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Study of Biopharmaceutical Properties and Stability of "Enformin" and "Sitmet" Tablets

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ABSTRACT
One of the biopharmaceutical studies assessing the therapeutic effect of drugs is their biological efficacy. One of the main methods for evaluating the biopharmaceutical properties of drugs in in vitro experiments is the "Rotating Basket" method, which is included in the State Pharmacopoeia of the Republic of Uzbekistan. It is known from the literature that the release rate of the active substance is influenced by various factors, including the excipients used, the volume and pH of the solvent medium, and the basket rotation speed

Keyword: *solvent medium, biologically active, biopharmaceutical properties..*

1. INTRODUCTION

To select a suitable pH value, solvent media with different pH values were used in the studies.

In the experiments, the volume of the dissolving medium was 1000 ml, and the temperature was 37±1 °C.

MATERIALS AND METHODS

The following solvents were used as the solvent medium under 3 different conditions: a neutral medium - purified water, an acidic medium - a 0.1 mol/L solution of hydrogen chloride, and an alkaline medium - a 0.1 mol/L solution of sodium hydroxide.

The results of studies on the effect of the solvent medium on the dissolution of the recommended tablets are presented in Figures 1 and 2.

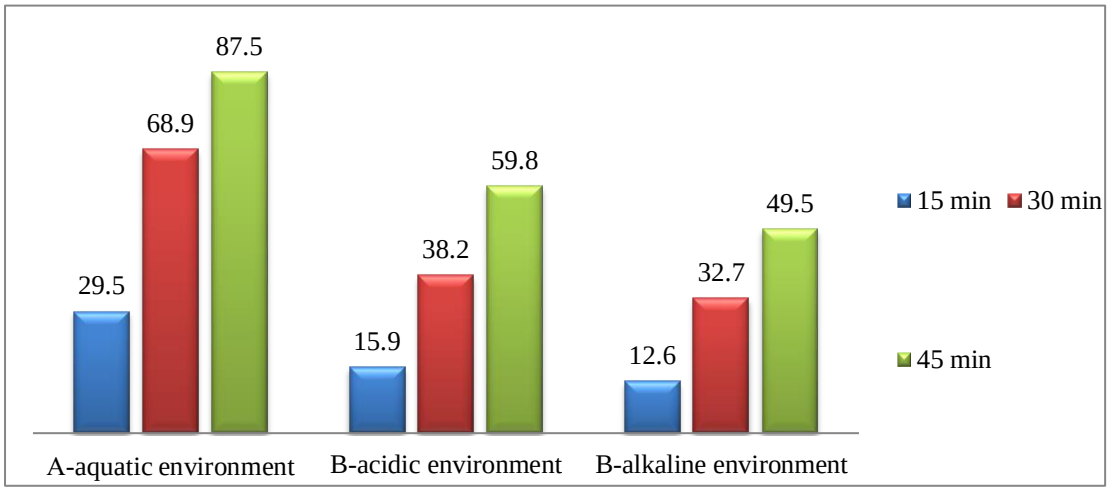


Figure 1. The effect of the solvent medium on the solubility of the tablets "Enformin

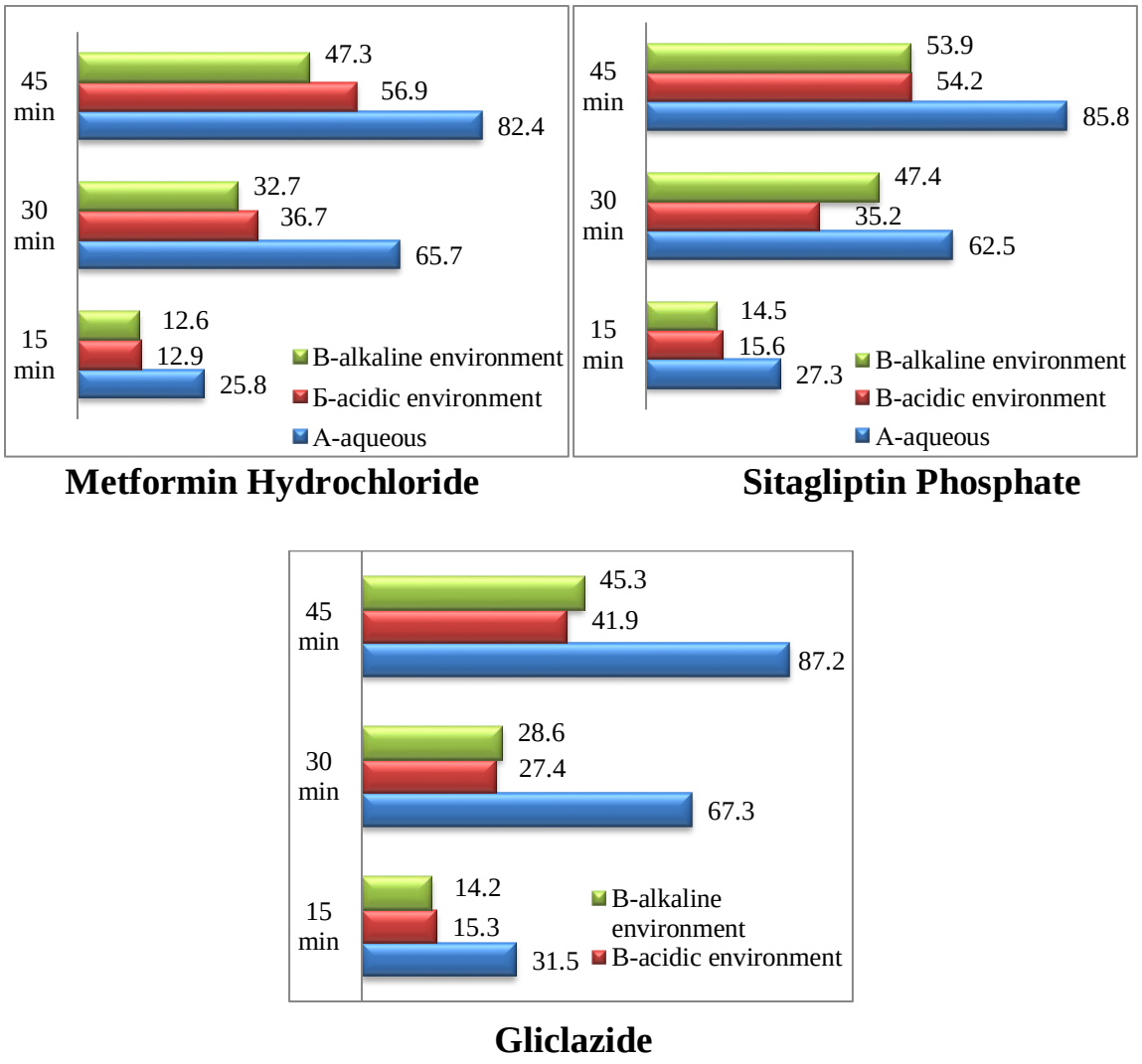


Figure 2. The effect of the solvent medium on the solubility of Sitmet tablets »

1. Neutral medium (purified water)

2. Acidic medium (0.1 N HCl solution)

3. Alkaline medium (0.1 N NaOH solution)

As can be seen from the results above, the release of metformin hydrochloride from Enformin tablets in 45 minutes was 87.5% in a neutral medium, 59.8% in an acidic medium, and 49.5% in an alkaline medium. In the case of "Sitmet" tablets, by the 45th minute of the incubation period, the release of bioactive substances into the neutral medium was 82.4%, 85.8%, and 87.2%, respectively. It was also found that these indicators are not at the required level in acidic (56.9%, 54.2%, and 41.9%, respectively) and alkaline (47.3%, 53.9%, and 45.3%, respectively) media.

According to the research results, it was established that water as a solvent is a neutral medium for the recommended "Enformin" and "Sitmet" tablets, and this is included in the regulatory documentation.

The next stage of research was continued by studying the effect of rotation speed using the "Rotating Basket" method on the release of active substances into the solvent medium from "Enformin" and "Sitmet" tablets [10, 17, 20].

When developing the "solubility test," studies on the selection of a moderate basket rotation speed were carried out at speeds of 50, 100, 150, and 200 rpm. The obtained results are presented in Figures 3 and 4.

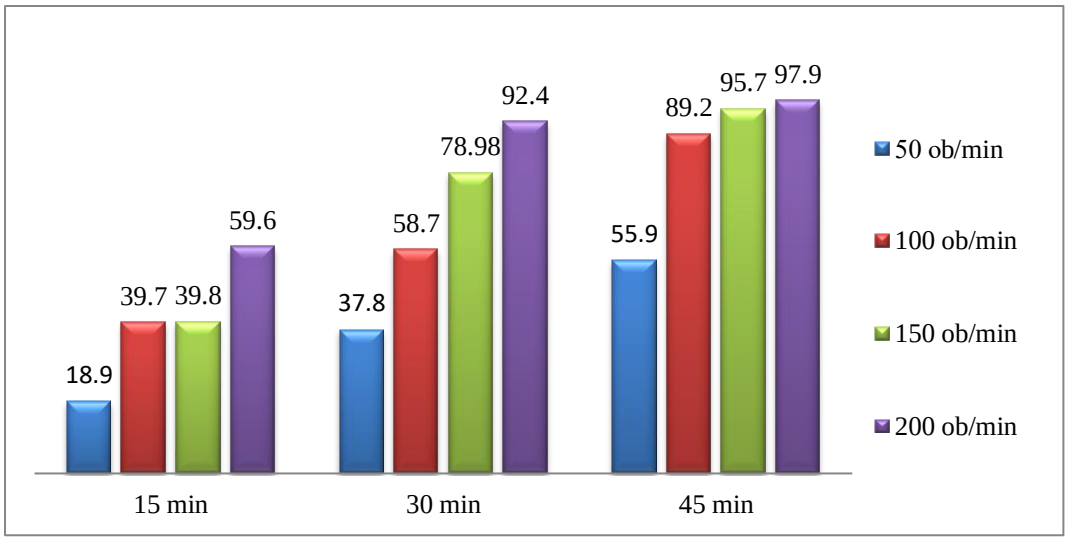
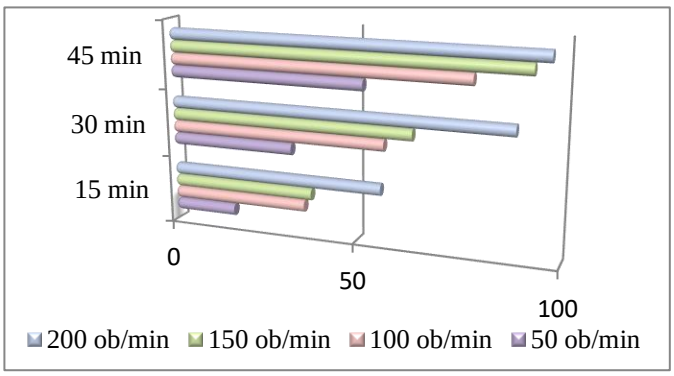


Figure 3. The effect of the rotation speed of the basket on the rate of release of biologically active substances from the tablets "Enformin »

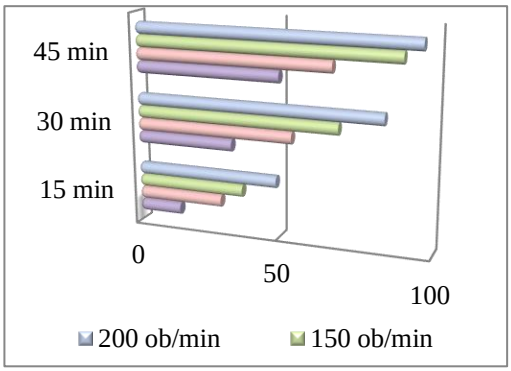
1. Basket rotation speed 50 rpm.
2. Basket rotation speed 100 rpm.
3. Basket rotation speed 150 rpm.
4. Basket rotation speed 200 rpm.

According to the data presented in Figure 3, as the basket rotation speed increases, the release of the main active ingredient from "Enformin" tablets into the solution also increases. According to the results obtained, the release rate of metformin hydrochloride from Enformin tablets was 18.9%, 37.8%, and 55.9% at 15, 30, and 45 minutes, respectively. At a basket rotation speed of 100 rpm, the indicators were 39.7%, 58.7%, and 89.2%, respectively. It was found that these indicators increase at higher speeds. We considered that even if the basket rotation speed meets the requirements, it is desirable to conserve unnecessary energy.

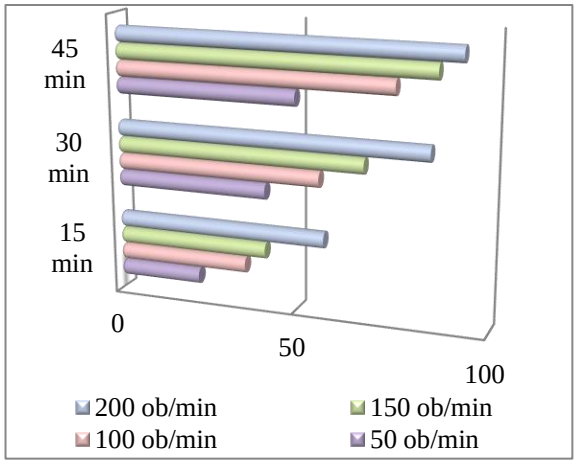
As a result of studying the effect of basket rotation speed on the release rate of biologically active substances from "Sitmet" tablets, an intensive release was noted with increasing basket rotation speed. By 45 minutes, the release of all three bioactive substances into the dissolution medium was observed at a basket rotation speed of 100 rpm. It turned out that the indicators meet the requirements for the rotation limit (≈75%). Since a basket rotation speed of 150 rpm showed relatively large indicators from the limit level of requirements, a basket rotation speed of 150 rpm was set for the dissolution test and was included in the regulatory documents (Figure 4).



Metformin Hydrochloride



Sitagliptin Phosphate



Gliclazide

Figure 4. The effect of the basket's rotation speed on the rate of release of biologically active substances from Sitmet tablets »

1 - Basket rotation speed 50 rpm.

2 - Basket rotation speed 100 rpm.

3 - Basket rotation speed 150 rpm.

4 - Basket rotation speed 200 rpm.

Based on the results of biopharmaceutical studies, considering that the "rotating basket" results for "Enformin" tablets at a speed of 100 rpm and the results for "Sitmet" tablets at a speed of 150 rpm meet the requirements of the State Pharmacopoeia of the Republic of Uzbekistan, we established these speeds as defined and selected them for further research.

Thus, based on the results of the above studies, a "Dissolution Test" was created for both recommended tablets. To assess the quality of the finished product from a biopharmaceutical point of view, the basket rotation speed for "Enformin" tablets was chosen to be 100 rpm, and for "Sitmet" tablets - 150 rpm, the volume of solvent - 1000 ml, and the medium was neutral.

RESULTS AND DISCUSSION

Studying the shelf life and storage conditions of "Enformin" and "Sitmet" tablets. Ensuring the stability of drugs for a certain period of time is one of the urgent tasks of pharmaceutical technology. During storage, solid dosage forms are affected by the temperature of the external sulfur, humidity, light, etc. [2,3,4,5,13,14,15,16].

When creating medicines, the pharmaceutical industry requires great attention to packaging materials. Packaging materials are the main barrier protecting tablets from the external environment and contributing to extending their shelf life. Accordingly, the correct selection of packaging materials helps to preserve the qualitative and quantitative indicators of the tablet [6,8,9,17].

Based on the foregoing, the following four types of packaging, widely used today in pharmaceutical practice, were used in the study:

packaging 1: container made of colorless glass (TU-64-228-84) with a plastic lid (TU-64-2-250-75);

packaging 2: flame-colored glass container (OST 64-2-71-8) with a plastic lid (TU-64-2-250-75);

packaging 3: packaging made of paper laminated with polyethylene, without a contour cell (TU13-7308001-477-85);

packaging 4: packaging made of contour-cellular polyvinyl chloride (EP-73) and aluminum foil (TU 48-21-270-78).

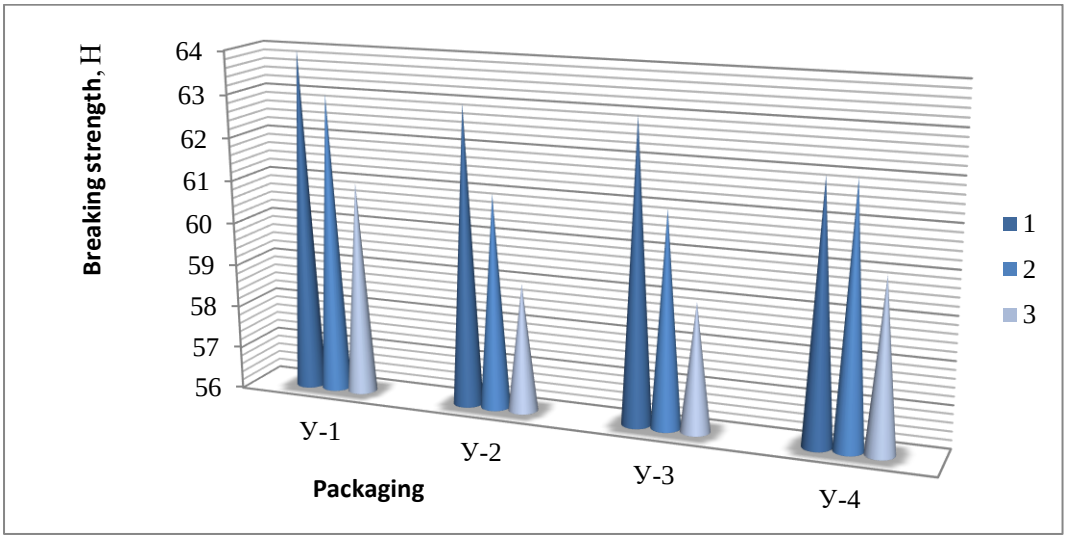
The study initially began with examining the quality of the recommended tablets.

The quality indicators studied were: the appearance of the tablets, the strength indicators in relation to fracture and abrasion, the disintegration index, the solubility of the tablets, etc. Then, the tablets were placed in the above-mentioned packaging and studied by the natural method and the method of "accelerated aging" [15,19].

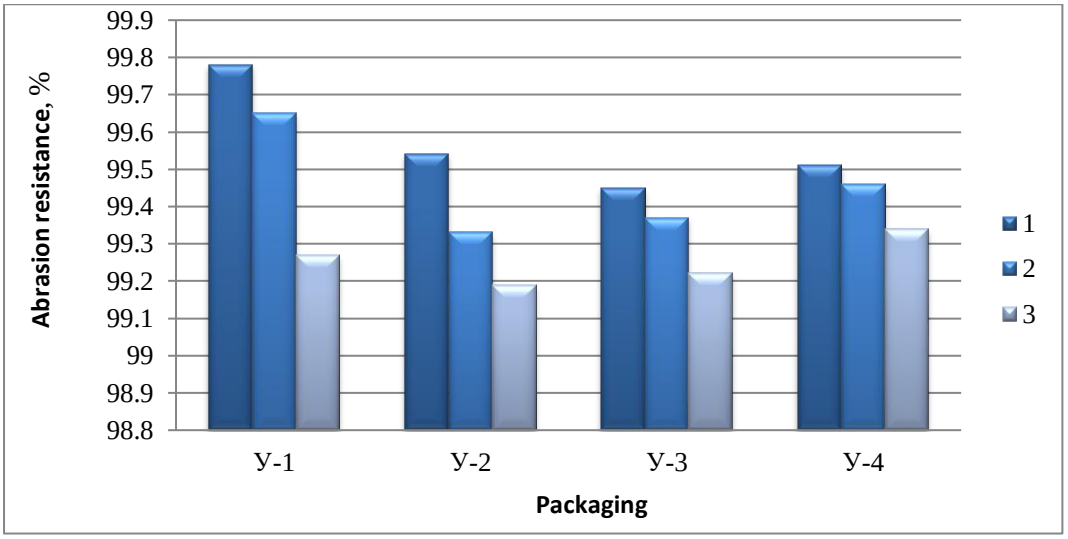
When assessing the appearance of tablets with the naked eye, it was noted that they are cylindrical tablets without color or odor.

First, the stability, abrasion resistance, and fracture resistance of "Enformin" tablets were tested under storage conditions.

The results are presented in Figure 5..



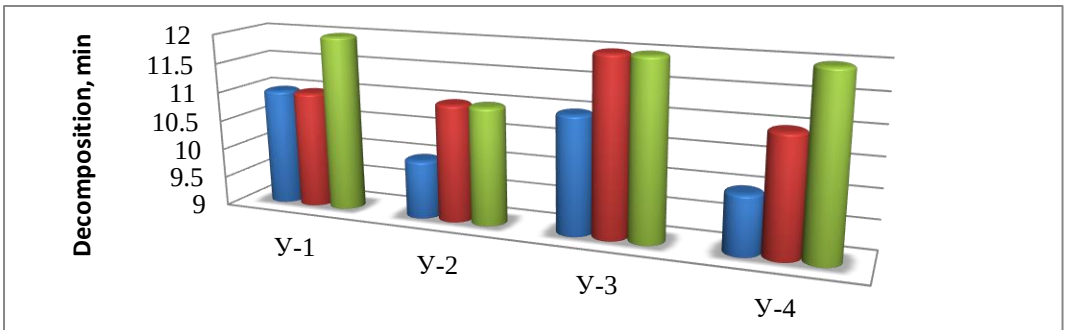
A



B

Figure 5. The results of the study of the strength of tablets "Enformin" for breaking (A) and abrasion (B) under storage conditions of 3 years.

As can be seen from the indicators shown in Figure 5, the results of a study of the strength of the "Enformin" tablets for breaking (64-59 N) and abrasion (99.78-99.19%) under storage conditions for 3 years during a 4-year incubation period have positive indicators. The results of the study of the indicators of the disintegration of tablets "Enformin" under 3-year storage conditions are shown in Figure 6. The results of the study showed that these indicators are at the required level.



	У-1	У-2	У-3	У-4
1	11	10	11	10
2	11	11	12	11
3	12	11	12	12

Figure 6. Results of a study of decay rates in 3-year storage of tablets "Enformin ».

The results shown in Figure 6 showed that the disintegration index of the recommended tablets in all packages was at the required level (9-12 min). The research results also showed that their decomposition increased relatively with increasing storage time, and the effect of time on this indicator was intense. The results of studying the solubility of "Enformin" tablets during storage for 3 years also showed positive indicators (Fig. 7).

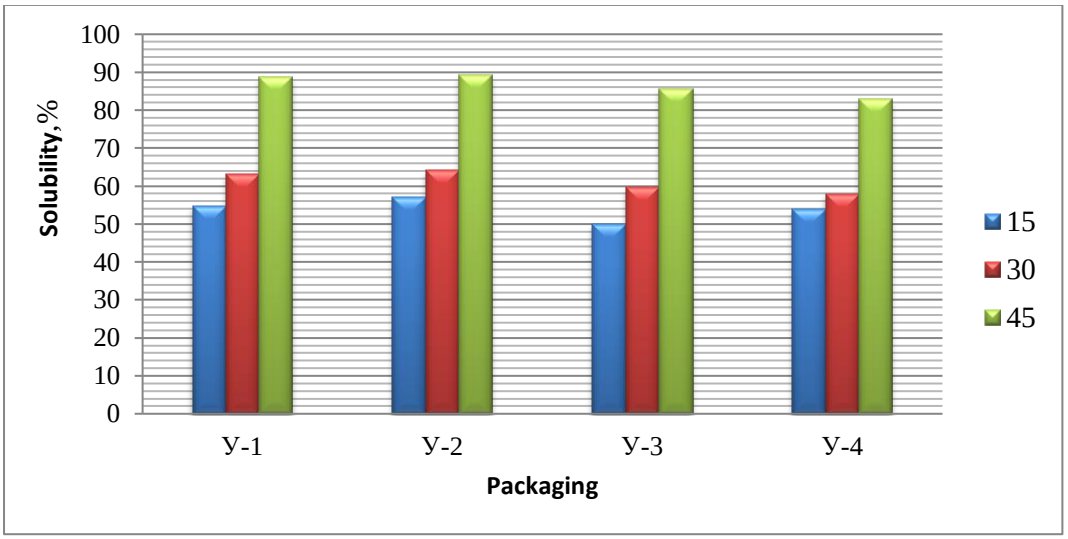
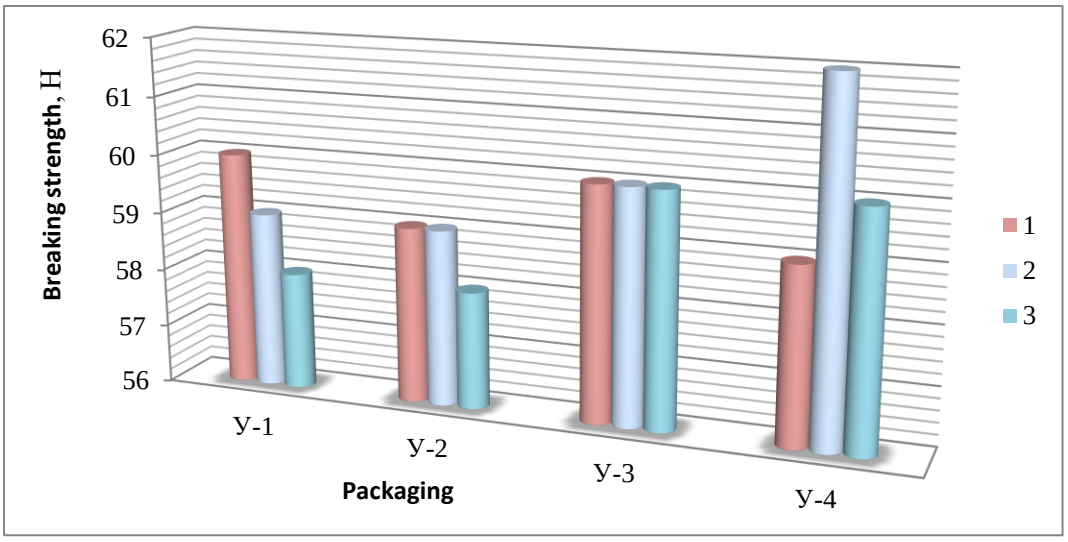
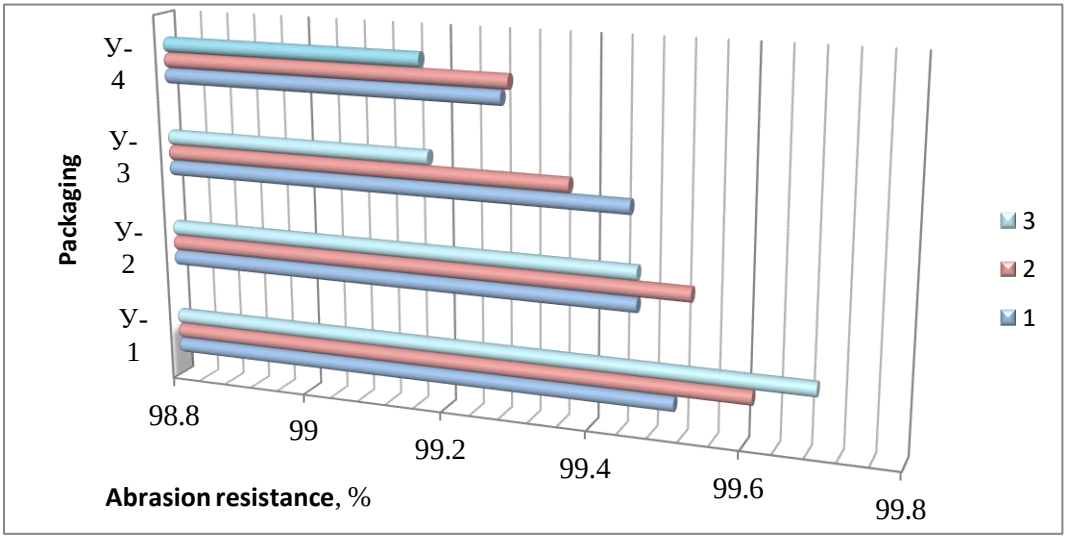


Figure 7. The results of the study of the solubility of tablets "Enformin" during 3-year storage.

The indicators shown in Figure 7 showed that the release of the bioactive substance into the solvent environment of the recommended "Enformin" tablets increased intensively during the experiment for 45 minutes and was at the required level (>75%) after 45 minutes. The next stage of research was conducted to study the quality indicators of Sitmet tablets obtained under the conditions and shelf life of the recommended composition and technology in the conditions of the above studies. First, the stability of the Sitmet tablet under storage conditions, abrasion resistance and breaking strength were tested. The results of a study of the strength of Sitmet tablets placed in four different packages for breaking (A) and abrasion (B) are shown in Figure 8.



A



B

Figure 8. Results of a study of the strength of Sitmet tablets for breaking (A) and abrasion (B) under 3-year storage conditions.

As can be seen from the indicators shown in Figure 8, the results of studying the strength of Sitmet tablets for breaking (59-61 N) and friction (99.17-99.69%) under 3-year storage conditions during the three-year incubation period have positive indicators. Also, unlike the "Enformin" tablets, the results of the study of the abrasion resistance of the "Sitmet" tablets in all packages meet the requirements, but the "U-1" package showed the highest rates (99.69%). The results of a study of the decay rates of the Sitmet tablet under 3-year storage conditions are shown in Figure 9.

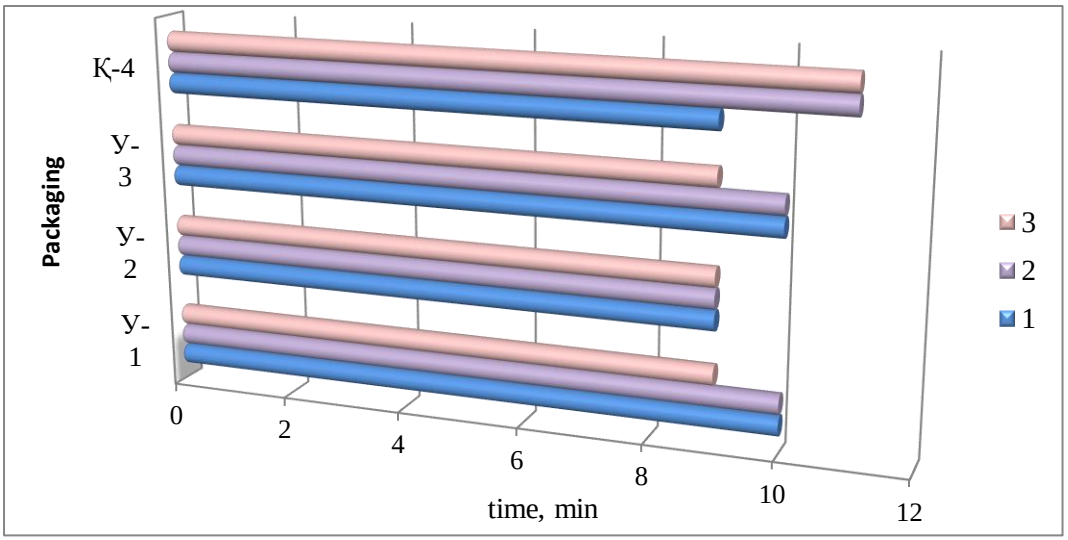


Figure 9. The results of a study of the decay rates of the Sitmet tablet during storage for 3 years.

"The results presented in Figure 9 showed that the disintegration time of the recommended tablets met the requirements (9-11 minutes) in all packaging types. In addition, the storage period had virtually no effect. When the storage period reached the 3rd year, the disintegration time of the tested tablets still met the required standards, decreasing by only one minute.

The results of subsequent studies on the solubility of 'Sitmet' tablets showed that their stability had a positive effect on solubility over 3 years.

The results of the solubility study are presented in Figure 10.".

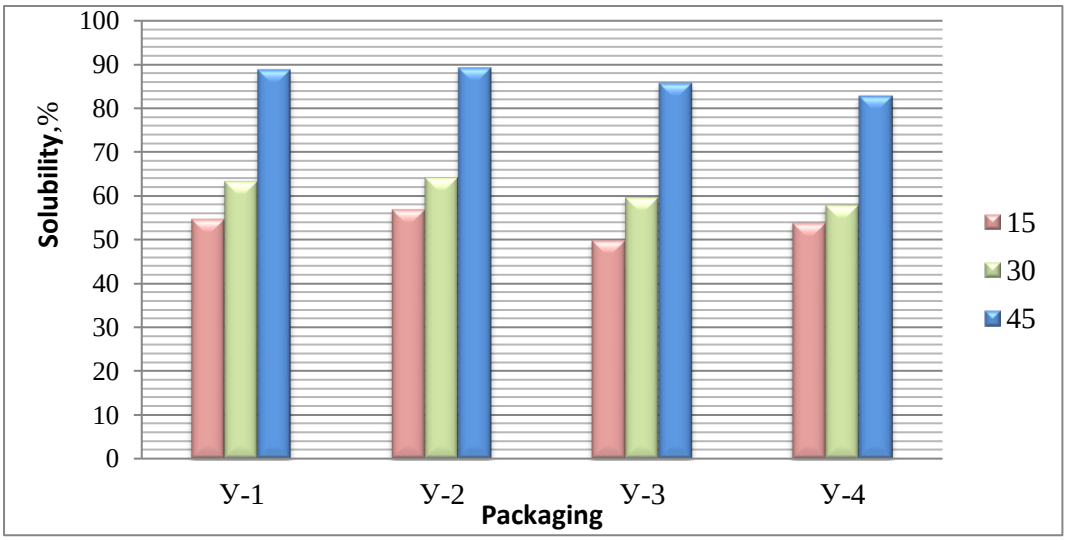


Figure 10. The results of the study of the solubility parameters of the Sitmet tablet during 3-year storage.

"The solubility indicators of the recommended 'Sitmet' tablets, as shown in Figure 10, demonstrated that the release of the bioactive substance into the dissolution medium within 45 minutes is at the required level (88.75-89.21%).

The indicators from the figures above were combined, and the results of the stability study of 'Enformin' and 'Sitmet' tablets using the natural method are presented in Tables 1 and 2.

The disintegration time of the tested 'Enformin' tablets was 10 minutes compared to the initial tablets, and it changed by only one minute (to 11 minutes) over 2 years. After 2 years, the quality of the tablets changed, and the study noted that both tablets

exhibited lower abrasion values than the required level.

The preservation of the quality of the recommended tablets for 3 years, in turn, indicates the correct choice of composition and technology."

Table-1 The results of the study of the shelf life and conditions of tablets "Enformin" in a natural way (22±2ºC)

Investigated indicators	Tablets "Enformin »							
	Types of packages							
	У-№1, У-№2, У-№3, У-№4							
	Shelf life, month							
	Initial samples of tablets	3	6	9	12	24	36	48
		Average values						
Appearance	The tablets are white in color	The tablets are white in color						
Average weight and deviations from it, g, %	1144±3,23	1258±2,08	1142±3,15	1149±2,07	1144±3,51	1153±2,37	1153±0,28	1148±3,11
Disintegration rate, min.	9	9	9	10	10	10	11	12
Abrasion resistance,%	99,32	99,74	99,12	99,15	99,35	98,22	99,00	69,87
Breaking strength,%	64	64	63	64	63	60	59	43
Solubility, %								
Amount of active substance, %	99,23	99,78	99,11	99,42	99,28	99,74	99,67	99,35

Table-2 The results of studying the shelf life and storage conditions of Sitmet tablets in a natural way (22±2oC)

Investigated indicators	Sitmet Tablets »							
	Types of packages							
	У-№1, У-№2, У-№3, У-№4							
	Shelf life, month							
	Initial samples of tablets	3	6	9	12	24	36	48
		Average values						
Appearance	The tablets are light	The tablets are light white in color						

		white in color							
Average weight and deviations from it, g, %		1041±2,12	1052±0,23	1043±2,65	1045±2,08	1044±1,34	1050±4,31	968±3,22	1047±2,07
Disintegration rate, min.		9	9	10	10	10	11	12	12
Abrasion resistance, %		99,22	99,31	99,63	99,87	99,41	99,39	99,27	98,99
Breaking strength, %		60	60	58	58	55	55	53	47
Solubility, %		88,78	88,43	88,36	88,54	98,49	88,62	88,31	87,18
Amount of active substance, %	MGX	99,76	99,69	99,11	99,09	99,00	99,05	99,00	98,43
	SG	99,58	99,55	99,25	98,75	99,03	98,97	98,39	99,15
	GD	99,32	99,17	99,28	98,52	98,17	98,96	98,56	98,42

Investigated indicators	Tablets "Enformin »				Sitmet tablets			
	Types of packages							
	У-№1, У-№2, У-№3, У-№4				У-№1, У-№2, У-№3, У-№4			
	Shelf life, days							
	Initial samples of tablets	23	46	69	92	Initial samples of tablets	23	46	69	92
	Average values					Average values				
Appearance	The tablets are white in color	The tablets are white in color				The tablets are light white in color	The tablets are light white in color			
Average weight and deviations from it, r, %										
Disintegration rate, min.	10	10	11	12	15	9	9	10	11	12
Abrasion resistance, %	99,28	99,51	99,67	99,02	98,21	99,22	99,62	99,19	99,79	98,78
Breaking strength, %	60	60	62	58	55	58	58	55	55	52

Amount of active substance, %	99,87	99,73	99,49	99,88	99,22	MGX	99,76	99,21	99,37	99,54	99,03
						SG	99,28	99,09	98,99	98,79	98,65
						GD	99,76	99,17	99,00	98,44	99,00

"Thus, the results of the study demonstrate that 'Enformin' and 'Sitmet' tablets, prepared according to the selected composition and proposed technology, exhibit stability in all types of packaging for 2 years for 'Enformin' tablets and 3 years for 'Sitmet' tablets when stored under natural conditions and using the 'accelerated aging' methods. It has been established that they fully meet the requirements for tablets.".

2. CONCLUSION

1. A "Solubility Test" was created for the recommended tablets. To assess the quality of the finished product from a biopharmaceutical perspective, the rotation speed of the basket for "Enformin" tablets is 100 rpm, and for "Sitmet" tablets - 150 rpm. The volume of the dissolution medium is 1000 ml, and the medium is neutral.

2. The stability of the recommended tablets was studied using the natural method and the "accelerated aging" method. Their stability was determined to be 2 years for "Enformin" tablets and 3 years for "Sitmet" tablets in all types of packaging.

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