ISSN: 2322 - 0902 (P)
ISSN: 2322 - 0910 (O)

International Journal of Ayurveda and Pharma Research

Research Article

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLET CONTAINING COMBINATION OF PHOSPHODIESTERASE-5 INHIBITOR AND HERBAL APHRODISIAC

Pujari Vijayanand*, Sanikop Vandana, Surve Rashmi
Department of Pharmaceutics, Rani Chennamma College of Pharmacy, Belagavi, Karnataka, India.

Article info

Article History:
Received: 21-01-2023
Revised: 05-02-2023
Accepted: 15-02-2023

KEYWORDS:
Orodispersible Tablets, Taste masking, Solubility enhancement, Sildenafil citrate, Ginseng, Erectile dysfunction.

ABSTRACT

Purpose: Sildenafil citrate is widely used drug for the treatment of Erectile Dysfunction (ED) and Ginseng is a natural aphrodisiac reported to benefit this condition. The objective of the present study was to develop orodispersible tablets (ODTs) containing combination of Sildenafil citrate and Ginseng extract to improve the bioavailability, reduce the dosing frequency and thereby maintaining the therapeutic efficacy of the drug. **Methods:** The ODTs were prepared using superdisintegrants such as Croscarmellose sodium (CCS), povidone, and sodium starch glycolate (SSG) at varying concentrations (2%, 4% and 6%) by direct compression. The bitter taste of Sildenafil citrate was masked by Doshion resin. The optimized formulation based on least disintegration time (DT) was chosen to reformulate using sublimating agents such as camphor, menthol or thymol at varying concentrations (1%, 2%, 3%) to further reduce the DT. The compatibility of drug with excipients was investigated and the prepared formulations were evaluated for pre and post-compression parameters. **Results:** The post-compression parameters such as weight variation, hardness, friability, DT and in-vitro drug release was found within specified limit. The formulation with camphor (2%) had DT of 12 sec and drug release >90% within 5 min hence was considered as optimized formulation. The accelerated stability study and kinetics modelling was performed for optimized formulation. **Conclusion:** The formulated Sildenafil citrate and Ginseng ODT's were found to be promising formulation with quicker DT and drug release which will eventually have higher bioavailability and better efficacy along with averting the issues of swallowing and improving patient compliance.

INTRODUCTION

Due to the high cost of developing a new chemical entity, the pharmaceutical companies are recently focusing on the development of new drug delivery systems for an existing drug with improved bioavailability and efficacy along with reduced dosing frequency to minimize side effects.[1,2] An ODT is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. For the past two decades, there has been an enriched demand for more patient compliance dosage forms like these.[3,4]

Access this article online	
Quick Response Code	
	https://doi.org/10.47070/ijapr.v11i2.2700

Sildenafil citrate is chemically known as 5-[2-ethoxy-5-(4-methylpiperazin-1-yl)sulfonylphenyl]-1-methyl-3-propyl-6H-pyrazolo[4,3-d]pyrimidin-7-one;2-hydroxypropane-1,2,3-tricarboxylic acid and its chemical structure is shown in Fig. 1 A.[5] It is a selective phosphodiesterase type-5 inhibitor that is approved for the treatment of male ED. Sildenafil citrate has a relatively low oral bioavailability (38–41%), which may be attributed to extensive gut and first-pass metabolism. Despite its long presence on the market, the development of novel formulations of Sildenafil citrate has poorly pursued may be due to its bitter taste.[6,7,8,9]

Ginseng (Fig. 2 B) is one of the most popular trade goods for health care and treatment of diseases in Asia, and is currently consumed in 35 countries around the world.[10] It belongs to the genus *Panax* and includes *Panax ginseng*, *Panax quinquefolius* and *Panax japonicus*. Endothelial nitric oxide release is promoted by Ginseng and ginsenosides, which exerts a direct effect on ED by triggering erection, mediated by

relaxation of the smooth muscles of the corpus cavernosum.[11,12,13]

The ED is a sign of a physical or psychological condition. The main symptom is a man's inability to get or keep an erection firm enough for sexual intercourse.[14] Over 50% of men aged 40 to 70 years will experience some degree of ED according to the data from the Massachusetts Male Aging Study and it is highly correlated with age.[15,16]

So the objectives of the present research work was to develop Doshion resin taste masked ODT of Sildenafil citrate with an additional benefit of Ginseng to reduce problem associated with conventional dosage form by combining suitable diluents and superdisintegrants.

MATERIALS AND METHODS

Material

Sildenafil citrate, *Panax ginseng* extract and Doshion were obtained as a gift sample from Empree Medicament Pvt Ltd, Belagavi, Karnataka. All the other solvents and chemicals used in this study were of analytical reagent grade.

Preformulation Studies

Differential Scanning Calorimetry (DSC) Studies

The thermal behaviour of Sildenafil citrate alone and in physical mixtures with tablet excipients was studied using DSC. Samples (3-5mg) were weighed and hermetically sealed in aluminium pans and heated at a constant rate of 10°C/min, in a temperature range from 25°C to 250°C. Thermograms of the samples were obtained using DSC (Shimadzu DSC 60). Thermal analysis data were recorded using a system with Shimadzu software programs. Nitrogen was used as the purging gas at a rate of 30 ml/min. [17,18]

Fourier Transform Infrared (FTIR) Spectroscopy

The study was carried on samples of pure Sildenafil citrate and physical mixture of CCS, povidone, SSG, thymol, menthol and camphor respectively. Spectra were obtained using potassium bromide disk method. About 2-3mg of dry sample were mixed with dried infrared grade potassium bromide powder and filled into the die cavity of sample holder and an FTIR spectrum was recorded. The spectrum was scanned over a frequency range 4,000–400 cm^{-1}.[17,18]

Identification test for Ginseng by Thin Layer Chromatography (TLC) method

Identification test of *Panax ginseng* extract powder was done by TLC method.[19] The Rf value was calculated using the below mentioned formula:

$$\text{Retention factor (Rf) of standard} = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

Spectrophotometric Method Development for Estimation of Sildenafil Citrate

The calibration curves for estimation of Sildenafil citrate in the dissolution medium were prepared in 0.01N hydrochloric acid (HCl). The drug exhibited λ-max at 294nm. The stock solution (100µg/ml) was further diluted to get concentration of Sildenafil citrate in the range of 10–35µg/ml and absorbance in the range of 0.2 - 0.8.[20] (Tomar et al. 2020)

Sildenafil Doshion Resin Preparation Method

Taste masking was attempted by forming a complex with ion exchange resin. Doshion was used with Sildenafil citrate in ratios of 1:1, 1:2 and 1:3. The complex was prepared by firstly dry mixing Sildenafil citrate with Doshion and passed through #60 mesh sieve. Purified water was added to make thick slurry and kept it overnight to form Sildenafil Resin complex. It was then dried in a tray dryer at 60℃ The semi dried mass was then passed through seive. The drying was continued until the loss on drying (LOD) was not more than (NMT) 2%.[21]

Formulation of ODTs

The ODTs were prepared by direct compression method. The formulation is given in Table 1.

Table 1: Formulation of Orodispersible Tablets of Sildenafil Citrate Using Superdisintegrating Agents

Formulation (mg)	Formulation Code								
	(F-1)	(F- 2)	(F-3)	(F-4)	(F-5)	(F-6)	(F-7)	(F- 8)	(F- 9)
Sildenafil citrate	35	35	35	35	35	35	35	35	35
Ginseng	10	10	10	10	10	10	10	10	10
Doshion	70	70	70	70	70	70	70	70	70
Mannitol	100	100	100	100	100	100	100	100	100
Microcrystalline cellulose	61	55	49	61	55	49	61	55	49
Sodium lauryl sulfate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Stevia powder	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Purified Talc	6	6	6	6	6	6	6	6	6
CCS	**6**	**12**	**18**	--	**--**	**--**	**--**	**--**	**--**

Povidone	**--**	**--**	**--**	**6**	**12**	**18**	**--**	**--**	**--**
SSG	**--**	**--**	**--**	--	**--**	**--**	**6**	**12**	**18**
Average Wt of tablets	300	300	300	300	300	300	300	300	300

Sildenafil citrate 25 mg ODT was prepared using povidone, CCS and SSG as super disintegrants, Sodium lauryl sulfate (SLS) was used as surfactant, mannitol and microcrystalline cellulose (MCC) as diluents, stevia as sweetening agent and magnesium stearate as lubricant. Drug and all the ingredients were weighed accurately and passed through sieve no #60 before mixing. All the ingredients were transferred to mortar and well ground for 15 min. The resulting mixture was compressed in single punch compression machine using 8mm flat punch with breakline on rotary tablet compression machine. Based on DT and drug release profile, one formulation was optimized and further chosen for sublimation studies as shown in Table 2. Camphor, menthol and thymol were used as sublimating agents and the tablets were prepared and vacuum dried at 60℃ for 24 hours to facilitate the sublimation. All the prepared formulations were suitably packed and stored until further evaluation.

Table 2: Formulation of ODTS of Sildenafil Citrate using Sublimating Agent

Formulation (mg)	**Formulation Code**								
	(F-10)	**(F- 11)**	**(F-12)**	**(F-13)**	**(F-14)**	**(F-15)**	**(F-16)**	**(F- 17)**	**(F- 18)**
Sildenafil citrate	35	35	35	35	35	35	35	35	35
Ginseng	10	10	10	10	10	10	10	10	10
Doshion	70	70	70	70	70	70	70	70	70
Mannitol	100	100	100	100	100	100	100	100	100
MCC	55	55	55	55	55	55	55	55	55
SLS	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Stevia powder	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
Magnesium stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Purified talc	6	6	6	6	6	6	6	6	6
CCS	12	12	12	12	12	12	12	12	12
Camphor	1	2	3	--	--	--	--	--	--
Menthol	--	--	--	1	2	3	--	--	--
Thymol	--	--	--	--	--	--	1	2	3
Average Wt of tablets	301	302	303	301	302	303	301	302	303

Determination of pre-compression and post compression parameters

Different pre compressional and post compressional properties like angle of repose, bulk density, tapped density, percent compressibility index (Carr's index), Hausner's ratio, weight variation, friability, hardness, thickness, DT, wetting time, assay and *in vitro* dissolution studies were performed for drug and excipients. [17,18,22-27]

Angle of Repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following formula.

$$tan\ \theta = h/r$$

Bulk Density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density (ρb) was calculated using following formula:

$$\rho b = M/Vb$$

Tapped Density

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tappings). The volume (Vt) occupied in the cylinder after tapping was measured. The tapped density (ρt) was calculated in g/ml using following formula:

$$\rho t = M/Vt$$

Compressibility Index (Carr's Index)

The simplest method of measurement of free flow of powder is compressibility. It is an indication of the ease with which material can be induced to flow which is calculated as follows:

$$I = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

The value below 15% indicates a powder which usually give rise to excellent flow characteristics, whereas above 25% indicate poor flow ability.

Hausner's Ratio (HR)

The HR is correlated to the flow ability of a powder material and is related to the inter particle

friction. It was calculated from bulk density and tapped density by using the following formula:

$$HR = \frac{\text{tapped density}}{\text{bulk densityy}}$$

Determination of Post Compression Parameters

Weight Variation

Random 20 tablets were individually weighed and average weight was calculated. All the 20 tablets were compared with the average weight. The tablets meet United States Pharmacopeia (USP) specifications if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Friability

Twenty tablets were taken and their weight was determined. Then they were placed in the Roche friabilator. The chamber rotates at a speed of 25 rpm for 4 min and drops the tablets by a distance of 15cm. The tablets were then de-dusted and reweighed. The percentage friability was calculated as below:

Percentage Friability = (W1 – W2) x 100/W1

Where, W1 = Initial weight of the 20 tablets.

W2 = Final weight of the 20 tablets after testing.

Friability values below 1% are generally acceptable.

Hardness

From each batch 5 tablets were taken and subjected to Stokes Monsanto hardness tester for measuring the hardness. The mean of the 5 tablets were calculated. The breaking strength (in kg) of each tablet was tested. After the dial on the tester was set to zero, a tablet was placed between the two jaws. The breaking point was determined by gradually increasing the force on the tester. Breaking strength is the force applied (in kg) to break the tablet radially into two halves.

Thickness of Tablets

Thickness was measured by using digital vernier calipers. Randomly 10 tablets were taken and thickness was measured for each tablet by placing between two anvils and rotating sliding knob until the tablet was tightly fitted and the reading was noted on the digital scale.

In vitro Dispersion Time

In vitro dispersion time was measured by dropping a tablet in 20ml of simulated salivary fluid (Phosphate Buffer of pH – 6.8) in a beaker. The time for the tablet to completely disintegrate into fine particles was noted. Overall 3 tablets from each batch were randomly selected and *in vitro* dispersion time was performed.

Assay

The assay was carried out by liquid chromatography technique by the following procedure.

- Disperse 10 tablets in the minimum volume of water (not exceeding 10% of the overall solvent mixture) and add sufficient acetonitrile to produce a solution expected to contain the equivalent of 0.1%w/v of Sildenafil citrate and filter. Dilute 1 volume of this solution to 50 volumes with acetonitrile.
- 0.0028% w/v of Sildenafil citrate European Pharmacopeial Commision of Reference Standard (EPCRS) in the mobile phase.
- Dissolve 70mg of sildenafil citrate EPCRS in 1ml of a mixture containing 1 volume of formic acid and 2 volumes of hydrogen peroxide solution (100 vol) and allow to stand for 10 min. Dilute the resulting solution to 250ml with the mobile phase (in-situ degradation of sildenafil citrate to produce impurity B).
- Chromatographic Conditions
  a. Column size: 15 cm X 3.9 mm packed with octadecylsilyl silica gel
  b. Flow rate: 1ml per min
  c. Column Temperature : 30℃
  d. Wavelength: 290nm

Dissolution

The in vitro dissolution studies were performed using USP apparatus type I rotating basket at 50rpm. The dissolution medium used was pH 1.2 HCl (900ml) maintained at 37±0.5℃ Aliquots of dissolution media were withdrawn at different intervals and drug content was measured by determining absorbance at 290nm.

Determination of Drug Content

The total content of sildenafil, $C_{22}H_{30}N_6O_4S$, in the medium using the declared content of sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$, in sildenafil citrate EPCRS was calculated. Each mg of $C_{28}H_{38}N_6O_{11}S$ is equivalent to 0.7118mg of $C_{22}H_{30}N_6O_4S$.

Limits: The amount of sildenafil released is not less than 75% (Q) of the stated amount.

Identification test for Ginseng by TLC method

Panax ginseng extract powder identification test was done by TLC method. The Rf value was calculated by using formula:

$$\text{Retention factor(Rf)} = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

TLC condition

a) TLC plate of Silica gel G 60

b) Mobile phase: $CHCl_3$:MeOH:H_20 (65:35:10 v/v lower phase)

c) Sprayed with 20% aqueous H_2SO_4

d) Heated at 105℃for 10 min.

Stability Study

Stability study of optimized orodispersible Sildenafil tablet of batch F11 was conducted at accelerated condition (40℃ ± 2℃ and 75±5% RH) in the stability chamber for 3 months and 6 months. Tablets were packed and sealed in polybag and were loaded at each station. All evaluation parameters like weight variation, hardness, thickness, friability, DT test, assay and dissolution test were performed at the interval of 3 month and 6 month for monitoring the degradation of the drug.

RESULTS AND DISCUSSION

Preformulation Studies

Differential Scanning Calorimetry studies

DSC thermogram of pure drug Sildenafil citrate was carried out using DSC instrument Shimadzu DSC 60. DSC thermogram of Sildenafil citrate revealed a sharp endothermic peak at 196.68°C as shown in Fig. 3.

Drug-Excipient Compatibility Study by DSC Method

DSC thermogram of Sildenafil citrate drug-excipient combination are as shown in Fig. 3 to Fig. 8

The DSC curves of drug and drug–excipient mixtures are as shown in Fig. 2 to Fig. 8. DSC thermogram of Sildenafil citrate Fig. 2 revealed a sharp endothermic peak at 196.68°C. The thermal behaviour of pure drug, respective excipient, and the combination of drug and excipients were compared in the DSC curves. In drug-excipient mixture (Fig. 3 to Fig. 8), sharp endotherm of Sildenafil citrate was very slightly shifted from 196.68℃ to 170°C with retained characteristic peak. There may be a change in the shape of the peaks of DSC curve and enthalpy due to the mixing of drug and excipients and may not necessarily indicate potential incompatibility.[28,29]

Fourier Transform Infrared Spectroscopy

The compatibility of drug was carried out by taking FTIR spectra of drug sample and excipients using dispersive FTIR as shown in Table 3 and 4.

Table 3: IR Spectra Interpretation of Sildenafil Citrate Compared with Excipient-CCS, SSG and Povidone

Functional Group	Std Wave Number at [cm^{-1}] of Sildenafil Citrate	Major Peak at Wave Number at [cm^{-1}] of Sildenafil Citrate	Major Peak at Wave Number at [cm^{-1}] of Sildenafil Citrate+ CCS	Major Peak at Wave Number at [cm^{-1}] of Sildenafil Citrate+ SSG	Major Peak at Wave Number at [cm^{-1}] of Sildenafil Citrate+ Povidone
C=O stretch (Carboxylate)	1697	1685.196	1698.40	1699.36	1699.36
N-H Stretch (Aromatic)	3294	3205.00	3256.02	3250.00	3250.00
-C-0 Stretch	1170	1165.00	1158.30	1157.59	1157.59
-CH_3 group Methyl Umbrella bend	1390	1395.00	1392.66	1394.59	1394.59
SO_2 Stretch	1358	1359.87	1357.94	1356.98	1359.87

Table 4: IR Spectra Interpretation of Sildenafil Citrate Compared with Excipient- Camphor, Menthol, Thymol and Optimised Formulation

Functional Group	Std Wave Number at [cm^{-1}] of Sildenafil Citrate	Major Peak at Wave Number at [cm^{-1}] of Sildenafil Citrate	Major Peak at Wave Number at [cm^{-1}] of Sildenafil Citrate+ Camphor	Major Peak at Wave Number at [cm^{-1}] of Sildenafil Citrate+ Menthol	Major Peak at Wave Number at [cm^{-1}] of Sildenafil Citrate+ Thymol	Major Peak at Wave Number at [cm^{-1}] of Optimised Formulation
C=O stretch (Carboxylate)	1697	1685.196	1698.40	1694.54	1698.40	1701.29
N-H Stretch (Aromatic)	3294	3205.00	3296.49	3422.83	3432.48	3296.49
-C-0 Stretch	1170	1165.00	1157.34	1145.77	1140.94	1173.73
-CH_3 group Methyl Umbrella bend	1390	1395.00	1394.59	1395.56	1394.59	1392.66
SO_2 Stretch	1358	1359.87	1361.80	1395.56	1361.80	1359.87

The spectra were overlaid for drug-excipient interaction study as shown in Fig. 9-19. The peaks produced are due to stretching and bending vibrations that occur within molecules when placed in the infrared field due to specific

group present in sample. There was no interaction found in the spectrum. In all spectrums of mixture the characteristic peak of Sildenafil citrate was in the same region as that of the pure drug. This revealed that there was no major interaction with each other.

Calibration curve of Sildenafil citrate

Calibration curve of Sildenafil citrate was prepared in pH 1.2 HCl buffer, the details of which are given in Table. 5 and Fig. 20. Regression coefficient, slope and intercept were calculated from the plot. The regression equation was calculated as Y= 0.1103x - 0.0501 with regression coefficient value 0.9786 which was found to obey Lambert–Beer's law.

Table 5: Calibration Curve Data of Sildenafil Citrate in 0.01 N Hydrochloric Acid

Sr. No	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1.	0	0	0	0	
2.	10	0.212	0.208	0.210	0.210 ± 0.002
3.	15	0.295	0.292	0.298	0.295 ± 0.003
4.	20	0.429	0.429	0.429	0.429 ± 0.000
5.	25	0.504	0.503	0.502	0.503 ± 0.001
6.	30	0.600	0.600	0.600	0.600 ± 0.000
7.	10	0.700	0.698	0.702	0.700 ± 0.002

Identification test for Ginseng by TLC method

Retention factor was calculated for standard drug and optimized batch. Blue spots observed through the UV light for standard sample and optimized batch sample are shown in the Fig. 21. The Rf value found was in the range of 0-1. The Rf value obtained was near to 1 hence the sample was said to be less polar. The Rf value was calculated as follows:

$$\text{Retention factor(Rf)} = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

Distance travelled by standard = 6.0

Distance travelled by sample = 4.8

Distance travelled by solvent 7.5

Retention factor (Rf) of standard = 0.8

Retention factor (Rf) of sample of optimized batch = 0.64

Sildenafil Citrate and Doshion Complex

The complex of Sildenafil citrate and Doshion in varying concentration was prepared for taste masking before compression as shown in Table 6. White granules were obtained in formulation D1 and D2 whereas pale yellow granules were obtained in D3 formulation. However the LOD of D1 formulation was beyond the limit (NMT 2%) hence formulation D2 with concentration ratio of 1:2 was selected for further processing.

Table 6: Sildenafil Citrate-Doshion Complex

Resin	Batch No	Ratio of concentration	LOD (1-2%)	Appearance
Doshion	D1	1:1	2.5	White Granules
	D2	1:2	2.0	White Granules
	D3	1:3	1.8	Pale Yellow granules

The ODTs were prepared by direct compression method with the formulation code as shown in Table 1. The pre-compression test parameters like bulk density, tap density, carrs index, HR and angle of repose have been used to study the flowability and cohesivity of powder blend. Values of these micromeritic parameters are given in Table 7. Result stated in the table show that the flow property of the batches F2, F4 and F8 has excellent flow while other batches showed good flow within acceptable limit.

Table 7: Pre-Compression of Formulations Prepared Using Different Super Disintegrant Agents by Direct Compression

Formulation Code	Bulk Density (gm/cc)±SD	Tap density (gm/cc)±SD	Carrs Index±SD	Hausner's Ratio±SD	Angle of Repose(Ø)	Flow Property
F1	0.34±0.01	0.39±0.02	12.75±0.45	1.14±0.02	31.45±0.93	Good
F2	0.32±0.02	0.33±0.02	2.39±0.12	1.02±0.01	26.32±1.45	Excellent
F3	0.34±0.01	0.38±0.04	11.62±0.76	1.13±0.01	31.35±1.04	Good
F4	0.32±0.02	0.33±0.02	3.89±0.35	1.04±0.01	26.54±1.24	Excellent
F5	0.43±0.01	0.48±0.02	11.49±0.30	1.12±0.02	33.38±2.84	Good
F6	0.37±0.02	0.43±0.02	13.56±0.33	1.15±0.03	33.32±2.84	Good
F7	0.36±0.02	0.42±0.01	12.82±0.02	1.14±0.02	34.53±0.86	Good
F8	0.33±0.03	0.34±0.02	4.022±0.08	1.04±0.01	27.41±1.67	Excellent
F9	0.34±0.01	0.38±0.04	11.39±0.30	1.12±0.02	32.21±1.37	Good

CCS, Povidone and SSG were used as superdisintegrants in 3 different concentrations. There is an inverse linear relation between concentration used in the formulation and DT. The formulation with 4% concentration of CCS showed lowest mean DT (32 sec) compared with the formulation with Povidone (1 min 15 sec) and SSG (48 sec) as shown in **Table 8.**

Table 8: Post Compression Test of Formulations Prepared Using Different Super Disintegrant Agents by Direct Compression

Parameters	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Average weight (mg)***	299.5 ±1	300.0 ±2	301.0 ±1.5	300.0 ±1	298.5 ±2	299.0 ±1	299.5 ±1.5	300.0 ±1.5	301.5 ±2
Hardness (kg/cm2)*	1.0 ±0.5	2.5 ±1.0	3.0 ±1.0	3.0 ±0.5	3.5 ±1.0	3.0 ±0.5	2.5 ±1.0	3.0 ±0.5	2.5 ±1.0
Friablity (%)*	1.08 ±0.02	0.60 ±0.04	1.05 ±0.03	0.18 ±0.02	0.20 ±0.05	0.32 ±0.04	0.42 ±0.06	0.50 ±0.02	0.48 ±0.04
Disintegration test** (sec)	42±4	32±2	40±2	80±5	75±6	82±2	52±4	50±6	48±2

Values are expressed as Mean ± SD ***n= 20, **n= 6 , * n=3

Interestingly, with higher concentration of SSG, the DT of formulation increased. This could be attributed to the mechanism of disintegration of SSG (swell and burst) versus CCS and povidone (winking mechanism). It has been reported that, with increase in concentration of SSG, a gel like matrix is produced that hinders, rather than accelerating DT. Therefore, based on the data available, CCS was selected for sublimation to achieve a target DT of less than 30 sec. The precompression and post compression test results of formulations prepared using sublimating agents by direct compression are as shown in Table 9 and 10 respectively. The precompression test data revealed that all formulations had adequate flow properties within the acceptable limit.

Table 9: Pre-compression Tests of Formulations Prepared Using Sublimating Agents by Direct Compression

Formulation code	Bulk density (gm/cc)±SD	Tap density (gm/cc)±SD	Carrs index±SD	Hausner's Ratio±SD	Angle of Repose(Ø)	Flow Property
F10	0.38±0.04	0.44±0.02	12.44±0.57	1.14±0.05	28.46±0.62	Good
F11	0.33±0.03	0.34±0.02	4.61±0.30	1.04±0.02	25.46±0.32	Excellent
F12	0.44±0.02	0.49±0.02	11.42±0.90	1.12±0.04	29.46±0.78	Good
F13	0.32±0.02	0.33±0.03	1.8±0.30	1.01±0.02	25.21±0.48	Excellent
F14	0.32±0.02	0.34±0.01	4.09±0.10	1.04±0.05	28.46±0.80	Excellent
F15	0.34±0.01	0.38±0.04	12.08±0.01	1.13±0.05	31.46±0.57	Good
F16	0.35±0.03	0.41±0.01	14.55±0.28	1.17±0.06	32.46±0.86	Good
F17	0.32±0.02	0.33±0.03	2.39±0.10	1.02±0.04	26.46±0.65	Excellent
F18	0.37±0.02	0.42±0.01	12.47±0.10	1.14±0.05	32.36±0.30	Good

Table 10: Post Compression of Formulations Prepared Using Sublimating Agents by Direct Compression

Parameters	Formulation Code								
	F10	F11	F12	F13	F14	F15	F16	F17	F18
Average weight (mg)***	301.0 ±1	302.0 ±1	301.0 ±2	303.0 ±1	302.0 ±1	302.0 ±2	304.0 ±1	303.0 ±2	302.0 ±1
Hardness (kg/cm²)*	2.0 ±0.5	1.5 ±1.0	2.0 ±0.5	2.0 ±1.0	2.5 ±0.5	2.5 ±1.0	2.5 ±0.5	2.5 ±1.0	3.0 ±0.5
Friablity (%)*	1.2 ±0.02	0.65 ±0.06	1.5 ±0.02	1.05 ±0.04	0.58 ±0.02	1.10 ±0.04	0.40 ±0.04	0.42 ±0.08	0.36 ±0.02
Disintegration test** (sec)	14±2	12±5	10±3	22±6	25±2	24±4	36±6	30±4	32±6

Values are expressed as Mean ± SD ***n= 20, **n=6, * n=3

The sublimating agents used were camphor, menthol and thymol in 3 different concentrations (1%, 2% and 3%) and DT was studied. It was observed that, with increase in concentration of sublimating agent, there was a linear decrease in DT. This could be due to formation of a porous structure in the tablet matrix. As the sublimating agent leaves the system and escapes into the atmosphere, it will leave behind a void which increases porosity of the tablet thus decreasing the DT. The formulation containing 4% camphor (F12) showed least DT (10 sec), but failed in the friability test (1.05%w/w). Therefore the formulation containing 2% w/w camphor (F11) with DT 12 sec was considered to be optimized and taken for statistical comparison with the formulation containing superdisintegrants (4% CCS).

Assay

Liquid chromatography technique was used to carry out the assay. The data obtained from the below Fig. 26-31 are summarized in Table 11.

Table 11: Assay Results of Batches Optimised with Camphor

B.No	Assay (%)	Limit (%) NLT	Limit (%) NMT
F10	97.54	95	105
F11	99.50	95	105
F12	99.03	95	105

*NLT: Not Less Than *NMT: Not More Than

Dissolution

The in vitro dissolution studies were performed using USP apparatus type I rotating basket at 50 rpm. The dissolution medium used was pH 1.2 HCl (900ml) maintained at 37 ± 0.5℃ The results are as shown in Table 12.

Table 12: Dissolution Profile of Selected Formulation

Batch No	Time (Min)	Result (%)	Standard deviation (SD)	Limit (%)
F10	5	97.24	0.81	NLT 80
	10	98.89		
	15	98.15		
F11	5	97.07	0.82	NLT 80
	10	100.10		
	15	102.40		
F12	5	97.46	0.70	NLT 80
	10	98.84		
	15	97.46		

Table 13: Details of Dissolution Study

Time (hrs.)	Square root of Time	Log Time	Absorbance	Cumulative Drug Release	% Cumulative Drug Release	% Cumulative Drug Retained	Log % Cumulative Drug Release	Log % Cumulative Drug Retained
5	2.236	0.699	0.274	18.269	73.077	26.923	1.864	1.430
10	3.162	1.000	0.282	19.024	76.094	23.906	1.881	1.379
15	3.873	1.176	0.288	19.618	78.473	21.527	1.895	1.333

Table 14: Release Kinetic Parameters for Prepared Tablets

S. No.	Model Name	R^2 (Regression coefficient)
1.	Zero order	0.995
2.	First order	0.998
3.	Higuchi	0.999
4.	Korsmeyer-Peppas	0.994
5.	Hixson–crowel	0.997

Mathematical models play a vital role in the interpretation of mechanism of drug release from a dosage form. The matrix tablets of Sildenafil citrate 25mg were formulated to show quick release of drug profile with the polymer CCS and sublimating agent camphor. Comparing with first and second order kinetics model, drug release mechanism was best fitted for First order kinetic model as the data obtained are plotted as log cumulative percentage of drug remaining Vs time which yields a straight line with a slope hence this relationship describes the drug dissolution of ODT formulation with porous matrix.

Further comparing the Higuchi's model, Korsemeyer-Pepas model and Hixon Crowel Cube root model, the drug release mechanism follows Higuchi Peppas plot as the data obtained were plotted as cumulative drug release versus square root of time, hence the relationship describes the matrix system formulation in which the initial concentration in the matrix is much higher than drug solubility, drug diffusion takes place only in one dimension.

Stability Study

The stability studies of the optimized formulation of ODTs revealed that there was no significant change in the physical parameters when stored at accelerated conditions (40℃/75% RH) for a period of 3 months and 6 months as shown in Table 15.

Table 15: Stability Testing Results for Accelerated Conditions

Batch. No	**F11**			
Test	**Results (Initial)**	**Results (3 month)**	**Results (6 month)**	**Limit**
Weight Variation	301.0	301.25	301.50	301-303mg
Hardness	1.5	2.0	2.5	Not More than 5 Kg/cm^2
DT	12	12 sec	14 sec	Not more than 3 min
Friability (%)	0.65	0.68	0.70	1.0%
Assay	99.50	98.89	97.51	95- 105%
Dissolution	102.40	101.10	100.20	NLT 80%

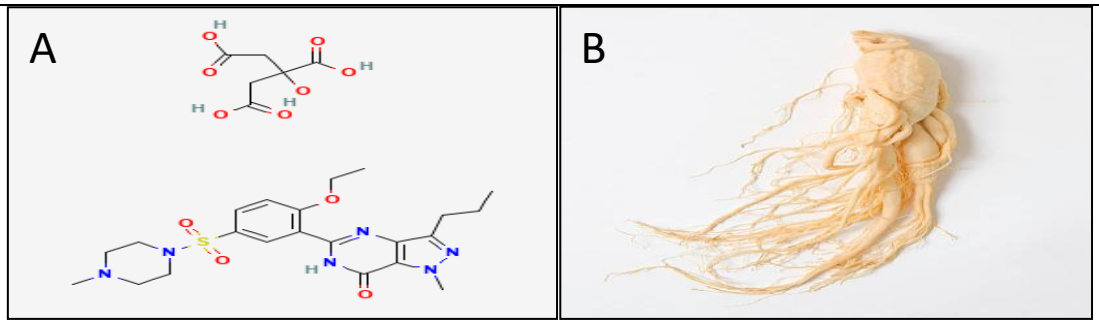

Fig. 1 A: Sildenafil citrate; B: Ginseng

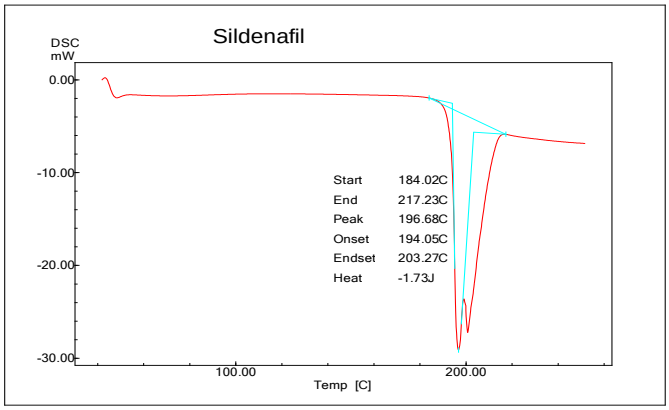

Fig. 2 DSC of Sildenafil citrate

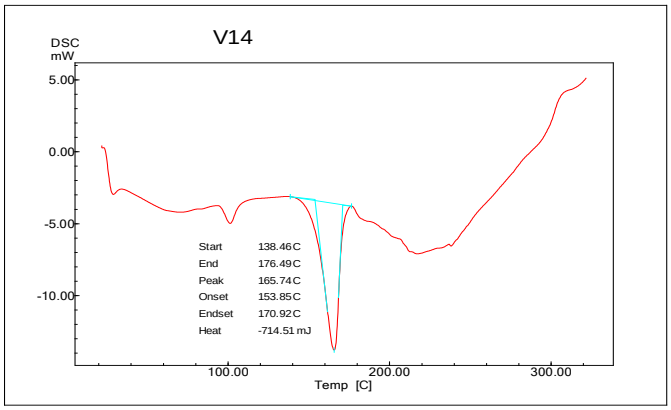

Fig. 3 Sildenafil citrate+Ginseng+Mannitol+MCC+SLS+CCS

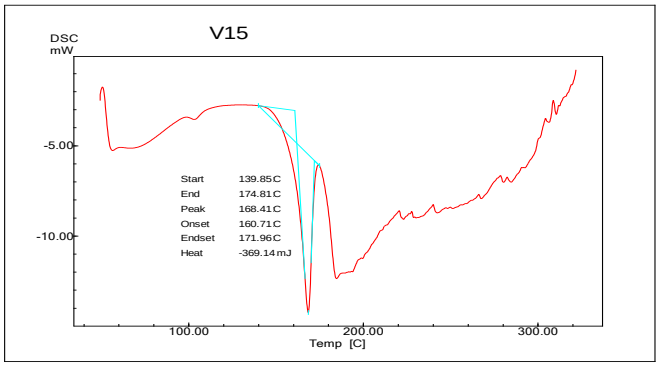

Fig. 4 Sildenafil citrate+Ginseng+Mannitol+MCC+SLS+Povidone

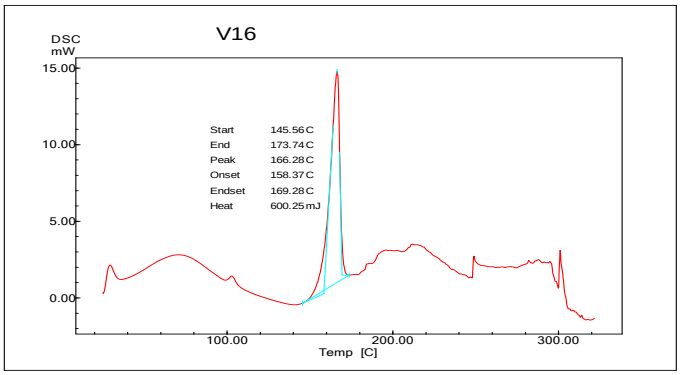

Fig. 5 Sildenafil citrate+Ginseng+Mannitol+MCC+SLS+SSG

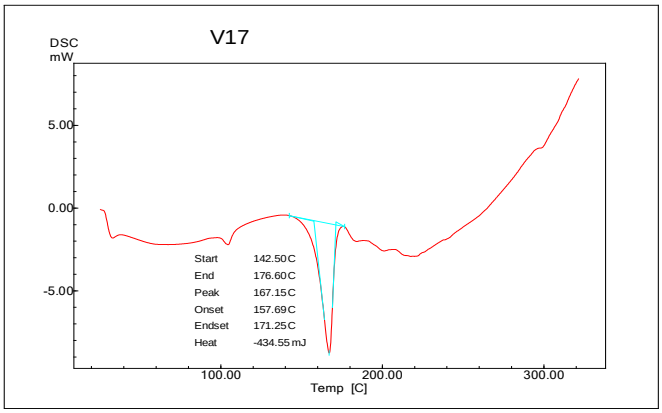

Fig. 6 Sildenafil citrate+Ginseng+Mannitol+MCC+SLS+CCS+Menthol

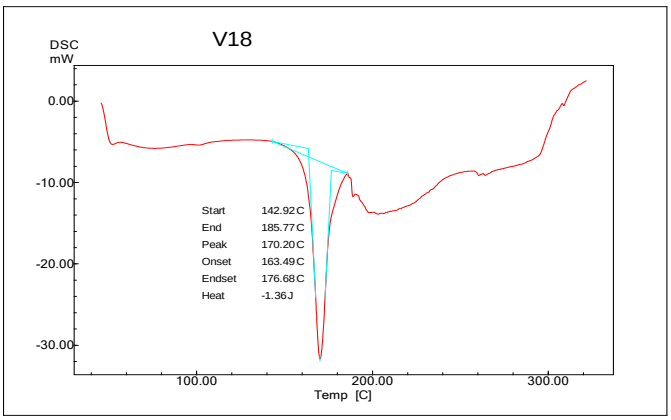

Fig. 7 Sildenafil citrate+Ginseng+Mannitol+MCC+SLS+CCS+Camphor

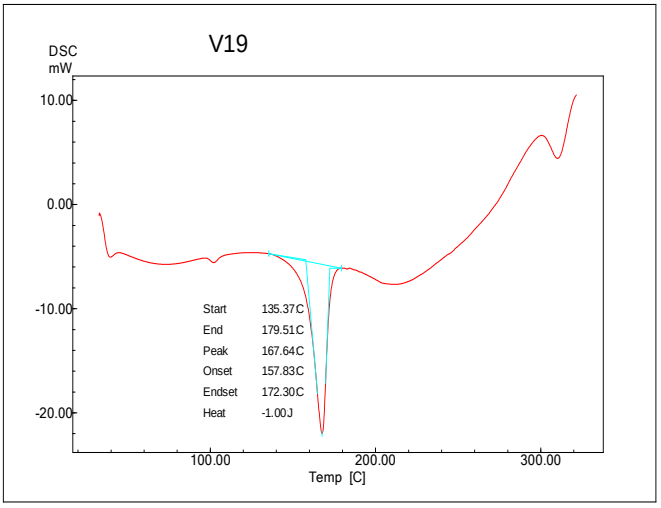

Fig. 8 Sildenafil citrate+Ginseng+Mannitol+MCC+SLS+CCS+Thymol

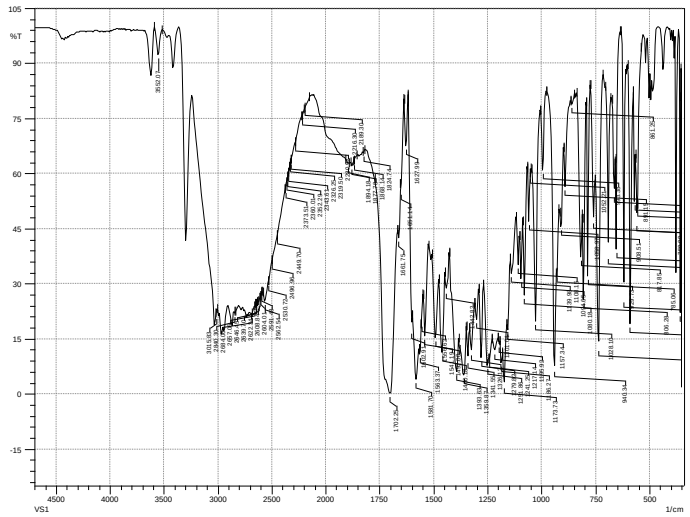

Fig. 9 FTIR Spectrum of Sildenafil Citrate

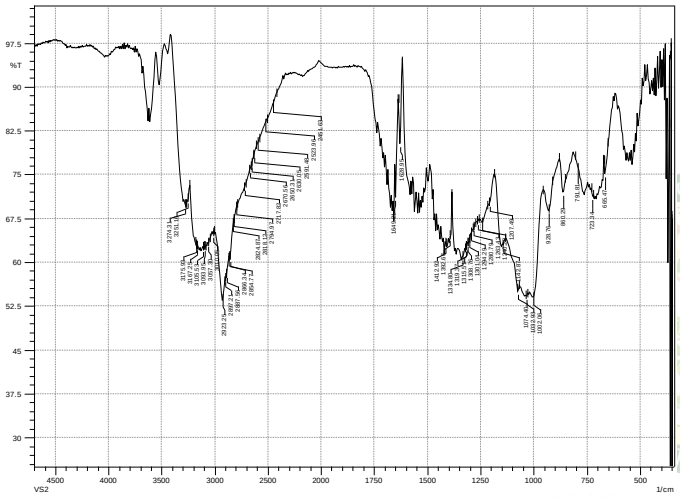

Fig. 10 FTIR Spectrum of Ginseng

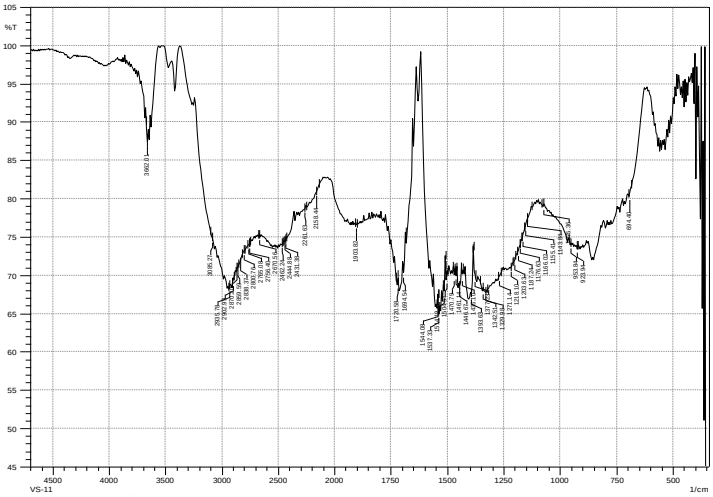

Fig. 11 FTIR Spectrum of Doshion

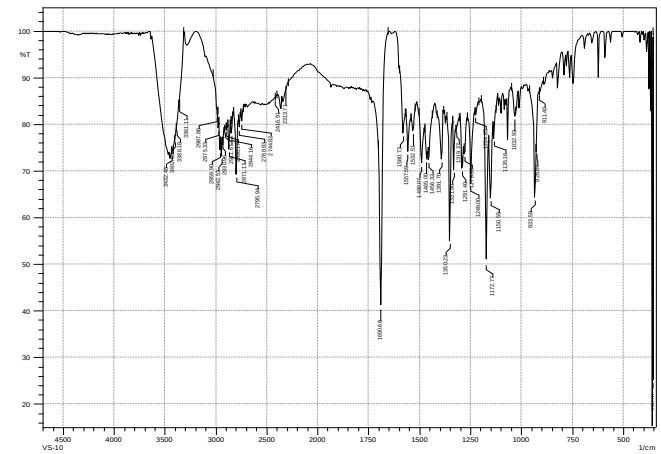

Fig. 12 FTIR Spectrum of Sildenafil Citrate+ Doshion

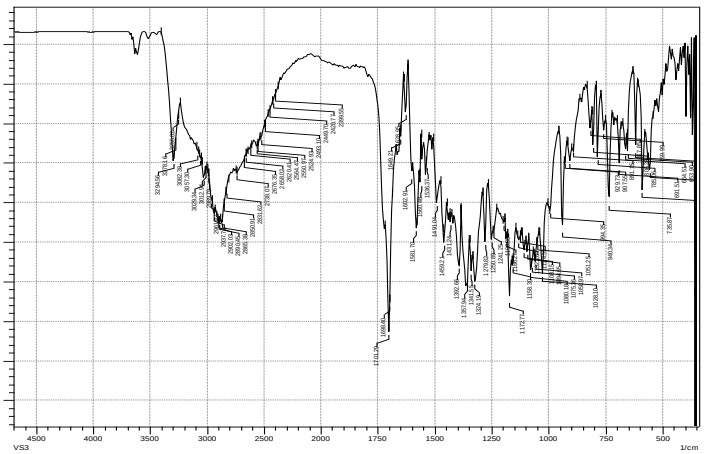

Fig. 13 FTIR Spectrum of Sildenafil Citrate + CCS

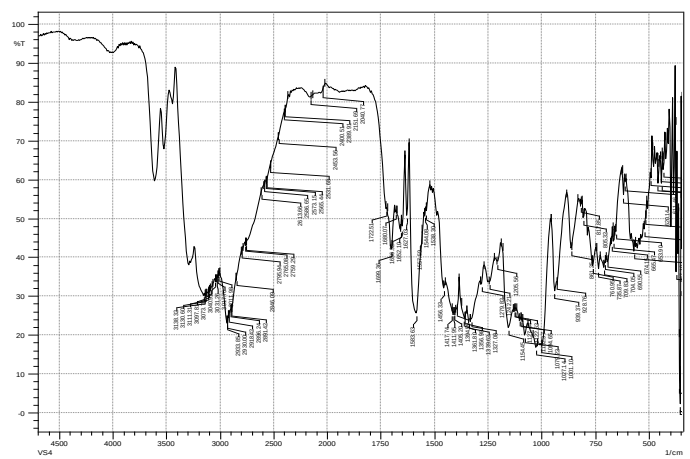

Fig. 14 FTIR Spectrum of Sildenafil Citrate + SSG

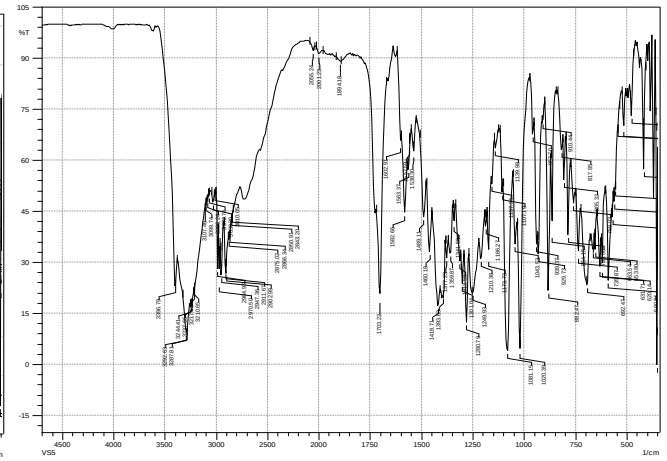

Fig. 15 FTIR Spectrum of Sildenafil Citrate + Povidone

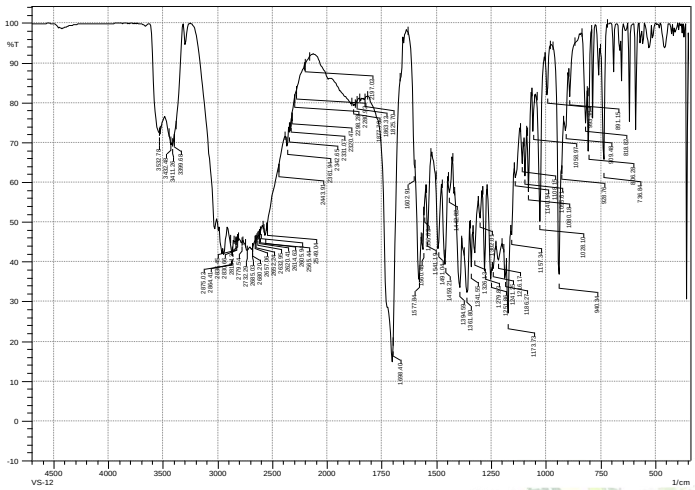

Fig. 16 FTIR Spectrum of Sildenafil Citrate +Camphor

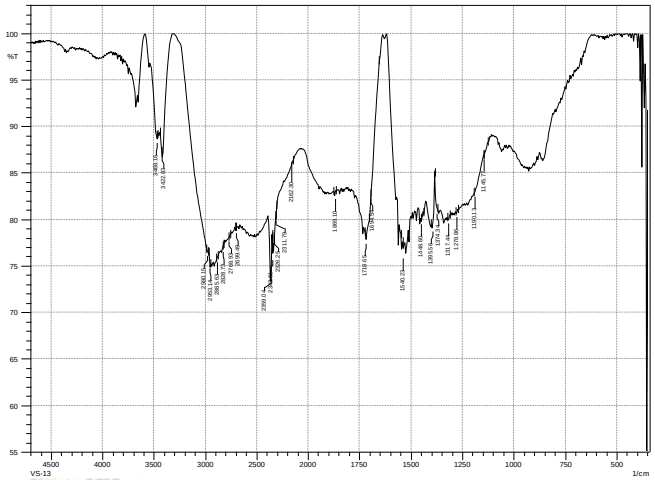

Fig. 17 FTIR Spectrum of Sildenafil Citrate +Menthol

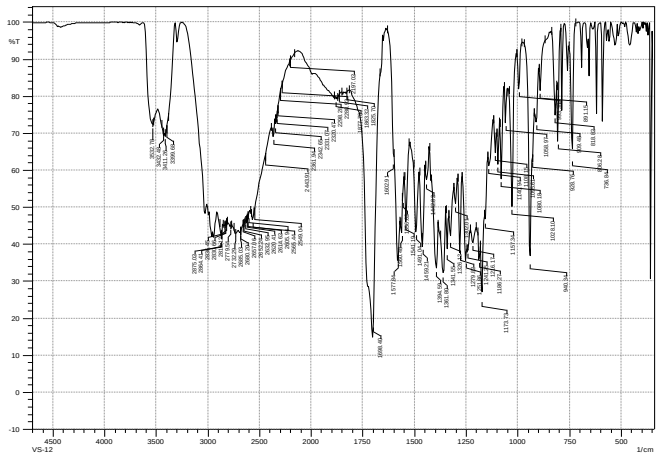

Fig. 18 FTIR Spectrum of Sildenafil Citrate + Thymol

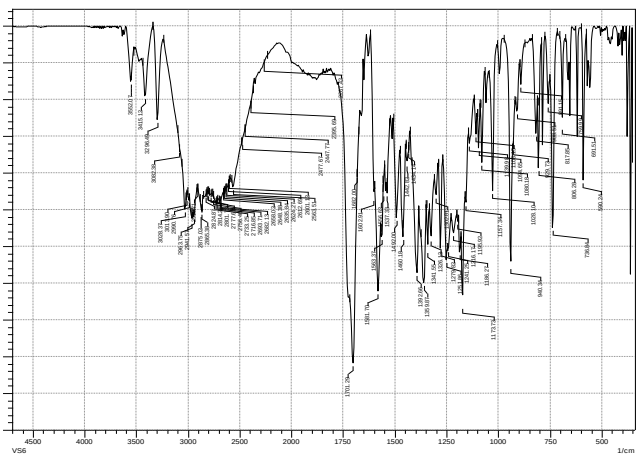

Fig. 19 FTIR Spectrum of Optimised Final Formulation

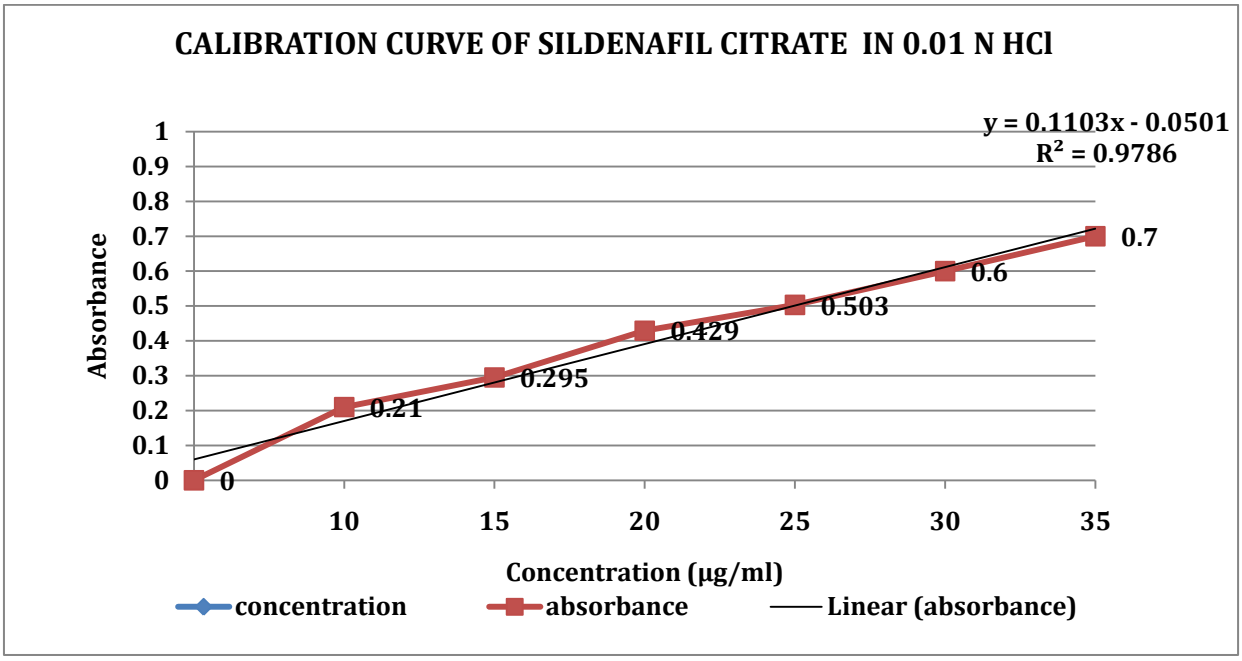

Fig. 20 Calibration Curve Data of Sildenafil Citrate in 0.01 N Hydrochloric Acid

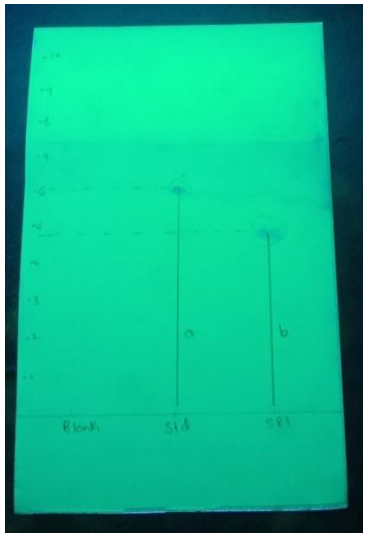

Fig. 21 Identification of Ginseng by TLC method

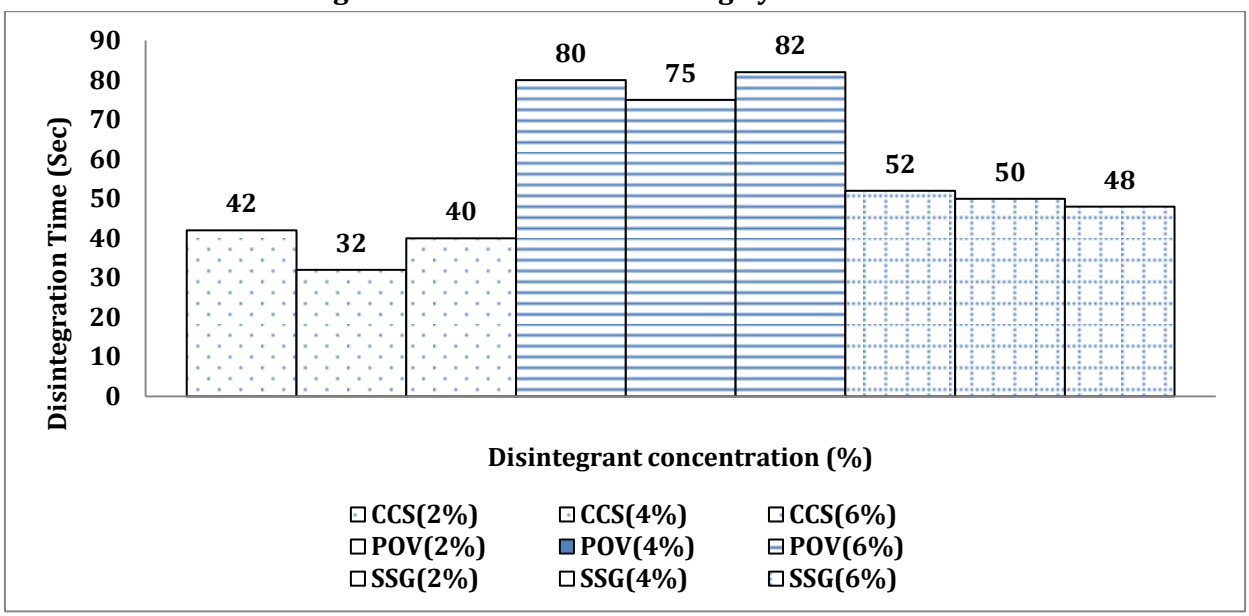

Fig. 22 Comparison of DT of formulations prepared using different super disintegrant by direct compression.

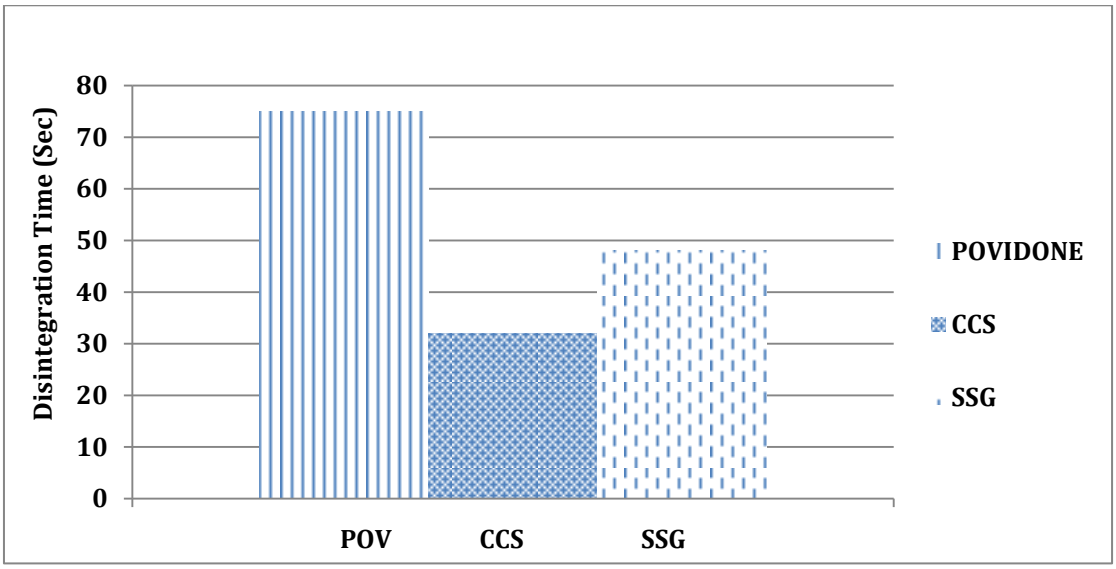

Fig. 23 Comparison of Superdisintegrant with the lowest obtained DT

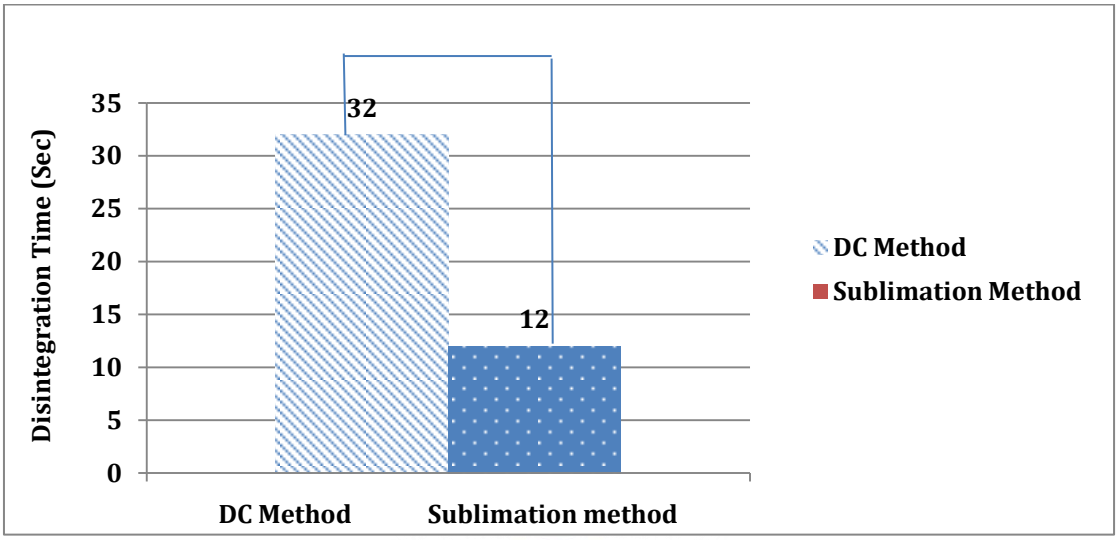

Fig. 24 Comparison of DT of formulations prepared using super disintegrant (CCS 4%) by direct compression and using sublimating agent (camphor 2%)

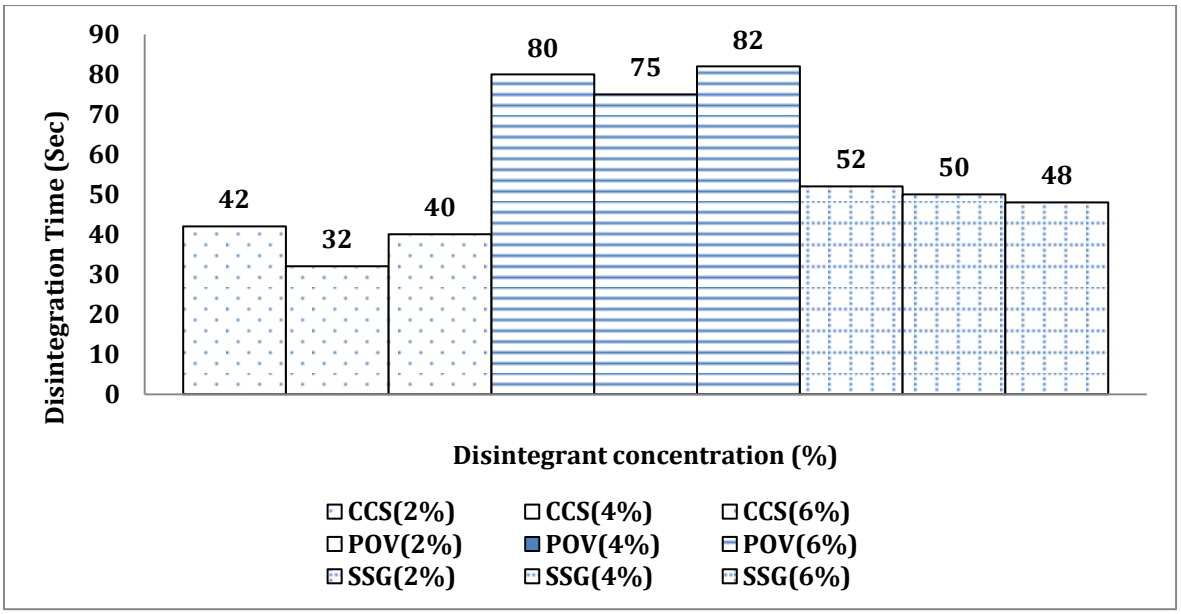

Fig. 25 Comparison of DT of formulations prepared using different super disintegrant by direct compression.

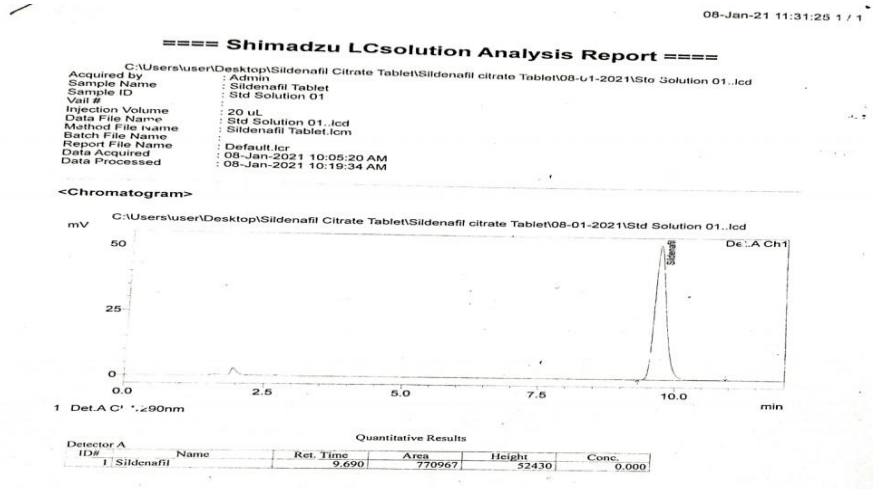

Fig. 26 HPLC analysis data for Standard sample of B.No- F10

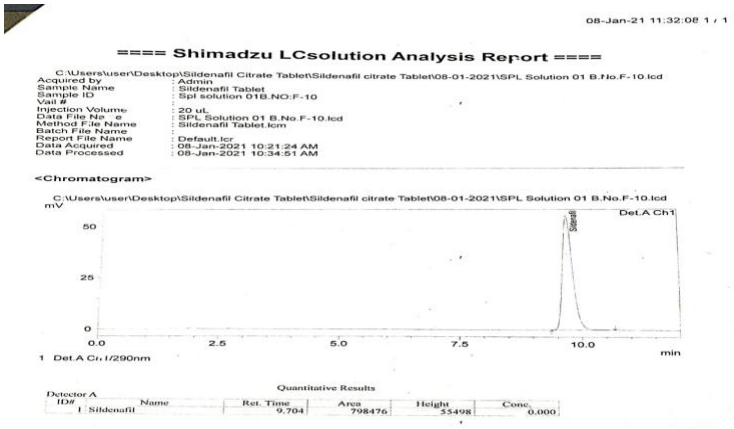

Fig. 27 HPLC analysis data for Sample of B.No- F10

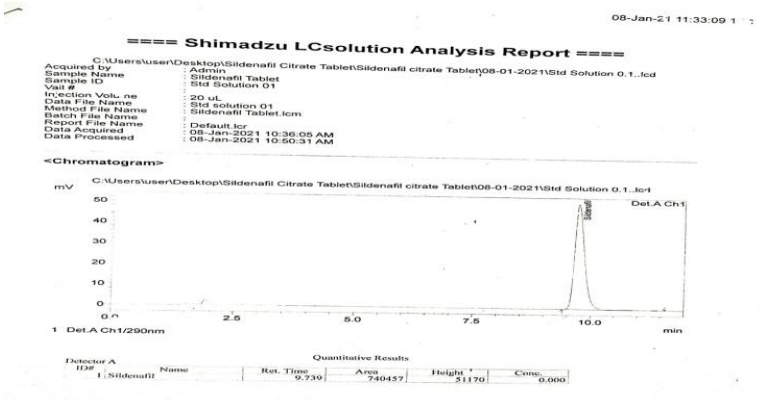

Fig. 28 HPLC analysis data for Standard sample of B.No- F11

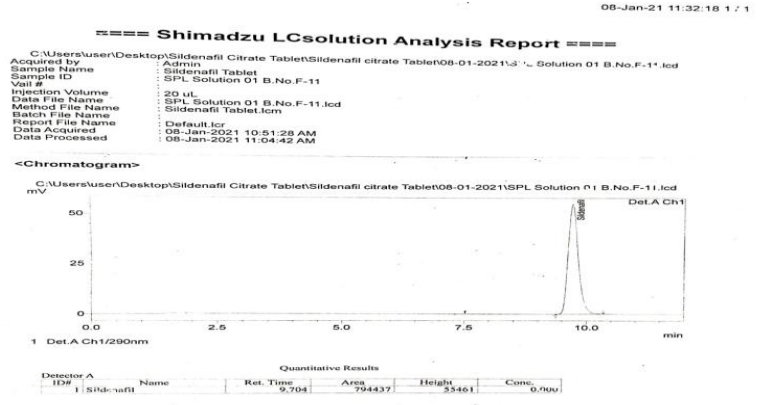

Fig. 29 HPLC analysis data for Sample of B.No- F11

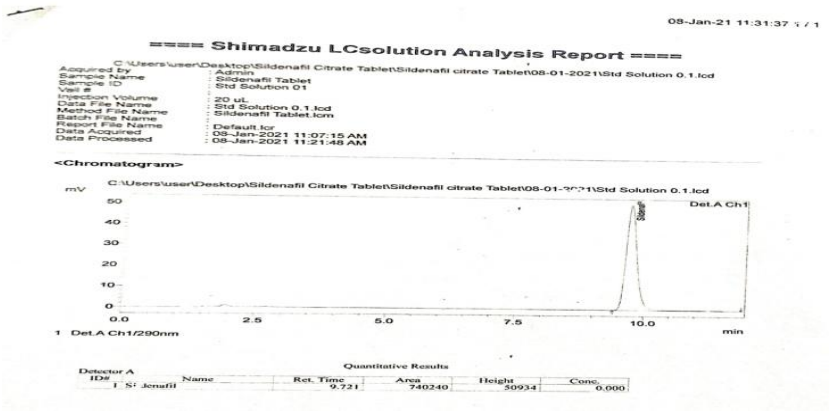

Fig. 30 HPLC analysis data for Sample of B.No- F12

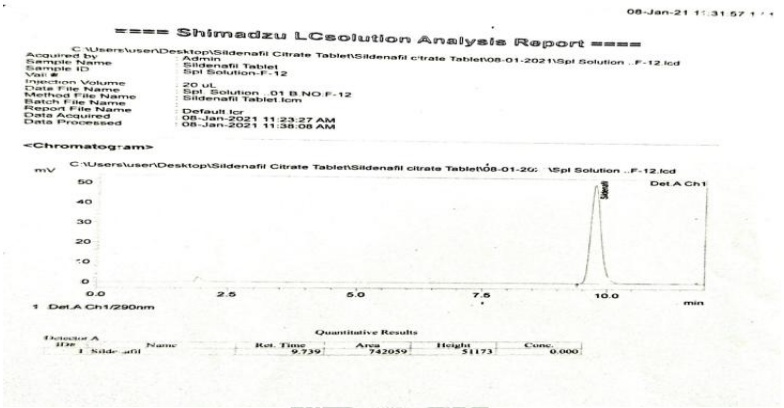

Fig. 31 HPLC analysis data for Standard sample of B.No- F12

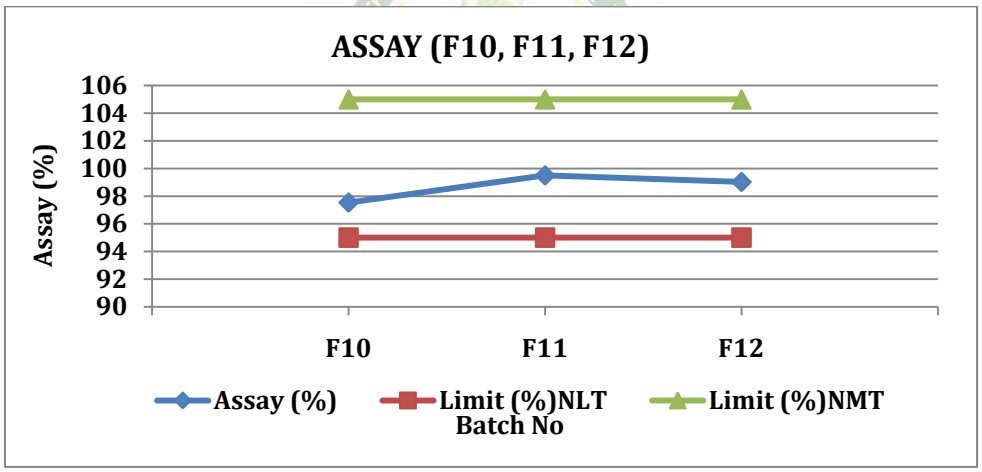

Fig. 32 Graphical representation of Assay of all the three batches optimised with 4% CCS and 1%, 2% and 3% Camphor

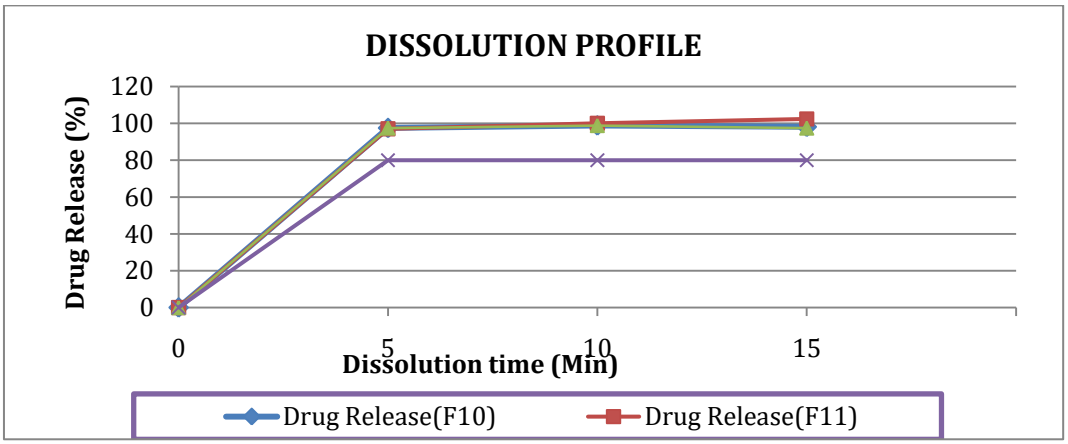

Fig. 33 In vitro Drug Release pattern of the formulation with sublimating agents (1% camphor B.No-F10, F11 and F12)

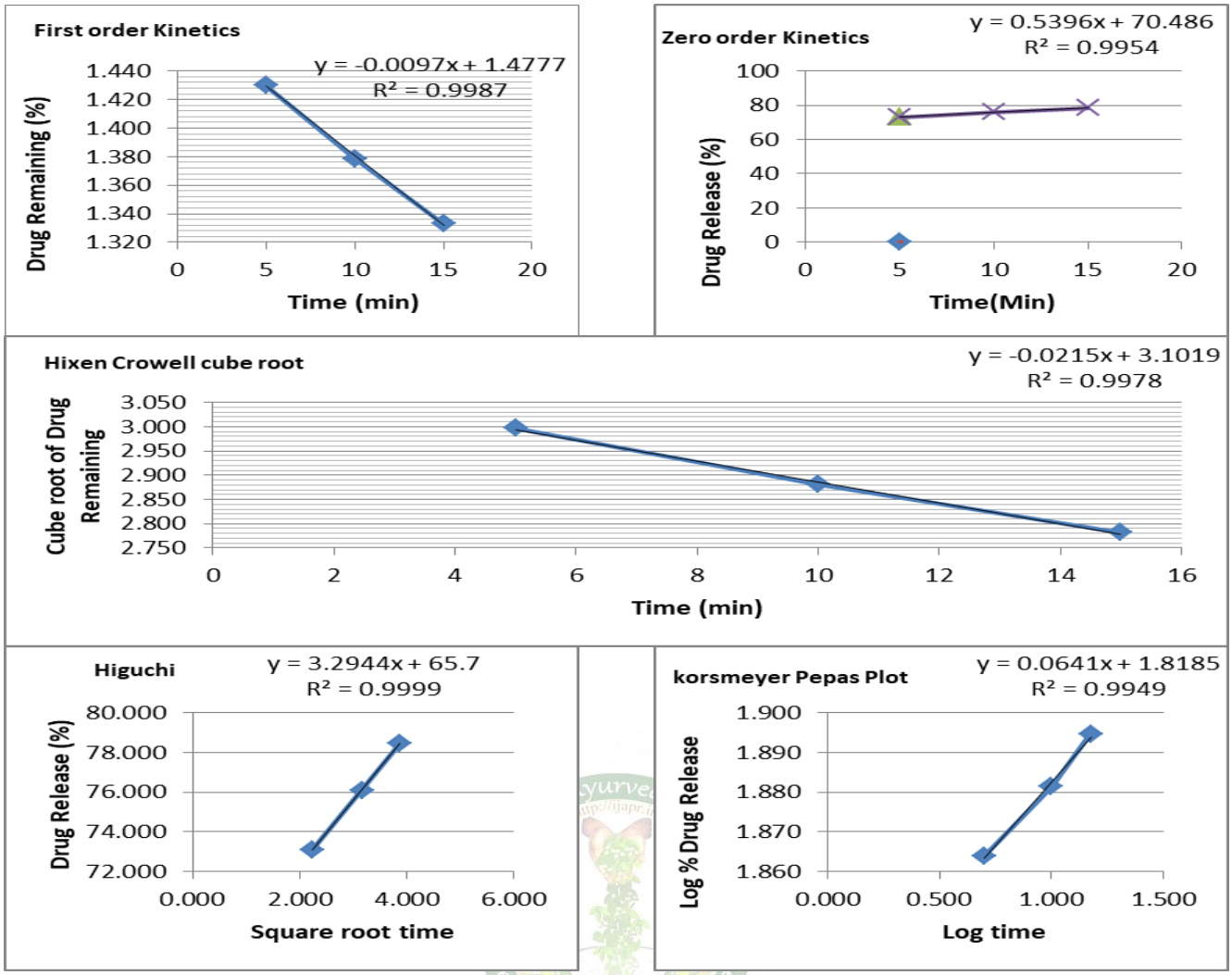

Fig. 34 *In-vitro* drug release kinetic models of optimised batch F11

CONCLUSION

From all above study it can be determined that taste masked ODT of Sildenafil citrate and Ginseng containing camphor and CCS which have released more than 90% within 5 min indicated higher drug release which in turn attributes to enhanced bioavailability and better efficacy. This would also obviate the problem of swallowing and consequently improving patient compliance.

Acknowledgements

The authors are thankful to Empree Medicament Pvt Ltd, Belagavi, Karnataka for providing laboratory facilities to conduct the research work. We are also very grateful to Rani Chennamma College of Pharmacy, Belagavi for providing facilities to carry out the research work.

REFERENCES

1. Bhowmik D, Bhanot R and Kumar KPS: Recent trends in role of superdisintegrants to formulation of solid oral dosage form. Research Journal of Pharmaceutical Dosage Forms and Technology 2018; 10(4): 245-52.
2. Ghori Y, Gupta AR and Maan M: Formulation and in-vitro evaluation of orodispersible tablets of telmisartan. Journal of Drug Delivery and Therapeutics 2019; 9(2): 53-5.
3. Kaur T, Gill B, Kumar S, Gupta G. Mouth dissoving tablets: A novel approach to drug delivery. International Journal of Pharmaceutical Research. 2011; 3(1): 1-7.
4. Siddiqui M, Garg G, Sharma P. Fast dissolving tablets: Preparation, characterization and evaluation: over view. International Journal of Pharmaceutical Sciences Review and Research. 2021; 4(2): 87-96.
5. Sawatdee S, Srichana T. Analytical validation of sildenafil citrate inhaler preparation. Chiang Mai J Sci. 2013 Oct 1;40(4):660-9.
6. Boolell M, Allen M, Ballard S. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. 1996; 8(2): 47-52.
7. Dunn PJ, Galvin S, Hettenbach K. The development of an environmentally benign synthesis of sildenafil citrate (Viagra™) and its assessment by Green Chemistry metrics. Green chemistry. 2004; 6(1): 43-8.
8. Gupta M, Kovar A, Meibohm B. The Clinical Pharmacokinetics of Phosphodiesterase-5 Inhibitors

for Erectile Dysfunction. The Journal of Clinical Pharmacology. 2005; 45(9): 987-1003.
9. De Toni L, De Rocco Ponce M, Franceschinis E, Dall'Acqua S, Padrini R, Realdon N et al. Sublingual Administration of Sildenafil Oro-dispersible Film: New Profiles of Drug Tolerability and Pharmacokinetics for PDE5 Inhibitors. Frontiers in Pharmacology. 2018; 9.
10. Baeg IH, So SH. The world ginseng market and the ginseng (Korea). Journal of ginseng research. 2013 Mar; 37(1): 1.
11. Lee H, Lee M, Kim T, Alraek T, Zaslawski C, Kim J et al. Ginseng for erectile dysfunction. Cochrane Database of Systematic Reviews. 2017;.
12. CHOI Y, RHA K, CHOI H. In vitro and in vivo experimental effect of Korean red ginseng on erection. 162. 1999; 4.
13. de Andrade E, de Mesquita A, de Almeida Claro J, de Andrade P, Ortiz V, Paranhos M et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. Asian Journal of Andrology. 2007; 9(2): 241-244.
14. Lue TF, Tanagho EA. Physiology of erection and pharmacological management of impotence. The Journal of urology. 1987 May; 137(5): 829-36.
15. Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F et al. Guidelines on Male Sexual Dysfunction: Erectile Dysfunction and Premature Ejaculation. European Urology. 2010; 57(5): 804-814.
16. Feldman H, Goldstein I, Hatzichristou D, Krane R, McKinlay J. Impotence and Its Medical and Psychosocial Correlates: Results of the Massachusetts Male Aging Study. Journal of Urology. 1994; 151(1): 54-61.
17. Al-Shadeedi M, Samein L, Shehab M. Formulation and Evaluation of Carbimazole Orodispersible Tablet. International Journal of Pharmacy and Pharmaceutical Science. 2013; 5(1).
18. Mahrous G, Kassem M, Ibrahim M, Auda S. Formulation and evaluation of orally disintegrating clopidogrel tablets. Brazilian Journal of Pharmaceutical Science. 2016; 52(2).
19. Choi HJ, Zhang YB, An BJ, Choi C. Identification of biologically active compounds from *Panax ginseng* CA Meyer. Korean Journal of Food Science and Technology. 2002; 34(3): 493-7.
20. Tomar D, Kaushik P, Mishra A, Sah L. Development of Analytical Method and its Validation for Sildenafil Citrate by Uv-Spectrophotometry. Int. Res. J. Pharm. 2020; 11 (12)
21. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug development and industrial pharmacy. 2004 Jan 1; 30(5): 429
22. Puttewar TY, Kshirsagar MD, Chandewar AV, Chikhale RV (2010) Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin. J King Saud Univ Sci 22: 229–240
23. Manivannan R. Oral disintegrating tablets: A future compaction. Drug Invention Today. 2009 Nov 1;1(1): 61-5.
24. Sohn S, Kim S, Kim Y, Kim H, Shin Y. and Yang S. A Comparison of antioxidant activity of lorean White and Red Ginsengs on H202- induced oxidative stress in HepG2 hepatoma cells. Journal of Ginseng Research, 2013, 37(4); 442-450.
25. Basu B, Aviya KR, Bhattacharya A. Development and characterization of mouth dissolving tablets of prednisolone. Journal of Pharmaceutical Investigation. 2014 Apr; 44(2): 79-102.
26. Mohanachandran PS, Krishnamohan PR, Fels S, Bini KB, Beenu B, Shalina KK (2010) Formulation and evaluation of mouth dispersible tablets of amlodipine besylate. Int J Appl Pharm; 2(3): 1–6
27. British Pharmacopoeia Commission. Formulated Preparation, specific monograph, Orodispersible Sidenafil Tablet. 1st ed. 2019.
28. Malan CE, de Villiers MM, Lotter AP. Application of differential scanning calorimetry and high performance liquid chromatography to determine the effects of mixture composition and preparation during the evaluation of niclosamide–excipient compatibility. J Pharm Biomed Anal. 1997; 15: 549–57.
29. Smith A. Use of thermal analysis in predicting drug–excipient interactions. Anal Proc. 1982; 19: 559–61.

Cite this article as:
Pujari Vijayanand, Sanikop Vandana, Surve Rashmi. Formulation and Evaluation of Orodispersible Tablet Containing Combination of Phosphodiesterase-5 Inhibitor and Herbal Aphrodisiac. International Journal of Ayurveda and Pharma Research. 2023;11(2):13-30.
https://doi.org/10.47070/ijapr.v11i2.2700
Source of support: Nil, Conflict of interest: None Declared

***Address for correspondence**
Dr. Pujari Vijayanand
Department of Pharmaceutics, Rani Chennamma College of Pharmacy, Belagavi, Karnataka, India.
Email: vijay.rccp@gmail.com
Mob: 9542185209