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Formulation and In-vitro Evaluation of Extended Release Tamsulosin Hydrochloride and Solifenacin Succinate Combined Tablet as an Effective Drug for Benign Prostatic Hyperplasia

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Abstract

Benign prostatic hyperplasia (BPH) is one of the common diseases in men. This disease includes characteristics such as the size of the prostate index, lower urinary tract problems (frequency, urgency in emptying urine, nocturnal urination, the feeling of incomplete emptying of the bladder and decreased urine flow pressure) and bladder outlet obstruction. Tamsulosin hydrochloride (**I**), which is an antagonist of alpha-receptors, and solifenacin succinate (**II**), which is an antagonist of muscarinic receptors, have been approved for the treatment of this disease and related problems. The simultaneous use of two drugs in the form of fixed dose combined tablets (FD) in addition to improving patients' compliance with treatment, leads to cost reduction and improvement of symptoms. Dry granulation method was used to make the rapid release layer of solifenacin succinate and polymer composition was used to make the tamsulosin hydrochloride release control layer by wet granulation method. Then the tablets were pressed and coated. Necessary standard tests were performed for all formulations. The results showed that the formulation containing 6 mg of solifenacin succinate and 0.4 mg of tamsulosin hydrochloride was selected as the superior formulation, which is similar to the Vesomni® brand sample.

Keywords: Benign Prostatic Hyperplasia, Combined Controlled Release Tablet, Tamsulosin Hydrochloride, Solifenacin Succinate.

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Introduction

Benign prostatic hyperplasia is common and costly in human societies. Disease symptoms, such as problems related to the lower urinary tract, severely affect the quality of life of men [1].

The treatment of benign prostatic hyperplasia can vary depending on the severity of the symptoms, the patient's preference and the amount of suffering. Patients with mild symptoms receive guidance on lifestyle changes, but patients with moderate and severe symptoms need drug therapy in addition to lifestyle changes.

The simultaneous use of anticholinergic drugs with alpha-receptor inhibitors is considered as the preferred option in benign prostatic hyperplasia patients who suffer from overactive bladder. Taking drugs from the category of alpha-blockers and 5 alpha reductase inhibitors is recommended as treatment options in patients with lower urinary tract problems and prostate enlargement. Finally, surgery [2] or laser [3] were considered as a treatment options for patients.

On the other hand, the absorption, distribution, metabolism and excretion of drugs in the body is dynamic, and the increase or decrease in the concentration of the drug leads to the occurrence of side effects and the reduction of therapeutic effects. To solve this problem, frequent and periodic use of medicine is needed, which is not possible in many patients. Recently, the use of continuous-release drugs has led to the satisfaction of patients' needs and is economically beneficial for them [4].

Tamsulosin with the generic name tamsulosin hydrochloride (5-[(2R)-2-[{2-(2-Ethoxyphenoxy)ethyljaminolpropyl)-2-methoxybe:nzenesulfonamide hydrochloride, **I**) and with an antagonistic effect on α1A adrenoreceptors in the prostate tissue, is used as an effective and safe drug to improve symptoms related to the lower urinary tract caused by benign prostatic hyperplasia. Also, by blocking the α1A and 1Dα receptors in the bladder, this drug leads to the inhibition of detrusor smooth muscle contraction and thus leads to the reduction of symptoms related to urinary retention [5].

Tamsulosin, as a fast-release drug, leads to rapid absorption and a sudden increase in the concentration of the drug in the plasma, and ultimately leads to the occurrence of side effects related to the heart and blood vessels. This issue led to the expansion of the use of this drug in the form of controlled release. Absorption of tamsulosin is a gradual release control and provides good safety and tolerability [6]. In addition, taking the drug as a controlled release after a meal leads to a more appropriate response against orthostatic stress [7].

Solifenacin with the generic name solifenacin succinate ((3R)-I-Azabicydo[2.2.2Joctan-3-yl(IS)-I-phenyl-3,4-dihydroisoquinoline-2(IH),arboxylate hydrogen butanedioatc, **II**) by antagonizing the specific M1 and M3 receptors in the bladder, improves the symptoms of overactive bladder

syndrome, which includes frequent urination, urgency in emptying urine, nocturnal enuresis, and urinary incontinence. It improves the quality of life of patients [8].

Many studies on the effectiveness of solifenacin succinate in the treatment of Overactive Bladder (OAB) [9-14], tamsulosin hydrochloride in the treatment of BPH [15-18] and simultaneous use of two drugs, solifenacin and tamsulosin, in the treatment of BPH [19-21] have been conducted so far.

The simultaneous use of two drugs, solifenacin and tamsulosin, as a rational, efficient and safe option, leads to the improvement of lower urinary tract symptoms and, as a result, improves the quality of life in patients [22].

Also, the simultaneous use of two drugs leads to synergism in the recovery of detrusor muscle hyperactivity [23] and symptoms such as retention (frequency of urination, nocturia, incontinence and urgency in urination) as well as problems related to urination (slow It improves urinary flow, delay in starting urination, interruption of urine flow, excretion of urine drops after termination). The simultaneous use of two drugs has been considered in patients who suffer from moderate to severe problems related to the urinary tract and do not show sufficient response to each of the two drugs separately [24].

Fixed-dose combination drugs provide the possibility of combining two or more drug molecules with different pharmacology categories. One of the advantages of using fixed-dose combined pills, which has led to the popularity of such drugs, is cost reduction, increased patient acceptance and comfort [25].

The above-mentioned benefits for fixed-dose combined drugs and the effort to improve the quality of life of people with benign prostatic hyperplasia and the existence of a pharmaceutical form of these two pharmaceutical substances in the world pharmaceutical market and the lack of it in the country are the basis for conducting this research on making pills. Tamsulosin-Solifenacin combination.

According to the conducted studies, there is no history of this product's formulation in Iran. Therefore, in this research, several formulations of solifenacin succinate-tamsulocin hydrochloride controlled release tablets were made and then in terms of physicochemical properties such as appearance, weight, hardness, thickness, diameter, erosion, opening time, percentage of released drug , quantity determination, drug content uniformity, similarity and difference factors were investigated and finally, the superior formulation in terms of physicochemical properties and selected release profile, which had the most similarity with the foreign sample of Vesomni®, was selected.

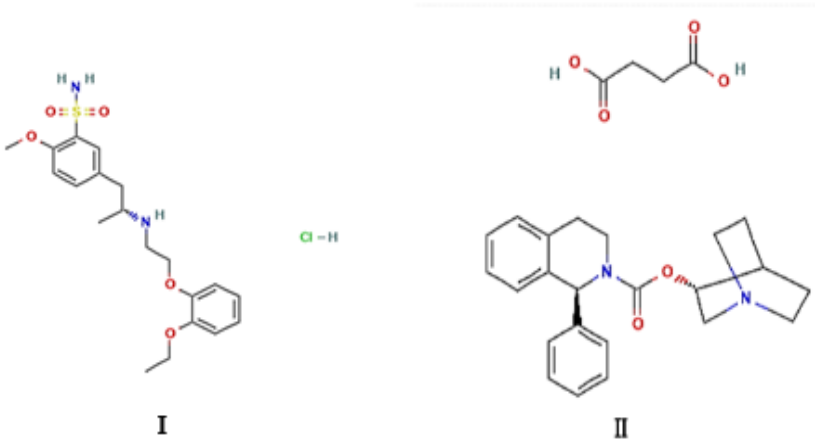


Figure 1. Structure formula of Tamsulosin Hydrochloride (**I**) and Solifenacin Succinate (**II**).

Experimental

Chemicals

Solifenacin Succinate (**I**) and Tamsulosin Hydrochloride (**II**) were prepared from Hetero Drugs Limited and Symed Labs Limited (India) companies. Other chemicals and reagents such as Polyvinyl pyrrolidone (PVP), Ethanol, Lactose, Magnesium stearate, Mannitol, Lactose monohydrate, Pregelatinized Starch, Silicon dioxide, Compritol 888 ATO and Hydroxypropyl Methyl cellulose (HPMC K100) were prepared from Merck (Germany) company.

Apparatus and instruments

HPLC (Shimadzu, Japan), Oven (Memmert, Germany), Magnetic stirrer (Heidolph, Germany), Analytical balance (Satorious, Germany), DT-800 dissolution, Hardness, Erosion and Opening time measuring devices (Erweka, Germany) instruments were used in this research.

Preparation of formulations

Quick release tablets of Solifenacin Succinate

In this section, the components, quantities, percentages and performance of quick release tablets of Solifenacin Succinate (SF_1 and SF_2) are given in Tables 1 and 2.

Table 1. Components, amounts, percentage and performance of SF_1 formulation.

	Drug dose			6 mg
	Formulation components	**Content**		**Role**
		mg	%	
1	Solifenacin Succinate	6	6	Active pharmaceutical ingredient
2	Lactose SD	78	78	Filler
3	Corn Starch	7.5	7.5	Adhesive
4	Gelatinous starch	7.5	7.5	Releasing agent
5	Magnesium stearate	1	1	Lubricant
The total components of the core		100	100	

Table 2. Components, amounts, percentage and performance of SF_2 formulation.

	Drug dose			6 mg
	Formulation components	**Content**		**Role**
		mg	%	
1	Solifenacin Succinate	6	6	Active pharmaceutical ingredient
2	Lactose SD	77	77	Filler
3	Corn Starch	7.5	7.5	Adhesive
4	Gelatinous starch	7.5	7.5	Releasing agent
5	Magnesium stearate	1	1	Lubricant
6	Colloidal silicon dioxide	1	1	Glidant
The total components of the core		100	100	

Quick release tablets of Tamsulosin Hydrochloride

In this section, the components, quantities, percentages and performance of quick release tablets of Tamsulosin Hydrochloride (TF_1-TF_6) are given in Tables 3-8.

Table 3. Components, amounts, percentage and performance of TF_1 formulation.

	Drug dose			0.4 mg
	Formulation components	**Content**		**Role**
		mg	%	
1	Tamsulosin Hydrochloride	0.4	0.2	Active pharmaceutical ingredient
2	Lactose monohydrate	50	25	Filler
3	Mannitol	50	25	Solvent
4	Spray Dried Mannitol	27.6	13.8	Solvent
5	Compritol 888 ATO	56	28	Release control polymer
6	PVP K30	14	7	Adhesive
7	Magnesium stearate	2	1	Lubricant
8	Distilled water	−	−	Solvent
The total components of the core		200	100	

Table 4. Components, amounts, percentage and performance of TF_2 formulation.

	Drug dose			0.4 mg
	Formulation components	**Content**		**Role**
		mg	%	
1	Tamsulosin Hydrochloride	0.4	0.16	Active pharmaceutical ingredient
2	Lactose monohydrate	50	20	Filler
3	Mannitol	50	20	Solvent
4	Spray Dried Mannitol	29.6	11.84	Solvent
5	Compritol 888 ATO	100	40	Release control polymer
6	PVP K30	17.5	7	Adhesive
7	Magnesium stearate	2.5	1	Lubricant
8	Distilled water	−	−	Solvent
The total components of the core		250	100	

Table 5. Components, amounts, percentage and performance of TF_3 formulation.

	Drug dose			0.4 mg
	Formulation components	**Content**		**Role**
		mg	%	
1	Tamsulosin Hydrochloride	0.4	0.16	Active pharmaceutical ingredient
2	Lactose monohydrate	40	16	Filler
3	Mannitol	40	16	Solvent
4	Spray Dried Mannitol	24.6	9.84	Solvent
5	Compritol 888 ATO	125	50	Release control polymer
6	PVP K30	17.5	7	Adhesive
7	Magnesium stearate	2.5	1	Lubricant
8	Distilled water	–	–	Solvent
The total components of the core		250	100	

Table 6. Components, amounts, percentage and performance of TF_4 formulation.

	Drug dose			0.4 mg
	Formulation components	**Content**		**Role**
		mg	%	
1	Tamsulosin Hydrochloride	0.4	0.16	Active pharmaceutical ingredient
2	Lactose monohydrate	40	16	Filler
3	Mannitol	40	16	Solvent
4	Spray Dried Mannitol	24.6	9.84	Solvent
5	Compritol 888 ATO	125	50	Release control polymer
6	PVP K30	17.5	7	Adhesive
7	Magnesium stearate	2.5	1	Lubricant
8	Distilled water	–	–	Solvent
The total components of the core		250	100	

Table 7. Components, amounts, percentage and performance of TF_5 formulation.

	Drug dose			0.4 mg
	Formulation components	**Content**		**Role**
		mg	%	
1	Tamsulosin Hydrochloride	0.4	0.16	Active pharmaceutical ingredient
2	Lactose monohydrate	40	16	Filler
3	Mannitol	40	16	Solvent
4	Spray Dried Mannitol	24.6	9.84	Solvent
5	Compritol 888 ATO	100	40	Release control polymer
6	HPMC K 100	25	10	Release control polymer
7	PVP K30	17.5	7	Adhesive
8	Magnesium stearate	2.5	1	Lubricant
9	Distilled water	–	–	Solvent
The total components of the core		250	100	

Table 8. Components, amounts, percentage and performance of TF_6 formulation.

	Drug dose			0.4 mg
	Formulation components	**Content**		**Role**
		mg	%	
1	Tamsulosin Hydrochloride	0.4	0.16	Active pharmaceutical ingredient
2	Lactose monohydrate	40	16	Filler
3	Mannitol	40	16	Solvent
4	Spray Dried Mannitol	24.6	9.84	Solvent
5	Compritol 888 ATO	75	30	Release control polymer
6	HPMC K 100	50	20	Release control polymer
7	PVP K30	17.5	7	Adhesive
8	Magnesium stearate	2.5	1	Lubricant
9	Distilled water	–	–	Solvent
The total components of the core		250	100	

Final formulation

The final formulation was formed by pressing the two formulas of SF_2 and TF_6 in two layers using 100 mg of solifenacin and 250 mg of tamsulosin by a double layer tablet press machine. At this stage, the ability to press the granules of solifenacin and tamsulosin as tablets with two layers on top of each other, the soundness of the appearance of the tablets after pressing, physicochemical tests such as measuring weight, thickness, hardness, diameter, erosion, determining amount of active pharmaceutical ingredient, dissolution and the degree of similarity and difference to the foreign brand sample were investigated [26].

Results

Physicochemical properties of quick release tablets of Solifenacin Succinate in SF_1 and SF_2 formulations

At first, samples were randomly selected from each series of formulations, their appearance properties such as shape, smell and color were examined, and all the tablets were healthy.

Then, using an analytical scale, digital caliper and hardness tester, the weight, thickness and hardness of random samples were measured and their average is given in table 9. The opening time was measured by a special device for 6 tablets and their average was calculated. Erosion was also calculated by erosion meter.

Table 9. The results of physical tests of solifnacin succinate formulations.

Formulation	Weight (mg)	Thickness (mm)	Hardness (kP)	Diameter (mm)	Friability (%)	Disintegration (s)
SF_1	104.8 1.09 ±	2.83 0.10 ±	10.18 1.18 ±	6.12 0.30 ±	0.41 0.25±	20
SF_2	104.40 1.14±	2.74 0.10 ±	10.51 1.25±	6.24 0.53 ±	0.38 0.19±	25

According to the results of the tests, the weight of all tablets was within ±10%. The weight of the solifenacin succinate layer is 100 mg. Considering that this amount is less than 130 mg which is given in the weight fluctuations table, the weight of this layer can be within ±10% of the average weight, so the weight of this layer should be in the range of 90-110 mg. should be warm Therefore, all formulations pass the weight uniformity test.

The opening time for uncoated tablets should be less than 15 minutes. In both formulations, both series of tablets were opened in less than 15 minutes, so the opening time of the tablets is

acceptable. Due to their small size, the hardness of the tablets was considered in the range of 9-11 kp. The erosion of both formulations was below 1%.

Quantitative determination of active ingredient in quick release tablets of solifenacin succinate

This test was done using the HPLC device (Table 10)**.**

Table 10. Amount of active pharmaceutical ingredient in the quick release tablet of Solifazine Succinate (n=2, Mean±SD).

Formulation name	Amount of active pharmaceutical ingredient
SF_1	1.13 ±52.53
SF_2	2.39 ±97.55

Considering that the final granule in the SF1 formulation was not completely separated from the metal tray due to organoleptic problems, the result of this test for the SF1 formulation was not within the acceptable range.

Drug release from solifenacin succinate quick release tablets

This test was performed using a dissolution device, which shows the release speed of the drug from pressed tablets of solifenacin succinate (Table 11).

Table 11. The percentage of drug released from Solifazine succinate quick release tablet: 6 mg in 120 minutes (n=2, Mean±SD).

Formulation name	The percentage of drug released in 120 minutes
SF_2	2.04 ±99.5

Physicochemical properties of quick release tablets of Tamsulosin Hydrochloride in TF_1-TF_6 formulations

At first, samples were randomly selected from each series of formulations, their appearance properties such as shape, smell and color were examined, and all the tablets were healthy.

Then, using an analytical scale, digital caliper and hardness tester, the weight, thickness and hardness of random samples were measured and their average is given in Table 12. The opening time was measured by a special device for 6 tablets and their average was calculated. Erosion was also calculated by erosion meter.

Table 12. The results of physical tests of Tamsulosin Hydrochloride formulations.

Formulation	Weight (mg)	Thickness (mm)	Hardness (kP)	Diameter (mm)	Friability (%)
TF_1	205.40 ± 1.95	3.73 ± 0.03	8.00 ± 0.42	8.02 ± 0.07	0.34
TF_2	255.20 ± 2.95	4.73 ± 0.07	8.52 ± 0.27	8.12 ± 0.12	0.51
TF_3	253.40 ± 1.52	4.87 ± 0.03	7.75 ± 0.1	8.00 ± 0.25	0.69
TF_4	258.60 ± 1.82	4.93 ± 0.03	7.99 ± 0.11	8.22 ± 0.62	0.60
TF_5	253.80 ± 3.03	4.74 ± 0.03	8.19 ± 0.17	8.14 ± 0.36	0.42
TF_6	252.80 ± 2.59	4.72 ± 0.03	8.17 ± 0.35	8.10 ± 0.8	0.48

According to the results of the tests, the weight of all tablets was in the range of ±7.5%. The weight of the Tamsulosin hydrochloride layer is 250 mg (except for the TF1 formulation, which has a tablet weight of 200 mg). Therefore, considering that these values are in the weight range of 130-324 mg which is given in the weight fluctuations table, so the weight of this layer can be in the range of ±7.5% (for 250 mg tablets, in the weight range of 268.75-231 mg and for 200 mg tablets, in the weight range of 215-185 mg). Therefore, all formulations pass the weight uniformity test. The hardness of the tablets that were pressed using the maximum pressure of the machine (one degree before the machine stuck) was considered in the range of 7-9 kp. Erosion was also below 1% in all formulations**.**

Quantitative determination of active ingredient in quick release tablets of Tamsulosin hydrochloride

This test was done using the HPLC device (Table 13)**.**

Table 13. Amount of active pharmaceutical ingredient in the quick release tablet of Tamsulosin hydrochloride (n=3, Mean±SD).

Formulation name	Amount of active pharmaceutical ingredient
TF_1	3.43 ± 98.64
TF_2	2.83 ± 97.42
TF_3	2.22 ± 96.65
TF_4	1.76 ± 98.28
TF_5	2.01 ± 97.71
TF_6	2.04 ± 96.79

Drug release from Tamsulosin hydrochloride quick release tablets

This test was performed using a dissolution device, which shows the release speed of the drug from pressed tablets of Tamsulosin hydrochloride (Table 14).

Table 14. The percentage of drug released from Tamsulosin hydrochloride quick release tablet: 0.4 mg after 2 h in acidic medium and 14 h in buffer medium (n=3, Mean±SD).

Formulation name	The drug released after 2 hours in acidic medium (%)	The drug released after 14 hours in buffer medium (%)	The drug released after 16 hours in acidic and buffer medium (%)
TF1	0.89 ±72.95	0.07± 31.13	104.08
TF2	1.83±55.38	1.57± 45.22	100.60
TF3	0.08±44.17	1± 45.95	90.12
TF4	0.42±45.47	0.57± 54.03	99.50
TF5	0.63±42.65	2.92± 47.58	90.23
TF6	0.31± 31.20	0.50± 61.05	92.69

Final formulation (FF: SF_2 and TF_6 combined tablets)

Table 15. Results of physical tests of the final formulation.

Formulation	Weight (mg)	Thickness (mm)	Hardness (kP)	Diameter (mm)	Friability (%)
FF	351.17 1.17±	5.05 0.09±	9.89 0.36±	9.00 0.08±	0.82

According to the results of the tests, the weight of all tablets was within ±5%. The weight of this formulation is 350 mg. Considering that this amount is more than 324 mg given in the table of weight fluctuations, therefore the weight of this layer can be in the range of ±5% (332.5 - 367.5 mg). Therefore, all formulations pass the weight uniformity test. Erosion was also 1% in this formula**.**

Table 16. The results of amount and uniformity determining of the drug content for solifenacin and tamsulosin.

Sample	Solifenacin (%)	Tamsulosin (%)
	Quantitative test	
1	99.8	97
Sample	**Drug content uniformity test**	
1	99.3	102.5
2	100	95.8
3	98.2	104.1
4	96.9	92.7
5	95.4	95.9

Table 17. Drug released in the final formulation.

	Tamsulosin (%)			Solifenacin (%)
Formulation name	**The drug released after 2 hours in acidic medium (%)**	**The drug released after 14 hours in buffer medium (%)**	**The drug released after 16 hours in acidic and buffer medium (%)**	**The percentage of drug released in 120 minutes**
FF	31.78±0.92	60.56±0.99	92.34	99.5±0.26

Table 18. Drug released in the brand sample and test for solifenacin succinate.

Time (min)	Drug released in the brand sample	Drug released in the test sample
5	35	32.92±0.16
15	78	83.11±0.93
30	88	91.1±28.06
60	92	93.73±0.6
120	95	99.5±0.54

Table 18. Drug released in the brand sample and test for Tamsulosin hydrochloride.

Time (h)	Drug released in the brand sample	Drug released in the test sample
2	30	0.96 ±31.78
3	35	0.72 ±40.39
6	58	2.13 ±61.45
9	72	2.73 ±76.12
12	80	1.50 ±85.73
16	91	1.99 ±92.34

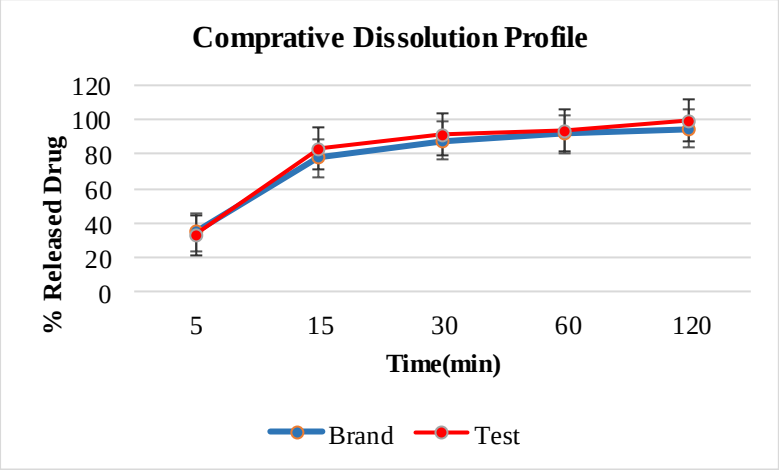


Figure 2. Comparative linear graph of solifenacin release from brand and test samples.

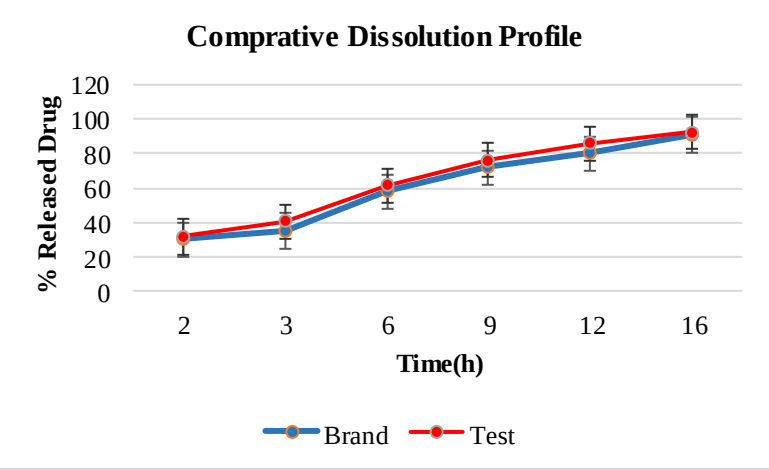
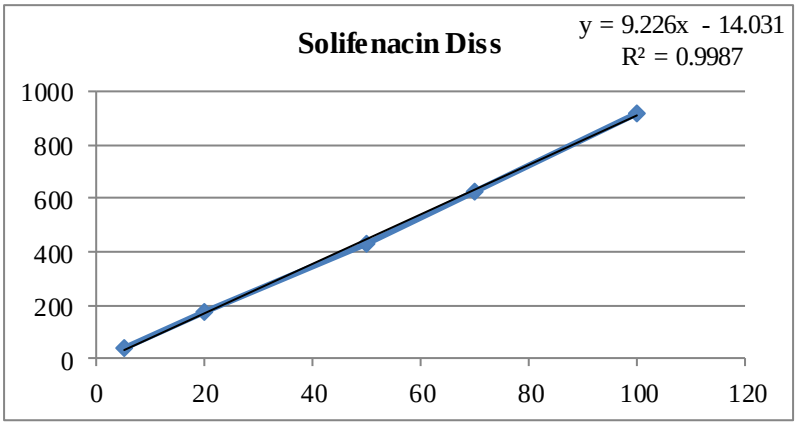


Figure 3. Comparative linear graph of Tamsulosin release from brand and test samples.

Validation and standard charting for solubility

The results of the concentration-absorption ratio were drawn in two graphs and the first-degree equation with the correlation coefficient R2>0.99 was obtained for both drugs.



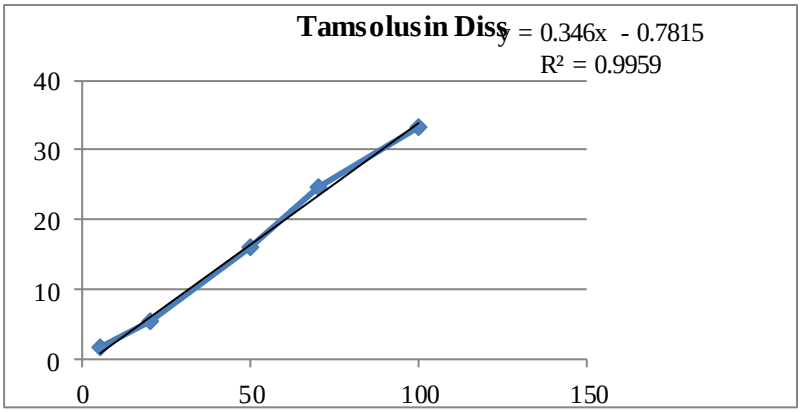


Figure 4. Tamsulosin and solifenacin standard charts.

Accuracy and Precision tests for dissolution

Table 19. Precision test results for solifenacin dissolution.

	Mean Area±SD	Mean Concentration	SD	RSD
1	1014.7±19.61	100.90		
2	1036.6±10.348	102.50		
3	1016.9±9.269	100.53	1.16	1.15
4	1054±14.021	100.93		
5	1040.9±3.065	100.97		
6	1014.7±13.692	100.93		

Table 20. Precision test results for Tamsulosin dissolution.

	Mean Area±SD	Mean Concentration	SD	RSD
1	32.9±1.384	101.30	0.80	0.80
2	31.5±1.334	99.53		
3	33.3±1.078	100.97		
4	32.4±1.602	100.43		
5	34±2.648	101.2		
6	33.3±1.724	100.60		

Table 21. Accuracy test results for solifenacin dissolution.

	C Actual (%)	Mean Area	C Theory (%)	Recovery (%)	Mean Recovery	SD	RSD
50	46.67	418.03	46.83	100.35	100.37	0.51	0.51
	46.67	420.35	47.08	100.89			
	50	446.63	49.93	86.99			
100	106.67	973.96	107.09	100.39	99.95	0.4	0.4
	107.67	968.58	106.50	99.85			
	108.33	981.58	107.91	99.61			
120	120	1082.90	118.89	99.08	10011	0.97	0.97
	123.33	1126.56	123.63	100.24			
	126.67	1166.33	127.94	101			

Table 22. Accuracy test results for Tamsulosin dissolution.

	C Actual (%)	Mean Area	C Theory (%)	Recovery (%)	Mean Recovery	SD	RSD
50	56.25	18.63	56.10	99.73	100.56	0.74	0.74
	52.5	17.53	52.92	100.80			
	50	16.72	50.58	101.16			
100	97.5	32.49	96.16	98.62	99.04	0.56	0.56
	110	37.15	109.64	99.67			
	97.5	32.55	96.35	98.982			

120	120	40.75	120.03	100.03	99.88	0.12	0.12
	117.5	39.8	117.28	99.82			
	115	38.93	114.78	99.81			

Table 23. Results of limit of detection and limit of quantification for Solifenacin and Tamsulosin.

	Solifenacin		**Tamsulosin**	
	LoD	LoQ	LoD	LoQ
S/N	54	48	17	31

Discussion

The purpose of this research is to achieve the optimal formulation of tamsulosin hydrochloride-sulfinasin succinate combined release control tablet and to examine the in vitro tests of this product. This combined pill is used to treat benign prostatic hyperplasia and related problems. Formulation of this pill in a combined way leads to improvement of patients' adherence to treatment and reduction of costs.

SD lactose (filler), corn starch (adhesive), pregelatinized starch (opening agent) and magnesium stearate (lubricant) were used to make the quick release layer of solifenacin in SF_1 formula and the results of the tests such as weight, hardness, erosion, opening time, diameter and thickness were within the acceptable range, but the amount of the active medicinal substance was out of range due to the adhesion of some of the raw material to the metal tray which was intended. The problem related to the organoleptic properties of solifenacin in SF_1 formulation was solved by adding 1% colloidal silicon dioxide (glidant). To prevent the change of the total weight of tablets in the SF_2 formulation, 1% of the solvent of this formulation was reduced. The results of physicochemical tests for this formulation were acceptable.

Lactose monohydrate (filler), SD mannitol and mannitol (solvent), Compritol 888 ATO (release control polymer), PVP (adhesive) and magnesium stearate (lubricant) were used to make the TF_1 formula. The first formulation was made by adding dry adhesive and tamsulosin as a suspension in water. Tests such as weight, hardness, erosion, diameter, thickness and active pharmaceutical ingredient determination were within the acceptable range, but the amount of drug released was more than the brand sample. In TF_2 formulation, 12% Compritol and 5% of lactose monohydrate and mannitol were added more and 2% of SD mannitol was decresed to reduction of drug released within two hours in an acidic medium. The amount of released drug was reduced by 17% compared to the previous formulation. The total weight of the formulation increased by 50 mg compared to the previous formula (the total weight in the brand drug for the tamsulosin formula was 250 mg).

In formula TF3, 10% polymer was added more (4% of lactose monohydrate and mannitol and 2% of SD mannitol were reduced). The release of the drug in this formula was reduced by 10% compared to the previous formula, but this amount was still more than the brand drug.

Addition of water-soluble binder in TF_4 formulation led to improvement of the properties of prepared granule and improvement of physico-chemical properties of the formulation. The release of the drug did not change compared to the previous formula. Addition of 50% polymer in TF_3 and TF_4 formulations led to the creation of gum-like properties in the granule. Therefore, in TF_5 formulation, to improve organoleptic problems and improve drug release, the amount of Compritol was reduced by 10% and HPMCK100 was used as a new release control polymer. The results of the physicochemical tests of this formulation were similar to the TF_4 formulation. Reducing Compritol by 10% and adding it to HPMCK100 in the final formulation resulted in a drug release profile similar to the brand sample. The results of the tests of weight, hardness, erosion, diameter, thickness and effective medicinal substance determination were acceptable.

The final formulation was formed by pressing the SF_2 and TF_6 formulas in two layers, and this formula was covered with a brown coating, similar to the brand sample. The weight of the final tablet was 350 mg, and each tablet was coated with 3% of its weight, which is equivalent to 10.5 mg. Tests of weight, hardness, diameter, thickness, erosion, percentage of drug released, effective substance determination and uniformity of drug content were performed for this formulation. The results of these tests were acceptable and within the mentioned limits. This formula was evaluated and confirmed in terms of the degree of similarity and difference with the brand sample.

Conclusion

The purpose of this research was to prepare and evaluate tamsulosin hydrochloride (0.4 mg) and solifenacin succinate (6 mg) controlled release tablets.

It can be concluded that, according to the results of the physicochemical tests at each stage, the problems of the formula were improved by changing the method and changing the amount and type of auxiliary materials. The tablets prepared in the superior two formulas passed the in vitro tests well and were acceptable compared to the brand sample.

It is suggested that, final formulation could be in vivo evaluated for effectiveness in the future studies.

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