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FORMULATION AND EVALUATION OF SILDENAFIL FAST DISSOLVING TABLETS COMBINED WITH SHILAJIT USING CROSCARMELLOSE AND CROSPOVIDONE AS SUPERDISINTEGRANTS

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ABSTRACT

Sildenafil citrate is the drug of choice for the treatment of erectile dysfunction. Bioavailability of Sildenafil citrate is 41% of orally administered dose. The objective of the present study was to develop fast dissolving tablets of sildenafil citrate combined with Shilajit and to improve its bioavailability, reduce the dosing frequency and thereby maximizing the therapeutic effect of the drug. Sildenafil fast dissolving tablets was prepared by wet granulation method using a combination of superdisintegrants, cfrosspovidone and croscarmellose sodium, shilajit and along with various other excipients in order to confer a therapeutic enhancement on the drug and provide organoleptic characteristics in the final dosage form. Compatibility of the drug and the excipients was investigated by FTIR and DSC studies. Seven formulations (F1-F7) were prepared and subjected to various pre compression and post compression parameters. The results of the formulations were examined after subjecting to variousevaluation parameters. Among all the formulations, batch F7 produced promising results in terms of fast disintegration and dissolution. Hence it was considered as the optimized formulation. Kinetic modeling were carried out on the formulations. Sildenafil citrate fast dissolving tablets were found to be the promising ones,as they increase bioavailability, rapid onset of action, avert the problem of swallowimg and improve the patient compliance.

KEYWORDS: Sildenafil Citrate, Fast Dissolving Tablets, Super Disintegrants, Shilajit

INTRODUCTION

Tablets and capsules are the most preferable, convenient and extensively used dosage forms as it offers versatile advantages when compared to other dosage forms. On the other hand they face one important drawback for some patients, which is the difficulty to swallow and access to water for easy swallowing of dosage form.

Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop FDTs with improved patient compliance and convenience. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. FDTs or orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules.

FDTs are known by different names such as mouth dissolving, oral disintegrating or orodisperse tablets. Apart from erectile dysfunction FDTs are also valuable as cardiovascular agents, analgesics, antiallergics, and neuroleptics.

Oral bioavailability of sildenafil is~40%, peak blood levels are attained in 1-2 hr; it is metabolized largely by CYP3A4 and an active metabolite is produced; t1/2 in men <65 years average 4 hours. It is recommended in a dose of 50mg (for men> 65 years 25mg), if not effective then 100mg 1 hour before intercourse. Duration and degree of penile erection is increased in 74-82% men with ED including diabetic neuropathy cases. Over 20 controlled trials have confirmed its efficacy. However, sildenafil is effective in men who have lost libido or when ED is due to cord injury or damaged nervi eregantis.

Like many medical conditions, there is not necessarily only one means to cure or reduce symptoms of ED. For men wishing to avoid the use of medication, there are a number of lifestyle changes that can be tried first, followed by some potential natural remedies and additional therapies.[1]

Shilajit is a sticky like substance with a colour ranging from white to dark brown (the latter is more common), found predominantly in Himalaya, Karakuram, Tibet mountains, Caucasus mountains, and mountains of Gilgit Baltistan. Shilajit is a blackish-brown exudation, of variable consistency, obtained from steep rocks of different formations found in the Altai Mountains. It is used in Ayurveda, the traditional Indian system of medicine. It has been reported to contain at least 85 minerals in ionic form, as well as triterpenes and humic acids.[2]

Shilajit as a dietary supplement may also improve heart health. Researchers tested the cardiac performance of shilajit on lab rats. After receiving a pretreatment of shilajit, some rats were injected with isoproterenol to induce heart injury. The study found that rats given shilajit prior to cardiac injury had fewer cardiac lesions.

Shilajit is also a safe supplement for male infertility. In one study, a group of 60 infertile men took shilajit twice a day for 90 days after meals. At the end of the 90-day period, more than 60 percent of the study participants showed an increase in total sperm count. More than 12 percent had an increase in sperm motility. Sperm motility refers to the ability of the sperm in a sample to move adequately, an important part of fertility.[3]

Sildenafil citrate allows greater blood flow to the penis. But in the heart, the it can prevent heart muscle thickening and early-stage heart failure, according to research published today in the open access journal BMC Medicine.[4]

A recent study using animal models tested how well shilajit protects the heart. The animals who received the herb showed less cardiovascular damage, with researchers concluding the effect must come from more than simply its antioxidant activity.[5]

So the combination of Sildenafil citrate and shilajit can be done so as to shilajit can subdue the effect of Sildenafil citrate.

5. MATERIALS AND METHOD

5.1. Materials

All the chemicals used in the project was procured from Girijananda Chowdhry Institute of Pharmaceutical Science chemical store. The natural Ayurvedic powder was being ordered from Amazon.

5.2. Methods

5.2.1. Preparation of standard curve of Sildenafil citrate

Various concentrations of sildenafil citrate (5-30 µg/ml) in pH 6.8 phosphate buffer were prepared and the absorbance was measured at 290 nm. For the standared curve 100 mg of Sildenafil citrate was accurately weighed and dissolved in 100 ml of pH 6.8 phosphate buffer. Then 10 ml of the resulting solution was diluted to 100 ml with the phosphate buffer to make a stock solution of concentration 100 µg/ml. Further serial dilutions were made by transferring 5, 10, 15, 20, 25 and 30 ml of the resultant solution to 100 ml volumetric flasks and diluted with pH 6.8 phosphate buffer up to the mark to obtain the concentrations 5, 10, 15, 20, 25 µg/ml. The absorbance of dilutions was measured against pH 6.8 phosphate buffer as a blank at 291 nm using UV spectrophotometer. A standard curve of absorbance vs standard curve was plotted.

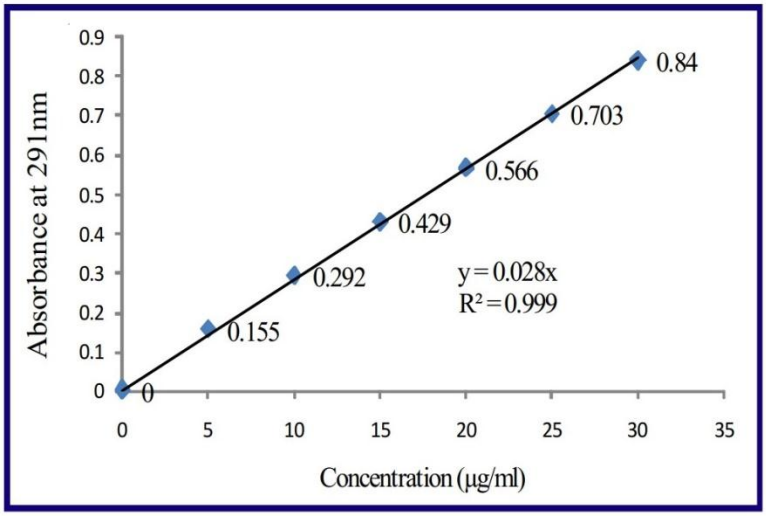

Figure 1: Standard curve of Sildenafil citrate./

5.2.2. Characterization of drug and excipients

5.2.2.1. Drug-excipient compatibility studies by FTIR

Compatibility studies were carried out to study the possible interactions in the pure drug (Sildenafil citrate) and Shilajit,and the admixture and other excipients and the optimized formulation by FTIR spectroscopy.

5.2.3. Formulation of FDTs

Sildenafil citrate fast dissolving tablets were prepared by using wet granulation method. In this method a liquid binder is used to lightly agglomerate the powder blend. The quantity of liquid must be properly controlled, because over wetting will cause the granules to be too

hard and and under wetting will cause them to be soft and friable. Sildenafil citrate, calcium carbonate, croscarmellose sodium, mannitol were sieved through #40 mesh and transferred into the mortar and pastle, dry mixed for 10 minutes. Binder solution was prepared by mixing PVP K-30 powder with sufficient quantity of purified water and the mixing was continued so as to get a clear solution. The binder solution so prepared was added to the dry mixed powder blend and mixed for 5 minutes. The wet granules were unloaded into fluid bed drier bowel, air dried for 5 minutes followed by drying at 60 ^{0}C in fluid bed drier for 15 minutes.

The dried granules were loaded into the double cone blender Crospovidone, Shilajit, aspartame, peppermint oil, colour brilliant green were loaded into the blender for 20 minutes. Magnesium stearate was sifted through #66, loaded into double cone blender containing the dried granules and blended for 5 minutes. The granules were poured into the hopper and the tablets were compressed at 550 mg using 12 mm round shaped punches. The tablets were collected in a cleaned double polybag indicating the batch number.

Table 1: Formulation of Sildenafil citrate FDTs.

Ingredients/batches	F1	F2	F3	F4	F5	F6	F7
Sildenafil citrate	100	100	100	100	100	100	100
Shilajit	100	100	100	100	100	100	100
Calcium carbonate	125	125	125	125	125	125	125
Croscarmellose sodium	20	22	24	26	28	30	32
Mannitol	90	92	85	87	89	79	76
PVP-30	17	15	13	11	7	9	13
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Crospovidone	15	17	19	21	23	25	27
Aspartame	40	40	40	40	40	40	40
Aerosil	18	14	19	15	13	17	12
Magnesium stearate	10	10	10	10	10	10	10
Pippermint oil	10	10	10	10	10	10	10
Brilliant green lake	5	5	5	5	5	5	5

5.2.4. Pre-compression evaluation of drug-excipient powder blend[6,7]

The drug-excipient powder blend was characterized for different flow property parameters such as bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio.

5.2.4.1 Bulk Density (D_b)

5 gm of drug-excipient powder blend from each formulation was weighed and transferred into 25 ml measuring cylinder. Then it was shaken lightly to break the agglomerate that may

have formed and the initial volume was noted and expressed in gm/ml and calculated by using the following formula

$D_b = M / V_o$

where, M is the mass of powder blend and V_o is the bulk volume of the powder blend.

5.2.4.2. Tapped Density (D_t)

Tapped density of the powder blend was determined by placing a measuring cylinder, containing a known mass of drug-excipient pow-der blend, on a mechanical tapping apparatus. The tapped volume of the powder blend was measured by tapping the powder to a constant volume. It was expressed in gm/ml and calculated by using the following formula

$D_t = M / V_t$

where, M is the mass of powder blend and Vt is the tapped volume of the powder blend.

5.2.4.3 Angle of Repose (θ)

Angle of repose of the drug-excipient powder blend was determined by using fixed funnel method. A known quantity of drug-excipient powder blend was taken in a funnel, which was maintained at a height where the tip of the funnel touches the apex of the pile of the powder blend. Powder blend was allowed to flow freely from the funnel, the height and the diameter of the pile was measured. The angle of repose, θ was calculated by using the formula

$\theta = \tan^{-1} (h / r)$

where, θ is the angle of repose, h is the height in cm and r is the radius in cm.

5.2.4.5. Hausner's Ratio (H)

The ratio of tapped density to bulk density of the drug-excipient powder blend gives Hausner's ratio. It was expressed in % and calculated by using the following formula

$H = D_t / D_b$

where, D_t is the tapped density of the powder blend and D_b is the bulk density of the powder blend.

5.2.5. Post-compression evaluation of Sildenafil citrate FDTs

5.2.5.1. Average weight

20 tablets are weighed. The average weight was determined. Then, tablets was weighed individually and for each tablet, the percentage of deviation of its weight from the average weight was determined.

Average weight = Weight of 20 tablets in mg/20

5.2.5.2. Weight variation

20 tablets are weighed at a time and the average weight is taken. Then the tablet is weighed individually in a digital balance. The percentage deviation can be determined by using the following formula. The percentage deviation can be determined by using the following formula.

% Deviation=Average weight-Individual weight/Average weight*100[8]

5.2.5.3. Hardness

Hardness of the tablet is one of the most important parameter on which the resistance of the tablet to chipping, abrasion or breakage during manufacturing, storage and handling depends. It is the force required to break a tablet in a diametric compression. The test was performed by selected three tablets randomly from each batch, their hardness was measured using Pfizer digital tablet hardness tester and was expressed in kg/cm^2.

5.2.5.4. Thickness

Three tablets were selected randomly from each batch, their thickness was measured by placing the tablet between the two arms of the digital vernier calipers and was expressed in mm.

5.2.5.5. Friability

Rosche friabilator was used to determine the friability of the tablet. . With the help of this apparatus the tablets were subjected to the combined effect of abrasion and shock in a chamber which revolves at a speed of 25 rpm and drops the tablet from a height of 6 inches in every revolution. Twenty tablets were selected randomly from the each batch, weighed and placed in the friabilator. The apparatus was allowed to run for 4 minutes i.e., 100 revolutions. The tablets were de-dusting, reweighed and the percentage of weight loss was calculated by using the following formula

Friability%=$W_{initial}$-W_{final}/$W_{initial}$*100[9]

5.2.5.6. Drug content

Twenty tablets were selected randomly from each batch, weighed and made into fine powder. The quantity of powder was equivalent to 50 mg of Sildenafil citrate and 50 mg of shilajit was dissolved in a 100 ml of pH 6.8 phosphate buffer and the resultant solution was filtered and the filtrate obtained was suitably diluted with pH 6.8 buffer. The content was determined

spectrometrically by measuring the absorbance at 291 nm. The drug content was calculated and reported.

5.2.5.7. In-vitro disintegration time

USP disintegration test apparatus was used to determine the in-vitro disintegration time. The chamber of the apparatus was filled with distilled water and the temperature was set to 37±0.5^{0}C. To each of the six tubes of the apparatus, one tablet was placed and allowed to run till the tablet completely disintegrated into fine particles. Time was noted down in seconds and the disintegration test was carried out for all the formulations and the disintegration time was reported.

5.2.5.8 In-vitro dissolution studies

In-vitro dissolution studies were carried out by using USP dissolution test apparatus type 2 (paddle) pH 6.8 phosphate buffer was the dissolution medium used. 900 ml of pH 6.8 phosphate buffer was taken in each vessel, the temperature was maintained at 37±0.5^{0}C and rpm 100. One tablet was added to each vessel and the system was allowed to run for 45 minutes. 10 ml of the sample was withdrawn from each vessel at regular interval of time (5, 10, 15, 20, 25, 30 minutes) and the same volume of fresh dissolution medium was replaced in the vessel. The withdrawn samples were analyzed spectrometrically by measuring the absorbance at 290 nm using suitable dilution. The dissolved drug was expressed as cumulative percentage of drug release and the test was carried out for all formulations. The cumulative percentage of drug release data was reported.

RESULTS AND DISCUSSION

Sildenafil citrate FDTs were prepared by wet granulation method using Shilajit, crospovidone and croscarmellose sodium as superdisintegrants. The excipients were chosen by taking preformulation studies into amount andtheir concentrations were built up on the premise of a broad literature survey. Calcium carbonate was chosen as a diluent, PVP K 30 was used as a granulating agent. Mannitol was selected as it bestows multidimensional advantages as it has good aqueous solubility and good wetting properties facilitating the tablet's breakdown and in addition negative heats of solution giving cooling effect in the mouth. Aerosil was selected as an adsorbent and glidant, peppermint was used as a flavouring agent. The bitter taste of Sildenafil citrate has been masked by using aspartame. Magnesium stearate was chosen as a lubricant to enhance the flow properties of the blend. Shilajit can subdue the effect of Sildenafil citrate.

6.1. Drug-excipient compatibility studies by FTIR

Sildenafil citrate and the admixture of drug with Shilajit, crospovidone, croscarmellose sodium were characterized by FTIR spectroscopy to test the compatibility and the spectras were shown in figure 2-5. There was no significant interaction between drug and excipients. Similarly the DSC was performed shown in figure 3 where no interaction was found.

6.1.1. Fourier-transform infrared spectroscopy (FTIR)

It is a technique used to obtain an infrared spectrum of absorption or emission of a solid, liquid or gas. An FTIR spectrometer simultaneously collects high-spectral-resolution data over a wide spectral range. This confers a significant advantage over a dispersive spectrometer, which measures intensity over a narrow range of wavelengths at a time.

The term Fourier-transform infrared spectroscopy originates from the fact that a Fourier transform (a mathematical process) is required to convert the raw data into the actual spectrum. For other uses of this kind of technique, see Fourier-transform spectroscopy.[10]

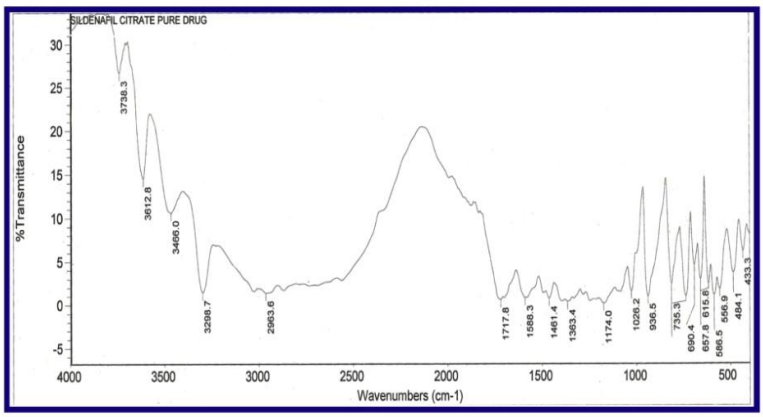

Figure 4: FTIR of pure drug Sildenafil citrate.

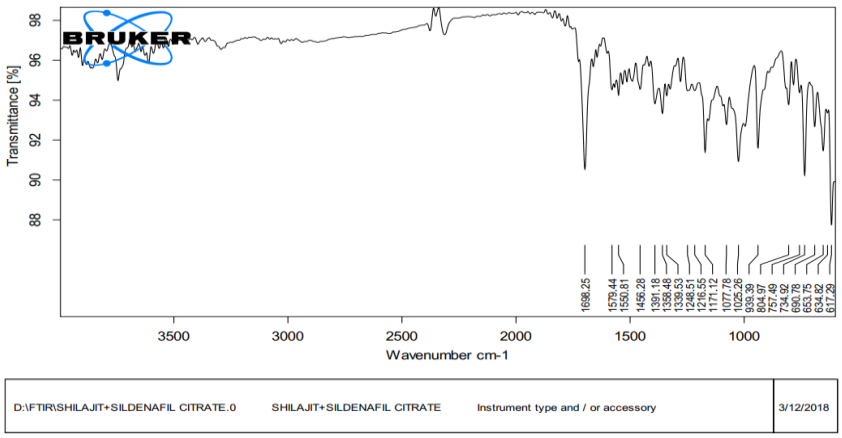

Figure 5: FTIR of drug+ Shilajit.

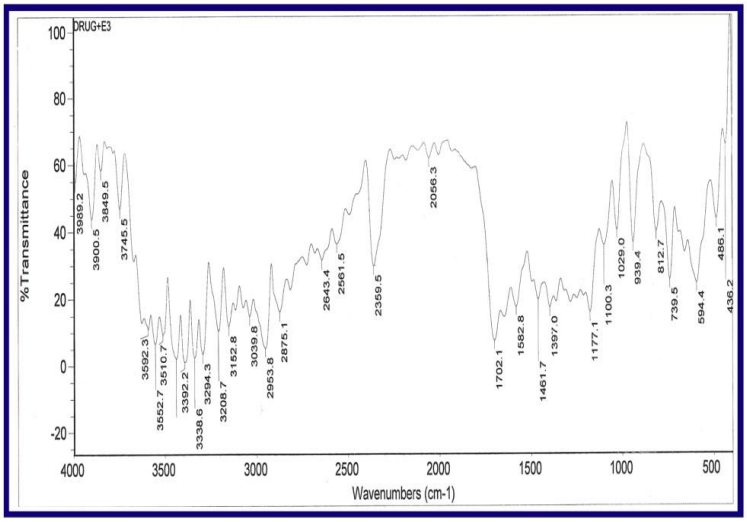

Figure 4: FTIR of drug+ Crospovidone.

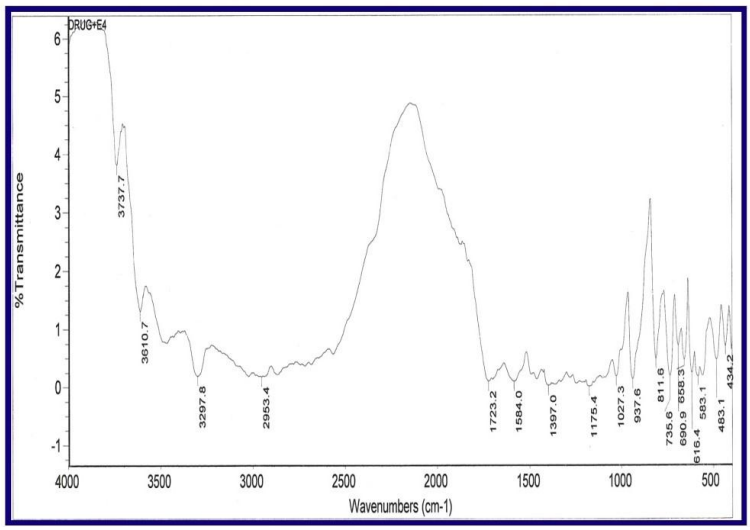

Figure 5: FTIR of drug+Croscarmellose sodium.

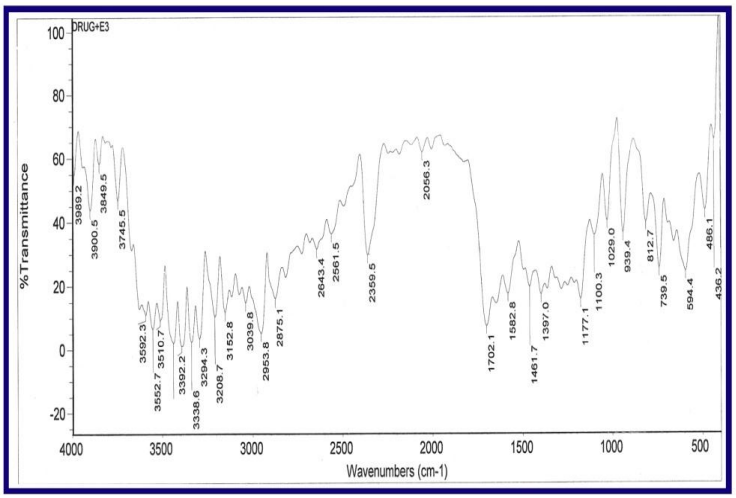

Figure 6: FTIR of optimized formulation.

6.1.2 Differential scanning calorimetry

DSC, is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned.[11]

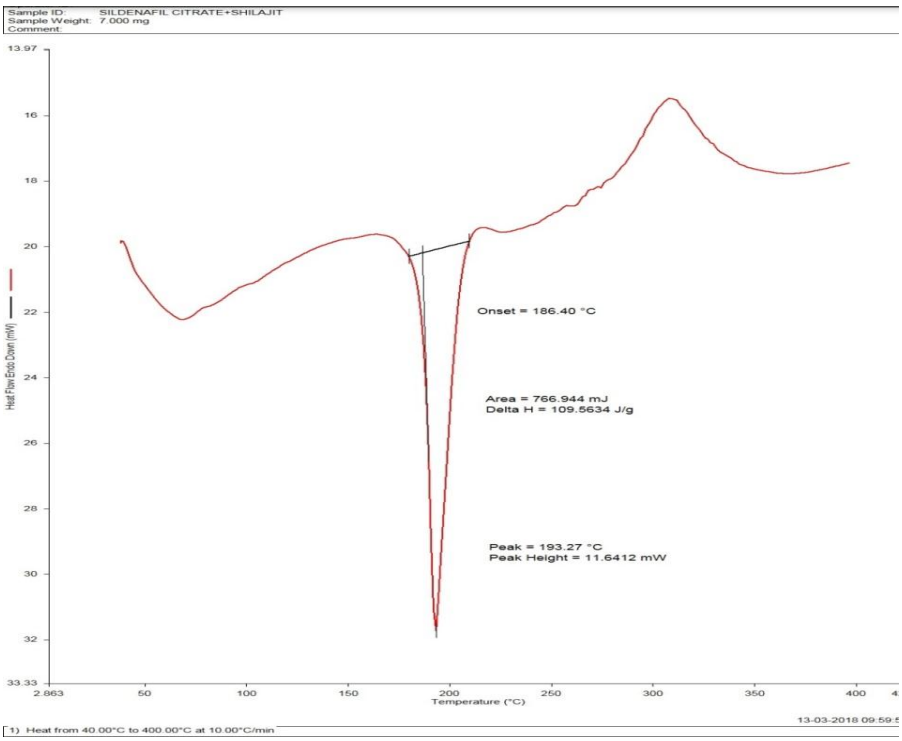

Figure 7: DSC of Drug+Shilajit.

DSC thermogram of Sildenafil citrate, shilajit, crosspovidone, croscarmellose sodium and mixture was done. The DSC thermogram of Sildenafil and shilajit are depicted in figure 7. The thermogram of combined drug indicates a sharp endothermic peak at 193.27^{0}C similar to the melting point of the other excipients so there is no possible interactions. The melting point of Sildenafil citrate is 197^{0}C.

6.2. Pre-compression evaluation of drug-excipient powder blend

The tablet blend showed the bulk density and tapped density in the range of 0.317 to 0.426 and 0.356 to 0.450 gm/ml respectively which represents that all formulations have good packability of granules. In terms of flow properties, all the formulations showed excellent to

good flowability. The angle of repose was found to be in the range of 26.52 to 35.13, Carr's index in the range of 08.855 to 17.326 and Hausner's ratio in the range of 0.704 to 1.168 The results of pre-compression parameters of drug-excipient powder blends represent free flowing properties of the powder blends (Table 2).

Table 2: Pre-compression parameters of drug-excipient powder blends.

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of Repose (θ)	Carr's index %	Hausner's Ratio %
API	0.594	0.752	41.48	21.306	0.789
F1	0.416	0.356	35.12	11.890	1.168
F2	0.364	0.433	34.96	12.74	0.840
F3	0.380	0.459	33.43	13.140	0.827
F4	0.317	0.450	35.13	12.974	0.704
F5	0.383	0.467	30.96	17.326	0.820
F6	0.394	0.365	34.27	14.186	1.079
F7	0.357	0.367	26.52	08.855	0.972

6.3. Post-compression evaluation of Sildenafil citrate FDTs

The average weight of the tablets varies from 548.8 to 552.2. All the formulations passed weight variation test as the results were found to be within the IP limits of ± 5% weight. The maximum thickness of the formulations was found to be 5.42 mm and the minimum thickness of the formulation was found to be 5.07 mm. The hardness of all the formulated tablets was determined and was found to be in the range of 3.05 to 6.05 kg/cm^2. Friability of the formulated tablets was found to be in between 0.265 to 0.085. The results of friability were much less than the specified limits in all the formulations ensuring the mechanical stability of the tablets. The maximum percentage of the drug content from all the formulations was found to be and the minimum percentage was found to be, ensuring the uniformity of the drug content in all the formulations.

In-vitro disintegration time is an important parameter for FDTs which is desired to be less than one minute. Rapid disintegration of the FDT assists in swallowing without the need of water and also plays an important role in the absorption of drug in the buccal cavity, thus promoting bioavailability. In-vitro disintegration time for all the formulated tablets were found to be in the range 34.13 to 56.60 seconds. From all formulations, F7 showed 34.11 seconds in-vitro disintegration time which facilitates rapid disintegration in the mouth. The results of post-compression evaluation of Sildenafil citrate FDTs are summarized in table 3.

Table 3: Post-compression parameters of drug-excipient powder blends.

Batch Code	Avg-wt	Weight variation (%)	Thickness	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	In-vitro disintegration time (sec)
F1	552	1.003	5.42	6.05	0.134	98.8	56.60
F2	549	0.998	5.34	5.54	0.135	98.4	54.70
F3	550	1.000	5.07	4.32	0.085	99.1	47.53
F4	548	0.996	5.21	3.58	0.124	99.6	50.63
F5	551	1.002	5.11	4.21	0.101	98.3	55.53
F6	549	0.998	5.15	3.32	0.138	99.3	44.13
F7	550	1.000	5.20	3.05	0.265	100.6	34.11

Table 4- In-vitro drug release profile of prepared formulations.

Batch code	0 mins	5 mins	10 mins	15 mins	20 mins	30 mins	45 mins
F1	0	40.47	43.65	48.41	54.37	57.89	59.09
F2	0	45.13	47.97	49.76	56.93	65.90	65.78
F3	0	50.67	56.32	58.65	61.38	68.34	69.32
F4	0	56.89	61.54	68.52	64.33	71.45	76.98
F5	0	60.36	69.76	71.89	72.18	75.23	80.12
F6	0	65.43	75.76	84.78	85.16	87.18	86.76
F7	0	71.83	84.48	92.90	100.1	100.6	100.7

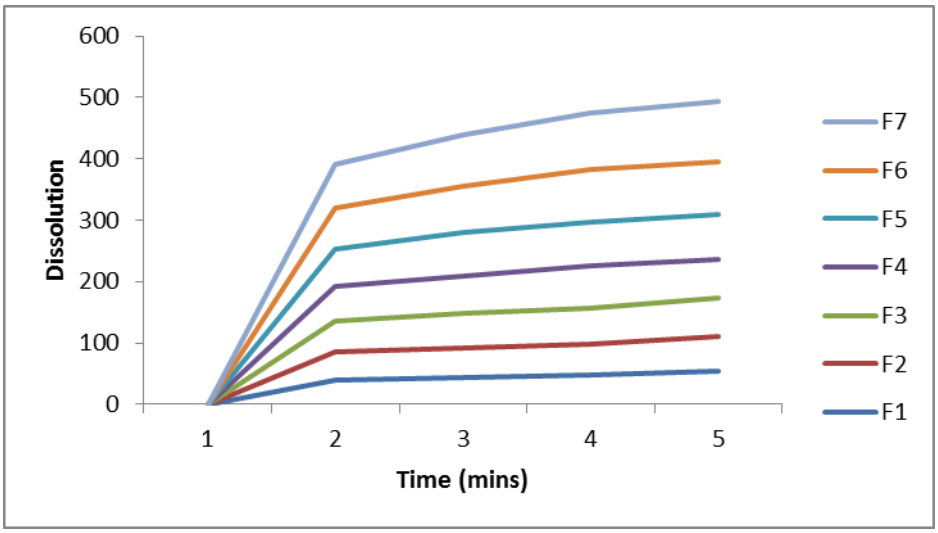

Figure 8: % Drug release of Sildenafil Citrate.

The *in-vitro* drug release kinetics i.e., zero-order, first order, Higuchi, and Hixson Crowell were conducted for the optimized formulation.[12]

Table 5: In-vitro drug release kinetic.

Batch no	Zero order rate constant (K_o)	First order rate constant (K_1)	Higuchi square root rate constant (K_2)	Hixson-Crowell rate constant (K_3)
F1	10.255 r=0.941	0.332 r=0.994	38.014 r=0.983	0.356 r=0.997
F2	9.858 r=0.914	0.280 r=0.973	37.010 r=0.968	0.321 r=0.982
F3	5.349 r=0.955	0.086 r=0.973	19.667 r=0.990	0.121 r=0.989
F4	6.836 r=0.917	0.300 r=0.994	25.686 r=0.972	0.290 r=0.990
F5	4.248 r=0.962	0.074 r=0.980	15.555 r=0.993	0.102 r=0.992
F6	3.950 r=0.990	0.053 r=0.965	13.110 r=0.983	0.077 r=0.970
F7	3.550 r=0.948	0.050 r=0.995	14.073 r=0.995	0.075 r=0.998

CONCLUSION

Sildenafil citrate fast dissolving tablets were prepared by the wet granulation method using crosspovidone and crosscarmellose sodium as superdisintegrants. Drug excipient compatibility studies were performed by the FTIR and DSC. The unpleasant taste of the Sildenafil citrate was masked by intra-granular addition of calcium carbonate and extra-granular addition of sweeteners and flavouring agents. Shilajit was added so as to show synergistic effect with the drug and mask its side effect. The prepared Sildenafil citrate fast dissolving tablets were characterized based upon their physico-chemical characteristics like average weight, weight variation, thickness, hardness, friability, wetting time, in-vitro disintegration time,in-vitro dissolution profile thereby rapid onset of action when compared to other formulations. Hence rapid onset of action compared to other formulations. Hence Sildenafil citrate fast dissolving tablets could be promising one as they increase the bioavailability, avert the problems of swallowing and improve the patient compliance.

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