Formulation and Evaluation of Sublingual Tablet of Desvenlafaxine for Antidepressant Activity.

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ABSTRACT:

The objective of the present study is to formulate and evaluate the mouth-dissolving sublingual tablet of Desvenlafaxine by direct compression method.The sublingual tabletwas manufactured using a direct compression method and using various super disintegrant concentrations. Superdisintegrant such as Sodium starch glycolate (SSG) and Croscarmellose sodium (CCS) is used. IR Spectroscopy and Differential scanning calorimetry were used to conduct compatibility tests on drugs and polymers. The tablet was evaluated for pre-compression studies such as Tapped density, Bulk density, Angle of repose, Carr's index, and Hausner's ratio &post-compressions studies like Hardness, Thickness,Weight variation, Friability, Wetting time, Drug content, Disintegration time and In vitro drug release study.There was an interaction between drug-polymerin accordance with FTIR spectra and DSC studies.Precompression variables passed pharmacopoeial specifications and were all within acceptable ranges. An optimized formulation is an F3 batch among all theformulations. The obtained results showed that the disintegration time of the optimized batch (was 30 sec.to 68 sec). The best in vitro drug release was found to be in the F3 batch is102%.Sublingual tablets of Desvenlafaxine were successfully prepared by using two different super disintegrants with good bioavailability.

KEYWORDS: Sublingual tablet, Desvenlafaxine, Superdisintegrant, Depression

INTRODUCTION:

Sublingual tablets are a form of medication that is designed to dissolve under the tongue for absorption, rather than being swallowed and absorbed through the digestive system. This method allows the medication to enter the bloodstream more quickly, as the membrane under the tongue is highly permeable[1].The parenteral method accelerates drug permeation while the oral route provides convenience. Subsequently, it's unable to make use of painful parenteral injections or the oral route's first-pass metabolism[2, 3, 4]. Drug mobility is facilitated more effectively in the sublingual region than in other

parts of the oral cavity because it has a thin epithelial surface and abundant blood supply[5, 6].By delivering drugs sublingually, first-passmetabolism can be avoided, and thereby fast drug absorption into the bloodstream.

Sublingual drug administration allows direct systemic absorption of the medication without first going through the digestive tract or liver to undergo enzymatic hydrolysis. These formulations will be most beneficial to the pediatric and geriatrics who use them[7, 8].

Among the most common and well-known psychotic illnesses, depression is characterized by low self-esteem, difficulty concentrating, insomnia, a feeling of hopelessness, sadness, and thoughts of suicide after losing enthusiasm for social activities. Around 16% of people experience depression, which is the primary reason for death in more than 60% of scenarios[9]. Despite the fact that melancholy is not a life-threatening disease, reported suicide attempts have occurred in the most extreme cases[10].

Desvenlafaxine, an (SNRI) class serotonin-norepinephrine reuptake inhibitor, is the active derivative of Venlafaxine. It belongs to the class BCS class 1 medication.Desvenlafaxine was given the FDA's permission in 2008 to be used in the therapy of severe depressive disorder[11]. Desvenlafaxine is also used to manage migraine headaches, vasoconstrictor signs of postmenopausal, and anxiousness[12].

Sublingual tablet advantages:

1. **Faster onset of action**: Drugs that are administered sublingually are absorbed directly into the bloodstream, bypassing the digestive system and liver, leading to more rapid onset of action.
2. **Better bioavailability:** By avoiding the digestive system and liver, drugs administered sublingually can maintain their chemical structure better and not be metabolized as much, increasing their bioavailability.
3. **Avoiding first-pass metabolism:** The first-pass metabolism that occurs when drugs are administered orally can lead to the breakdown of some of the active drug before it reaches the systemic circulation. By administering drugs sublingually, this metabolism can be avoided.
4. **Easy and convenient administration:** Sublingual tablets are small and easy to administer, making them a convenient option for patients who have difficulty swallowing pills or who need fast-acting medication.
5. **Precise dosing:** Sublingual tablet doses can be easily measured and adjusted, leading to more accurate and precise dosing.
6. **Reduced side effects:** Sublingual drug administration allows for lower doses of medication to be used, reducing the potential for side effects.

MATERIAL AND METHODS

Materials:

A gift sample of Desvenlafaxine was received from Lupin Limited,Verna-Goa, India. Sodium Starch Glycolate, Microcrystalline Cellulose, Mannitol, Sucrose, and Talc.All other chemicals used were of the highest analytical grades.

Methods:

Desvenlafaxine sublingual tablets were manufactured using the direct compression technique employing a variety of super disintegrants, including Sodium Starch Glycolate (SSG) and Croscarmellose Sodium (CSS).Fillers like microcrystalline cellulose (MCC) were used to make the tablets. Mannitol is used as a diluent and the flavoring agent is sucrose. The preparation of all nine batch of formulations involved the usage of different concentrations of super disintegrants, such as CSS and SSG.

All of the components were thoroughly mixed in a porcelain pestle and mortar before being passed through Sieve No. 80 to obtain fine particles.

The resulting mixture was then compressed into tablets using a 10-station single-punch rotating Rimek Minipress-11 MT made by Karnavati Engineering Ltd. Tablets were manufactured using a flat-faced punch with a 10mm diameter their hardness ranged from 3.04 to 4.2 kg/cm2. The approximate 200mg weight of each of the 25mg drug-containing formulations F1 through F9 was produced using a punch.

Optimization:

The super disintegrant ratio is optimized by using the central composite factorial designs. The quantity of the super disintegrant, either Sodium starch glycolate or Croscarmellose sodium, was selected as an independent factor. The -1 and +1 values of each component were evaluated and shown in Tables 1 and 2.

Table 1: Table for batch design

Levels	Low value (-1)	Medium value	High value (+1)
Sodium Starch Glycolate	5	0	8
Croscarmellose Sodium	1	0	5

Table 2: Formulation batches of Superdisintegrant as per Central Composite factorial Design:

Run	Factor 1	Factor 2
	Sodium Starch Glycolate	Croscarmellose Sodium
	mg	mg
1	0	0
2	+1	0
3	-1	+1
4	-1	+1
5	+1	-1
6	+1	+1
7	-1	0
8	-1	0
9	0	-1

Table 3: Formulation Composition Table of Sublingual Tablet of Desvenlafaxine

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	25	25	25	25	25	25	25	25	25
CCS	**0**	**0**	**+1**	**+1**	**-1**	**+1**	**0**	**0**	**-1**
SSG	**0**	**+1**	**-1**	**-1**	**+1**	**+1**	**-1**	**-1**	**0**
Mannitol	100.25	91.76	93.18	97	95	91	98.83	96	101
MCC	50	50	50	50	50	50	50	50	50
Sucrose	15	15	15	15	15	15	15	15	15
Talc	6	6	6	6	6	6	6	6	6
Total**(mg)**	200	200	200	200	200	200	200	200	200

All quantities in table are being expressed in mg. Quantities for the CCS and SSG are coded.

PRE-FORMULATION EVALUATION:

An infrared Fourier-transform spectroscopy (FT-IR) study was conducted to determine the drug's purity and analyze its interaction with the active components. The melting point was determined using the capillary method.

Evaluation prior to compression:

The Angle of repose, Carr's index, and Hausner's ratio were used to characterize the powder flow properties.

POST-FORMULATION [4-8]:

Weight Variation Test:

A uniformity test was performed according tothe procedure to determine the weight's uniformity. After compression, the average weight of 20 randomly selected tablets from each formulation was determined using an analytical balance. By comparing the individual weights with the average, the weight variance is calculated.

Hardness test:

A Monsanto hardness apparatus was used to measure each tablet sample's strength. The hardness was given in kg/cm^2 measurements. The hardness of three randomly selected tablets was measured. The average was calculated.

Friability Test:

The % friability of tablets was calculated with a Roche friabilitor (Electrolab). 20 previously weighted tablets were rotated at a speed of 25 rpm for 4 minutes. Prior to and following observations, the weight reduction of the tablets was calculated using the followingformula.

$$\%\mathbf{Friability} = \text{Initial weight of tablet} - \text{Final weight of tablet} / \text{Initial weight of tablet} * 100$$

Thickness:

The thickness of the tablet is important in order to keep uniformity in tablet measurements. The thickness was measured with Vernier Calipers. 10 tablets from each batch were tested for thickness.

Drug content uniformity:

Randomly selected five tablets from each batch were thoroughly crushed, and a powder containing equivalent to 100 mg of the drug desvenlafaxine was measured and diluted in 100ml of a solution containing phosphate buffer at pH 6.8. The mixture was stirred up vigorously. Whatman No. 41 filter paper was used in filtration to remove the insoluble substance. After that, the dilutions were repeated. The absorbance of thesolutions was measured at 224 nm. The drug content was calculated using the Desvenlafaxine standard calibration curve in a phosphate buffer solution at pH 6.8.

Wetting Time:

In a Petri dish with an interior diameter of 8.5 cm and 6 ml of a buffer solution with a pH of 6.8, a piece of tissue paper that was twice folded has been placed inside. In seconds after being placed on this paper, the time that it required for the tablet to become fully wet was noted.

Disintegration Test:

*In-Vitro*disintegration test was determined using the disintegration test apparatus. The apparatus was operated using pH 6.8 simulated saliva buffer solution maintained at 37±2°C as the immersion liquid, and each of the 6 sections of the basket had one tablet and a disc in it. The time in seconds required for the tablet to fully dissolve was recorded once there was no visible mass remaining inside the instrument.

In- vitro drug release study[13]:

*In-Vitro*drug release was calculated using USP-II dissolution testingapparatus (Paddle method). At 37°C and 50 rpm, the dissolution test was conducted using 900 ml of 6.8 pH phosphate buffer. At 5, 10, 15, 20, 25, and 30 minutes, a sample (5 ml) of the fluid was removed from the dissolution test apparatus. The samples were replaced witha fresh solution of the same volume. The samples had been filtered through whatman filter paper No. 40 before being subjected to a UV spectroscopic analysisat 224 nm for the content of Desvenlafaxine. The % of drug release was determined using data from the calibration graph.

RESULT AND DISCUSSION:

The Central Composite Design was used to design and formulate 9batchesofsublingual tablet ofDesvenlafaxine. Independentvariables such as sodium starch glycolate and croscarmellose sodium concentration were selected.

Pre-formulation studies:

λmax of Desvenlafaxine stock solution in Phosphate Buffer pH 6.8 by UV spectrophotometer was found at 224 nm. For determination of calibration curve, concentration of 2–10 µg/ml were prepared. R^2 was found to be 0.9994.

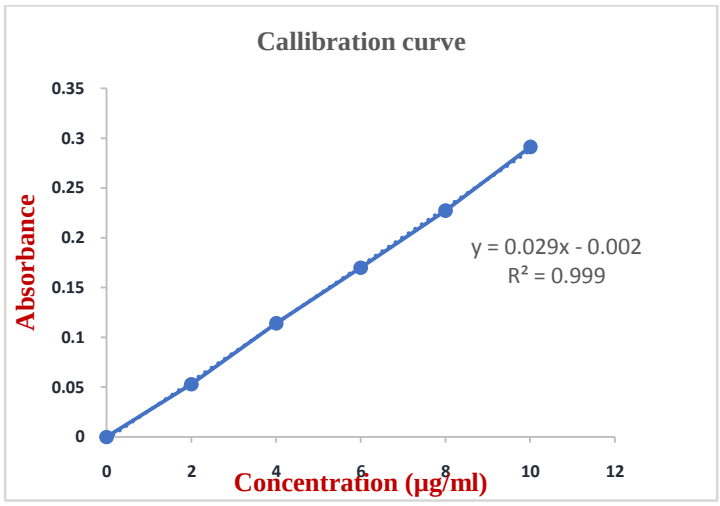

Fig. 1: Standard Calibration curve of Desvenlafaxine in pH 6.8

Compatibility studies:

Drug excipient compatibility studies were performed using an FTIR study drug for compatibility both individually and in combination with super disintegrant and physical mixtures. Both the pure drug and drug-excipientmixtureshowed that there is no chemical interaction between the drug and the super disintegrant used in the formulation.

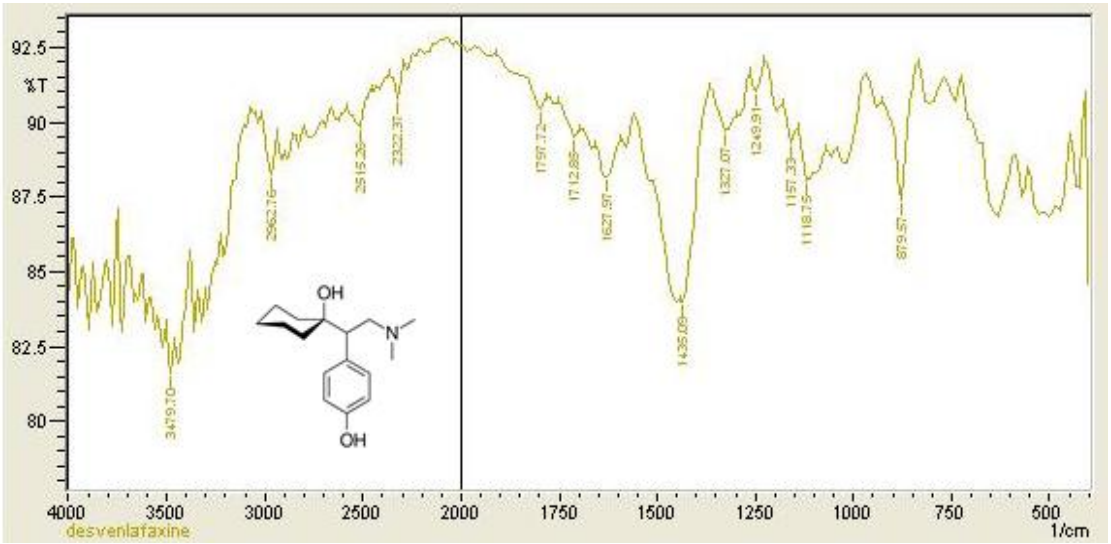

Fig.2: FTIR Spectra of Desvenlafaxine

Table 4: FTIR Spectrum data of Desvenlafaxine

Sr. No.	Functional groups	Wave Number (cm^{-1})
1	-OH group	3479
2	-CH, Ar	2962
3	C=C, Ar	1627
4	C-C Aliphatic	1249

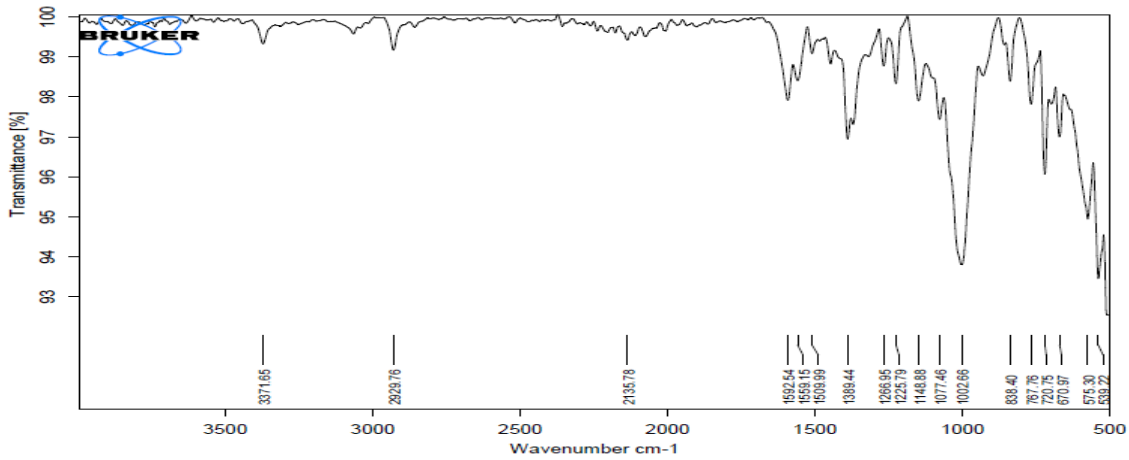

Fig. 3: FTIR Spectra of Desvenlafaxine and SSG

Table 5: FTIR Spectrum of Desvenlafaxine and Sodium Starch glycolate

Sr.No.	Functional group	Wavenumber in cm^{-1}
1	-OH group	3371
2	C-H, Ar	2929
3	C=C	1592
4	C-O-C	1002

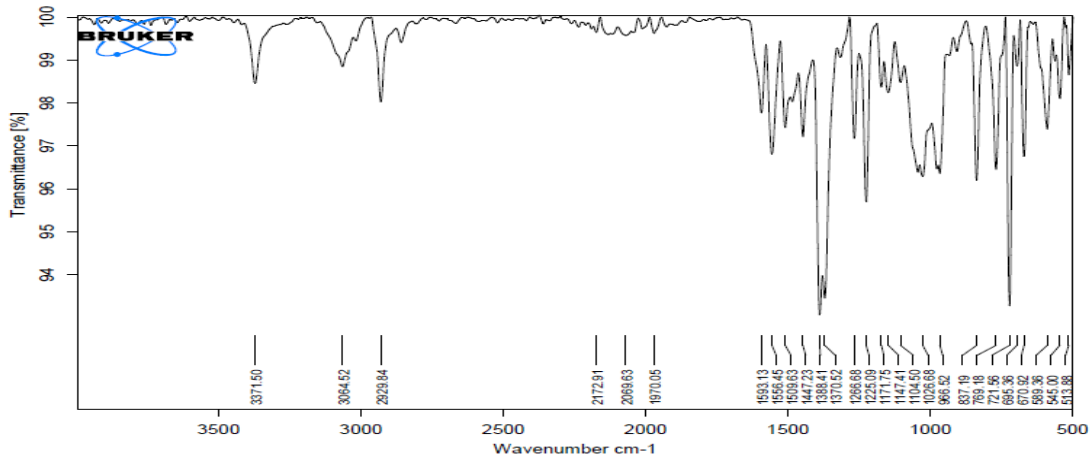

Fig. 4: FTIR Spectra of Desvenlafaxine and CCS

Table 6: FTIR Spectrum of Desvenlafaxine and Croscarmellose Sodium

Sr.No.	Functional group	Wavenumber in cm^{-1}
1	-OH group	3371
2	C-H, Ar	2929
3	C=C	1593
4	C-O-C	1026

Differential scanning calorimetry:

The DSC thermogram of pure Desvenlafaxine shows the peak at 129^0C-136^0C, respectively, which indicated the melting point that was documented in the literature. The drug's melting point did not significantly change. Consequently, there was no interaction between the superdisintegrant and the drug.

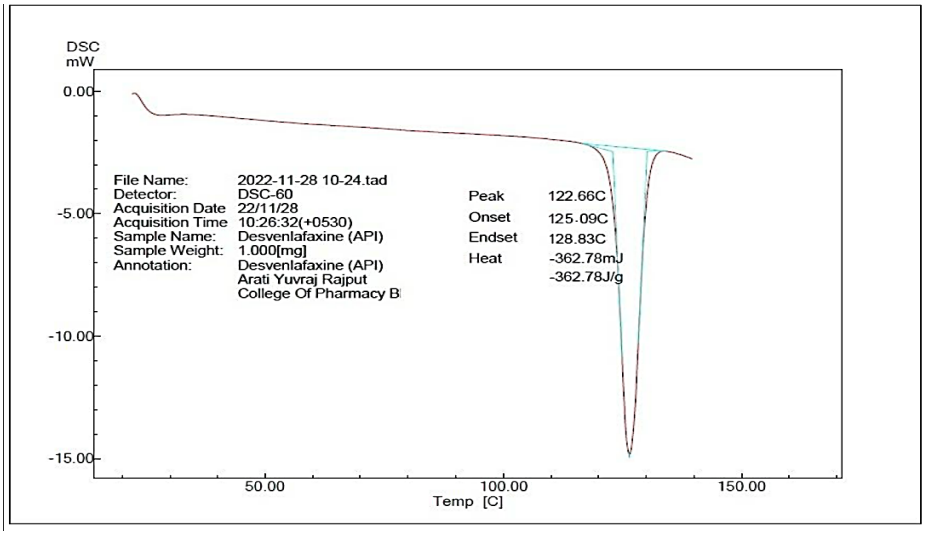

Fig. 5: Differential Scanning Calorimetry

Table 7: Evaluation of Flow properties of powder:

Parameter	F1	F2	F3	F4	F5	F6	F7	F7	F9
Bulk density (gm/ml)	0.34± 0.02	0.31± 0.01	0.29± 0.012	0.31± 0.01	0.35±0. 013	0.37± 0.015	0.37± 0.014	0.38± 0.01	0.36± 0.01
Tapped density(mg/ml)	0.42± 0.015	0.30± 0.01	0.34± 0.15	0.41± 0.017	0.40±0. 014	0.40± 0.011	0.40± 0.011	0.43± 0.015	0.41± 0.02
Angle of Repose (0)	31.55± 0.012	23.22± 0.02	30.40± 0.12	28.5±0. 3	28.02±0 .02	24.69± 0.01	25.40± 0.015	28.43± 0.90	27.54± 1.55
Carr's index (%)	13.52± 0.11	15.31± 0.01	7.56± 0.16	16.13±0 .09	11.17±0 .013	7.5±0.08	7.5± 0.07	17.23± 1.09	14.55± 3.16
Hausner's ratio	1.58± 0.13	1.16± 0.015	1.07± 0.17	1.21±0. 014	1.13± 0.025	1.08± 0.011	1.08± 0.011	1.24± 0.04	1.17± 0.03

Table 8: Post-Compression Study Result:

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm) ±SD	2.81± 0.012	2.85± 0.013	2.26± 0.014	2.79± 0.015	2.22± 0.017	2.69± 0.019	2.53± 0.030	2.32± 0.026	2.85± 0.17
Hardness (Kg/cm^2) ±SD	3.4± 0.18	3.3± 0.23	3.1± 0.16	3.7± 0.16	3.8± 0.19	3.6± 0.19	3.9± 0.20	4.1± 0.22	3.8± 0.21
% Friability (%)±SD	0.75± 0.018	0.77± 0.019	0.40± 0.022	0.50± 0.016	0.73± 0.018	0.43± 0.027	0.45± 0.030	0.60± 0.016	0.38± 0.005
Weight variation (mg) ±SD	202± 0.54	198± 1.04	199± 0.55	201± 0.80	206± 1.05	198± 0.78	210± 1.05	220± 0.90	200± 1.06

Table 9: Other Evaluation Parameter:

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Disintegration Time (sec)	58	52	30	39	44	32	57	50	60
Wetting Time (sec)	69	62	38	45	52	40	68	57	72
Drug content(%)	97.05	98.77	99.98	99.34	97.17	95.9	98.91	96.88	98.89

The weight and hardness of the tablets were found to be in a range from 190 to 200 mg and 3.1 to 4.1 mm, respectively. The composition with the greatest tapped density overall is shown to be the F3 batch.Each tablet's friability value ranged from 0.5 to 0.8%. The tablets from Formulation F3 were less hard than other formulations.

Wetting time:

Wetting time and the tablet's internal structure are closely related. Table No.9 illustrates the wetting time result. Each formulation demonstrated fast wetting in the time range of 38 to 69 seconds.

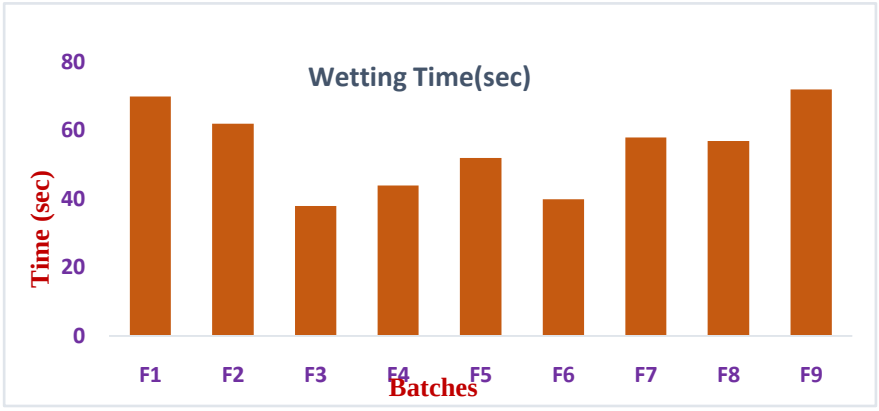

Fig.7: Wetting Time Profile of Desvenlafaxine Formulation F1 To F9

Disintegration Time:

Sublingual tablets should dissolve more quickly because they should completely dissolve in a short time.The disintegration time in the formulations F1 to F9 was found to be between 30 and 60 seconds by using various super disintegrants. Table 9 and Fig. 8 show the data. The batch F3 tablets showed the best results, demonstrating a 30-second disintegration time.

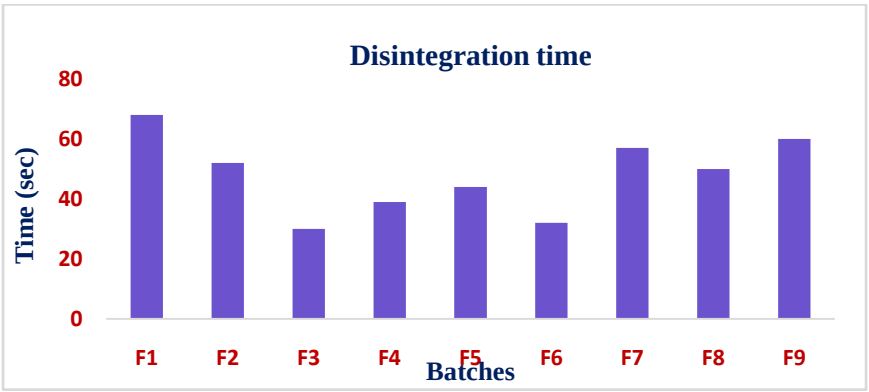

Figure8:Disintegration Time Profile of Desvenlafaxine Formulations F1 To F9

Table 10*: In-vitro* drug release studies of sublingual tablets of Desvenlafaxine:

Sr.No.	Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**5**	15.33	19.58	22.86	24.64	23.85	25.22	21.14	25.75	26.03
2	**10**	28.16	27.12	44.73	38.64	29.78	38.47	41.99	39.99	44.65
3	**15**	36.91	39.83	54.43	51.45	44.59	59.31	54.36	53.65	50.61
4	**20**	54.38	53.36	72.91	64.13	57.51	68.11	68.16	67.55	63.95
5	**25**	68.84	58.95	87.33	81.86	73.67	83.44	84.37	81.49	80
6	**30**	83.90	85.42	102	99.29	94.89	97.17	95.9	98.91	93.25

In-vitro release study:

Graphical data for the *In-vitro* drug releasegiven in Fig.9.For formulations F1 to F9, the percentage of drug release was determined to be 15.33% to 102% over the period of 5 to 30 minutes. In formulation F3, the maximum percentage of drug release was determined to be 102% over a 30-minute period.The percentage of drug release increased with an increase in the concentration of the super disintegrant Croscarmellose sodium, according to the studies mentioned above. Formulation F3 showed the best in-vitro drug release of any of the formulations (F1 to F9), with increased croscarmellose concentration as a result of its rapid disintegration.

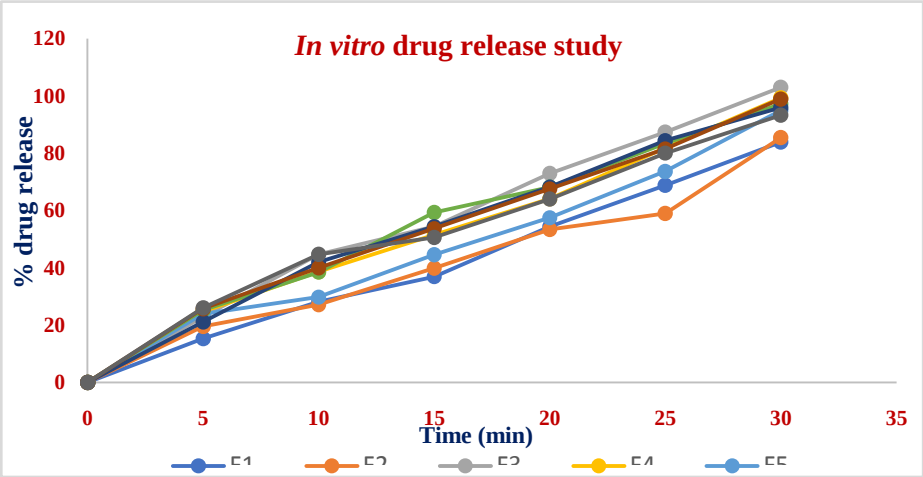

Figure. 9: In-Vitro Dissolution Time of Desvenlafaxine Formulations F1 to F9

Stability Study:

According to the results of the in-vitro disintegration time and wetting time tests, along with their high cumulative % drug release, the formulation F3 batch was selected for stability studies. The tablet was stored according to the ICH guidelines [40 ^{0}C±2 ^{0}C and 75 ± 5%RH (Q1C)]. There was no physical parameter variance in this formulation**.**

CONCLUSION:

Desvenlafaxine BCS first class of drug used in the treatment of depression, anxiety, stress, and psychological disorder. It belongs to the SNRI (serotonin-norepinephrine reuptake inhibitor) family of antidepressants and is administered orally. To get fast relief from depression, an effort was put into in the present research to make Desvenlafaxine sublingual tablets using various super disintegrants. Each of the nine formulations contained 25 mg of the drug along with 2 differentsuper disintegrants at different ratios. The data from the pre-andpost-formulation tests were acceptable. Further, formulation no. F3 was determined to be the best formulation and was kept for three months of stability testing. The formulation was constant, according to the observations of the stability studies. The Desvenlafaxine sublingual tablet that dissolves in the mouth has a faster onset of action, immediate release, maximal absorption, and enhanced bioavailability at pH 6.8. For patients who are unable to ingest, the aged, paralyzed patients, and patients who decline to swallow like pediatric, geriatric, and psychiatric patients, they provide greater cooperation.

CONFLICT OF INTEREST:

None

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