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Formulation and In Vitro Characterization of Vardenafil Hcl Sublingual Tablets

Bhautik R. Teli[1], Manish J. Pandav[2], Suraj R. Chauhan[3], Gazala Y. Ansari[4], Bhumi A. Raval[5], Jitendra O. Bhangale[6]

[1-2] Student, Smt. N. M. Padalia Pharmacy College, Navapura, Ahmedabad, Gujarat, India 382210
[3]Associate Professor, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat, 382210, India
[4]Assistant Professor, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat, 382210, India
[5]Professor, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat, 382210, India
[6]Professor and Principal, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat, 382210, India

Corresponding Author:
Dr. Jitendra O. Bhangale
Email: jitu2586@gmail.com

ABSTRACT

Vardenafil HCl, is mainly prescribed for erectile dysfunction (ED) in men. As a phosphodiesterase type 5 (PDE5) inhibitor, it boosts blood flow to the penis during arousal, aiding in achieving an erection. Typically taken orally, it takes effect within 30 to 60 minutes, lasting for about four to five hours. While known for its effectiveness and quick response, it's crucial to use Vardenafil HCl under healthcare supervision due to potential side effects and interactions. In the current study sublingual tablet of Vardenafil HCl was prepared by direct compression using various super disintegrants like Sodium starch glycolate & Kyron T-314. All precompression parameter like Carr's index, Hauser's ratio, and angle of repose meets the standard, values of powder indicating good flow properties. The friability and hardness were within compendial limit which showed that all formulation possessed good mechanical strength. Drug content uniformity was within acceptable limit, which indicates a homogeneous distribution of drug in tablets. The formulation F9 was optimized from the evaluation, which showed minimum disintegrating time of 16.00 ± 1.59, % CDR was 99.85 in 12 min among all other batches of tablets. The results of stability study of the batch F9 showed that there was no significant change in hardness, in vitro disintegration time, % drug content and in vitro dissolution (% CDR) profile for a period of one mouth when stored at 40° ± 2°C / 75 ± 5% relative humidity. From the study it was concluded that sublingual tablet of Vardenafil HCl can be successfully prepared which will be help to improve patient compliance.

KEYWORDS: Erectile Dysfunction, Vardenafil HCl, Sublingual Tablet, Kyron T-314, Sodium Starch Glycolate.

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INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. It is one of the most common male sexual disorders and has a significant impact on quality of life, self-esteem, and intimate relationships. ED is a multifactorial condition resulting from physical, psychological, and lifestyle-related factors.

ED is broadly classified into organic and psychogenic types. Organic ED is more prevalent, particularly in older men, and is associated with vascular, neurological, hormonal, or structural penile abnormalities. Common risk factors include aging, diabetes mellitus, cardiovascular disease, hypertension, obesity, dyslipidemia, smoking, alcohol consumption, and certain medications. Hormonal disturbances such as testosterone deficiency and hyperprolactinemia, as well as neurological disorders, also contribute. Psychogenic ED arises from stress, anxiety, depression, and relationship problems and may coexist with organic causes.

Penile erection is a complex neurovascular process mediated by nitric oxide (NO) release, which stimulates cyclic guanosine monophosphate (cGMP) formation, leading to relaxation of cavernosal smooth muscle and increased penile blood flow. Detumescence occurs through phosphodiesterase-5 (PDE-5)-mediated degradation of cGMP. Any disruption in neural signaling, vascular function, hormonal balance, or smooth muscle integrity can result in ED.

Clinically, ED presents as difficulty in achieving or maintaining an erection or complete erectile failure persisting for at least three months. Reduced or absent morning erections often suggest an organic etiology. Epidemiological studies indicate that approximately 40% of men at 40 years of age and up to 70% at 70 years' experience ED, with more than 150 million men affected worldwide, although the true prevalence is likely underestimated.

Diagnosis is based on medical and sexual history, physical examination, laboratory investigations, and specialized tests such as penile Doppler ultrasonography and nocturnal penile tumescence testing. Management includes lifestyle modification, psychological counselling, oral PDE-5 inhibitors, hormone therapy when indicated, intracavernosal injections, vacuum devices, and surgical interventions in refractory cases. Preventive measures emphasize cardiovascular health, regular physical activity, weight control, smoking cessation, and stress management.[1-4]

MATERIALS AND METHODS

Materials

Vardenafil HCl was supplied by West coast pharmaceutical, Gujarat, Ahmedabad. Crosspovidone, Sodium starch glycolate, Mannitol & MCC were provided by Chemdyes corporation, Rajkot, Gujarat. Kyron T 314 was supplied by Coral Pharma Chem, Ahmedabad, Gujarat, India.

Fabrication of Sublingual tablets [5-8]

The sublingual tablets were prepared using the direct compression method. Following passage through filter #60, geometric dilution was used to combine the exact amount of the active component and all additions evenly. The blend was directly compressed using a multi-rotatory tableting machine (Cronimach) equipped with a die set and an 8 mm flat-faced punch. The mass and compression force of each pill did not change. Each tablet contained 10 milligrams of vardenafil HCl. All formulations' compositions are listed in Table No. 1.

Table 1 Formulation table of Sublingual Tablets:

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Vardenafil HCl	10	10	10	10	10	10	10	10	10
Kyron T-314	0.6	0.6	0.6	1.8	1.8	1.8	3	3	3
SSG	3	7.5	12	3	7.5	12	3	7.5	12
D-Mannitol	59.2	54.7	50.2	58	53.5	49	56.8	52.3	47.8
Avicel PH 102 (MCC)	30	30	30	30	30	30	30	30	30
Sodium bi carbonate	30	30	30	30	30	30	30	30	30
Aspartame	10	10	10	10	10	10	10	10	10
SLS	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3
Total weight	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Determination of melting point of Vardenafil HCl [9]

Melting point of Vardenafil HCl was measured by capillary apparatus. A small quantity of the drug was placed in a sealed thin-walled capillary tube and heated, and the temperature range over which melting occurred was recorded. The experiment was carried out in triplicate.

Identification by UV Spectroscopy [10]

Calibration curve of Vardenafil HCl in Phosphate buffer pH 6.8

Ten milligrams of Vardenafil HCl were dissolved in one hundred milliliters of phosphate buffer (pH 6.8) to create a standard stock solution with a concentration of 100 µg/ml. By pipetting out 2, 3, 4, 5, and 6 ml of the stock solution of 100 µg/ml and diluting it up to 10 ml in a volumetric flask, working solutions with concentrations of 5, 10, 15, 20 and 25 µg/ml were created. Working solutions' absorbance was measured three times at λ max 250 nm using phosphate buffer pH 6.8 as a blank.

Determination of precompression parameters [11]

Hausner's ratio, bulk density, tapered density, compressibility index, and angle of repose were all measured. Good flow qualities were indicated by the powder mixture's minimum Carr's index, Hausner's ratio, and angle of repose.

Determination of post compression parameters [12]

Thickness and diameter

The diameter and thickness of the tablets were determined using digital Vernier calipers. Six tablets were randomly selected, and measurements were taken using the upper and lower jaws of the calipers. Uniformity of tablet dimensions was assessed, and the mean diameter and thickness were calculated.

Hardness

Hardness provides insight about the tablet's mechanical strength. A Monsanto hardness tester was used to measure the tablets' hardness. Each formulation's six tablets were chosen at random, and the tablets' hardness was assessed.

Weight Variation

From each batch, twenty tablets were removed and weighed separately. Then, using the Indian Pharmacopoeia's parameters, the average weight and standard deviation of the tablets were calculated. (Table 2)

Table 2 Weight variation limit

Average weight of tablet	% Deviation
130 mg or less	± 10
130 mg through 324 mg	± 7.5
324 mg or more	± 5

% Friability

Tablet friability was evaluated using a Roche friabilator. A preweighed sample of tablets (W_0) was placed in the friabilator and subjected to 100 revolutions at 25 rpm for 4 minutes. The tablets were then removed, dedusted, and reweighed (Wf). Friability was calculated as the percentage weight loss using the standard formula. A weight loss exceeding 1% was considered unacceptable. The % friability was calculated by using formula:

$\%F = 100 (1- W_{Final} / W_{Initial})$

Drug content

An accurately weighed quantity of tablet powder, equivalent to the average tablet weight, was prepared by crushing randomly selected tablets in a glass mortar. The powder was initially dissolved in a small volume of methanol, diluted with phosphate buffer (pH 6.8), and filtered through Whatman filter paper. The filtrate was analyzed using a UV–visible spectrophotometer (Shimadzu 1900, dual beam) at 250 nm. Drug concentration was calculated using a previously established calibration curve.

Wetting Time

A petridish container was stuffed with six circular tissue papers, each approximately 10 cm in diameter. To the petridish, ten milliliters of phosphate buffer (pH 6.8) was added. On atop of the tissue paper, a tablet was softly placed. Wetting time is characterized as the amount of time it required for water to reach the tablet's upper surface.

***In Vitro* Disintegration test**

Using a digital tablet disintegration test device, this test was conducted on six tablets. As a disintegration medium, phosphate buffer pH 6.8 at 37°±0.5 °C was utilized, and the amount of time in seconds it took for the tablet to completely dissolve and leave no residue in the device was noted.

***In Vitro* Drug release study [14-17]**

Vardenafil HCl's percentage in vitro drug release from sublingual tablets was assessed using a USP type II (paddle type) dissolution device. 900 milliliters of phosphate buffer pH 6.8 at 37° ± 0.5 °C and 50 rpm were used for this test. At regular intervals, 5 ml of the sample solution was taken out of the dissolution equipment and replaced with the same amount of new dissolution medium. A 0.45µm membrane filter was used to filter the sample. These samples' absorbance was measured at 250 nm using a UV spectrophotometer.

Stability study

In the current investigation, the optimized batch's stability was investigated for one month at 40° ± 2°C / 75 ± 5% relative humidity. The formulation was shielded from light by being wrapped in aluminum foil. Tablets were assessed for hardness, friability, weight fluctuation, drug content, in vitro disintegration time, and in vitro drug release study after a 30-day period.

RESULTS AND DISCUSSION

Melting point of Vardenafil HCl

One common method for identifying drugs is melting point determination, which uses melting point apparatus. The melting point of Vardenafil HCl was determined to be between 230-233°C The melting temperature of Vardenafil HCl is comparable to the reported melting point of 230-235°C.

Identification of drug by UV Spectroscopy Method

Drug overlay spectra were acquired by scanning solutions with varying concentrations (5, 10, 15, 20, and 25 µg/ml) at 200–400 nm. Given that the reported λ max is 250 nm, it can be inferred that the medication was Vardenafil HCl. (Figure 1 and Table 3,4)

Table 3: UV Absorbance data for calibration curve of Vardenafil HCl in phosphate buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance			Mean Absorbance ± SD
		I	II	III	
1	5	0.161	0.164	0.163	0.163 ± 0.00125
2	10	0.326	0.323	0.324	0.324 ± 0.00125
3	15	0.480	0.481	0.479	0.480 ± 0.00082
4	20	0.596	0.598	0.599	0.598 ± 0.00125
5	25	0.758	0.759	0.758	0.758 ± 0.00047

Figure 1: Calibration curve of Vardenafil HCl in phosphate buffer pH 6.8

Table 4: Regression Analysis of Vardenafil HCl in Phosphate Buffer At pH 6.8

Sr. No.	Parameters	Result
1.	Regression equation	y = 0.0293x + 0.0252
2.	Correlation coefficient	0.9975
3.	Calibration curve range	5 - 25 ppm

Precompression Parameters

The powder blend's bulk density, taped density, Hausner's ratio, Carr's index, and angle of repose were all measured. It was discovered that every parameter had acceptable flow characteristics. Blend's flow characteristics have been tested and documented in Table 5. The tapped density ranged from 0.54 to 0.73 gm/ml, while the bulk density was found to be between 0.45 and 0.64 gm/ml. Carr's compressibility index was computed using the two data points mentioned above. The range of the compressibility index was 10.76 to 19.44 percent. Data on compressibility and flow ability showed that all powder mixes had excellent to fair characteristics. Angle of repose also demonstrated the superior flow characteristics of all powder blends. The angle of repose was range of 29.14º to 33.55° so it indicates excellent to good flow property (Table 5).

Table 5 Precompression Parameters

Batch	Bulk Density ± S.D. (gm/ml)	Tapped Density ± S.D. (gm/ml)	Carr's index (%)	Hausner's Ratio	Angle of repose (°θ)
F1	0.52 ± 0.01	0.64 ± 0.01	16.66 ± 0.14	1.23 ± 0.35	30.23 ± 0.22
F2	0.59 ± 0.03	0.69 ± 0.02	14.49 ± 0.23	1.16 ± 0.20	33.14 ± 0.21
F3	0.45 ± 0.01	0.54 ± 0.01	16.66 ± 0.26	1.23 ± 0.30	29.14 ± 0.17
F4	0.58 ± 0.02	0.64 ± 0.02	10.76 ± 0.12	1.11 ± 0.05	30.65 ± 0.30
F5	0.63 ± 0.01	0.73 ± 0.07	13.69 ± 0.09	1.15 ± 0.01	33.41 ± 0.28
F6	0.64 ± 0.03	0.72 ± 0.01	11.11 ± 0.12	1.10 ± 0.10	32.56 ± 0.20
F7	0.60 ± 0.19	0.71 ± 0.04	15.49 ± 0.25	1.18 ± 0.19	32.44 ± 0.35
F8	0.58 ± 0.02	0.72 ± 0.03	19.44 ± 0.26	1.24 ± 0.25	33.55 ± 0.25
F9	0.60 ± 0.01	0.70 ± 0.02	18.52 ± 0.21	1.20 ± 0.20	33.02 ± 0.21

Physical parameters

Physical characteristics such as hardness, friability, weight fluctuation, thickness, and diameter were measured. It was discovered that the improved batch's friability was 0.68%, meeting Pharmacopeia standards. The optimal batch's hardness was 2.68 ± 0.13. This was enough to keep the tablet from shattering while being transported. The weight variation was 150.79± 1.47, in accordance with the Indian Pharmacopeia (Table 6).

Table 6 Post compression parameters of Vardenafil HCl Sublingual tablets

Batch	Thickness (mm ± S.D.)	Diameter (mm ± S.D.)	Weight Variation (mg ± S.D.)	Hardness (kg/cm^2 ± S.D.)	Friability (%)
F1	1.58 ± 0.02	8.20 ± 0.01	151.04 ± 2.11	2.68 ± 0.05	0.77
F2	1.54 ± 0.02	8.14 ± 0.02	150.02 ± 2.72	2.66 ± 0.021	0.70
F3	1.48 ± 0.03	8.02 ± 0.01	150.00 ± 1.82	2.67 ± 0.04	0.69
F4	1.57 ± 0.02	8.24 ± 0.06	151.24 ± 1.37	2.65 ± 0.67	0.68
F5	1.56 ± 0.01	8.06 ± 0.07	151.85 ± 1.81	2.66 ± 0.081	0.66
F6	1.52 ± 0.01	8.01 ± 0.04	150.00 ± 1.76	2.70 ± 0.13	0.61

F7	1.50 ± 0.02	8.38 ± 0.06	152.14 ± 2.20	2.71 ± 0.14	0.61
F8	1.48 ± 0.01	8.21 ± 0.02	150.59 ± 1.79	2.73 ± 0.12	0.59
F9	1.50 ± 0.03	8.24 ± 0.05	150.79 ± 1.47	2.68 ± 0.13	0.68

All values are expressed as mean ± SD; (n=6)

Post compression parameters

The prepared batches' in vitro disintegration time ranged from 16.00 ± 1.59 to 41.12 ± 2.00 seconds. Wetting time of the formulated batches was found to be in the range of 12.10 ± 1.42 sec. to 37.53 ± 1.68 sec. The drug content of the tablets, which were made using the direct compression method, was determined to be between 97.67% to 100.67%. These drug content results showed that the active component was evenly distributed and at the right dosage in the sublingual tablet (Table 7).

Table 7 *In-Vitro* disintegration time, wetting time and drug Content

Batch	*In vitro* disintegrating time (sec. ± S.D.)	Wetting time (sec. ± S.D.)	Drug content (%)
F1	38.00 ± 2.01	34.14 ± 1.27	98.29
F2	34.33 ± 1.62	31.75 ± 1.58	98.78
F3	29.00 ± 1.12	24.23 ± 2.01	99.02
F4	41.12 ± 2.00	37.53 ± 1.68	98.21
F5	35.33 ± 2.14	30.86 ± 2.01	99.33
F6	32.00 ± 3.02	27.01 ± 2.63	97.67
F7	28.67 ± 3.04	22.47 ± 1.48	100.00
F8	22.00 ± 1.75	19.34 ± 1.24	99.67
F9	16.00 ± 1.59	12.10 ± 1.42	100.67

All values are expressed as mean ± SD; (n=6)

***In Vitro* Drug Release study**

The study assessed drug release using a dissolution test apparatus in a phosphate buffer solution at pH 6.8, with controlled temperature and stirring. Results showed that increasing the concentration of a superdisintegrant in the tablet led to higher drug release. Over 50% of the drug was released within 4 minutes, and over 90% within 12 minutes. For formulations F1 to F3, the drug release started at 36.59 % - 41.08 % after 2 minutes, reaching 98.01 % - 99.02 % by the end of 14 to 16 minutes. Formulations F4 to F6 displayed initial drug release percentages of 33.78 % - 43.93% at 2 minutes, which increased to 96.17 % - 99.17 % by 14 to 16 minutes. In formulations F7 to F9, the drug release ranged from 42.28 % - 54.15 % at 2 minutes, escalating to 99.02 % - 99.85 % by 12 to 16 minutes, respectively. The optimized batch F9 shows 99.85% drug release at 12 minutes, which was formulated using super disintegrants like Kyron T-314 (03 mg) and Sodium starch glycolate (12 mg) (Figure 2, 3 and 4).

Figure 2: *In-vitro* drug release of Batches F1 to F3

Figure 3: In-vitro drug release of Batches F4 to F6

Figure 4: In-vitro drug release of Batches F7 to F9

Stability studies

As indicated in tables 8 and 9, the optimized tablet underwent a month of stability testing and was determined to be stable in terms of hardness, friability, weight variation, percentage drug content, in vitro disintegration time, and in vitro drug release research.

Comparison study between the result of optimized batch and after time period of stability is graphically illustrated in Figure 5.

Table 8 Post compression parameters of F9 batch after stability study

Evaluation parameter	Results of optimized batch	Result after 1 month at 40 ± 2°C and 75 ± 5 % RH
Hardness (kg/cm^2± S.D.)	2.68 ± 0.13	2.66 ± 0.11
Wetting Time (sec. ± S.D.)	12.10 ± 1.42	12.01 ± 1.14
In vitro Disintegration Time (sec. ± S.D.)	16.00 ± 1.59	16.15 ± 0.58
Drug Content (%)	100.67	100.18

Table 9 *In Vitro* Drug Release study of Stability batch

Time (Min.)	% CDR of Optimized Batch (% ± S.D.)	% CDR of batch After Time Period of 1 Month (% ± S.D.)
0	0.0	0.0
2	54.15 ± 1.25	51.98 ± 2.05
4	69.47 ± 2.27	68.02 ± 1.19
6	79.18 ± 1.64	77.87 ± 1.08
8	89.46 ± 2.10	88.41 ± 1.98
10	92.47 ± 1.63	91.22 ± 1.70
12	99.85 ±1.89	98.67 ± 1.36

All values are expressed as mean ± SD; (n=6)

Figure 5: Comparison of *in Vitro* Drug Release study of Optimized batch and After Stability

CONCLUSION

The current analysis comes to the conclusion that Vardenafil HCl sublingual tablets were made utilizing a multi-tablet compression machine and the direct compression method. Pre and after compression characteristics were assessed for each formulation. Properties of the flow, such as bulk density, tapped density, angle of repose, and percentage All formulations were tested for Carr's compressibility, and the findings demonstrated satisfactory flow properties. On the basis of various precompression and post compression parameters, batch F9 was selected as optimized batch, because it is a Super disintegrant which gave disintegration in minimum time at just 16.00 ± 1.59 seconds, wetting time of 12.10 ± 1.42 seconds, and a cumulative drug release percentage of 99.85% within just 12 minutes among all other batches of tablets. The result of stability study of the batch F9 showed that there were no significant changes in all post compression parameters after one month at 40° ± 2 °C and 75 ± 5% RH. So, this work has been able to produce a formulation of Sublingual tablets of Vardenafil HCl.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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