MAIN FACTORS AFFECTING THE QUALITY OF THE RECOMMENDED COMBINED ANTISPASMODIC TABLETS

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ABSTRACT

The results of research on the development of combined tablets recommended as an antispasmodic drug based on simethicone and drotaverine hydrochloride are presented. The main factors influencing the quality of the recommended combined antispasmodic tablets have been studied.

Key words: combined tablets, moisture, technological properties, drotaverine hydrochloride, simethicone, antispasmodic action

INTRODUCTION

In recent years, advances in pharmacy and pharmacology, as well as the rapid development of chemistry and the pharmaceutical industry, have significantly expanded the range of domestically produced medicinal products, giving a strong impetus to the growth of their assortment. According to data from the World Health Organization, today, functional gastrointestinal disorders are observed in 15–20% of the world's population. The growth of the antispasmodic drug market is largely attributed to the increasing demand for these medications among the elderly population. One of the key and urgent tasks in the pharmaceutical sector is to provide the population with high-quality, locally produced drugs with high bioactivity from a biopharmaceutical perspective. Therefore, improving the biopharmaceutical properties of antispasmodic drugs and developing combination drug forms, as well as implementing them into practice, is of great significance [1,4,11,15,16,18].

On a global scale, the complex nature of irritable bowel syndrome highlights the need for a multifaceted approach for future successful drug

discoveries. Additionally, the growing demand for combination drugs is driving the development of new methods in this area. The development of technology for combination drug forms used in the treatment of functional gastrointestinal diseases, along with establishing methods for their analysis, ensuring their bio efficacy and stability, are among the pressing issues in the field. Solving these challenges involves the development of innovative technologies for combination antispasmodic drugs and their implementation in the pharmaceutical industry [1,2,3,5,7,19].

Drotaverine hydrochloride plays a significant role in the accurate diagnosis and effective treatment of functional gastrointestinal disorders and is one of the most frequently recommended medications for such conditions. Combinations of drotaverine hydrochloride with non-steroidal anti-inflammatory drugs (NSAIDs) are available, forming part of a wide range of antispasmodic and analgesic medicines used for various etiologies of diseases [6,8,9,12,13,15,18].

The combination we propose consists of drotaverine hydrochloride and simethicone, which has carminative (gas-reducing) properties. This combination is intended for use in gastrointestinal spasms that are increasingly common today due to global issues such as a sedentary lifestyle and poor dietary habits [5,10,14,17].

When determining the bioactivity of medicinal products, tablet quality is considered one of the main factors. Tablet quality depends on many variables, including the manufacturing technology, which makes the selection of appropriate production conditions a crucial task [7,9,10,18].

Pharmaceutical factors influence the pharmacological effect, shelf life, and bio efficacy of tablets, thereby determining their overall quality. To obtain high-quality medications, researchers must study and provide recommendations on the factors affecting their quality. Several factors influence the quality of finished tablets, such as compression pressure,

residual and environmental humidity, excipients, and technological processes [].

Objective of the Study:

To investigate the factors affecting the quality of the recommended combined tablet with spasmolytic effect.

Materials and Methods:

The research objects were **simethicone** and **drotaverine hydrochloride**. In the process of obtaining the recommended tablets, the following equipment was used: a laboratory hydraulic press with a pressing force of up to 250 kgf/cm^2, a pointer micrometer "MKI" with a measurement accuracy of 0.01 mm; tablet abrasion resistance was determined using the device 545P-AK-8; bulk flowability of tablet masses – VP-12A; disintegration – 545-AK-1; dissolution – 545-AK-7; breaking strength – TVN-200/TD; and a laboratory coating kettle.

To solve the objectives of this study, physical and pharmaco-technological methods were used, along with logical and graphical research methods: determination of bulk density, flowability, angle of repose, average tablet mass, and quality control of the recommended combined spasmolytic tablets, taking into account the scientific approach to the problem of creating combination drugs.

Experimental Section

This study presents the results of examining certain factors influencing the quality of the recommended combined tablets named **"Simverin."** The effects of compression pressure and residual moisture on tablet quality were studied, and the technological process parameters were established [11].

The tablet masses were prepared based on the proposed formulations using the selected research objects (simethicone and drotaverine hydrochloride). These factors were studied in accordance with the requirements for tablets specified in the State Pharmacopoeia of the Republic

of Uzbekistan (UzR DPh) and using methods described in the scientific literature [11, 5, 17].

The initial experiments were focused on investigating the impact of **compression pressure** on the quality of the spasmolytic tablets "Simverin." In this part of the study, tablets were produced using different compression pressures ranging from **50 to 300 MPa**. The following pharmaco-technological properties were analyzed for the obtained tablets: **disintegration time**, **hardness (resistance to breaking and abrasion)**, and **dissolution rate**.

One of the key indicators of tablet quality is **hardness**. This indicator is closely related to other quality parameters and also ensures the stability of the tablets [11].

The results of the analysis of tablets compressed at **50–300 MPa**, including their **hardness**, **abrasion resistance**, and **breaking strength**, are presented in **Figures 1 and 2**.

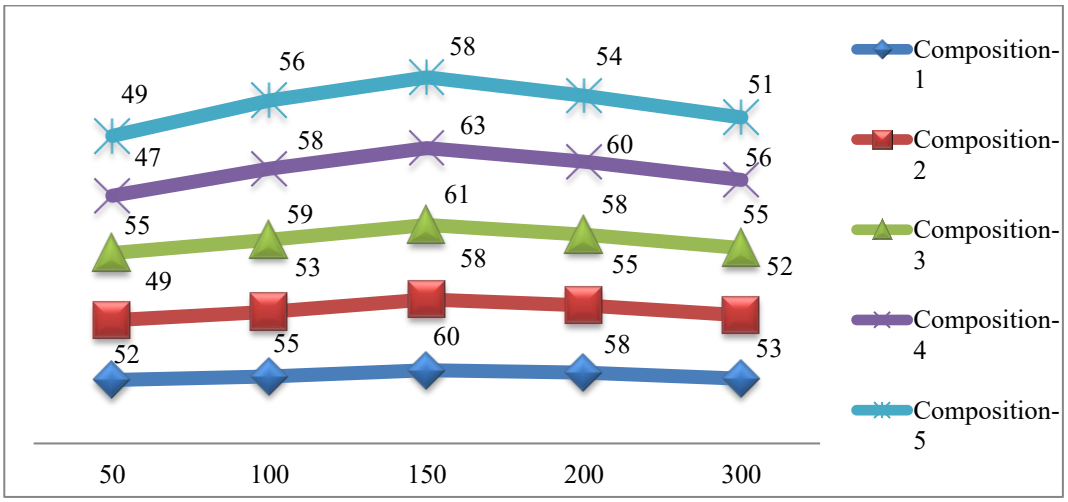

Figure 1. Results of studying the breaking hardness of "Simverin" tablets compressed at 50–300 MPa pressure

In all recommended formulations, the research showed a direct relationship between compression pressure and the breaking hardness of the tablets.

The tablets obtained from the recommended formulations demonstrated the following breaking hardness values under various pressures: at 50 MPa —

47–55 N, at 100 MPa — 53–59 N, at 150 MPa — 58–61 N, at 200 MPa — 54–59 N, and at 300 MPa — 51–56 N.

The results indicate that the tablets produced from all recommended formulations meet the required specifications for this indicator.

Furthermore, it was observed that when the compression pressure exceeded 200 MPa, the breaking hardness of tablets decreased across all formulations, although still within acceptable limits. Among the formulations, the highest breaking hardness (60 N) was observed in tablets obtained from formulation 4.

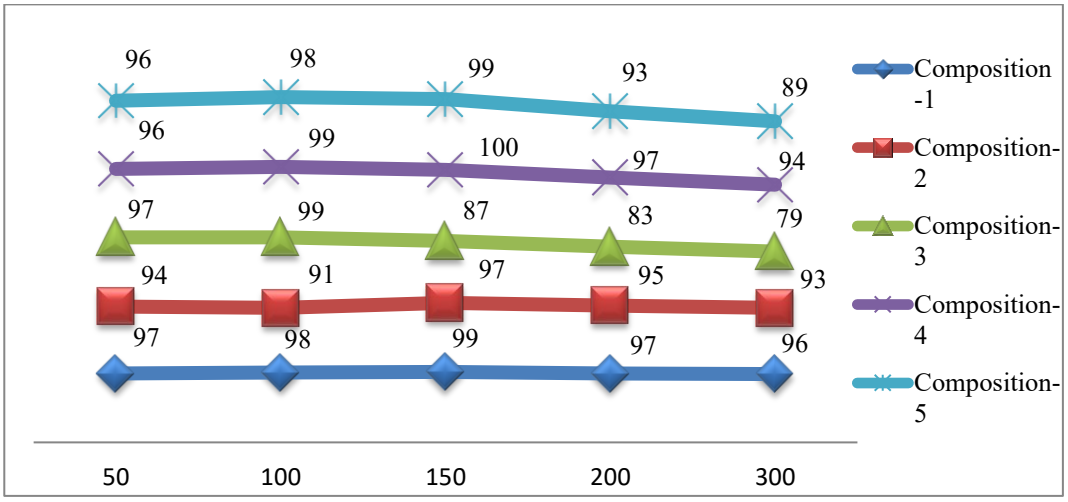

Figure 2. Results of studying the friability (resistance to abrasion) of "Simverin" tablets compressed at 50–300 MPa.

The results of studying the resistance to abrasion (friability) of "Simverin" tablets compressed at 50–300 MPa are presented in Figure 3.2. It was found that the results were nearly identical to those described above. These indicators also showed a decrease as the compression pressure exceeded 200 MPa.

At 50 MPa pressure, the resistance to abrasion for all recommended formulations ranged from 94% to 97%; at 100 MPa – from 91% to 99%; at 150 MPa – from 87% to 100%; at 200 MPa – from 83% to 97%; and at 300 MPa – from 79.96% to 96.53%, according to the research findings.

In addition, it was noted that the tablets obtained from formulation 4 at 150 MPa demonstrated the most optimal values in terms of this indicator.

In the next stage, the research focused on studying the effect of compression pressure on the disintegration of “Simverin” tablets. Disintegration is one of the key quality indicators of tablets, as it is among the factors determining the bioavailability of the drug.

Table 1 presents the results of studying the effect of compression pressure on the disintegration of the tablets.

.1-table

Results of Studying the Effect of Compression at 50–300 MPa on the Disintegration of 'Simverin' Tablets

Pressure, MPa	Disintegration time, minutes				
	Composition -1	**Composition -2**	**Composition -3**	**Composition -4**	**Composition -5**
50	10	9	10	10	8
100	10	11	12	9	10
150	9	11	11	11	11
200	9	9	10	14	9
300	9	10	9	14	10

The indicators presented in Table 3.1 show that compression pressure has almost no effect on the disintegration of the recommended tablets.

Thus, based on the conducted research, the obtained results indicate that compression pressure directly affects quality indicators such as the breaking and friability resistance of the *Simverin* tablet, while it has almost no influence on the disintegration indicator. For the production of these tablets, a compression pressure range of 100–180 MPa was determined as optimal.

Additionally, based on the research findings mentioned above, the tablets obtained from formulation 4 were evaluated as having good quality.

Studying the impact of residual moisture on the quality of Simverin tablets:

The residual moisture in the tablet mass was examined in formulation 4 using the gravimetric method as outlined in the State Pharmacopoeia of the Republic of Uzbekistan.

The results of studying the effect of residual moisture on tablet quality at various compression pressures are presented in **Table 2**.

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2-table

The results of studying the effect of residual moisture on the quality of "Simverin" tablets obtained from the proposed formulations

Residual moisture,%	Compositions				
	1	2	3	4	5
	Hardness against friction, %				
1-2	98,21±0,67	99,77±0,34	99,25±0,92	99,11±0,15	98,79±0,31
2-3	96,34±0,92	98,22±0,67	98,99±0,85	98,34±0,73	97,56±0,22
3-4	95,97±0,48	97,99±0,43	98,08±0,97	97,65±0,49	96,83±0,51
4-5	95,11±0,52	97,21±0,11	97,73±0.64	97,09±0,23	96,31±0.35
Hardness against breakage, *H*					
1-2	39	49	55	60	47
2-3	37	46	52	59	44
3-4	33	38	47	55	39
4-5	31	35	43	48	28
Disintegration, minutes					
1-2	14	9	9	10	12
2-3	16	10	10	11	14
3-4	14	11	10	11	14
4-5	15	11	10	12	14

Residual moisture is one of the factors affecting tablet quality, and this stage of the study continued by investigating its impact on the quality of the proposed tablets. In these experiments, tablets were produced from masses of different compositions with varying residual moisture content, and the

relationship between their hardness (resistance to abrasion and breaking) and disintegration time was examined.

The research results presented in Table 2 demonstrated that residual moisture has a direct effect on the quality of the proposed tablets and that this effect also depends on compression pressure. Based on the obtained results, it was determined that for future studies, the residual moisture of the tablets should be maintained between 1–2%, and the compression pressure should range from 100–180 MPa.

In the subsequent studies, the quality indicators of tablets produced under these selected conditions were evaluated comprehensively.

Based on a series of studies conducted to develop the "Simverin" tablet, tablets were produced by direct compression using the recommended formulations, with modifications in the sequence of the technological process.

The mixture of drotaverine hydrochloride with adsorbents, microcrystalline cellulose, and starch powder was gradually added and compressed. In the first stage, the ingredients were brought to an agglomerate state using a viscous liquid, then granulated through a sieve with a pore size of 160 μm. The dry drotaverine hydrochloride powder was gradually added in small amounts to this mass and mixed thoroughly. At the final stage of the technological process, magnesium stearate was added, and the mixture was compressed into tablets. The residual moisture of the tablet mass was maintained at 2.5%, and the compression pressure was set at 100–180 MPa.
The results of the quality evaluation of the proposed "Simverin" tablet are presented in Table 3.

Based on the requirements for tablets outlined in the State Pharmacopoeia of the Republic of Uzbekistan, the following quality indicators affecting the bioavailability of the proposed tablets were studied: visual appearance, disintegration characteristics, hardness (resistance to breaking and abrasion), and solubility.

According to the indicators in Table 3, the tablets produced with the proposed compositions had a light lemon-yellow color and an intact cylindrical shape with smooth edges.

The hardness indicators for abrasion resistance in tablets produced using compositions 1, 2, 3, and 5 ranged from 96.98% to 98.22%, which was below the required standard. However, tablets produced using formulation 4 demonstrated an abrasion resistance of 99.45%, thus meeting the requirement.

Furthermore, when the breaking strength of the tablets was analyzed, those produced using formulation 2.7 showed a value of 29 N, while tablets from other formulations had values ranging from 35 to 50 N. It was found that the tablets produced using formulation 1 did not meet the standard limit, whereas the others complied with the requirement.

Model tablets produced using formulations 4 and 5 showed disintegration times of 11–14 minutes (<15), which met the required standard. In contrast, tablets from formulations 1 to 3 disintegrated within 15–21 minutes (>15), thus failing to meet the requirement.

When studying the height-to-diameter ratio of the tablets, those produced using formulations 1–3 showed values in the range of 24.31–29.94 mm, which were below the acceptable range (<30–40%). However, tablets from formulations 4 and 5 demonstrated values of 37.83 mm and 35.89 mm, respectively, indicating compliance with the required standard.

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3-table

Results of the study of quality indicators of "Simverin" tablets

Bioactive substances	№	Formulations	Studied indicators			
			Қаттиқлик		Disintegration, minutes	Tablet diameter-to-height ratio, mm
			Abrasion resistance %	Crushing strength, N		

Simethicone + Drotaverine hydrochloride	1	Dibasic calcium phosphate Potato starch MCC (Microcrystalline cellulose) Magnesium stearate	97,09±1,76	29	21	25,98 ± 2,14
	2	Potato starch (P) Colloidal silicon dioxide Croscarmellose Magnesium stearate	96,98±1,67	35	16	24,31 ± 1,87
	3	Magnesium aluminum silicate Lactose monohydrate Croscarmellose Magnesium stearate	97,87±1,83	38	15	29,94 ± 2,11
	4	Dibasic calcium phosphate Magnesium aluminum silicate Potato starch MCC (Microcrystalline cellulose) Magnesium stearate	99,45±0,65	50	11	37,83 ± 2,44
	5	Dibasic calcium phosphate Peptidized potato starch MCC (Microcrystalline cellulose) Magnesium stearate	98,22±0,21	50	14	35,89 ± 1,67

In the subsequent stages of the research, based on the above-mentioned results, tablets were produced according to the selected fourth formulation. The following quality indicators of these tablets were studied in accordance with the requirements for tablet dosage forms specified in the State Pharmacopoeia of the Republic of Uzbekistan. It was proven that the tablets met these standards. The following parameters were examined: visual appearance of the tablets with the naked eye, average weight and its deviation, the ratio of tablet diameter to thickness, disintegration characteristics, hardness in relation to breaking and abrasion. The obtained results confirmed compliance.

The compliance of the proposed combined “Simverin” tablets with the quality requirements for tablets specified in the State Pharmacopoeia of the Republic of Uzbekistan is presented in tabular form in Table 3.5.

The analysis of the results presented in Table 4 confirmed the correctness of the selected formulation.

The tablets obtained using the proposed composition and technology fully comply with all the quality and quantitative requirements for tablet dosage forms set by the State Pharmacopoeia of the Republic of Uzbekistan.

3.5-table

Results of Studying the Quality Indicators of "Simverin" Combination Tablets

TLV standards	**Tablet Compression Conditions: Compression pressure 100-180 MPa and residual moisture content 1-2%**	**Analysis Results**	**Methods**
	Studied Indicators		
Light lemon in	***Appearance***		

color, with intact cylindrical edges	Light lemon-colored tablets with intact, cylindrical edges	Complies	With the naked eye
Friability (or Resistance to Abrasion), %			
> 99	99,45	Complies	UzSP (п.2.9.7.)
Hardness (or Resistance to Crushing), H			
> 30 H	55 H	Complies	UzSP (п.2.9.7.)
Average weight and its deviation, %			
0,5225 from 0,5775(0,5г) 5%	0,5211± 2,57	Complies	UzSP (п.2.9.5.)
Disintegration, min.			
< 15	11± 0,74	Complies	UzSP (п.2.9.1.)
Dissolution,%			
Not less than 75% in 45 minutes	99,22± 0,38	Complies	Spectrophotometry and HPLC
Amount of active ingredients, g			
Drotaverine hydrochloride	From 36.0 mg to 44.0 mg per tablet	39,65 ± 3,21	Spectrophotometry
Simethicone	From 67.5 mg to 82.5 mg per tablet	77,83± 4,39	UV and IR Spectroscopy

Thus, it was determined that the combined “Simethicone” tablets obtained using the proposed composition and technology meet all the requirements for tablet dosage forms as specified in the State Pharmacopoeia of the Republic of Uzbekistan in terms of quality and quantitative indicators. The conducted studies confirmed that the tablets produced with the selected composition and technology can serve as a basis for further stage research.

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