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Study Of The Influence Of Excipients On The Quality Of "Simverin" Tablets

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Abstract
In these studies, the effect of excipients on the pharmacotechnological properties of the recommended tablets was examined, as well as their influence in different ratios during the development of the recommended tablets. The impact of excipients with various chemical structures was studied to obtain the combined tablets "Simverin."
In order to improve the technological process of manufacturing the recommended tablets, a comparative evaluation of the pharmacotechnological properties of the tablets was carried out using different excipients.
The most well-known excipients used in the composition of pharmaceutical dosage forms available on the pharmaceutical market were selected for this study.
Key words: *Drotaverine hydrochloride, simethicone, antispasmodic effect, excipients*

INTRODUCTION

The President and Government of the Republic of Uzbekistan are paying great attention to the development of domestic pharmaceutical production. According to the strategic directions of the pharmaceutical policy of the Republic of Uzbekistan, production volumes are increasing at a rapid pace. The technology of pharmaceutical products has a significant impact on the future economic indicators of production and practical application. As a result of the growing role and potential of pharmaceutical technology, the time from the emergence of an idea and the first results of scientific research to their industrial implementation is being reduced [2,5].

In Uzbekistan, plans have been made to reduce the volume of imported consumer goods by expanding their production at domestic enterprises [1,3,6,9].

Thanks to research in the field of tablet manufacturing both in our country and abroad, this branch of pharmaceutical science is moving beyond empiricism and is becoming an important field of science in addressing issues related to improving the pharmaceutical services provided to the population [9,10,15,16].

Based on the above, the creation of highly effective pharmaceutical products is the main goal of the pharmaceutical industry.

There are many approaches through which it is considered possible and economically feasible to develop a pharmaceutical dosage form with the desired pharmacological effect based on the combination of substances that have demonstrated pharmacological efficacy over an extended period [17,18,20].

There are several factors driving the increased demand among patients for combination drugs, such as: increased effectiveness of combinations compared to monotherapy due to the synergistic effect of the components included; faster onset of action; improved safety while maintaining efficacy at the level of separate application; one component neutralizing adverse drug reactions (ADRs) caused by another; and simplified therapy [3,10,19].

The market of combination drugs for the treatment of abdominal pain includes numerous medications that provide both symptomatic and pathogenetic therapy [12,13,14,15].

Drotaverine hydrochloride is one of the most in-demand drugs with a broad spectrum of antispasmodic activity, commonly prescribed for diseases of various etiologies. It belongs to the group of myotropic non-selective agents. Its action is based on the inhibition of phosphodiesterase (PDE), which breaks down the intracellular signal mediator (cAMP). As a result, the contractile capacity of myofibrils decreases. Drotaverine partially blocks calcium and sodium channels, reduces smooth muscle tone, dilates blood vessels, and normalizes intestinal peristalsis. The drug is well-tolerated by patients and is considered a fast-acting antispasmodic. It is prescribed regardless of the cause of pain in cases where the pain syndrome is

caused by spasms of the smooth muscles located in internal organs. The drug is actively used to relieve renal, intestinal, and hepatic colic, as well as spastic constipation. According to statistics, the cause of abdominal spasms often lies in various pathological reactions associated with flatulence [4,5,6,9,11].
Developing a combination of antispasmodic and carminative (anti-flatulent) drugs will increase the effectiveness of pharmacological treatment of functional gastrointestinal disorders, as assessed by the Rome criteria [7,12].
As the carminative component in the combination, we selected the drug simethicone. Simethicone is an organosilicon compound from the polydimethylsiloxane group with defoaming properties, used to reduce bloating, discomfort, or pain caused by excessive gas formation [8,9,10].
Based on the above, the aim of this research was to study the effect of excipients with the necessary structural-mechanical and technological properties that enhance the technological characteristics of the combination of drotaverine hydrochloride and simethicone.
Excipients in tablet manufacturing are substances included in the tablet mass to impart the required technological properties, ensuring dosage accuracy, tablet strength, and disintegration. All quality parameters of a pharmaceutical product depend, to some extent, on the excipients used, which is why greater attention is being paid to their optimal selection [].

MATERIALS AND METHODS

At this stage of our research, in order to select the tablet composition, more than twenty formulations were studied separately and in combinations, using auxiliary substances that modify the negative technological properties of the raw materials currently widely used and planned to be obtained in practice. The technological properties of the auxiliary substances on the technological indicators of drotaverine hydrochloride and simethicone agglomerates were studied, selected, and included in the formulation.
In the selection of auxiliary substances, compositions were prepared based on excipients that are readily available, inexpensive, widely used in current pharmaceutical practice, and inert (do not react) with the bioactive substances.
As auxiliary substances, we used dibasic calcium phosphate, magnesium aluminum silicate, potato starch, peptidated potato starch, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and magnesium stearate.
More than twenty compositions were studied in the research..

EXPERIMENTAL PART

The results of the study on the effect of disintegrants such as potato starch, corn starch, and peptidized potato starch on tablet disintegration are presented in Figure 1.

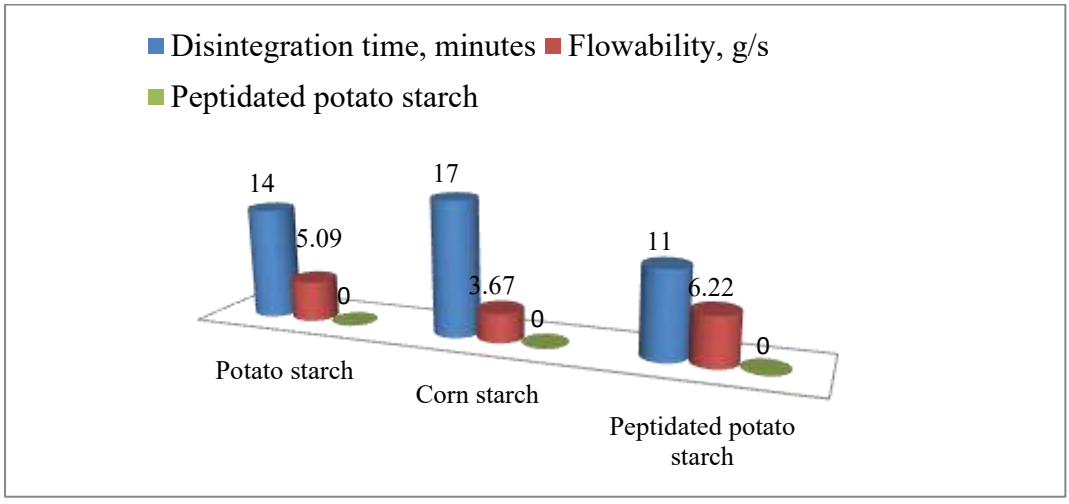


Figure 1. Results of the Study on the Effect of Disintegrants on the Friability of the "Simverin" Tablet Mass and Tablet Disintegration

Analyzing the obtained results shows that all three disintegrants had varying effects on the disintegration and friability of the "Simverin" tablets. Among the studied disintegrants, corn starch demonstrated a positive friability value of 3.67 g/s for the tablet mass, while its disintegration time was 17 minutes, which exceeds the required limit (<15 minutes).
Potato starch and modified (peptized) potato starch showed disintegration times of 14 and 11 minutes, respectively. Their friability values were 5.09 and 6.22 g/s, respectively. Both of these indicators showed

positive results for the two disintegrants, which was considered favorable based on the research findings. However, when comparing the two disintegrants with positive results, it was found that potato starch's effect on disintegration was at the borderline of the required limit (<15 minutes), and its friability was lower compared to modified potato starch.

Modified potato starch has moisture-retaining properties and solubility in cold water, which makes it convenient for direct compression tablet manufacturing. Modified potato starch—Driamyl VP—is a modified product of potato starch that also serves as a preservative.

Based on the above, modified potato starch was selected as the disintegrant for the "Simverin" tablet formulation.

Methylcellulose and microcrystalline cellulose are widely used as dry binders in tablet manufacturing and are suitable for direct compression tablets. Additionally, methylcellulose improves the compressibility and friability of the tablet mass. In tablets produced by wet granulation, methylcellulose is used in pharmacy due to its water-soluble binding or thickening properties.

The study comparatively investigated the compressibility, friability, and natural angle of repose of microcrystalline cellulose and methylcellulose.

The results obtained are presented in Figure 2 below.

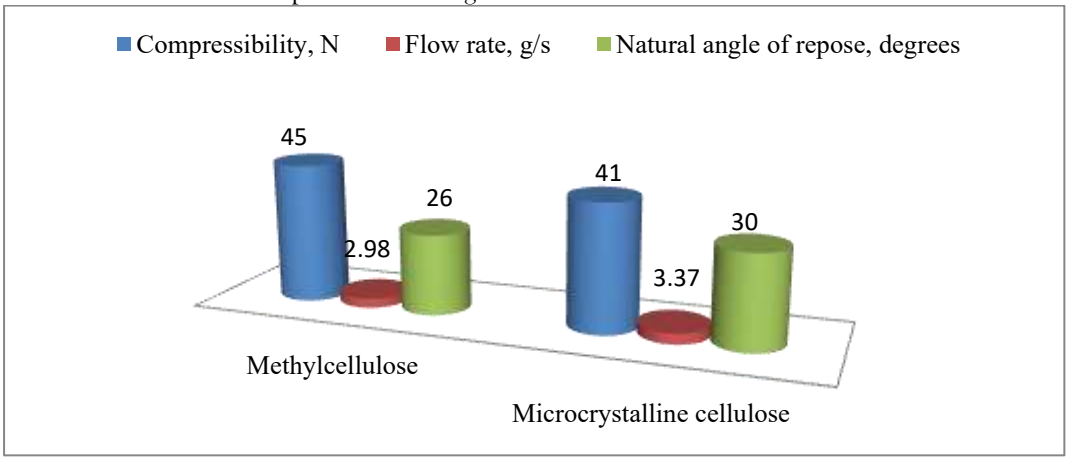


Figure 2. Comparative study results of the effect of microcrystalline cellulose and methylcellulose on the compressibility, friability, and natural angle of repose of the tablet mass

The results presented in Figure 2 show that methylcellulose exhibited a higher compressibility value of 45 N compared to microcrystalline cellulose, which showed 41 N, indicating a positive performance. Both powders demonstrated friability values at the required level (2.98 and 3.37, respectively), with methylcellulose showing relatively better friability characteristics.

Additionally, when studying the natural angle of repose of both powders, methylcellulose showed a value of 35 degrees, while microcrystalline cellulose showed 31 degrees. These values further confirmed that the friability was indeed within the acceptable range. These results also indicated that methylcellulose has a relatively more stable positive effect.

Based on the above research results, it was predicted that the technological indicators would improve when using methylcellulose.

Subsequent studies continued on the selection of anti-friction agents. Stearic acid, calcium stearate, and magnesium stearate were taken as anti-friction agents, and their effect on improving the ejection of tablets from the mold was studied.

The results of the study on the effect of anti-friction agents on the friability and natural angle of repose of the recommended tablet compressible mass are presented in Figure 3

Based on the indicators obtained in the studies, we concluded that magnesium stearate should be included as an anti-friction agent in the formulation. This is because calcium stearate has lubricating and adhesion properties, as well as electrostatic forces.

Both stearic acid and magnesium stearate act as lubricants providing anti-friction effects. It was observed in the studies that magnesium stearate, a derivative of stearic acid, had a positive effect on the detachment of the finished tablets from the punch. For this reason, we included magnesium stearate in the formulation for further studies and used it in the recommended production technology.

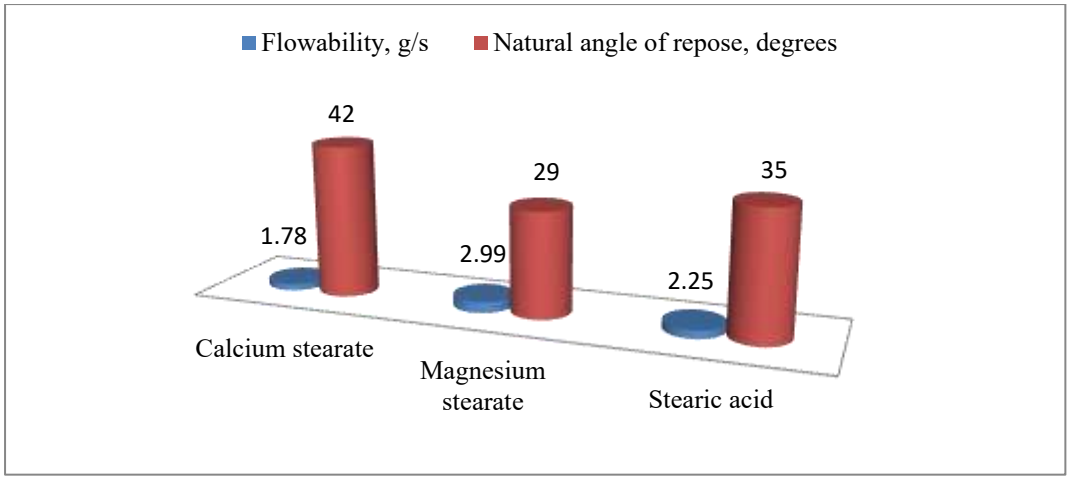


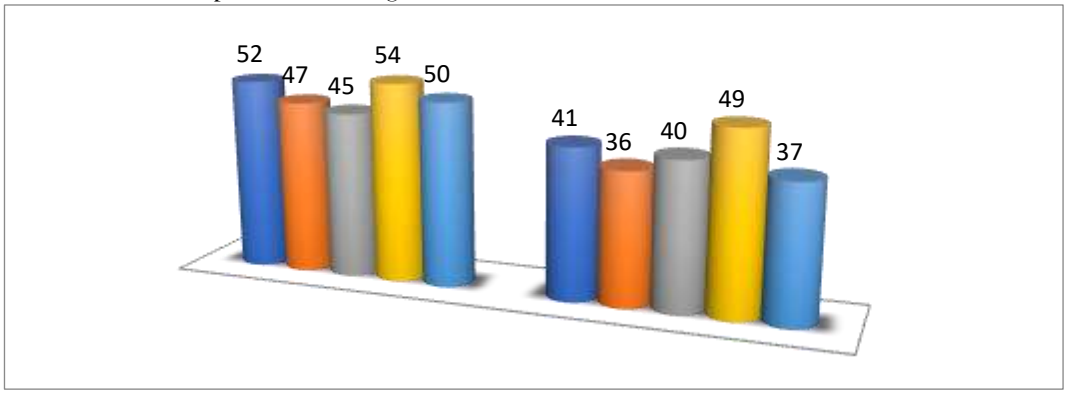
Figure 3. Comparative study results of the effect of anti-friction agents on the friability and natural angle of repose of the tablet mass

Below are five formulations that exhibited similar technological properties to each other (Table 1).

Table 1 Formulation compositions studied for the preparation of "Simverin" combined tablets

Ingredients	Formulations				
	1	2	3	4	5
Simethicone	0,075	0,075	0,075	**0,075**	0,075
Drotaverine hydrochloride	0,040	0,040	0,040	**0,040**	0,040
Dibasic calcium phosphate	0,265			**0,265**	0,265
Magnesium aluminum silicate			0,265		
Potato starch	0,038				
Peptidated potato starch (Drillamyl VP VPP)		0,038		**0,038**	0,038
Lactose monohydrate			0,038		
Microcrystalline cellulose	0,077				0,077
Methyl cellulose				**0,077**	
Colloidal silicon dioxide		0,265			
Croscarmellose		0,077	0,077		
Magnesium stearate	0,005	0,005	0,005	**0,005**	0,005
Average weight	0,5	0,5	0,5	**0,5**	0,5

Thus, based on the above research results, a number of formulations were studied. The study continued by investigating the technological properties of the mass obtained from the bioactive substances and auxiliary materials presented in Table 1, focusing on friability, natural angle of repose, and bulk density. The results obtained are presented in Figure 4.



4- Figure. Study results of the compressibility and natural angle of repose of the five recommended formulations

The research results presented in Figure 4 show that, compared to the initial raw materials, the technological property indicators have shifted positively, especially clearly observed in the mass obtained in formulation 4.

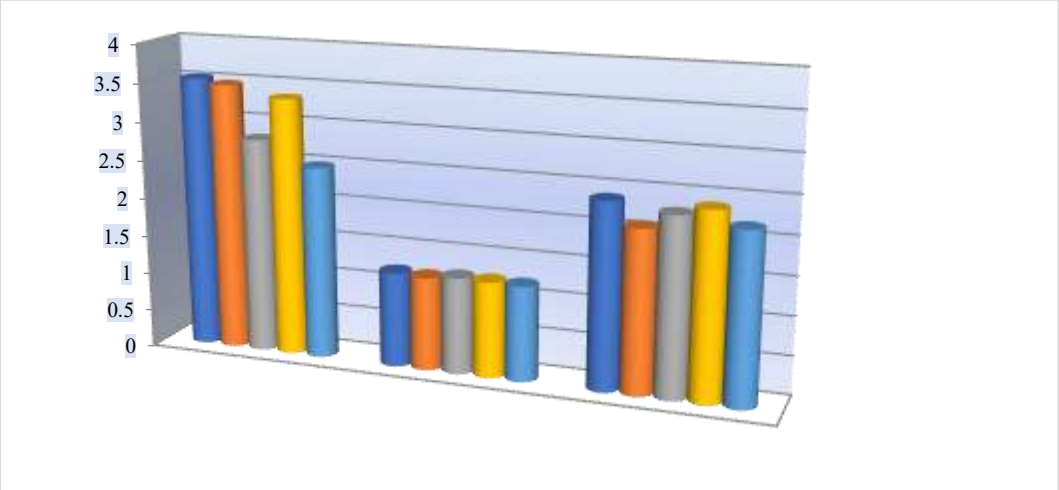
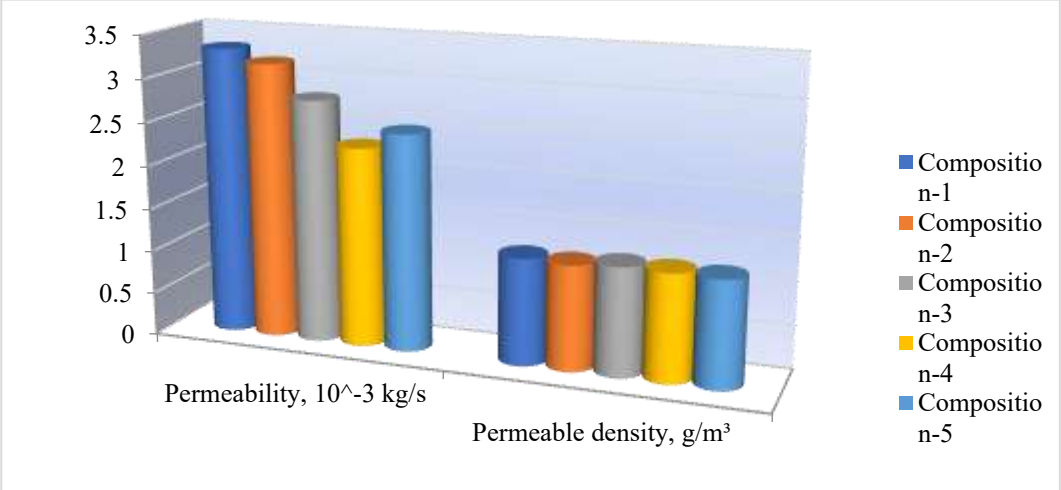


Figure 5. Study results of residual moisture, compressibility, and densification coefficient of the five recommended formulations

The results obtained show that the residual moisture, compressibility, and densification indicators of the mass obtained in the five formulations are within the required standards.



6 - Figure. Results of the study on the friability and bulk density of the five recommended formulations

The results of the study on the uniformity of tablet masses and flowability showed a positive change in indicators, as can be seen from the data in Figure 6. However, the degree of flowability remained relatively low, although it was within acceptable limits.

Taking the above into consideration, the tablets obtained from the proposed formulation were prepared using the direct compression method through the following stages:

Adsorbents (dibasic calcium phosphate, magnesium aluminum silicate, and colloidal silicon dioxide), passed through a sieve with a 160 µm mesh diameter, were mixed in a double-cone mixer rotating at 90 rpm. Simethicone was added in a fibrous form and mixed for 30 minutes. To the resulting agglomerate, drotaverine hydrochloride, fillers, and disintegrants (microcrystalline cellulose, methylcellulose, lactose monohydrate, croscarmellose, potato starch) — all pre-sieved through a 160 µm sieve — were added and mixed until a uniform mass was achieved.

At the final stage of the technological process, magnesium stearate was added and the mixture was compressed into tablets.

The resulting tablets were light lemon-colored with intact, cylindrical shapes, clearly visible to the naked eye. The average weight of the tablets and its deviation were within acceptable limits. However, the height-to-diameter ratio of the prepared tablets was low, ranging between 25–29 mm. In addition, it was found that the disintegration time of the tablets was between 16–21 minutes and their solubility ranged from 58% to 67%, which did not meet the required standards.

Based on the results of several studies conducted on the development of "Simverin" tablets, the sequence of the technological process was modified in the proposed formulations, and tablets were obtained by direct compression.

Drotaverine hydrochloride, along with adsorbents, microcrystalline cellulose, and starch powders, was gradually added to the formulation and compressed. In the first stage, the ingredients were agglomerated into a fibrous liquid form as described earlier, granulated through a 160 μm sieve, and then small portions of dry drotaverine hydrochloride powder were added and mixed.

At the final stage of the process, magnesium stearate was added, and the mixture was compressed. The residual moisture of the tablet mass was maintained at 2.5%, and the compression pressure was set at 100–180 MPa.

The quality indicators of the proposed "Simverin" tablets continued to be studied, and the results are presented in Table 2 below.

Based on the standards set in the State Pharmacopoeia of the Republic of Uzbekistan, the key quality indicators affecting the bioavailability of the tablets were examined. These include external appearance, disintegration time, resistance to breaking and friction (hardness), and solubility.

As shown in Table 2, the tablets obtained from the proposed formulations had a light lemon color with intact, cylindrical edges.

The resistance to friction (friability) in the tablets from formulations 1, 2, 3, and 5 ranged from 96.98% to 98.22%, which did not meet the required standards. Tablets from formulation 4, however, showed a result of 99.45%, meeting the required specifications.

Moreover, when analyzing the resistance to breaking (hardness), it was found that tablets from formulation 2.7 showed a hardness of 29 N, while those from the other formulations ranged between 35–50 N. Tablets from formulation 1 were found to be below the acceptable threshold (i.e., not in compliance with normative requirements), while the others met the required standards.

As for the model tablets, those from formulations 4 and 5 disintegrated in 11–14 minutes (<15), which met the required standards. Meanwhile, tablets from formulations 1–3 disintegrated in 15–21 minutes (>15), thus failing to meet the standard criteria.

2-table

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

Bioactive substances	№	Ingredients	Studied indicators			
			Hardness		Disintegration, minutes	Ratio of tablet diameter to height, mm
			With respect to friction%	With respect to breaking, N		
Simethicone , Drotaverine hydrochloride	1	Dicalcium phosphate Potato starch Microcrystalline cellulose (MCC) Magnesium stearate	97,09±1,76	29	21	25,98 ± 2,14
	2	— Potato starch (P) Colloidal silicon dioxide Croscarmellose sodium Magnesium stearate	96,98±1,67	35	16	24,31 ± 1,87
	3	Magnesium aluminum silicate Lactose monohydrate	97,87±1,83	38	15	29,94 ± 2,11

		Croscarmellose sodium Magnesium stearate				
	4	Dicalcium phosphate Magnesium aluminum silicate Potato starch Microcrystalline cellulose (MCC) Magnesium stearate	99,45±0,65	50	11	37,83 ± 2,44
	5	Dicalcium phosphate Peptidated potato starch Microcrystalline cellulose (MCC) Magnesium stearate	98,22±0,21	50	14	35,89 ± 1,67

When studying the height-to-diameter ratio of the tablets, it was found that the tablets obtained from compositions 1 to 3 showed values below the required range (24.31–29.94 mm, which is less than the acceptable 30–40%). In contrast, the tablets from compositions 4 and 5 demonstrated acceptable values of 37.83 mm and 35.89 mm, respectively, meeting the standard requirements. Thus, based on the results of studying the quality indicators of the "Simverin" tablets obtained from the proposed compositions, composition 4 was selected and served as the basis for further research.

CONCLUSION

Based on the results of the above-mentioned research, it was determined that the composition and technology of the recommended tablets were correctly developed, as the quality indicators of the proposed tablets meet the required standards.

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