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Research Article **Novel drug delivery system**

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NOVEL ANTI-DEPRESSANT FAST DISSOLVING TABLET: DESIGN AND DEVELOPMENT

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ABSTRACT

The purpose of the present investigation is to formulate taste masked fast dissolving tablets of venlafaxine hydrochloride, a novel antidepressant, by wet granulation method. Nine formulations were prepared using sodium starch glycolate, croscarmellose sodium and crospovidone as superdisintegrants in different concentrations of 5%, 7.5% and 10%.ingredients like peppermint oil, menthol and sucralose aided in the taste masking process of the drug. The prepared batches were then evaluated for various physical and chemical attributes. Amongst the nine formulations CP-3 emerged as an overall the best formulation showing release profile of almost 100%. Accelerated stability studies were conducted for this batch at 40±2^{o}C and 75±5% RH for one month period.

KEYWORDS: Fast dissolving tablets, venlafaxine hydrochloride, peppermint oil, wet granulation, superdisintegrants and cumulative percent drug release.

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INTRODUCTION

Fast dissolving drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages over both the traditional dosage forms. Fast dispersible drug delivery system offers the luxury of much more accurate dosing than the primary alternative. This segment of formulation is especially designed for dysphagia, geriatric, pediatric and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations. The fast dissolving tablet (FDT) has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within few seconds. When an FDT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration. FDTs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or to deliver sustained release multi-particulate system to those who cannot swallow intact sustained action tablets/capsules. The active ingredient, venlafaxine hydrochloride, belongs to the pharmaco-therapeutic group of drugs called 'other antidepressants'. Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. These products are indicated for the treatment of depressive illness including depression accompanied by anxiety. Following an initial response venlafaxine is indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes. The pharmacokinetics of venlafaxine is well described. It is well absorbed (>92%) and undergoes extensive first-pass metabolism. Bioavailability is unaffected by food. Considerable intra-subject variability is seen. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and is reached in approximately 2.4 hours. Venlafaxine is extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and ODV is approximately 5 and 11 hours, respectively. Mean peak ODV plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Venlafaxine and ODV are 27% and 30% bound to plasma proteins respectively. ODV, other minor venlafaxine metabolites, and non-metabolized venlafaxine are excreted primarily through the kidneys. Venlafaxine does not produce usual side effects of TCAs; tends to rise rather than depress blood pressure and is safer in overdose. Conventional tablets of venlafaxine hydrochloride are available in 25, 37.5, 75, and 150 mg doses in the market. Venlafaxine is a white to off-white crystalline solid with solubility of 572 mg/ml in water. However the main limitation to its therapeutic effectiveness is its poor bioavailability (45%), molecular weight (313.87 gm/mol), basic nature of the drug and short biological half-life (5 hours) necessitating the administration, two or three times daily so as to maintain adequate plasma levels of the drug. These biopharmaceutical and physicochemical properties reveal that venlafaxine hydrochloride is an ideal candidate for the development of fast dissolving tablets. In our present study, we have investigated that the superdisintegrant crospovidone when used in higher concentrations as compared to other superdisintegrants like croscarmellose sodium and sodium starch glycolate gave a drug release profile of almost 100% and also the in vitro dispersion time and wetting time was found to be the least among the nine formulations.

MATERIALS AND METHODS

Venlafaxine hydrochloride was obtained as a gift sample from Accutest Research Laboratories Ltd. Sodium starch glycolate (SSG), Croscarmellose sodium (CCS), Crospovidone (CP), Microcrystalline cellulose (Avicel PH 102), Mannitol (directly compressible), Menthol and Peppermint oil were obtained from Divakar Chemicals Ltd. All

other ingredients used were of analytical grades.

i. Preparation of venlafaxine hydrochloride fast dissolving tablets

Nine formulations were prepared by varying the percentage of the superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate; keeping the total weight of the tablet (200 mg) constant in all the formulations. Weighed quantity of MCC-102, DC- mannitol and half the quantity of superdisintegrant were mixed and passed through 40# sieve. The weighed amount of drug was dissolved separately in required quantity of distilled water and this drug solution was used as an aid in wet granulation. The granules so obtained from 24# sieve were tray dried at 60^{o}C for 30-40 minutes. Required quantity of menthol crystals were dissolved in peppermint oil and was then adsorbed on aerosol. The dried granules were then lubricated with this aerosol, talc and magnesium stearate and remaining quantity of the superdisintegrant. This procedure was applied for all the nine formulations. The final blends were then subjected to direct compression.

Table 1

Composition of the nine batches of venlafaxine hydrochloride fast dissolving tablets.

Ingredients	Formulation code								
	SSG-1	SSG-2	SSG-3	CCS-1	CCS-2	CCS-3	CP-1	CP-2	CP-3
Venlafaxine hydrochloride	25	25	25	25	25	25	25	25	25
Microcrystalline cellulose (Avicel PH 102)	30	30	30	30	30	30	30	30	30
Mannitol (directly compressible)	89.2	75.2	70.2	89.2	75.2	70.2	89.2	75.2	70.2
Sodium starch glycolate	10	15	20	-	-	-	-	-	
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Sucralose	5	5	5	5	5	5	5	5	
Menthol	40	40	40	40	40	40	40	40	40
Peppermint oil	2	2	2	2	2	2	2	2	2
Aerosil	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	
Total	200	200	200	200	200	200	200	200	200

- ***All quantities are in milligrams.***

EVALUATION

1. Granule properties

The powder blends of all the nine formulations were studied for their granule properties such as Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner's ratio and percent Loss on drying (% LOD); the results of which are mentioned in the following Table 2.

2. In – process parameters

i. Tablet dimensions (Tablet thickness and diameter)

Twenty tablets of each batch were picked randomly and its thickness and diameter was measured individually using Digimatic micrometer (Mitutuyo, Japan). The values of thickness were used to adjust the initial stages of compression

ii. Weight variation

10 tablets were selected at random, weighed and the average weight was calculated. Not more than the percentage as given in IP and none of the tablet deviates by more than twice that percentage.

ii. Hardness

The hardness of the tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm ^{2}. Five tablets were randomly picked from each batch and the hardness of the tablets was determined. The mean and standard deviation values were calculated for each batch.

iii. Friability

Roche friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in

the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined. The percent friability was determined using the following formula;

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where, W_1 = weight of the tablet before test and W_2 = weight of the tablets after test.

iv. 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 (R) was calculated using the formula,

$R = 100 \times [W_a - W_b] / W_b$

Where, W_a = weight of tablet after absorption and W_b = weight of tablet before absorption

v. Wetting time

Two circular tissue papers of 10 cm diameter were placed in a petri dish having the same inner diameter. 10 mL of phosphate buffer solution pH 6.8 containing Eosin, a water soluble dye, was added to petri dish. A tablet is carefully placed on the surface of the tissue paper so that complete tablet was not immersed in the solution Then, the time required for buffer to reach upper surface of the tablet was noted as wetting time.

In-vitro dispersion time

In vitro dispersion time was measured by dropping a tablet into a Petri dish containing 10 ml of phosphate buffer solution pH 6.8. Three tablets from each batch were randomly selected and tested. *In vitro* dispersion time was found and expressed in seconds.

3. Finished product parameters

vi. Content uniformity test

10 tablets were selected randomly. Each tablet was transferred into a 50mL volumetric flask, dissolved and diluted to 50 mL with phosphate buffer pH 6.8. One 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.

vii. In vitro dissolution studies

In vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 mL of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37 $\pm$ 0.5 ^oC and rpm of 50. One Venlafaxine hydrochloride tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 35 minutes. Samples measuring 5 mL were withdrawn after every 5, 10, 15, 20, 25, 30 and 35 minutes. Samples were filtered through 10 µm filter. The fresh dissolution medium was replaced every time with the same quantity of the sample. The collected samples were analyzed at 225 nm using dissolution medium as blank. The cumulative percentage drug release was calculated.

viii. Stability Studies

The stability of pharmaceutical preparation was evaluated by accelerated stability studies. The optimized formulation of Venlafaxine hydrochloride tablets (batch CP-3) was selected for the stability studies. The accelerated stability studies were carried out by packing the samples in strips and subjected the samples at 40 $\pm$ 2 ^oC and 75 $\pm$ 5% RH for a period of 1 month. The tablets were evaluated for hardness, wetting time, *in vitro* dispersion time, water absorption ratio and *in vitro* drug release.

RESULTS AND DISCUSSIONS

The compositions of different formulations are presented in Table 1. The granule properties, and the In-process parameters were found to

be satisfactory and within the limits. The results for the same are represented in Table 2, Table 3, Table 3.1, Table 4, Table 4.1, Table 4.2 and Table 4.3.

Table 2
Granule properties of the nine formulation powder blends.

Formulation code	Angle of repose (°)	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	% LOD	Hausner's ratio
SSG-1	29.40±0.31	0.43±0.25	0.55±0.24	21.74±o.29	0.79±0.02	1.36±0.07
SSG-2	31.05±0.32	0.43±0.18	0.51±0.19	23.11±0.36	0.87±0.44	1.35±0.02
SSG-3	30.10±0.19	0.42±0.34	0.53±0.13	22.57±0.14	0.92±0.36	1.32±0.02
CCS-1	33.69±0.29	0.40±0.46	0.51±0.36	22.0±0.14	0.96±0.58	1.34±0.09
CCS-2	32.19±0.16	0.41±0.16	0.50±0.28	21.84±0.37	0.82±0.39	1.33±0.06
CCS-3	30.46±0.23	0.42±0.27	0.52±0.25	23.16±0.25	0.88±0.31	1.32±0.08
CP-1	29.81±0.22	0.38±0.24	0.52±0.27	21.07±0.33	1.10±0.52	1.19±0.07
CP-2	30.38±0.12	0.39±0.29	0.51±0.34	20.12±0.31	1.13±0.34	1.29±0.05
CP-3	30.46±0.23	0.38±0.35	0.47±0.33	19.24±0.28	1.09±0.40	1.27±0.05

Table 3
In-process parameters of the nine formulation batches.

Formulation code	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
SSG-1	199.6±0.54	3.80±0.19	7.78±0.01	3.90±0.21	0.85±0.07
SSG-2	199.9±0.39	3.75±0.16	7.75±0.02	3.71±0.23	0.88±0.05
SSG-3	200.2±0.71	3.81±0.24	7.76±0.02	3.44±0.18	0.89±0.15
CCS-1	200.7±0.36	3.83±0.27	7.78±0.01	3.75±0.19	0.79±0.06
CCS-2	199.8±0.87	3.81±0.31	7.77±0.03	3.60±0.19	0.78±0.10
CCS-3	200.2±0.84	3.75±0.39	7.80±0.02	3.86±0.21	0.81±0.15
CP-1	199.5±0.66	3.79±0.35	7.75±0.03	3.54±0.21	0.83±0.12
CP-2	200.4±0.52	3.80±0.36	7.81±0.02	3.40±0.23	0.86±0.17
CP-3	200.0±0.12	3.75±0.37	7.78±0.01	3.63±0.18	0.80±0.19

Table 3.1
In- process parameters of the nine formulation batches.

Formulation code	Water absorption ratio	Wetting time	*In vitro* dispersion time
SSG-1	75.82±2.42	33±0.14	38±0.63
SSG-2	101.95±2.06	32±0.17	37±0.25
SSG-3	108.22±3.40	30±0.12	35±0.21
CCS-1	47.37±2.50	31±0.54	34±0.63
CCS-2	54.73±0.42	29±0.63	33±0.45
CCS-3	60.19±3.26	24±0.32	32±0.26
CP-1	66.71±4.86	25±0.14	30±0.24
CP-2	95.13±2.39	22±0.32	27±0.42
CP-3	99.31±2.32	21±0.54	25±0.14

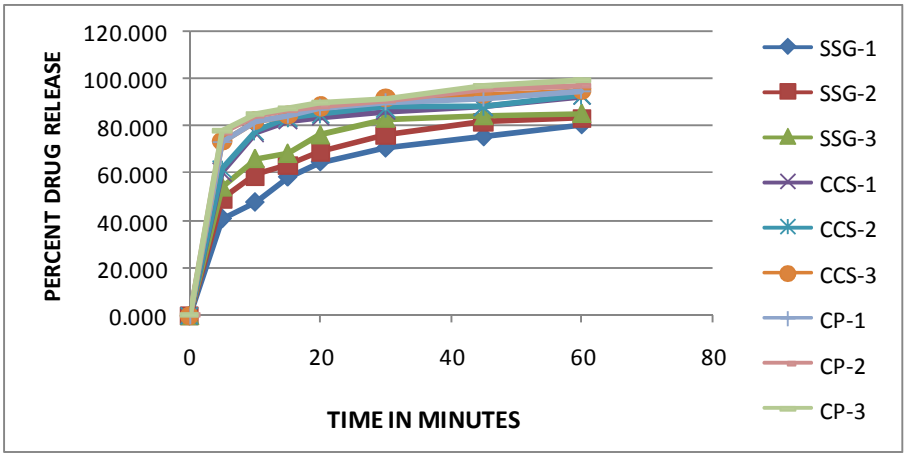
Table 4
Finished product parameters

Formulation code	Assay (%)
SSG-1	99.43±1.23
SSG-2	99.73±1.22
SSG-3	99.74±1.34
CCS-1	99.40±1.94
CCS-2	99.19±0.51
CCS-3	99.82±0.33
CP-1	100.25±2.94
CP-2	99.65±1.50
CP-3	100.55±0.58

Table 4.1
Cumulative percentage drug release of the nine formulations

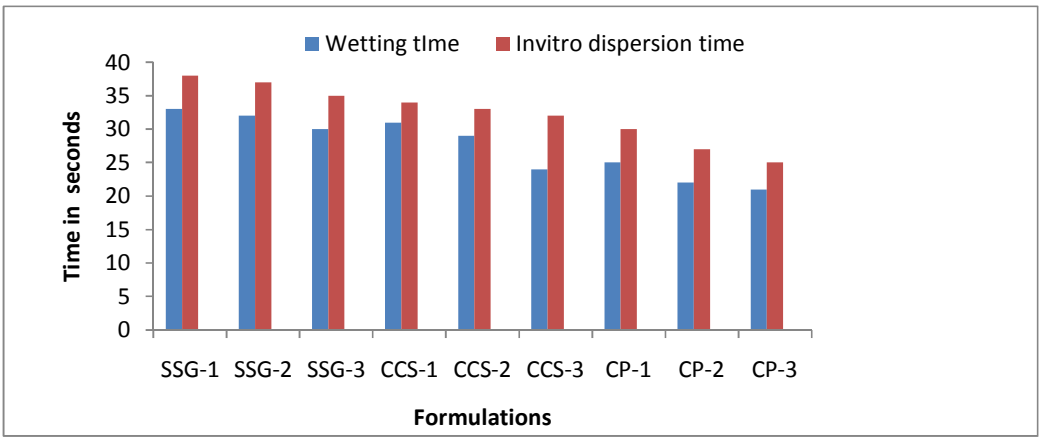
Time (minutes)	Cumulative percentage of drug release in pH 6.8 phosphate buffer								
	SSG-1	SSG-2	SSG-3	CCS-1	CCS-2	CCS-3	CP-1	CP-2	CP-3
0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
5	40.98±0.14	49.08±0.54	54.46±0.21	60.73±0.45	61.76±0.14	73.69±0.17	72.97±0.54	77.29±0.45	77.91±0.12
10	47.90±0.54	59.26±0.54	66.38±0.21	77.42±0.47	77.84±0.74	82.54±0.54	81.71±1.25	84.51±0.36	84.82±0.21
15	58.55±0.41	63.80±0.21	68.60±0.22	82.39±0.47	83.41±0.96	84.95±0.69	84.32±0.78	87.03±0.14	87.24±0.36
20	64.94±0.14	68.99±0.54	76.49±0.54	84.27±0.49	85.21±0.54	88.19±0.56	87.77±0.97	88.75±0.74	89.79±0.14
25	70.75±0.87	76.15±0.21	83.49±0.54	86.38±0.87	87.84±0.59	91.86±0.54	89.89±0.98	91.08±0.24	91.82±0.54
30	75.60±0.54	81.71±0.21	84.56±0.87	88.29±0.46	88.52±0.54	93.70±0.54	91.82±0.96	95.90±0.52	96.94±0.39
35	80.60±0.74	83.39±0.54	85.54±0.23	92.68±0.14	92.91±0.47	94.93±0.47	94.68±0.74	97.34±0.54	99.42±0.84

Graph 1
***In vitro* release of the drug from the nine formulations**



The tablets of SSG-1, SSG-2 and SSG-3 showed 80.598, 83.390 and 85.536% of drug release at the end of 35minutes. Drug release profile was not seen up to 100% which could be because of sodium starch glycolate (SSG). SSG is found to release the drug by swelling mechanism. SSG swells 7-12 folds in less than 30 seconds that is too much swelling takes place in three dimensions and therefore serves as a sustained release matrix. Due to this reason the 3 formulations showed lesser release rates. Further the tablets of CCS-1, CCS-2 and CCS-3 showed 92.676, 92.909 and 94.926% of drug release at the end of 35 minutes. In this case too, the drug release was not seen up to 100% because of Croscarmellose sodium (CCS). CCS swells 4-8 folds in less than 10 seconds and acts by swelling in 2 dimensions which helps in release of the drug. However, CCS when used alone was able to release the drug completely in 35 minutes and still the target release was not achieved and hence further attempts were made to improve the drug release profile. The tablets of CP-1, CP-2 and CP-3 showed 94.685, 97.345 and 99.423% of drug release at the end of 35 minutes. The maximum drug release was obtained since Crospovidone (CP) acts by both swelling and wicking actions which aids in the release of the drug. The drug release profile for all the nine formulations is shown above in Graph 1 and Table 4.1.

Graph 2
Comparison between Wetting Time (WT) and In Vitro Dispersion Time (IDT)



The formulations containing the lowest percentage of superdisintegrants have shown the highest wetting time and *in vitro* dispersion time. On the other hand formulations containing the highest percentage of superdisintegrants have shown the least wetting time and *in vitro* dispersion time. The results indicated that wetting time decreases with an increase in the concentration of superdisintegrants. This was due to the water absorbing capacity of the superdisintegrant, which in turn decreased the *in vitro* dispersion time. Comparison between wetting time (WT) and *in vitro* dispersion time (IDT) of the nine formulations is shown above in Graph 2.

Table 4.2
Stability data

Parameters	0 day	10 days	20 days	30 days
Hardness (kg/cm^2)	3.7	3.6	3.7	3.7
Wetting time (seconds)	21	23	22	21
In vitro dispersion time (seconds)	25	26	26	25
Water absorption ratio (%)	99.12	100.5	98.9	99.42

Table 4.3
Stability data (percent drug release)

Time (minutes)	0 day	10 days	20 days	30 days
0	0±0.00	0±0.00	0±0.00	0±0.00
5	77.910±2.13	74.92±1.36	74.43±1.50	76.81±1.13
10	84.822±1.05	86.71±1.01	84.57±1.88	86.40±2.04
15	87.245±0.98	88.78±1.18	88.16±1.14	87.89±0.73
20	89.782±1.42	89.37±0.94	89.66±1.10	89.59±2.86
25	91.816±2.10	90.15±0.77	90.76±2.04	91.89±0.85
30	96.944±1.36	95.79±2.21	96.28±0.91	96.96±1.09
35	99.423±1.13	99.61±1.21	100.46±1.03	99.56±0.98

CP-3 formulation was selected for the short term stability study under the conditions of 40^{o}C and 75% RH for four weeks. At every one week interval, the tablets were evaluated for hardness, wetting time, in vitro dispersion time, water absorption ratio and percent drug release. There were no significant changes observed when the values were compared with the initial parameters of the formulation. The results are seen above in Table 4.2 and Table 4.3.

CONCLUSION

Fast dissolving tablets of venlafaxine hydrochloride could be efficiently and

successfully be formulated by the method of wet granulation using suitable superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate. Amongst these three, crospovidone in the concentration of 10% was found to be the best. The proposed fast dissolving formulations possessed ideal and reproducible characteristics of in vitro dispersion time and percent drug release profile. Thus from above studies it can be concluded that fast dissolving drug delivery systems can be a suitable approach for the fast onset of action and better patient compliance.

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