of active substances.

As well as, according to the results of the test “Dissolution”, it was found that the number of active ingredients transferred to water purified from “Biomayrin” capsules is 87% on average, in acidic environment - 82.2% on average, in buffer medium - 81.6%. Comparison of the data allows us to conclude that the release of active substances in the buffer solution is slower than in a neutral environment (purified water). The results show that the method of “dissolution”: the degree of release of biologically active substances in 1 hour is at least 81%.

It was found that at the end of the shelf life (2 years) gradually reduces the rate of “dissolution” from 93.6% to 89.5% and changes the profile of release of active substances from the capsule forms of drugs.

Ethical Clearance: No ethical approval is needed.

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Conflict of Interest: Nil

References

1. General monograph. 1.1.0009.15 Time limits for medicinal products. .
2. S.Narasimha Murthy MAR. Excipient Stability: a Critical Aspect in Stability of Pharmaceuticals. An Official Journal of the American Association of Pharmaceutical Scientists. 2018 Jan; 19(1): p. 11.
3. Arzamastsev AP, Sadchikova NP, Ledovskikh EB, Nechaeva EBao. Investigation of stability of the cyclosporin capsule drug forms (in Russian). Russian biotherapeutic journal. 2006; 1: p. 80-85.
4. Yalkaev AG, Kildiyarov FH, Kataev VA, Khalikov RA, Fedotova AA. Research of stability of the 11-deoxymisoprostol tablets//Vestnik VolgGMU. 2017;(3(63)): p. 109-112.
5. (M/XDR-TB)” Grosar”aedrT. WHO. 2010;: p. 1-71.
6. Krasnoselskikh I.V. SYA, GEV. Capsule form - a new approach for treatment of patients with tuberculosis. Farmatsiya. 2012; 7: p. 38.
7. Lebedeva MO, Sukhova EV. Formation of motivation for treatment in patients with lung tuberculosis. Invention bulletin, useful models. No.19 (1 part). 2008;: p. 17.
8. Kaur Kiptiral GARKNRSRM. Novel drug delivery systems: desired feat for tuberculosis. J. Adv. Pharm.Tech.Res. 2010; 1(2): p. 145-163.
9. Tsubota N. TS. A clinical experience of rifampicin suppository for the treatment of pulmonary tuberculosis. Kekkaku. 2015 Jun; 90(6): p. 543-547.
10. Organization WH. WHO report 2018 of 19th September. 2018 Sept.
11. Kim M.E. MKB, SEF. Antituberculosis drug

dosage forms: range, key benefits and prospects of technological improvement/pharmacy & pharmacology. 2016; 3: p. 38-53.

12. Shegokar Ranjita A. SLMK. Present Status of Nanoplasticle Researche for Treatment of Tuberculosis. J. Pharm. Pharmaceut Sci. 2011; 14(1).
13. Sabitha P. VRJaRRK. Design and evaluation of controlled release of chitosan-calcium alginate microcapsules of antitubercular drugs for oral use. Int.J.Chem.Technol.Res. 2010; 2(1): p. 88-98.
14. T.I. Morozova LEPONDONBON. Efficiency of combined chemical preparations in treatment of patients with tuberculosis in high risk of drug resistance m. Tuberculosi. Bulletin of modern clinical medicine. 2013; 2: p. 46-51.
15. al RPe. Fixed - dose comdinations for tuderculosis: lessons learned from a clinical, formulation and regulatory. Department of Pharmaceutics National Institute of Pharmaceutical Education and Research (NIPER). India. 2004.;: p. 1-40.
16. Application for Patent IAP 20160219 dated 07/06/2016. Shomurotov S.A. AOR, TAS"aaopa. .
17. Shomuratov S.A. AOR, MNE, SBT, TAS. Modified derivatives of polysaccharides having anti-terculosis activity. Austrian Journal of Technical and Natural Sciences. 2017; 1(2): p. 134-138.
18. Mamatmusaeva N.E. SSASBT, TAS. Study of technological properties of substance and basic composition for obtaining the drug product of Biomayrin. Pharmacy & pharmacology. 2017; 6: p. 532-542.
19. Anil Kumar K.N. BRS, nV, RAM. Encapsulation and release of rifampicin using poly (vinyl pyrrolidone)-poly (methacrylic acid) polyelectrolyte capsules. Materials Science and Engineering. 2009; 29: p. 2508-2513.
20. State Pharmacopoeia of the Russian Federation XIV edition, volume II, Moscow. 2018;: p. 1449.
21. Chizhova DA, Bunyatyan ND, Vasilenko GF. Release of substances from solid dosage forms. No. 2. 2008. 2008;: p. 50-52.