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FORMULATION DEVELOPMENT AND EVALUATION OF VENLAFAXINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

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ABSTRACT

The objective of the present study was to develop venlafaxine hydrochloride orodispersible tablet by using conventional techniques which are simple and cost effective such as use of superdisintegrant technology. In this, sodium starch glycollate and Crosscarmellose sodium were used in the rapid disintegration of the tablets. In this various trials were conducted for the selection of optimum concentration of superdisintegrant. The optimized formula aids in the stabilization of final product. The blend and compressed tablets were evaluated for physical characteristics like bulk density, tapped density, angle of repose, hardness, friability, disintegration time, wetting time, water absorption ratio, *In-vitro* dispersion time and chemical characteristics like *In-vitro* dissolution, content uniformity and assay. The stability study was conducted for the optimized batch. This design of dosage form will open a new era for rapid disintegration tablets.

INTRODUCTION: Orally disintegrating tablets are also called as orodispersible [1, 2, 3] tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. ODTs are the dosage forms containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute.

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications.

ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. These problems led to development of novel types of solid oral dosage forms that disintegrates and dissolves rapidly in saliva without the need of drinking water, disintegrates and dissolves rapidly in saliva without the need of drinking water. Orally disintegrating tablets offer all advantages [5, 6, 7] of solid dosage forms and liquid dosage forms along with special advantages, which include:

a. As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
b. No risk of obstruction of dosage form, which is beneficial for traveling patients. Various challenges in the develop ODT[7] are, rapid disintegration of tablet ,Avoid increase in tablet size, have sufficient mechanical strength, minimum or no residue in mouth, protection from moisture, good package design, dose lower than 20 mg, small to moderate molecular weight, which do not have access to water. In this superdisintegrants major function is to oppose the efficacy of the tablet binder and the physical forces that act under compression to form the tablet. The mechanism by which tablet is broken down into smaller particles and then produces a homogeneous suspension or solution. In this study direct compression method was selected for the formulation of venlafaxine 50mg orodispersible tablets by using different concentrations of Crosscarmellose sodium and Sodium starch glycollate as superdisintegrants.

MATERIALS AND METHODS:

Materials: Venlafaxine Hydrochloride was obtained from Orchid Chemicals and Pharmaceuticals Ltd., Sodium starch glycollate and Crosscarmellose sodium were obtained from Rankem limited, Mumbai. Other excipients used in this formulation were of analytical grade.

Methods:

Preparation of Venlafaxine Orodispersible tablets: Venlafaxine Hydrochloride, Microcrystalline cellulose, Superdisintegrants, Aerosil, Aspartame, Mannitol, Starch-1500 were sifted through # 40 mesh separately, collected in poly bags. Venlafaxine hydrochloride, Microcrystalline cellulose, Super-disintegrants, Aerosil, Aspartame, Mannitol, Starch-1500, Strawberry flavor were loaded into Octagonal blender and mixed. Sodium saccharine, Magnesium stearate, Talc were added to this and mixed for 10 minutes, then sifted through #60 mesh. Then the final blend was compressed in to tablets using Rotary press tablet compression machine. The formula for the preparation of various baches of Venlafaxine hydrochloride tablets were given in **table 1.**

TABLE 1: FORMULATION OF VENLAFAXINE HYDRCHLORIDE 50 MG ORODISPERSIBLE TABLETS

Ingredients	QUANTITY OF INGREDIENTS (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Venlafaxine Hydrochloride	50	50	50	50	50	50	50	50	50
Crosscarmellose sodium	10	15	20	-	-	-	-	-	-
Cross povidone	-	-	-	10	15	20	-	-	-
Sodium starch glycollate	-	-	-	-	-	-	10	15	20
Avicel PH 101	34	34	34	34	34	34	34	34	34
Mannitol	63	58	53	63	58	53	63	58	53
Starch-1500	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
Aspartame	20	20	20	20	20	20	20	20	20
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium stearate	2	2	2	2	2	2	2	2	2
Strawberry flavor	5	5	5	5	5	5	5	5	5
Sodium saccharin	5	5	5	5	5	5	5	5	5
TOTAL	200	200	200	200	200	200	200	200	200

Evaluation:

Pre-compression parameters [47]: The Angle of repose, Bulk density, Tapped density, Compressibility Index, Hausner's ratio and % LOD were determined and results were given in **Table 2** and **2.1**.

Post compression parameters [48, 49]: Thickness, Weight Variation Test, Hardness Test, Friability Test and Disintegration were determined as per the Standard Procedures and the results obtained are tabulated in **Table 3** and **3.1**.

TABLE 2: PRECOMPRESSION RESULTS OF VENALAFEXINE HYDROCHLORIDE TABLETS

Formulation	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index
F_1	32.15±0.12	0.40±0.16	0.51±0.24	0.22±0.14
F_2	30.46±0.22	0.40±0.35	0.50±0.28	20.00±0.18
F_3	27.89±0.17	0.43±0.18	0.42±0.13	19.57±0.25
F_4	32.05±0.31	0.43±0.24	0.55±0.19	21.74±0.33
F_5	29.82±0.24	0.41±0.27	0.52±0.24	20.84±0.37
F_6	27.21±0.15	0.38±0.34	0.47±0.32	19.24±0.28
F_7	33.69±0.19	0.40±0.25	0.51±0.27	0.22±0.26
F_8	32.05±0.21	0.41±0.26	0.52±0.34	20.84±0.34
F_9	28.49±0.23	0.40±0.41	0.50±0.26	20.00±0.21

Mean ± Standard deviation (n = 3)

TABLE 2.1: PRECOMPRESSION PROPERTIES

Formulation	Hausner's Ratio	% LOD
F_1	1.37 ± 0.16	0.82 ± 0.36
F_2	1.29 ± 0.05	1.06 ± 0.41
F_3	1.32 ± 0.02	0.96 ± 0.58
F_4	1.32 ± 0.02	0.62 ± 0.02
F_5	1.36 ± 0.07	0.88 ± 0.37
F_6	1.29 ± 0.05	1.15 ± 0.51
F_7	1.19 ± 0.07	1.1 ± 0.40
F_8	1.43 ± 0.21	1.03 ± 0.34
F_9	1.25 ± 0.05	1.08 ± 0.40

Mean ± Standard deviation (n = 3)

- The angle of repose of all formulations ranged from 27.21^o±0.5 to 32.15^o±0.5. The flow properties of all the formulations are in the increasing order of; $F_9 < F_5 < F_2 < F_6 < F_7 < F_4 < F_8 < F_1 < F_3$
- All the nine formulations exhibited good flow properties.
- The bulk density of all formulations ranged from 0.38 to 0.43.

- The tapped density of all formulations ranged from 0.42 to 0.55.
- The values of tapped and bulk density shown that the blends are not tightly packed
- The compressibility index of all formulations ranged from 0.22 to 21.74.
- For all the formulations the compressibility index of the formulations were found to comply within the limits specified and shown good compressibility index
- The Hausner's ratio of all formulations are ranged from 1.19 ± 0.07to 1.43 ± 0.21.
- The % LOD of all formulations is ranged from 0.62 ± 0.02 to 1.06 ± 0.41.
- For all the formulations the results of precompressional parameters were found to be within the limits specified.

TABLE 3: POST COMPRESSION PROPERTIES

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)
F_1	200.0 ± 0.12	4.71 ± 0.14	3.40 ± 0.14	0.74 ± 0.15	24 ± 0.01
F_2	199.8 ±1.12	4.90 ±0.74	3.90 ± 0.14	0.65 ± 0.07	28 ± 0.02
F_3	200.2 ± 0.54	4.88 ± 0.21	3.58 ±0.23	0.93 ±0.05	27 ± 0.14
F_4	200.3 ± 0.63	4.96 ± 0.14	3.86 ± 0.47	0.97 ± 0.02	26 ± 0.25
F_5	199.9 ± 0.87	4.87 ± 0.32	3.98 ± 0.21	0.83 ± 0.06	27 ± 0.14
F_6	200.5 ± 0.36	4.96 ± 0.47	3.62 ± 0.36	0.80 ± 0.12	25 ± 0.14
F_7	200.2 ± 0.74	4.63 ± 0.54	3.12 ± 0.41	0.79 ± 0.10	26 ± 0.36
F_8	200.4 ± 0.52	4.78 ± 0.47	3.10 ± 0.74	0.75 ± 0.15	24 ± 0.14
F_9	199.6 ± 0.14	4.66 ± 0.47	3.11 ± 0.74	0.81 ± 0.10	29 ± 0.14

Mean ± Standard deviation (n = 3)

TABLE 3.1: POST COMPRESSION PROPERTIES

Formulation	Water absorption Ratio	Assay	Wetting time (sec)	*In-vitro* dispersion time (Sec)
F_1	78.92 ± 0.14	99.19 ± 0.51	21 ± 0.24	32± 0.21
F_2	72.35 ± 0.41	98.42 ± 1.01	24 ± 0.14	32 ± 0.25
F_3	69.32 ± 0.58	97.77 ± 1.26	28 ± 0.17	31 ± 0.63
F_4	75.63 ± 0.47	97.53 ± 1.82	25 ± 0.12	29 ± 0.14
F_5	74.21 ± 0.25	99.82 ± 0.33	32 ± 0.32	32 ± 0.24
F_6	74.23 ± 0.14	100.55 ± 0.58	33 ± 0.54	28 ± 0.14
F_7	76.32 ± 0.25	100.25 ± 2.94	28 ± 0.36	29 ± 0.41
F_8	77.12 ± 0.54	99.40 ± 0.94	29 ± 0.65	33 ± 0. 63
F_9	74.12 ± 0.14	101.63 ±1.50	31 ± 0.14	32 ± 0.45

Water absorption Ratio: A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption Ratio = Initial weight/Final weight x 100

Content uniformity test: 10 tablets were selected randomly transfer each tablet in to a 50ml standard flask and dissolved and diluted to 50 ml with phosphate buffer pH 6.8.1 ml of this solution was diluted to 100 ml with phosphate buffer ph 6.8. The amount of drug present in each tablet was determined by UV spectroscopy at 225 nm.

Wetting time: A petri dish containing 6 ml of distilled water was taken and a tissue paper folded twice was placed in it. A tablet containing a small quantity of amaranth color was placed on this. Time required for the upper surface of the tablet to become complete red was noted.

***In-vitro* dispersion time** [50]: The test was performed by placing two tablets in 100 ml water and stirred gently, till the tablets get completely disintegrated. The formulation was taken in the form of a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710µm without leaving any residue on the mesh. Tablets were added to 100 ml of phosphate buffer solution, pH 6.8 at 37+0.5^{o}C, Time required for complete dispersion of a tablet was measured.

***In vitro* dissolution studies** [49, 50]:

Preparation of pH 6.8 phosphate buffer: 50 ml of monobasic potassium phosphate solution was placed in a 200 ml volumetric flask, to it 22.4 ml of 0.2 M sodium hydroxide was added and the volume was then made up to 200 ml with distilled water.

Standard curve of venlafaxine hydrochloride in phosphate buffer pH 6.8: 100mg of venlafaxine hydrochloride was dissolved in phosphate buffer pH 6.8 in a 100ml standard flask and filled up to the mark using phosphate buffer pH 6.8. Serial dilutions were made in phosphate buffer pH 6.8 in order to obtain 5 µg/ml, 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml. Absorbance of these solutions were measured at 225 nm using UV-Visible Spectrophotometer (Schimadzu 159) and standard graph was plotted.

Procedure: Tablet dissolution was assessed using standard USP dissolution apparatus type II. The dissolution media used was 900ml of 6.8 phosphate buffer. The temperature was maintained at 37±0.5^{o}C. At predetermined time intervals, an aliquot of 5 ml sample was withdrawn and made up to 10 ml with suitable diluents and results were given in **Table 4, 4.1, 4.2 and 4.3**.

TABLE 4: STANDARD PLOT OF VENLAFAXINE HCl IN 6.8 pH PHOSPHATE BUFFER

Concentration(µg/ml)	Absorbance at 254 nm
4	0.052
8	0.165
12	0.364
16	0.478
20	0.587

TABLE 4.1: CUMULATIVE PERCENTAGE DRUG RELEASE OF PDT_1 – PDT_3 IN pH 6.8 PHOSPHATE BUFFER

Sampling Time in min	Cumulative Percentage of Drug Release in pH 6.8 Phosphate Buffer		
	F_1	F_2	F_3
5	48.5 ± 0.45	74.2 ± 0.14	73.2 ± 0.17
10	76.1 ± 0.47	84.6 ± 0.74	87.4 ± 0.54
20	80.6 ± 0.47	89.8 ± 0.96	91.7 ± 0.69
30	80.6 ± 0.87	95.2 ± 0.54	95.8 ± 0.54
45	87.5 ± 0.47	93.3 ± 0.54	95.0 ± 0.69
60	91.1 ± 0.14	95.5 ± 0.47	97.5 ± 0.74

Mean ± Standard deviation (n = 3)

TABLE 4.2: CUMULATIVE PERCENTAGE DRUG RELEASE OF F_4 – F_6 IN pH 6.8 PHOSPHATE BUFFER

Sampling Time in min	Cumulative Percentage Of Drug Release in pH 6.8 Phosphate Buffer.		
	F_4	F_5	F_6
5	60.3 ± 0.54	65.4 ± 0.45	74.2 ± 0.12
10	71.2 ± 1.25	78.6 ± 0.36	80.3 ±0.21
20	78.7 ± .78	84.6 ± 0.14	86.7 ± 0.36
30	85.1 ± 0.97	89.8 ± 0.74	92.2 ± 0.14
45	90.5 ± 0.96	93.3 ± 0.14	95.7 ± 0.47
60	93.6 ± 0.74	95.2 ± 0.54	99.4 ± 0.54

Mean ± Standard deviation (n = 3)

TABLE 4.3: CUMULATIVE PERCENTAGE DRUG RELEASE OF F_7 – F_9 IN pH 6.8 PHOSPHATE BUFFER

Sampling Time in min	Cumulative Percentage of Drug Release in pH 6.8 Phosphate Buffer		
	F_7	F_8	F_9
5	49.9 ± 0.14	50.3 ± 0.54	58.3 ± 0.21
10	68.5 ± 0.54	69.3 ± 0.54	67.2 ± 0.21
20	69.3 ± 0.41	71.1 ± 0.21	75.3 ± 0.22
30	71.1 ± 0.14	75.6 ± 0.54	81.3 ± 0.54
45	87.5 ± 0.87	79.3 ± 0.21	86.3 ± 0.54
60	89.1 ± 0.54	89.3 ± 0.21	90.12 ± 0.87

Mean ± Standard deviation (n = 3)

- The *In vitro* drug release of tablets containing the crosspovidone as superdisintegrant shown the minimum drug release that is 93.6 ± 0.74 for F_4 and maximum drug release at 99.4±0.54 for F_6
- The *In vitro* drug release of tablets containing the Crosscarmellose sodium as superdisintegrant shown the minimum drug release that is 91.1±0.14 for $F_1$and maximum drug release at 97.5±0.74 for F_3
- The *In vitro* drug release of tablets containing the sodium starch glycollate as superdisintegrant shown the minimum drug release that is 89.1±0.54 for F_7 and maximum drug release at 90.12±0.87 for F_9
- Based on this *In vitro* drug release studies it was found that the formulation F_6 which contains cross povidone as superdisintegrant in the concentration of 10% showed maximum drug release 99.4±0.54 at the end of 1 hr.

RESULTS AND DISCUSSION:

Drug Excipient compatible studies: The results obtained with IR studies showed that there was no interaction between the drug and other excipients used in the formulation. The FTIR of venlafaxine HCl (drug) shown intense band at 1613.36 cm^{-1}, 1566.76 cm^{-1}, 1515.59 cm^{-1} and 1052.22 cm^{-1} corresponding to the functional groups C=O, COOH, NH and OH bending as shown in **Fig. 1**. The FTIR of drug + polymer shown intense bands at 1617.75 cm^{-1},1560.85 cm^{-1} , 1517.38 cm^{-1} and 1052.19 cm^{-1} indicates no change in the functional groups C=O, COOH, NH and OH as shown in **Fig. 3**. The FTIR of Placebo shown that there are no intense bands at groups C=O, COOH, NH and OH this shows that drug peaks are missing in it as shown in **Fig. 2**. From the above interpretation it is understood that there is no major shifting in the frequencies of above said functional groups. Hence these drug and polymers are compatible with each other.

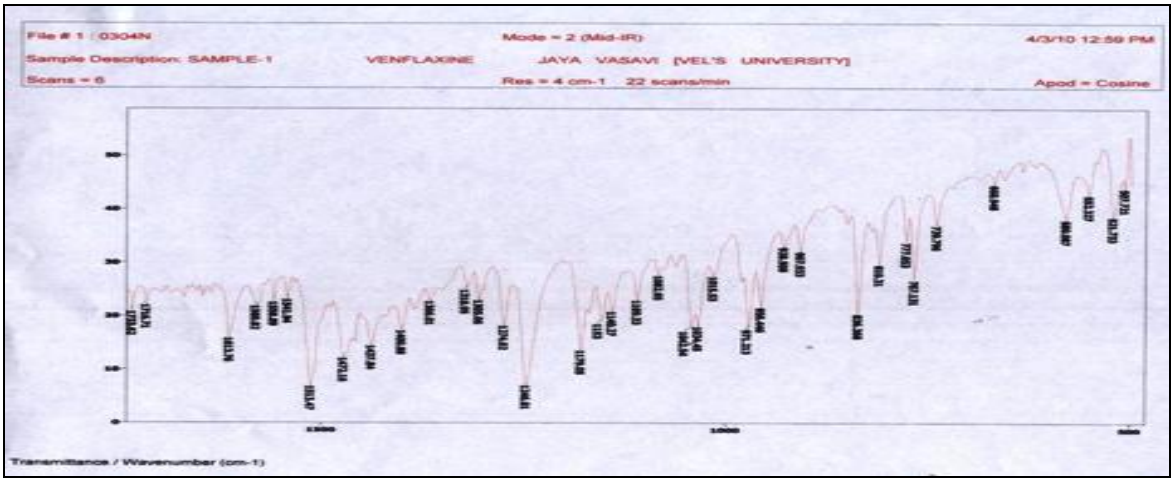

FIG. 1: FTIR OF VENLAFAXINE HCl

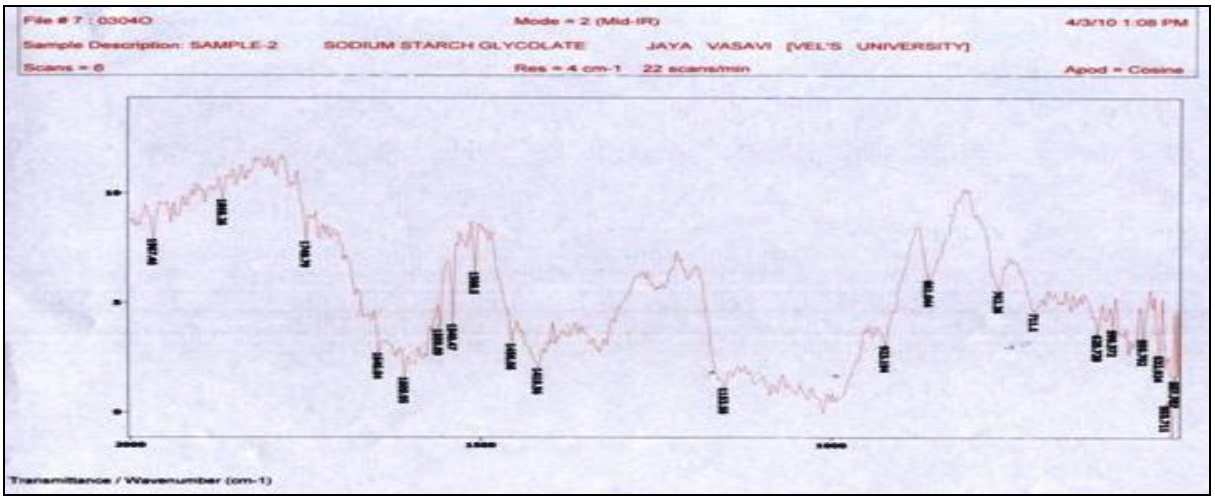

FIG. 2: FTIR OF PLACEBO

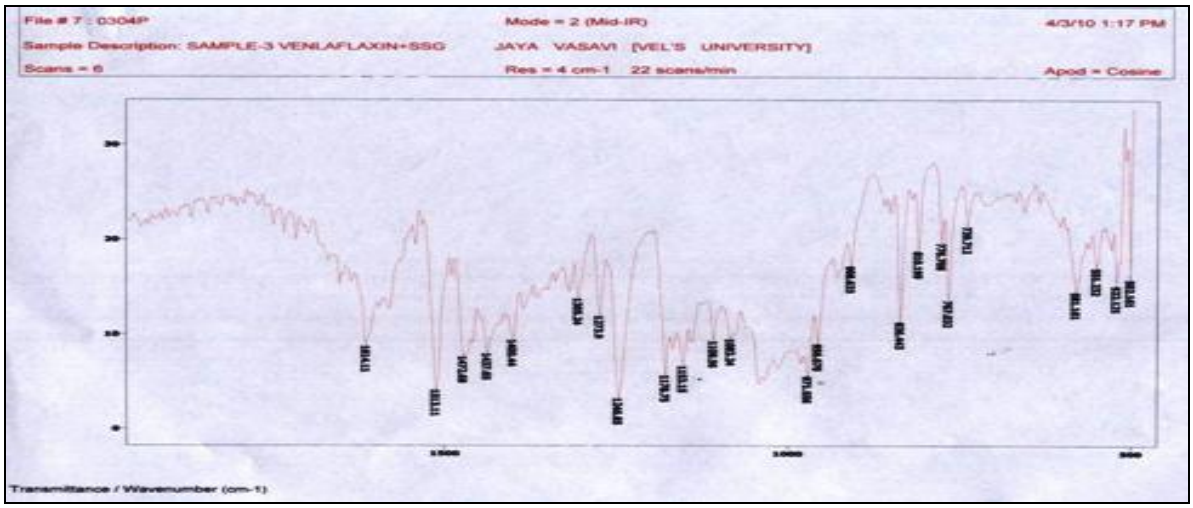

FIG. 3: FTIR OF DRUG + POLYMER

CONCLUSION: In present work an attempt was made to develop orodispersible tablets of venlafaxine hydrochloride by direct compression method using cross povidone, Crosscarmellose sodium and sodium starch glycollate as superdisintegrants and the optimum concentration were identified based on the *in vitro* drug release results. Based on the observation, it was concluded that batch F_6 exhibited desirable properties and optimized drug release. The results demonstrated the effective use of orodispersible tablets of venlafaxine hydrochloride and as an ideal drug release formulation for treatment of hypertension.

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