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Original Article

Formulation design and optimization of novel mouth dissolving tablets for venlafaxine hydrochloride using sublimation technique

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ARTICLE INFO

Article history:
Received 17 March 2013
Accepted 28 April 2013
Available online 27 June 2013

Keywords:
3^2 Factorial design
Mouth dissolving tablet
Sublimating agent
Superdisintegrant
Venlafaxine hydrochloride

ABSTRACT

Aim: Venlafaxine hydrochloride, commonly used as antidepressant, has poor bioavailability due to extensive first pass metabolism. The objective of present study is to develop novel method of preparing compressed tablets for venlafaxine hydrochloride with high porosity which dissolves rapidly in mouth, using camphor as sublimating agent.

Methods: A 3^2 factorial design was used to investigate effect of amount of camphor and superdisintegrant namely indion 234 as independent variable. Friability, disintegration time, percent drug release were taken as dependent variables. Different concentrations (3%, 4%, 5%)of superdisintegrant indion 234 and camphor (5%, 10%, 15%) were used respectively. Tablets were prepared by direct compression method. Pearlitol SD-200 was used as bulking agent. The compressed tablets were dried for 6 h to allow sublimation of camphor to increase the porosity of the tablets to improve their dissolution. The tablets were evaluated for hardness, thickness, friability, weight variation, porosity, wetting time, disintegration time, drug content and *in-vitro* drug release. Drug-excipient interaction was investigated by FTIR study. Optimized formulation was evaluated for stability as per ICH guideline.

Results: All tablets had hardness 3–3.5 kg/cm^2 and friability of all formulations was less than 1.08%. Weight variation and drug content were within USP limits. FTIR study revealed no drug-excipient interaction. SEM study showed the porous surface morphology of tablets. A stability study for optimized F3 formulation as per ICH guideline for 90 days showed no changes in drug content.

Conclusion: Therefore, it may be concluded that developed novel method of preparing compressed tablets for venlafaxine hydrochloride with high porosity which dissolve rapidly in mouth, could be industrially feasible.

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0974-6943/$ – see front matter
http://dx.doi.org/10.1016/j.jopr.2013.04.054

1. Introduction

Mouth dissolving tablet system can be defined as a tablet that disintegrates and dissolves rapidly in saliva within few seconds without need of drinking water or chewing.[1] In spite of tremendous development in drug delivery technology, oral route remains perfect route for administration of therapeutic reagents because of low cost of therapy, ease of administration, accurate dose, self medication, pain avoidance, leading to high level of patient compliance. Tablets and capsules are the most popular dosage forms[2] but main drawback of such dosage forms is dysphasia or difficulty in swallowing. This problem led to development of novel solid dosage forms such as mouth dissolving tablets that disintegrate and dissolve rapidly in saliva without need of water. Mouth dissolving tablets avoid first pass metabolism and enhance bioavailability of active ingredient.[3]

Venlafaxine hydrochloride is an antidepressant agent. It acts by inhibiting selectively the uptake of serotonin and noradrenaline.[4] Venlafaxine hydrochloride has poor bioavailability (40–45%) and short half life of 5 h, it shows 92% oral absorption and only 12.6% drug reaches to systemic circulation due to extensive first pass metabolism and gets converted into its active metabolite O–desmethylve nlafaxine.[5] O–desmethylvenlafaxine has same neural activity like venlafaxine hydrochloride but differs in its half life which is 11 h. It act as hypertensive agent and also interferes with ejaculation in men.[6] Therefore an attempt was made in present study to formulate mouth dissolving tablets of venlafaxine hydrochloride by using a combination of camphor as sublimating agent and indion 234 as superdisintegrant. The aim was to optimize a mouth dissolving formulation by 3^2 factorial design and developing a dosage form with enhanced bioavailability with high porosity.

2. Materials

Venlafaxine hydrochloride was obtained as gift sample from Lupin Ltd, Vadodara, India. Pearlitol SD-200, Sucralose, Kyron, Camphor, Magnesium stearate, and Talc were procured as gift samples from Lupin Ltd, Mumbai. Indion 234 was received from Ion Exchange India Ltd, Gujarat.

3. Methods

3.1. Preparation of tablet blend

Tablets containing 25 mg of venlafaxine hydrochloride were prepared by sublimation method. The various formulations used in the study are shown in Table 1. The drug, diluents, superdisintegrant, camphor and sucralose were passed through sieve # 40. All the above ingredients were properly mixed together (in a poly-bag). Talc and magnesium stearate were passed through sieve # 80, mixed, and blended with initial mixture in a poly-bag. The powder blend was compressed into tablets on tablet machine (Rimek mini press – DL) using 8 mm concave punch set. Compressed tablets were subjected to the process of sublimation in vaccume oven (Osworld Vaccume Oven IRIC-8) at 60 °C for 6 h.[7]

Table 1 – 3^2 factorial design formulation of venlafaxine hydrochloride prepared by sublimation method.

Ingredient (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine hydrochloride	25	25	25	25	25	25	25	25	25
Indion-234	3	4	5	3	4	5	3	4	5
Camphor	5	5	5	10	10	10	15	15	15
Sucralose	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Pearlitol SD-200	63	62	61	58	57	56	53	52	51
Total weight	100	100	100	100	100	100	100	100	100

3.2. Evaluation of mouth dissolving tablets

The formulated mouth dissolving tablets were evaluated for different parameters like thickness, weight variation test, drug content, hardness, friability, wetting time, disintegration time, dissolution test, porosity, and morphology by SEM.

3.3. Thickness

Tablet thickness was measured by using vernier calipers (Mitutoyo). Five tablets were randomly taken and their thickness was measured by placing between two arms of vernier caliper.

3.4. Hardness

The crushing strength of tablets was measured by using Monsanto hardness tester.[8]

3.5. Weight variation test

Twenty tablets were selected at random and average weight was determined using an electronic balance (Shimadzu-AUX 220). Tablets were weighed individually and compared with average weight.[9]

3.6. Drug content

Ten tablets were powdered and blend equivalent to 25 mg of venlafaxine hydrochloride was weighed and dissolved in suitable quantity of phosphate buffer pH 6.8. The solution was filtered through 0.45 μm membrane filter and drug content was analyzed using UV Spectrophotometer (UV- 1700 Pharmaspec Shimadzu) at λ_{max} 225 nm.

3.7. Friability test

The friability of tablets was measured in Roche friabilator. Twenty tablets were dedusted at 25 rpm for 4 min and weighed again.[8] Percentage friability was calculated from loss

in weight as given in equation below. The weight loss should not be more than 1%.

$$\% \text{ Friability} = [(\text{Initial weight} - \text{Final weight})/\text{Initial weight}] \times 100$$

3.8. *In- vitro disintegration test*

The test was carried out on 6 tablets using digital tablet disintegration test apparatus (Microprocess based-Electrolab). Distilled water at 37 °C ± 2 °C was used as a disintegration media and time in second taken for complete disintegration of tablet with no residue remaining in apparatus.[10]

3.9. *In-vitro dissolution study*

Percent drug release of venlafaxine hydrochloride mouth dissolving tablets was determined by USP dissolution test apparatus (Lab India – 2000) using paddle method. The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 at 37 °C ± 0.5 °C at 50 rpm. A sample of 5 ml solution was withdrawn from dissolution apparatus at regular interval of 30 s. The same quantity of sample was replaced with fresh dissolution medium. The samples were filtered through 0.45 μm membrane filter.[11,12] Absorbance of these samples was analyzed at λ_{max} 225 nm using UV–visible spectrophotometer.

3.10. *Wetting time*

Wetting time of tablets can be measured using simple procedure. Six circular tissue papers of 10 cm diameter were placed in a petridish. 10 ml of water containing amaranth dye was added to petridish. A tablet was carefully placed on the surface of tissue paper.[10] Time required for water to reach upper surface of the tablet was noted as wetting time.

3.11. *Measurement of tablet porosity*

The porosity of tablets was calculated from the weight of tablet (W), tablet volume (V), and true density of powder (ρ) using following equation,[13]

$$\% \text{ Porosity} = [1 - \text{weight of tablet (W)}/\text{Volume (V)} \times \text{Density } (\rho)]$$

The true density of powder was determined by a pycnometer. Photomicroscope (Olympus cx31) was used for pore analysis.

3.12. *Drug-excipient interaction study*

FTIR spectra of all formulations were obtained on IR-spectrophotometer (Prestige-21-shimadzu). The samples were prepared in KBr dish (2 mg of sample in 200 mg KBr). The sample scanning range was 500–4000 cm^{-1}.

3.13. *SEM analysis*

The surface morphology of optimized formulation before and after sublimation of camphor was studied using (GEOL Ltd. Japan-JSM-6360). The tablet surface was sputter coated for 10 min with gold by using fine coat ion sputter and examined under SEM.

3.14. *Stability study*

The stability of optimized formulation F3 was tested according to ICH guideline, at 40 °C ± 2 °C/75%RH ± 5% condition in stability camber (HMG, India) for 3 months.[14] Tablets were tested for drug content for 30, 60, and 90 days.

3.15. *Experimental design*

The 3^2 factorial design was used for the optimization of mouth dissolving tablets of venlafaxine hydrochloride (Design Expert 8.0.7.1). The two independent factors, concentration of Indion-234 (X_1) and concentration of camphor (X_2), were set to three different levels and experimental trials were performed for all nine possible combinations.[15] The dependent responses measured, were disintegration time, friability, and percent drug release.

3.16. *Validation of the experimental design*

In order to validate the experimental design using a polynomial equation, three parameters namely disintegration time, friability and percent drug release were selected. The following second order polynomial equation was applied as a tool of mathematical modeling.[16]

$$Y = b0 + b1X_1 + b_2X_2 + b12X_1X_2 + b11X_{12} + b22X_{22}$$

where, Y is the dependent variable, b0 is the arithmetic mean response of the nine runs and b1 (b1,b2,,b12,b11 and b22) is the estimated coefficient for corresponding factor X1 (X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity.

Table 2 – Tablet weight (mg) before and after sublimation of camphor.

Formulation code	Camphor (mg)	Sublimation	
		Before (mg ± S.D)	After (mg ± S.D)
F1	5	100.2 ± 0.83	96.66 ± 0.51
F2	5	99.4 ± 0.89	96.46 ± 0.87
F3	5	99.8 ± 0.83	96.56 ± 0.56
F4	10	100.4 ± 0.89	91.03 ± 0.66
F5	10	99.6 ± 0.89	90.96 ± 0.20
F6	10	101 ± 0.70	91.03 ± 0.73
F7	15	100.8 ± 0.44	86.33 ± 0.70
F8	15	99.2 ± 0.83	85.26 ± 0.55
F9	15	101.8 ± 0.44	86.70 ± 0.45

Table 3 – Evaluation of factorial design mouth dissolving tablets.

Batch code	Hardness (kg/cm^2)	Thickness (mg ± S.D)	Drug content (% ± S.D)	*In-vitro* DT (sec ± S.D)	Wetting time (sec ± S.D)	Friability (% ± S.D)	% Drug release in 1 min (% ± S.D)	% Porosity (% ± S.D)
F1	3–3.5	2.4 ± 0.20	100.3 ± 0.3	30.16 ± 0.98	28.33 ± 1.36	0.33 ± 0.12	75.04 ± 0.05	12.75 ± 1.01
F2	3–3.5	2.46 ± 0.35	98.71 ± 0.0	24.66 ± 0.81	23.00 ± 1.67	0.34 ± 0.10	78.13 ± 0.09	13.10 ± 1.38
F3	3–3.5	2.33 ± 0.30	101.38 ± 0.7	19.16 ± 0.75	17.16 ± 1.47	0.32 ± 0.10	85.21 ± 0.55	15.38 ± 1.46
F4	3–3.5	2.36 ± 0.20	98.83 ± 0.1	27.5 ± 1.04	24.66 ± 1.50	0.73 ± 0.16	77.31 ± 0.4	23.08 ± 1.36
F5	3–3.5	2.26 ± 0.15	98.60 ± 0.1	23.0 ± 0.89	22.5 ± 1.51	0.67 ± 0.12	78.76 ± 0.07	25.60 ± 1.63
F6	3–3.5	2.23 ± 0.32	98.77 ± 0.2	19.33 ± 1.03	17.83 ± 1.32	0.63 ± 0.24	84.92 ± 0.08	27.36 ± 1.58
F7	3–3.5	2.13 ± 0.15	98.44 ± 0.0	24.16 ± 0.98	22.66 ± 1.36	1.08 ± 0.13	82.23 ± 0.08	40.09 ± 1.84
F8	3–3.5	2.3 ± 0.20	98.85 ± 0.0	21.66 ± 0.81	19.16 ± 1.16	1.01 ± 0.10	79.09 ± 0.26	40.75 ± 1.14
F9	3–3.5	2.23 ± 0.15	99.33 ± 0.0	17.5 ± 1.04	15.5 ± 1.37	1.04 ± 0.13	88.57 ± 0.11	41.01 ± 1.25

4. Result and discussion

The aim of present study was to optimize a mouth dissolving formulation by 3^2 factorial design for developing a dosage form with high porosity and enhanced bioavailability. The decrease in mean weight of tablets after sublimation corresponds to weight of camphor added as shown in Table 2. This study revealed that almost all of camphor had sublimated from the tablets.

The weight variation, hardness, friability, porosity, and drug content of all tablet formulations were found to be satisfactory as shown in Table 3. All the formulated tablets were of uniform weight with acceptable weight variation. Hardness of all formulations was 3–3.5 kg/cm^2 and friability loss was found to be between 0.32 and 1.08%. Drug content was found to be high (≥98.44%) and uniform (coefficient of variation between 0.03 and 0.3%). The sublimating agent increased the friability of tablets probably by increasing porosity. The hardness and friability studies revealed that the tablets possessed good mechanical resistance.

4.1. *In-vitro disintegration test*

The most important parameter that needs to be optimized in the development of mouth dissolving tablets is the disintegration time of tablets. In present study all tablets disintegrated in less than 30 s as shown in Table 3 fulfilling the official requirement (<1 min) for mouth dissolving tablets.

4.2. *Wetting time*

Rapid disintegration of prepared tablets in saliva may be related to an improvement in the ability of water to penetrate into tablet due to high porosity achieved by the increase in number of pores after sublimation of camphor. The outcome of this study was that many porous cavities were formed in tablets due to sublimation of camphor.

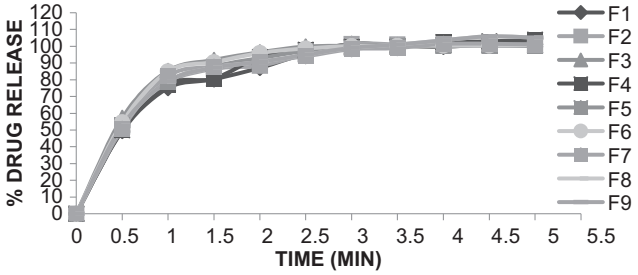

Fig. 1 – *In-vitro* dissolution profile of all formulation.

4.3. *Porosity*

Tablets exhibit % porosity in the range of 12.92–41.28 for camphor concentration in the range of 5–15 mg. Hence many porous structures are responsible for faster water uptake hence reduced wetting time; it also facilitates wicking action of Indion-234 bringing about faster disintegration.

4.4. *In-vitro dissolution test*

Disintegration time of tablet decreases with increase in concentration of camphor and Indion-234. Tablet showing lower disintegration time will show high drug release. *In-vitro* dissolution profile (Fig. 1) revealed faster and maximum drug from formulation F3. Formulation F3 prepared by direct sublimation of camphor shows release of 99.89% drug at 2.5 min. From above data F3 formulation was found to be optimized and used for further stability study.

4.5. *Stability study*

Stability study performed on optimized F3 formulation as per ICH guideline for 90 days at 40 °C ± 2 °C/75%RH ± 5%. The study found that no remarkable changes in the physical properties of tablets as well as no change in drug content as indicated in Table 4.

4.6. *Drug-excipient interaction study*

The FTIR of venlafaxine hydrochloride shows intense band at 16.1056 cm^{-1}, 1514.2 cm^{-1}, 1365.60 cm^{-1} and 1039.63 cm^{-1}

Table 4 – Drug content of mouth dissolving tablet of venlafaxine hydrochloride at 40 °C ± 2 °C/75% RH ± 5%.

Physical parameter	Factorial batch F3			
	0 days	30 days	60 days	90 days
% Drug content	101.20 ± 0.86	100.44 ± 0.52	99.28 ± 0.35	98.63 ± 0.80

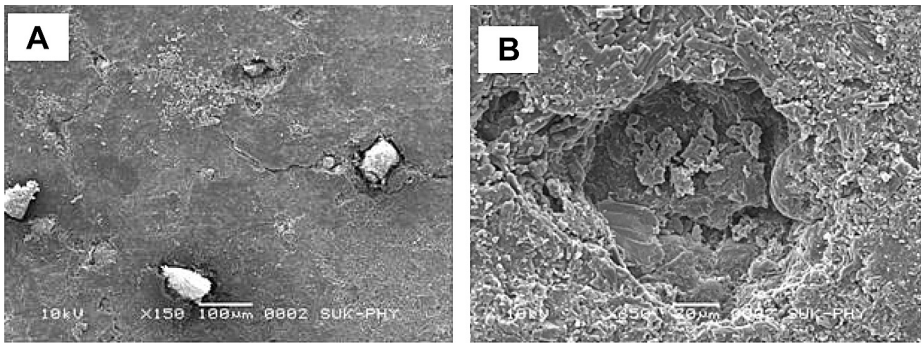

Fig. 2 – SEM images of optimized formulation F3 before sublimation (A) and after sublimation (B).

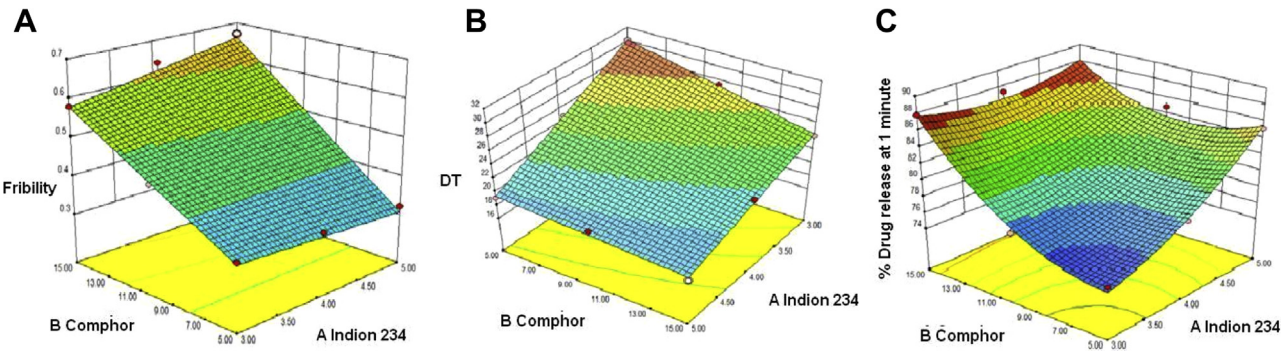

Fig. 3 – Response surface plot of factorial variable on friability (A),disintegration time (B) and % Drug release at 1 min (C).

corresponding to the functional groups C=O, COOH, NH and OH blending. The of drug and excipients shown intense band at 1695.43 cm^{-1}, 1583.56 cm^{-1}, 1485.19 cm^{-1} and 1080.14 cm^{-1} indicates no change in the functional groups C=O, COOH, NH and OH. From the above interpretation it is found that there is no major shifting in the frequencies of above said functional groups. Hence above result conclude that no drug and excipients interaction was found.

4.7. *Surface topography*

The image show formulation of pores on tablet surface that may have extended into the matrix after sublimation of the sublimating agent, thus providing a sufficiently porous structure to facilitate rapid penetration of dispersion medium. This is evident from the magnified tablet surface images (Fig. 2) of tablet before and after sublimation.

4.8. *Validation of experimental design*

The parameter disintegration time can be described by the model equation,

$$Y\,(\text{disintegration time}) = +23.03 - 4.31X1 - 1.80X2 + 1.09X1X2.$$

The negative sign for coefficient X1 and X2 indicates that as concentration of superdisintegrant and camphor increases, disintegration time decreases. R^2 value 0.9926 for disintegration time indicating good correlation between independent and dependent variable. The term with ($P < 0.0001$) were considered significant.

The parameter friability can be described by model equation,

$$Y\,(\text{Friability}) = +0.69 - 0.030X1 + 0.35X2.$$

The negative sign for coefficient X1 indicates that as concentration of superdisintegrant increases friability decreases and positive sign of X2 indicates that as concentration of camphor increases friability also increases. R^2 value 0.9955 for friability indicating good correlation between independent and dependent variable. The term with ($P < 0.0001$) were considered significant.

The % drug release can be described by the model equation,

$$Y(\%\ \text{Drug release}) = +79.31 + 2.88X1 + 3.98X_2 2.67X1X2 + 1.54(X1)^2 + 3.11(X2)^2$$

The positive sign for X1 and X2 indicates that as concentrations of Superdisintegrant and camphor increases, percent drug release also increases. R^2 value 0.9789 for percent drug release indicating good correlation between independent and dependent variable. The term with ($P < 0.01$) were considered significant. The computer generated response surface for dependent variables are shown in Fig. 3 respectively.

5. Conclusion

The formulation F3 using combine approach of sublimating agent and superdisintegrant was identified as optimized mouth

dissolving tablet formulation of venlafaxine hydrochloride. It appears that the use of superdisintegrant in higher concentration and camphor in lower concentration results in faster disintegration of the tablets with low friability. Camphor, used as sublimating agent, increases porosity of tablets due to which penetration of water takes place at high rate. This leads to faster disintegration of the tablets. Thus it may be concluded here that the developed novel method for preparing mouth dissolving tablets for venlafaxine hydrochloride increases the porosity and enhances the bioavailability.

Conflicts of interest

All authors have none to declare.

Acknowledgment

The authors express their sincere thanks to Principal Dr. S.S. Khadabadi, GCOP, Aurangabad, for providing the required facilities.

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