FORMULATION AND IN VITRO EVALUATION OF EXTENDED RELEASE MATRIX TABLET FOR THE EFFECTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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ABSTRACT:

The objectives of this investigation was to prepare and evaluate an extended-release matrix tablet of Desvenlafaxine Succinate for the efficient treatment of Major Depressive Disorder (MDD). Major Depressive Disorder (MDD) is a chronic condition requiring long-term treatment. Desvenlafaxine Succinate was chosen for this study due to its dual serotonin-norepinephrine reuptake inhibition (SNRI) action, stable pharmacokinetics, strong clinical efficacy, and better tolerability compared to other antidepressants. The matrix tablets of Desvenlafaxine Succinate were prepared by using hydrophilic polymers like Hydroxypropyl Methylcellulose (HPMC K100M, HPMC K15M), MCC, Talc, Colloidal Sillicon Dioxide, Magnesium stearate by direct compression. Core tablets further film coated with opadry II brown to hide bitter taste of Desvenlafaxine Succinate. A total of ten formulations (F01–F10) were prepared and evaluated for physical parameters and in vitro drug release in 0.9% NaCl in water. Out of them, batch F04 showed better drug release up to 24 hours, with a close similarity to the innovator product (Pristiq®). ICH stability study (Q1R2) confirmed the physicochemical stability of the optimized formulation. The ER matrix tablet successfully mitigated common side effects associated with peak plasma levels of Desvenlafaxine and improved patient compliance. These results indicate that the developed ER matrix formulation is a potential approach to sustained drug delivery in MDD treatment.

KEYWORDS: Desvenlafaxine Succinate, Extended-release, Matrix tablet, direct compression, Major Depressive Disorder, HPMC K100M, In vitro drug release

1. INTRODUCTION:

The phrase oral drug delivery refers to the delivery of a dosage form orally for local action or systemic absorption along the gastrointestinal (GI) tract. Oral drug delivery has been the most widely utilized route of administration for decades due to the fact that it is noninvasive, convenient, pain avoidance and patient compliance is high.. The traditional drug delivery systems have been characterized by immediate release and high frequency dosing of the drug, which may lead to the risk of fluctuation of doses thus, there is a need for formulation with controlled release that is experiencing a very constant or equated blood level. [1] [2] Modified release drug delivery systems are new drug forms which enable control over the rate and site of medication which release in the body.[3] Extended release drug delivery system is intended to produce a long-lasting therapeutic effect by releasing medication continuously over a long

period of time following administration of a single dose. This could improve patient compliance by reducing dosing frequency and could enhance therapeutic efficacy by maintaining more consistent drug levels in the bloodstream. [4] Major Depressive Disorder (MDD) or depression is a serious and prevalent mental disorder that affects mood, cognition, and physical function and requires chronic treatment. [5] Desvenlafaxine is an antidepressant that is an FDA-approved drug to treat major depressive disorder in adults. Desvenlafaxine Succinate was chosen for this study since it possesses dual serotonin-norepinephrine reuptake inhibition (SNRI) activity, stable pharmacokinetics, strong clinical efficacy, and enhanced tolerability in comparison to other antidepressants. This double-barreled activity is more effective than SSRIs, particularly in patients with symptoms of fatigue, loss of initiative, or poor thinking, which involve norepinephrine dysfunction. [6] By providing consistent drug levels, the extended-release provides easier treatment, lessens side effects, and improves the total therapeutic experience.

2. MATERIALS AND METHODS:

2.1 MATERIALS

Desvenlafaxine Succinate was obtained from Hetero Drugs Limited, Bonthapally. Hypromellose 2208 (Methocel K100M Premium CR) and Hypromellose 2208 (Methocel K15M Premium CR) were obtained from Dow Chemical company. Microcrystalline cellulose, (Microcel 102 SD) was obtained from Crest Cellulose Private Limited. Colloidal silicon dioxide, (cab-o-sil, grade M5) was obtained from Cabot Sanmar limited. Talc (Luzenac Pharma) was obtained from Imerys. Magnesium Stearate (LIGA-MF-2- V) was obtained from Peter Greven and Opadry II Brown was obtained from Colorcon.

2.2 METHODS:

Preformulation study:

Physical characterization of API sample:

The API sample was observed visually and viewed under microscope for the determination of its nature and then the result were compared with the official book. Then sample was evaluated for its colour, taste and odour. Melting point of Desvenlafaxine Succinate sample was determined by using DSC method using a DuPont 2100 thermal analyzer system. Content of water was measured on 0.5 gm of sample of Desvenlafaxine Succinate by Karl's Fischer titration method. Solubility study was carried out in various media such as 0.9 % NaCl in water,

0.1 N HCl, pH 4.5 Acetate buffer, pH 6.8 phosphate buffer, Distilled water. Flow of API was determined with the assistance of Bulk density, Tapped density, Carrs' (Compressibility) index, Hausner's ratio, Angle of repose.

Analytical characterization of API Desvenlafaxine Succinate:

Scanning of Desvenlafaxine Succinate in 0.9 % NaCl in water

10 ug/ml solution of Desvenlafaxine Succinate in 0.9 % NaCl was taken and scanned in range of 400-200 nm against 0.9 % NaCl in water as a blank using UV spectrophotometer.

Calibration curve of Desvenlafaxine Succinate 0.9 % NaCl in water:

Accurately weighed 100 mg of Desvenlafaxine Succinate and transfer into 100 ml volumetric flask and dissolve in suitable quantity of 0.9 % NaCl in water and lastly make the volume up to 100 ml using 0.9 % NaCl in water to obtain a 1000 µg/ml concentration stock solution.

About 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml of this stock solution (1000 µg/ml) was taken in 100 ml volumetric flask and diluted to 100 ml with 0.9 % NaCl in water solution to get 5 to 25 µg/ml drug concentration. Then they were analyzed spectrophotometrically by measuring the absorbance at 224 nm. A calibration curve of concentration Vs absorbance was plotted and its intercept and slope value were calculated. [7]

Drug excipient compatibility study:

Knowledge of drug-excipients interactions is very important to the formulators in selecting appropriate excipients with API. Compatibility between API and excipients were performed by preparing compatibility blends at different ratio of different excipients with API, based on the tentative average weight of tablet. The blends were stored in both open and close conditions at 25 ± 2°C/ 60 ± 5%RH and 40 ± 2°C/ 75 ± 5%RH in glass vials for 4 weeks and physical observation has been carried out visually. [8]

Formulation:

Desvenlafaxine Succinate, Hypromellose 2208 (Methocel K100M Premium CR), Hypromellose 2208 (Methocel K15M Premium CR), Microcrystalline cellulose, (Microcel 102 SD), Colloidal silicon dioxide, (cab-o-sil, grade M5), Talc (Luzenac Pharma) were weighed accurately using calibrated weighing balance. Co-shift above ingredient from sieve no. #30. Add above material into blender and blend of 15 minutes. Weight and shift Magnesium Stearate (LIGA-MF-2V) from sieve no. #60. Add shifted material into blender and lubricaed for 5 minutes. Then lubricated blend was compressed into tablet using 10.5 mm, round shape, bevel edge, biconvex punches, embossed with “D64” on upper punch and “H” on lower punch. Then core tablets were further film-coated with Opadry II brown. Finally Brown, round shaped, bevel edged biconvex film coated tablets, deposed with “D64” on one side and “H” on other side were prepared

Table No 1: Formulation trial of batch F01, F02, F03, F04, F05

Sr. NO.	Name of ingredient	F01 (mg/tab)	F02 (mg/tab)	F03 (mg/tab)	F04 (mg/tab)	F05 (mg/tab)
	Intra-granular material (Pre-lubrication)					
1	Desvenlafaxine succinate, USP	152	152	152	152	152
2	Hypromellose 2208 USP (Methocel K100M Premium CR)	75	100	150	175	200
3	Microcrystalline cellulose (Microcel 102 SD) USP-NF	136	111	61	36	31
4	Talc (Luzenac Pharma), USP	4	4	4	4	4
5	Colloidal silicon dioxide, (Cab-o-sil, grade M5), USP-NF	4	4	4	2	2
	Extra-granular material (Lubrication)					
6	Magnesium stearate (LIGA-MF-2-V), USP-NF	4	4	4	6	6
	Core Tablet Weight (mg)	375	375	375	375	375
	Sub-Coating (20%w/w solids)					
7	Opadry II Brown 85F565406-CN, IH	11.25	11.25	11.25	11.25	11.25
8	Purified water	45	45	45	45	45
	Sub coated Tablet Weight (mg)	386.25	386.25	386.25	386.25	386.25

Table No 2: Formulation trial of batch F06, F07, F08, F08, F09, F10

Sr. NO.	Name of ingredient	F06 (mg/tab)	F07 (mg/tab)	F08 (mg/tab)	F09 (mg/tab)	F10 (mg/tab)
	Intra-granular material (Pre-lubrication)					
1	Desvenlafaxine succinate, USP	152	152	152	152	152
2	Hypromellose 2208 USP (Methocel K100M Premium CR)	180	-	-	75	100
3	Hypromellose 2208 USP (Methocel K15M Premium CR)	-	100	200	75	100
4	Microcrystalline cellulose (Microcel 102 SD) USP-NF	31	111	11	61	11
5	Talc (Luzenac Pharma), USP	4	4	4	4	4
6	Colloidal silicon dioxide, (Cab-o-sil, grade M5), USP-NF	2	2	2	2	2
	Extra-granular material (Lubrication)					
7	Magnesium stearate (LIGA-MF-2-V), USP-NF	6	6	6	6	6
	Core Tablet Weight (mg)	375	375	375	375	375
	Sub-Coating (20%w/w solids)					
8	Opadry II Brown 85F565406-CN, IH	11.25	11.25	11.25	11.25	11.25
9	Purified water	45	45	45	45	45
	Sub coated Tablet Weight (mg)	386.25	386.25	386.25	386.25	386.25

Evaluation Studies:

Pre-compression evaluation parameters:

The powder blend of all formulations were evaluated for bulk density, tapped density, carr's index, hausner's ratio and angle of repose to determine its flow properties during compression.

Bulk density:

Apparent bulk density was determined by pouring the powder blend into a measuring cylinder and measuring the volume and weight and bulk density was determine by using formula

$$\mathbf{Db} = \frac{\mathbf{M}}{\mathbf{Vb}}$$

Tapped density:

The pre-weighed powder was filled in measuring cylinder. Then it was tapped in automated bulk density test apparatus. Carry out 10, 500, and 1250 taps on the same powder blend and read the corresponding volumes V10, V500, and V1250. If the difference between V500 and V1250 is less than or equal to 2 ml, V1250 is the final tapped volume. Tapped density was determined by [9]

$$\mathbf{Db} = \frac{\mathbf{M}}{\mathbf{Vt}}$$

Carr's index:

Tapped density (Dt) and bulk density (Db) of powder material was used to measure compressibility of a powder material. It was measure used to describe compression capability of the powder material. Carr's index was determined using following equation

$$\textbf{Carr's index} = \frac{\mathbf{Dt-Db}}{\mathbf{Dt}} \mathbf{X\ 100}$$

Hausner's ratio:

The Hausner's ratio is a number that measures the flowability of a powder material. It is calculated by dividing the tapped density of a material by its bulk density:

$$\mathbf{HR = \frac{Dt}{Db}}$$

Angle of repose:

The angle of repose was determined by using the funnel method. The accurately weight powder blend were taken in the funnel and tip of funnel was blocked by thumb at initially. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend (Almost 2 cm was fix from plane to tip of funnel). The powder blend was allowed to flow through the funnel freely on to the surface.. It is a measure used to describe flow ability of the powder material. The equation for determining angle of Repose, θ, is [10]

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

Post-compression evaluation parameters of finished product:

Weight variation:

The weight of the tablet was measured with the help of digital electronic balance. For determination of weight variation, ten tablets were selected randomly from a batch and average weight was determined.[11]

Thickness:

Ten tablets were selected in a batch for the determination of thickness variation with Vernier Caliper. [12]

Hardness:

Adequate hardness is necessary to withstand the mechanical shock of manufacturing packaging and shipping, and to ensure consumer acceptance. Hardness of tablet was determined using Ewereka hardness tester. The tablet was compressed between a holding ansil and a piston and digital screen showed hardness in kp.

Friability:

Friability of the tablets was determined using an Electrolab friabilator. The tablets should be carefully dedusted before testing. Accurately weigh the tablet sample and place the tablets in the drum. Rotate the drum at 25 rpm for 4 minutes, and remove the tablets.

Remove any loose dust from the surface of tablets as before and accurately weigh. Friability was determined by [13]

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial Weight}} \text{ X } 100$$

Limit: Not more than 1.0%

Percentage swelling:

The formulation showing maximum similarity with the innovator was selected along to perform swelling test in 0.9% w/v NaCl solution. Firstly weighed tablets and immersed in 500 ml of the 0.9 % NaCl and at selected time intervals the swollen tablets were collected on filter paper, the wet tablet weight was determined using analytical balance. The percentage swelling of tablets was calculated from the equation [14]

$$\textbf{Percentage Swelling} = \frac{Wt - Wo}{W0}$$

Drug content:

Five tablets were weighed individually from optimized formulation (F04), then placed in a mortar and powdered with a pestle. An amount equivalent to 100 mg drug was mixed with 100 ml of 0.9 % NaCl in water. The solution was filtered through a Whatmann filter paper (0.22 µm pore size), then diluted with 0.9 % NaCl in water and then take absorbance at 224 nm wavelength using UV spectrophotometer and the percentage of drug content was calculated by formula.[15]

$$\text{Drug Content (\%)} = \frac{\text{Actual Amount of Drug}}{\text{Theoretical Amount of Drug}} \text{ X } 100$$

In-vitro drug release studies:

In-vitro drug release studies of the Desvenlafaxine finished products were conducted using the USP Apparatus I (rotating basket method) at a stirring speed of 100 rpm. The dissolution was performed at 37 ± 0.5°C in 900 ml of 0.9% NaCl solution as the dissolution medium for 24 hours.

3 ml of sample withdrawn at interval of 1, 2, 4, 8, 12, 16, 20, 24 hours with the replacement of equal volume of dissolution media into dissolution flask. Filter the solution through 0.45

µm membrane. Dilute the sample with 0.9 % NaCl in water up to 30 ml into 100 ml volumetric flask. Then samples were analyzed at 224nm by UV spectrophotometer (UV-1800 SHIMADZU). [15]

Kinetics study:

Various kinetics models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, higuchi, Hixson-Crowell cube root law and korsmeyer-peppas release model. [16]

Similarity study:

The similarity factor (f2) was used to compare the dissolution profiles of the formulated batches with the innovator product. Similarity factor (f2) were calculated using equation and the dissolution profiles are considered to be similar when f2 value is between 50 and 100.

$$f_2 = 50 \times \log\left[\left(1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right)^{-0.5} \times 100\right]$$

Stability studies of the optimized formulation:

The selected HDPE Bottle packing formulations stored at 25°C/ 60% RH and 40°C/75% RH for 2 months and evaluated for their physical appearance and drug release at specified intervals of every month. [17]

3. RESULTS AND DISCUSSION:

Physical characterization of API sample:

Table No. 3: Physical characterization of API Desvenlafaxine Succinate (USP)

Sr. No.	Evaluation Parameters	Method Used	Observed Result
1	**Colour**	Self-observed	White to cremish
2	**State of matter**	Optical microscopy	Crystalline
3	**Odor**	Self-observed	Bitter

4	**Taste**	Self-observed	Highly Bitter
5	**Melting Point**	DSC	132 ± 3°C
6	**Water content**	KF reagent	4.5 % w/w

Solubility study:

The solubility of Desvenlafaxine Succinate (USP) in different media is presented in Table No. 4 and comparision of solubility with in solvent is shown in Figure No. 1.

Table No. 4: Solubility of Desvenlafaxine Succinate (USP) at 25^0C in different media

Sr. No.	Media	Solubility (mg/ml)
1	0.9 % NaCl in water	55.68
2	Purified Water	49.44
3	0.1N HCl	67.68
4	pH 4.5 Acetate Buffer	49.41
5	pH 6.8 Phosphate Buffer	51.63

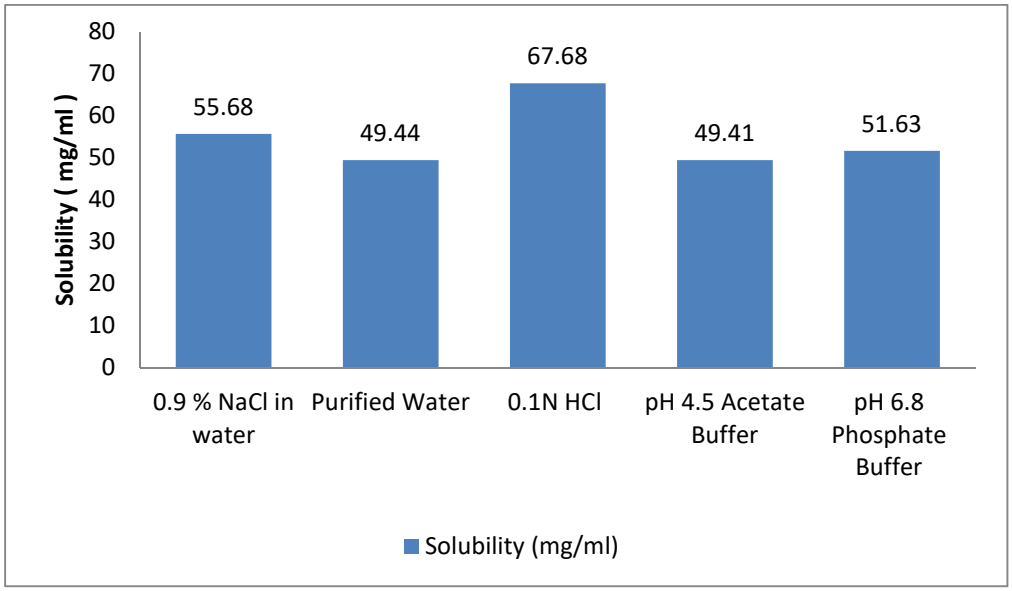

Figure No. 1: Solubility of Desvenlafaxine Succinate in different media

From table no. 4 it is showing that API have similar solubility in all the studied media store at 25°C.

Derived properties:

Table No. 5: Bulk density, Tapped density, Carr's index, Hausner's ratio, Angle of repose of API Desvenlafaxine Succinate

Sr. No	Derived properties	Results
1	**Bulk density**	0.40 gm/ml
2	**Tapped density**	0.60 gm/ml
3	**Carr's index**	33.33
4	**Hausner's ratio**	1.5
5	**Angle of repose**	57.38°

From Table no. 5 it is shown that API has **very poor flow**.

Analytical characterization of API Desvenlafaxine Succinate:

Scanning of Desvenlafaxine Succinate in 0.9 % NaCl in water

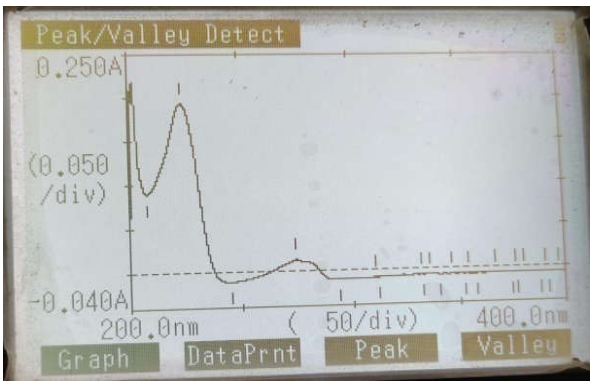

Figure No. 2: UV spectra of Desvenlafaxine Succinate in 0.9 % NaCl in water

From figure no. 2 it is found that maximum absorbance of **Desvenlafaxine Succinate** was at the wavelength **224 nm**.

Calibration curve of Desvenlafaxine Succinate 0.9 % NaCl in water:

A spectrophotometric method for estimation of Desvenlafaxine succinate, based on the measurement of absorbance at 224 nm in 0.9 % NaCl in water, gives a straight line with an equation: $y = 0.023x + 0.013$ and $r^2 = 0.999$ (Figure 3).

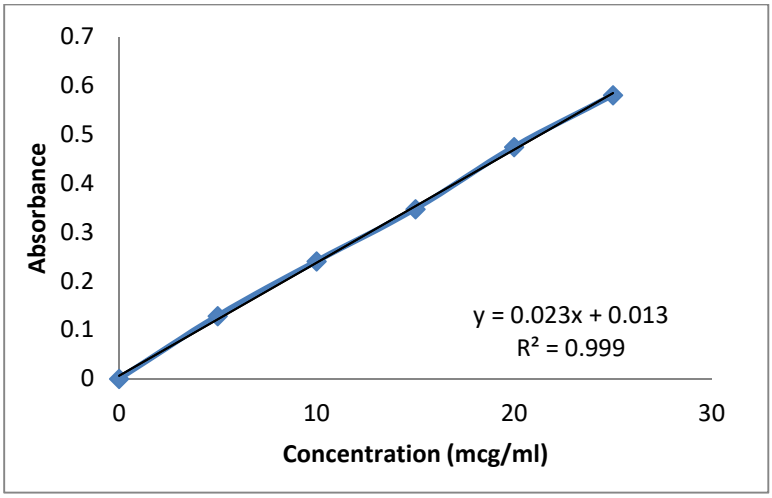

Figure No. 3: Standard calibration curve of DVS in 0.9% NaCl at 224 nm

Drug excipient compatibility study:

There was no significant physical change with any of selected excipients with API after 4 weeks of exposure at 25ºC/60%RH Open & Close and 40ºC/75%RH Open & Close conditions in vials when observed physicially.

Drug–excipient compatibility study by using FTIR spectroscopy-

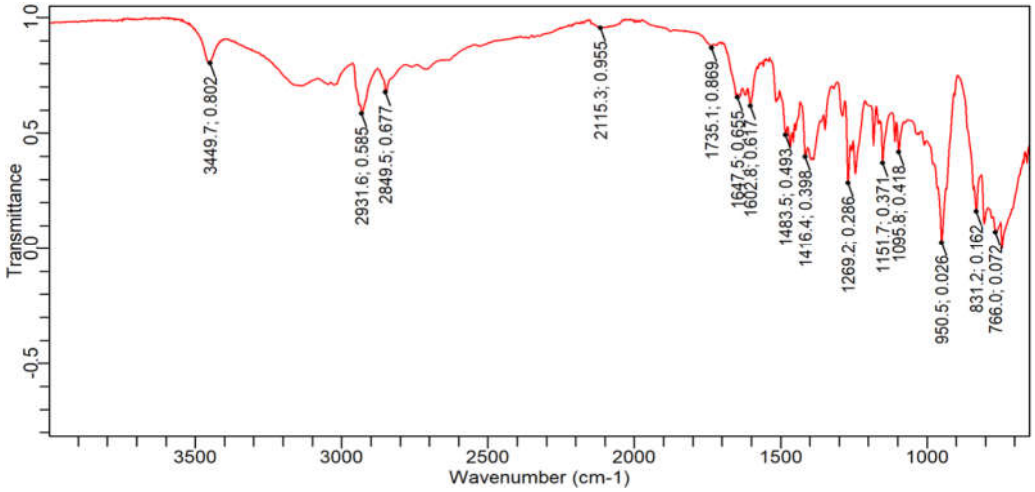

Figure No. 4: FTIR spectrum of pure API Desvenlafaxine Succinate

Table No. 6: Functional group and principle peaks present in API Desvenlafaxine Succinate

Wavenumber (cm^{-1})	Characteristics of functional groups
765.97	Aromatic C–H bending (out-of-plane)
1095.84	C–O stretching (Ether or Alcohol)
1151.75	C–O stretching (Ether or Carboxylate)
1416.39	C–H bending (Methyl or Methylene groups)
1483.48	C=C stretching (Aromatic ring)
1647.48	N–H bending (Amine) or C=O stretching (Amide)
1735.08	C=O stretching (Carbonyl group in Ester or Carboxyl)
2115.26	C≡C stretching (Alkyne) or C≡N stretching (Nitrile)
2849.55	C–H stretching (Alkane, Methyl, or Methylene groups)
3449.65	O–H stretching (Alcohol or Phenol) or N–H stretching (Amine)

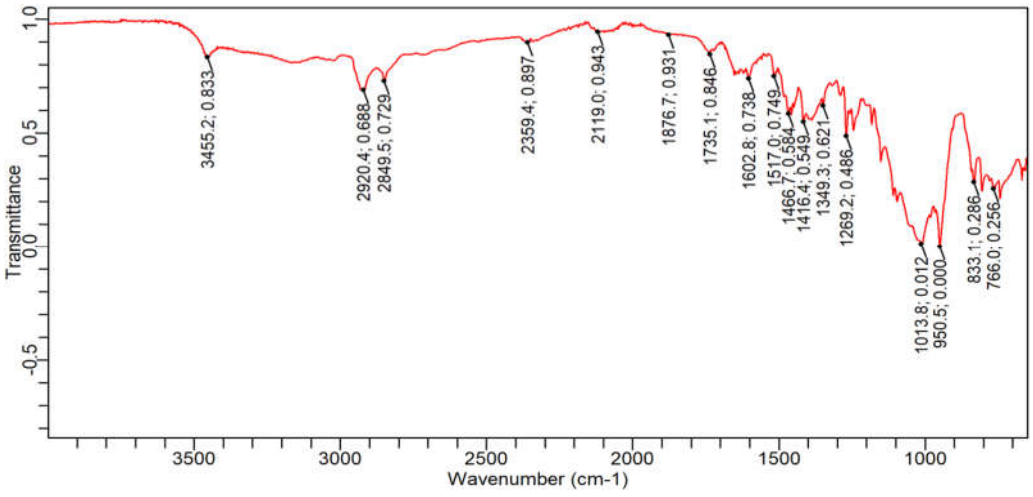

Figure No. 5: FTIR spectrum of API Desvenlafaxine Succinate and and all excipients

Table No. 7: Functional group and principle peaks present in physical mixture of API Desvenlafaxine Succinate and all excipients

Wavenumber (cm^{-1})	Characteristics of functional groups	Belongs to
765.97	Aromatic C–H bending (out-of-plane)	Desvenlafaxine Succinate
950.47	C–O stretching (Ether or Alcohol)	Desvenlafaxine, Cellulose-based excipients (Methocel, MCC)
1013.84	Si–O stretching (Silicon dioxide)	Colloidal Silicon Dioxide
1269.16	C–O stretching (Carboxylate or Ester)	Desvenlafaxine Succinate, MCC
1349.30	C–H bending (Alkane) or C–O stretching	Magnesium Stearate, MCC
1416.39	C–H bending (Methyl or Methylene groups)	Both (Desvenlafaxine, MCC, Methocel, Talc, Mg Stearate)
1466.71	CH_2 bending (Methylene groups)	Magnesium Stearate, MCC
1517.03	C=C stretching (Aromatic ring)	Desvenlafaxine Succinate
1735.08	C=O stretching (Carbonyl group in Ester or Carboxyl)	Desvenlafaxine Succinate, Magnesium Stearate
1876.71	Possibly combination band or overtone (Talc)	Talc
2849.55	C–H stretching (Alkane, Methyl, or Methylene groups)	Both (Desvenlafaxine, MCC, Methocel, Talc, Mg Stearate)
3455.24	O–H stretching (Alcohol or Hydroxyl from Cellulose, Talc)	Methocel K100M, MCC, Talc

From table no 6 and 7, FTIR spectral analysis of pure Desvenlafaxine Succinate, and its physical mixture with all excipients (Microcrystalline Cellulose, Talc, Colloidal Silicon Dioxide, Magnesium Stearate), no significant peak shifts, new interactions, or degradation products were observed. Thus, Desvenlafaxine Succinate is compatible with the selected excipients based on FTIR analysis, confirming its stability in the proposed formulation.

Evaluation Studies:

Pre-compression evaluation parameters:

From table no. 8 The evaluated powder blends (F01–F10) demonstrated varying flow properties based on their angle of repose, compressibility index, and Hausner's ratio. Most formulations exhibited passable to fair flow characteristics, indicating suitability for direct compression.

Table No. 8: Pre-compression evaluation parameters of the powder blend

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index	Hausner's ratio	Angle of repose (degree)	Flow property of powder blend
F01	0.360	0.450	20.00	1.25	36.52	Fair
F02	0.448	0.588	23.88	1.313	42.79	Passable
F03	0.508	0.667	23.73	1.311	39.80	Fair
F04	0.407	0.528	22.86	1.29	41.76	Passable
F05	0.428	0.541	20.93	1.26	41.76	Passable
F06	0.394	0.491	19.70	1.245	39.80	Fair
F07	0.391	0.472	17.19	1.2	41.76	Passable
F08	0.418	0.528	20.90	1.26	39.80	Fair
F09	0.353	0.453	22.06	1.283	37.99	Fair
F10	0.388	0.491	20.90	1.26	40.76	Passable

Post-compression evaluation parameters of finished product:

Physical parameters of batch from F01 to F10:

Table No. 9: Physical parameters of batch from F01 to F10

Formulation Code	Average Weight (mg)	Thickness (mm)	Hardness (kp)	Percentage Swelling	Drug content (%)
F01	387.5 – 391.3	4.73 – 4.76	10 - 11	256.56	97.56
F02	386.5 – 388.5	4.73 – 4.77	10 - 11	296.36	97.35
F03	387 – 390.5	4.70 – 4.75	10 - 11	354.36	98.49
F04	388 – 390.5	4.73 – 4.76	10 - 11	487.78	99.28
F05	388.5 – 391.5	4.73 – 4.77	9 - 10	489.36	97.86
F06	387 - 390	4.70 - 4.75	10 - 11	506.45	96.36
F07	386.25 - 388	4.73 – 4.76	10.5 - 11	186.63	98.36
F08	387.5 – 388	4.73 – 4.77	10 – 11.5	248.36	99.56
F09	386.25 – 390.5	4.70 – 4.75	10 – 11	564.23	97.96
F10	386.25 – 390.5	4.73 – 4.76	10 – 11.5	586.43	97.53

In-vitro drug release profile of batch F01, F02 and F03

Table No. 10: In-vitro drug release profile of batch F01, F02 and F03 in release media 0.9 % NaCl in water and comparision with innovator

Time (Hrs)	Release Specification	Innovator	F01	F02	F03
		Cumulative % drug release (Mean ± S.D.; n = 3)			
0		0	0	0	0
1	NMT 25%	15±0.5	18.03±0.4	16.05±0.1	18.03±0.1
2		24±0.4	31.08±0.4	29.10±0.2	23.17±0.2
4		39±0.2	52.04±0.6	48.08±0.5	45.71±0.1

8	50 – 75%	60±0.4	85.25±0.4	80.51±0.3	76.95±0.5
12		74±0.2	101.07±0.2	96.33±0.6	88.02±0.2
16		84±0.6	107.00±0.4	102.65±0.1	94.35±0.6
20		91±0.2	109.38±0.2	108.19±0.6	98.70±0.5
24	NLT 80%	95±0.2	108.98±0.1	112.54±0.2	103.05±0.4

Table No. 11: In-vitro drug release profile of batch F04, F05 and F06 in release media 0.9 % NaCl in water and comparision with innovator

Time (Hrs)	Release Specification	Innovator	F04	F05	F06
		Cumulative % drug release (Mean ± S.D.; n = 3)			
0		0	0.00	0.00	0.00
1	NMT 25%	15±0.5	16.05±0.8	13.29±0.3	15.26±0.2
2		24±0.4	23.96±0.4	21.20±0.8	22.38±0.1
4		39±0.2	41.36±0.9	37.01±0.5	43.34±0.6
8	50 – 75%	60±0.4	62.32±0.1	56.78±0.3	64.30±0.1
12		74±0.2	78.14±0.5	70.23±0.6	77.74±0.5
16		84±0.6	87.63±0.1	80.91±0.2	88.42±0.9
20		91±0.2	94.75±0.8	87.23±0.6	95.14±0.2
24	NLT 80%	95±0.2	99.09±0.7	91.19±0.2	98.30±0.07

Table No. 12: In-vitro drug release profile of batch F07, F08, F09 and F10

Time (Hrs)	Release Specification	Innovator	F07	F08	F09	F10
		Cumulative % drug release (Mean ± S.D.; n = 3)				
0		0	0.00	0.00	0.00	0.00
1	NMT 25%	15±0.5	24.36±0.2	19.61±0.5	12.10±0.2	10.91±0.2
2		24±0.4	33.45±0.5	27.13±0.5	21.59±0.5	18.82±0.4
4		39±0.2	51.25±0.4	46.11±0.6	32.27±0.6	29.10±0.5
8	50 – 75%	60±0.4	69.44±0.4	64.30±0.6	50.85±0.2	44.13±0.2

12		74±0.2	82.88±0.1	79.72±0.7	65.48±0.3	57.18±0.5
16		84±0.6	95.14±0.2	90.40±0.2	80.51±0.3	69.44±0.5
20		91±0.2	101.47±0.6	96.33±0.2	87.63±0.7	80.91±0.1
24	NLT 80%	95±0.2	101.07±0.2	97.91±0.2	94.75±0.3	88.81±0.3

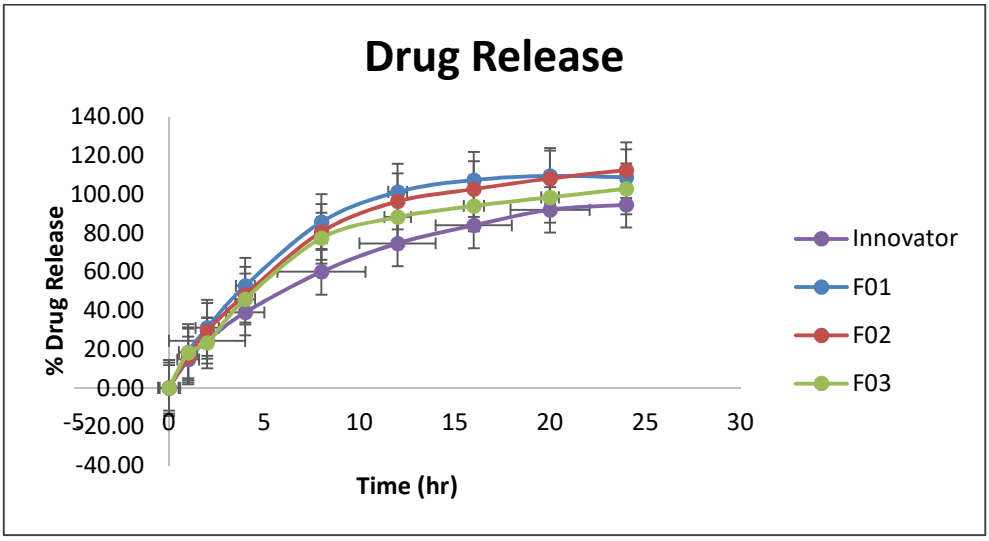

Figure No. 6: In-vitro drug release profile of batch F01, F02 and F03 in release media 0.9 % NaCl in water and comparision with innovator

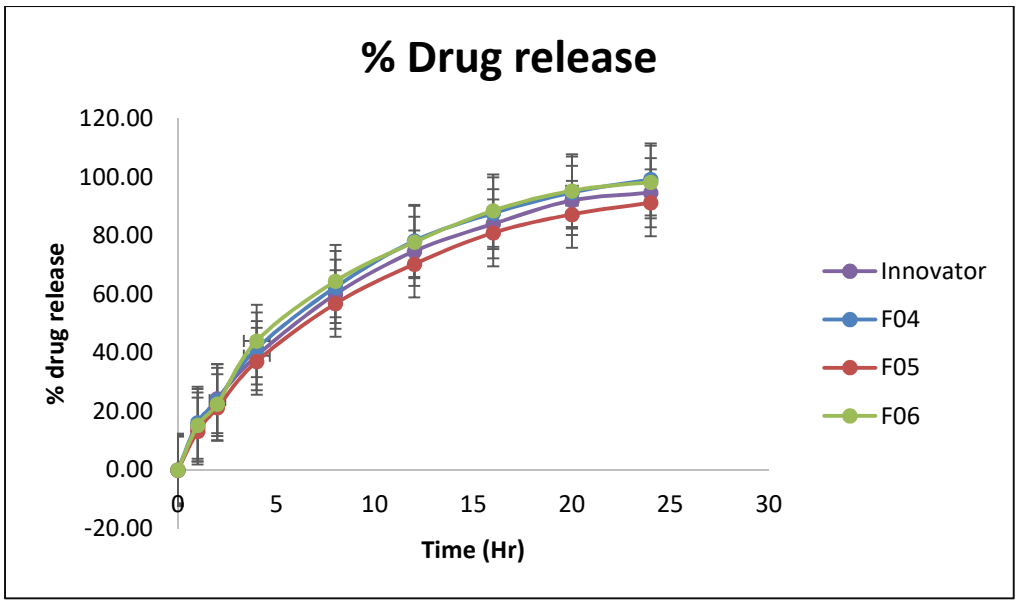

Figure No. 7: In-vitro drug release profile of batch F04, F05 and F06 in release media 0.9 % NaCl in water and comparision with innovator

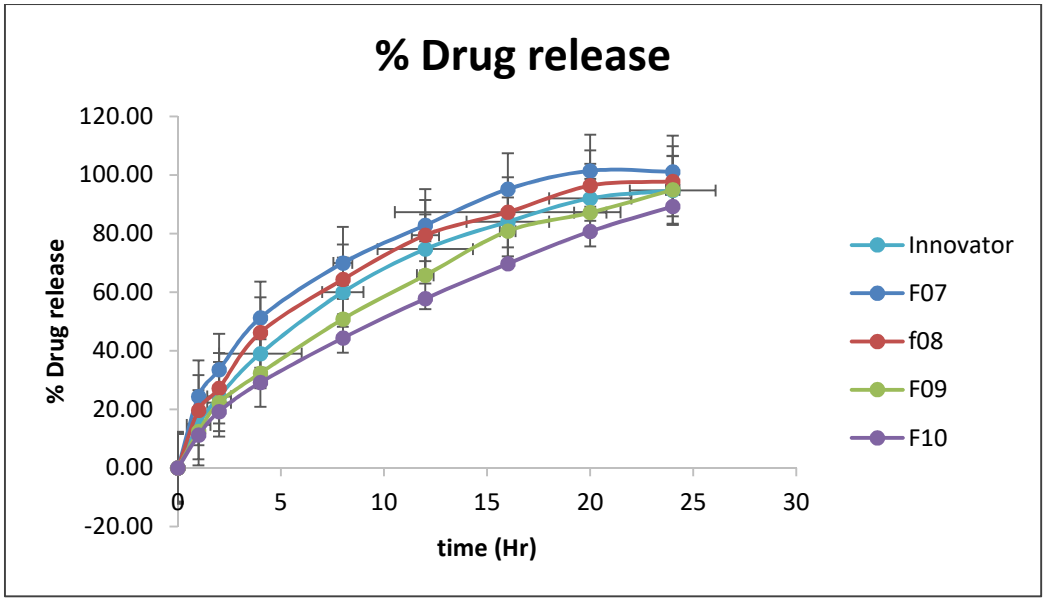

Figure No. 7: In-vitro drug release profile of batch F07, F08, F09 and F10 in release media 0.9 % NaCl in water and comparision with innovator

All ten formulations (F01–F10) showed sustained drug release of 24 hours in 0.9% NaCl medium with different control over release. Formulations F01–F03 released drugs rapidly, recording more than 100% at 16–20 hours, suggesting quicker release thn innovator. F04–F06 released 98–99% of the drug at 24 hours, which resembles the profile of the innovator, and represents the best possible sustained-release profile. F07–F10 showed more sustained release with lower cumulative percentages (88–101%), especially F10 (88.81%), which reflects extended release. Formulations F04 generally matched the most with the innovator, whereas F07–F10 provided more robust extended-release properties ideal for once-daily administration.

Kinetics study:

Table No. 13: Drug release kinetics of innovator and formulation F01 to F10

Formulation code	First order plot (R^2)	Zero order plot (R^2)	Higuchi plots (R^2)	Hixon-Crowel cube root plot (R^2)	Korsmeyer-peppas plots		Best fit model
					N	R^2	
Innovator	0.9920	0.9088	0.9908	0.9958	0.6421	0.9895	**Hixon-Crowel**
F01	0.9152	0.8252	0.9898	0.9160	0.7056	0.9528	**Higuchi plots**
F02	0.9356	0.8681	0.9818	0.9663	0.7285	0.9795	**Higuchi plots**
F03	0.9432	0.8323	0.9528	0.9430	0.6914	0.9895	**Korsmeyer-peppas**
F04	0.9405	0.9101	0.9900	0.9966	0.6501	0.9895	**Hixon-Crowel**
F05	0.9994	0.9163	0.9900	0.9876	0.6817	0.9898	**First order**
F06	0.9781	0.8995	0.9854	0.9965	0.6822	0.9895	**Hixon-Crowel**
F07	0.9145	0.8689	0.9844	0.9330	0.5016	0.9895	**Korsmeyer-peppas**
F08	0.9882	0.8881	0.9870	0.9913	0.5783	0.9895	**Hixon-Crowel**
F09	0.9757	0.9537	0.9924	0.9973	0.6674	0.9898	**Hixon-Crowel**
F10	0.9804	0.9708	0.9904	0.9958	0.6565	0.9895	**Hixon-Crowel**

From Table No. 13 it is shown that optimized batch (**F04**) follows **Hixon-Crowel cube root plot** with R^2 value **0.9966** which is identical to innovator**.**

Similarity study:

Table No. 14: Similarity factors of prepared formulations F01 to F10

Formulation code	F01	F02	F03	**F04**	F05	F06	F07	F08	F09	F10
Similarity factor (f2)	38.1	41.39	52.44	**75.99**	75.42	72.77	51.63	65.31	63.99	48.6

Among all batches, **F04 showed the highest f2 value (75.99)**, demonstrating dissolution most comparable to the innovator. Hence, **F04 was considered the optimized batch** based on its close match with the reference product.

Stability Studies of optimized formulation:

Stability studies was carried out at **25°C/60% RH** and **40°C/75% RH** for optimized formulation (F04) for 2 months. After each month physical changes like colour, drug content and dissolution profile were recorded.

Table No. 15: Stability study data of optimized formulation (F04) at 25°C/ 60% RH for 3 months

Formulation F04	**Initial**	**1M 25°C/60% RH HDPE Bottle**	**2M 25°C/60% RH HDPE Bottle**
(1) Physical stability	Brown, round shaped	Similar to initial	Similar to initial
(2) Drug content (%)	99.28 %	99.23 %	98.56 %
(3) Dissolution Parameters	Apparatus type: USP-I, rpm: 100, Media: 0.9 % NaCl in water, Media volume: 900 ml, Sampling points: 1, 2, 4, 8, 12, 16, 20, 24 hrs		

Time in Hrs	Cumulative percent drug release	Cumulative percent drug release	Cumulative percent drug release
1	16.05±0.8	16.05±0.4	17.64±0.3
2	23.96±0.4	23.96±0.6	24.75±0.6
4	41.36±0.9	44.53±0.4	45.71±0.9
8	62.32±0.1	65.48±0.8	65.88±0.4
12	78.14±0.5	79.72±0.4	81.70±0.5
16	87.63±0.1	89.21±0.5	90.40±0.4
20	94.75±0.8	96.33±0.3	93.16±0.7
24	99.09±0.7	98.30±1.12	96.72±0.5
Conclusion	**24 Hrs profile**	**Similar to initial**	**Similar to initial**

Table No. 15 shows the stability study findings of formulation F04 stored at 25°C/60% RH for 2 months. The physical condition of the tablets did not change during the course of the study, maintaining their original brown, rounded shape at both time points (1 and 2 months), showing no effects on physical integrity under these conditions of storage.

The first drug content was 99.28%, and it dropped slightly to 98.45% by the second month, remaining well within tolerable ranges. The first 24-hour drug release was 99.09%, whereas by comparison, it was 98.30%, 96.72% at 1 and 2 months. There was a minor fluctuation in early drug release points, but otherwise, the profile was consistent with the first. These results show that F04 retains its physical stability, drug content, and extended-release performance after long-term storage, validating its use for controlled room temperature storage for extended periods.

Table No. 16: Stability study data of optimized formulation (F04) at 40°C/ 75% RH for 3 months

Formulation F04	**Initial**	**1M 40°C/75% RH HDPE Bottle**	**2M 40°C/75% RH HDPE Bottle**
(1) Physical stability	Brown, round shaped	Similar to initial	Similar to initial
(2) Drug content (%)	99.28 %	98.76 %	98.56 %
(3) Dissolution Parameters	Apparatus type: USP-I, rpm: 100, Media: 0.9 % NaCl in water, Media volume: 900 ml, Sampling points: 1, 2, 4, 8, 12, 16, 20, 24 hrs		
Time in Hrs	**Cumulative percent drug release**	**Cumulative percent drug release**	**Cumulative percent drug release**
1	16.05±0.8	17.64±0.6	17.64±0.5
2	23.96±0.4	25.15±0.7	26.34±0.6
4	41.36±0.9	45.32±0.9	47.69±0.3
8	62.32±0.1	65.09±0.5	68.25±1.8
12	78.14±0.5	81.70±0.6	82.88±0.9
16	87.63±0.1	90.00±1.2	93.16±0.4
20	94.75±0.8	97.91±1.4	95.14±0.7
24	99.09±0.7	98.30±0.5	96.72±0.3
Conclusion	**24 Hrs profile**	**Similar to initial**	**Similar to initial**

Table No. 16 shows the stability performance of formulation F04 stored at 40°C/75% RH for 2 months. Initially, physical appearance remained consistent throughout the study. The tablets retained their original brown, round-shaped form at all checkpoints (1 and 2 months), indicating that the elevated temperature and humidity had no adverse effect on the physical integrity or external features of the dosage form.

The drug content was 99.28%, which slightly decreased to 97.58% by the second month. The initial drug release at 24 hours was 99.09% compared to 98.30%, 96.72% at 1 and 2 months. A slight increase in early time-point release was observed post-storage, likely due to minor changes in polymer behavior under high temperature and humidity.

4. SUMMARY AND CONCLUSION:

However, the overall drug release profile remained similar to the initial. These results confirm that **F04** maintains its physical stability, drug content and extended-release characteristics under accelerated conditions, supporting its robustness for long-term storage. The current research centered on the preparation and in vitro assessment of sustained-release matrix tablets of Desvenlafaxine with an aim to enhanced treatment of major depressive disorder through extended drug delivery. Ten formulations (F01–F10) were prepared employing different levels and blends of Methocel K100M Premium CR and Methocel K15M Premium CR as the matrix material. The tablets were compressed directly and film-coated using Opadry II Brown for appearance and protective reasons. The drug-excipient compatibility studies were conducted to affirm no notable interaction, validating the stability of the formulations.

Formulations F01–F03 contained increasing levels of Methocel K100M, with F03 having a more rapid drug release, the rationale for making further changes to polymer proportions. F04–F06 contained increased levels of Methocel K100M, with F04 having an optimal extended-release profile. F07–F08 employed Methocel K15M, which with its lower viscosity, resulted in quicker drug release. F09–F10 blended both forms of Methocel and resulted in slow release, suggesting a more intense retardation effect.

Among them, batch F04 was the best optimized formulation. It had outstanding physical characteristics and a drug release pattern very close to the reference product (Pristiq®), with an f2 similarity factor of 75.99. F04 also showed best swelling (487.78%), which is crucial for creating a uniform gel barrier and maintaining consistent drug diffusion without burst release. Stability studies assured its stability in accelerated and real-time conditions.

Finally, the optimized formula F04 was able to provide 24-hour controlled drug release, possibly reducing side effects and enhancing patient compliance. Therefore, it is a promising extended-release oral drug dosage form of Desvenlafaxine for effective once-daily therapy for major depressive disorder.

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