International Journal of Drug Delivery 2 (2010) 299-303

http://www.arjournals.org/ijdd.html

Research article

ISSN: 0975-0215

Development and characterization of gastroretentive mucoadhesive tablets of venlafaxine hydrochloride

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Abstract

The present study was undertaken with an aim to formulation development and evaluation of gastroretentive mucoadhesive sustained release tablet of Venlafaxine hydrochloride which releases the drug in a sustained manner over a period of 12 hours, by using Carbopol 971P in combination with eudragit RS-PO and ethyl cellulose as a mucoadhesive and release retardant respectively. Preformulation study was done initially and results directed for the further course of formulation. Based on Preformulation studies different batches of Venlafaxine hydrochloride were prepared using Carbopol 971P, Eudragit RS-PO and ethyl cellulose chosen for their different hydrophilic properties to calculate the sustained release properties. Sustained release tablets were prepared by direct compression and were evaluated for bioadhesion time, swelling index and matrix erosion, and in vitro drug release. The tablets of batch F3 and F6 had high swelling behaviors but release of drug is very less. And batch F2 having considerable swelling index and in vitro drug release (99.85%). Batch F2 can be taken as an ideal or optimized formulation of sustained release tablets for 12 hour release as it fulfills all the requirements for sustained release tablet. From the discussion it is concluded that use of carbopol as a release retardant and adhesive polymer is very effective; and also it act as strong release retardant in combination with hydrophobic polymers.

Keywords: Gastroretentive; Mucoadhesive; Venlafaxine hydrochloride; Tablet.

Introduction

Venlafaxine is a unique antidepressant, and is referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor [1]. It works by blocking the transporter reuptake proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitter in the synapse [2]. Venlafaxine inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine, but have no monoamine oxidase inhibitory activity and a low affinity for brain muscarinic, cholinergic, histaminergic or alpha-adrenergic receptors [3]. Hence, it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants [4]. The steady state half lives of venlafaxine are 5 hour, necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug.

doi:10.5138/ijdd.2010.0975.0215.02041

The objective of this present study is to develop a Gastroretentive mucoadhesive sustained release tablet of venlafaxine hydrochloride which releases the drug in a sustained manner over a period of 12 hours, by using Carbopol 971P and Eudragit RS-PO as a mucoadhesive and release retardant respectively.

- To formulate the mucoadhesive sustained release dosage form of venlafaxine hydrochloride.
- To study the effect of polymer concentration on tablet characteristic.
- To study the effect of combination and composition of various polymer materials on tablet characteristic.
- To study the effect of temperature and relative humidity on tablet characteristic.

Materials and methods

Materials

Venlafaxine hydrochloride was provided by Wokhardt pharmaceutical Ltd (Aurangabad, India) and Sodium carboxymethylcellulose (Na CMC) and Dicalcium phosphate was a gift from Ajanta pharmaceutical Ltd Aurangabad, Eudragit-RS PO a gift sample from Glenmark pharmaceutical Ltd Nashik, and other materials are analytical grade.

Methods

Tablets were made by direct compression. All ingredients were weighed accurately and passed through 40 mesh sieve. Drug was mixed with excipients in geometric proportion for 15 min. Weighed quantities of DCP and magnesium stearate were passed through 40 mesh sieve and then blended with the above mass for 3 min. Compression was done on a as Rimek multistation tablet compressing machine fitted with flat punches and dies (13 mm diameter).

Evaluation of tablets [5, 6, 7, 8]

The compressed matrix tablets were evaluated for thickness, weight variation, hardness and drug content.

Thickness

The thickness of tablet was determined using Vernier Caliper (Kayco, India). Six tablets from each batch of formulation were used and mean thickness value and SD was calculated for each formulation.

Hardness

For each formulation, the hardness of six tablets was measured using the Pfizer hardness tester (Cadmach, Ahemadabad, India) and mean value and SD was calculated for each formulation.

Weight variation:

To study the weight variation, 20 tablets of each formulation were weighed using an electronic digital balance. The average weight of each tablet was calculated.

Table 1. Formulation of venlafaxine HCl mucoadhesive tablets.

Ingredients(mg) /Formulatiom	F1	F2	F3	F4	F5	F6
Venlafaxine HCL	150	150	150	150	150	150
Carbopol971P	125	150	175	125	150	175
Eudragit-RS PO	175	150	125	150	125	100
Ethyl cellulose-cp7	-	-	-	50	50	50
DCP	40	40	40	15	15	15
Magnesium stearate	10	10	10	10	10	10

Friability

For each formulation the friability of 6 tablets was determined using Roche Friabilator (Remi Equipments).

Drug content

Five tablets were weighed and powdered. Weigh accurately a quantity of the powder equivalent to 0.1 g of venlafaxine hydrochloride shake with 50 ml of 1.2 pH for 10 minutes, and add sufficient 0.1N HCl to produce 100.0 ml and filter. After suitable dilution with solvent measure the absorbance of the resulting solution at the maximum at about 224.10 nm. Calculate the content of venlafaxine HCl, at the maximum at about 224.10 nm.

Swelling study of formulations [9]

Swelling study of individual polymers and combinations was carried out using USP type I dissolution apparatus (rotating paddle), DISSO 2000 LABINDIA at 100 rpm and 0.1 N HCl was used as medium, temperature was maintained at 37± 0.5^0 C.

Weight of individual tablet was taken prior to the swelling study (W1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 4, 8, 12 hours (W2). Percent hydration (swelling index) was calculated as shown in table 4 using following formula,

% of hydration = (W2-W1) X 100 / W2

Where W1:- initial weight of tablet, W2:- weight of tablet after 12 hours.

Table 2. Evaluation of venlafaxine HCl mucoadhesive tablets.

Formulation Code	Thickness (mm) (mean ±S.D)	Hardness (Kg/cm2) (mean ±S.D)	Weight Variation (%)	Friability (%) (mean ±S.D)	Drug Content (%)
F1	4.05 ±0.0034	7.8±0.0011	2.2	0.48±0.0043	99.05
F2	3.95 ±0.0012	8.00±0.0043	1.4	0.35±0.0023	100.03
F3	3.90 ±0.0023	7.95±0.0022	1.5	0.40±32	98.25
F4	4.00 ±0.0014	7.95±0.0015	1.8	0.41±0.0027	98.12
F5	3.95 ±0.0030	8.05±0.0034	1.4	0.35±0.0028	99.38
F6	3.9 ±0.0033	7.90±0.0020	2.5	0.42±0.0032	100.06

Measurement of matrix erosion [9]

The swollen tablet in swelling study at 12 hours was dried at 60^0 C for in vaccum oven. The tablet were air dried for 7 days and reweighed (W3). Matrix erosion or dissolution was calculated by using following formula,

DS= (W1-W3) X 100 / W1

Where, W1- initial weight of tablet, W3 = Weight of tablet dried at 60^0 C for 24 hrs in vacuum.

In-vitro mucoadhesion measurement [10]

Adhesion time of formulations were determined by using USP type VI (rotating cylinder method) apparatus, DISSO 2000 LABINDIA at 37 ± 0.5^0 C at 100 rpm using 0.1N HCl as a medium. The goat gastric mucosa was adhered to the cylinder by using cynoacrylate glue. The Tablet was pressed on the mucosa gently with the finger for 1 minute. Time upto which Tablet remains adhered to goat gastric mucosa was measured and shown in table 3.

In vitro drug release study [11, 12, 13]

In vitro dissolution of formulation was studied using the rotating basket method (USP Type I apparatus). In this method, 900 ml of 0.1 N HCl was used as the dissolution media. The rate of stirring was 100 rpm. The tablets were placed in dissolution media maintained at 37 ± 5°C for a period of 12 hours. At appropriate time interval up to 12hrs, 5 ml of each sample was taken and 0.45 membranes filtered.

Table 3. Adhesion time of venlafaxine HCl mucoadhesive tablets.

Formulation	Adhesion time in Hrs
F1	9.30
F2	12.00
F3	12.00
F4	10.35
F5	10.42
F6	12.05

The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume (sink condition).

Table 4. Swelling index of tablets.

Formulation	Percent swelling index in hours			% Matrix erosion or dissolution after 12 hours
	4	8	12	
F1	23	39	48	24
F2	29	43	59	27
F3	32	46	61	31
F4	24	40	47	24
F5	31	44	58	29
F6	31	45	61	30

Table 5. Drug release profile of mucoadhesive tablets.

Time	F1	F2	F3	F4	F5	F6
1	42.42857	23	20.57143	18	23	23.28571
2	48.80714	31.84206	33.1142	36.67143	31.12778	32.27222
3	57.64841	42.16111	41.444	41.58889	44.3	42.73651
4	55.39444	54.96508	51.24	53.24683	45.83016	48.40079
5	64.84048	58.5754	56.807	57.25397	55.36746	52.38095
6	68.432	64.30238	63.54762	64.85317	66.24206	58.09603
7	72.14286	79.08175	73.60873	72.20714	69.74683	64.453
8	79.40079	85.36984	79.15238	77.45714	75.4119	69.26984
10	92.69683	91.21746	81.7246	80.01984	76.24921	73.93254
12	107.4929	98.85397	90.7373	85.02302	83.3746	81.47619

The amount of drug present in the samples was calculated with the help of calibration curve constructed.

Result and discussion

Evaluation of tablets

The thickness of all the formulations were varies within ranges from 3.8 - 4.10 mm. All the formulation showed uniform thickness. The weight variation test was carried out as per official method and it was found that all formulation to be within the limit (as per pharmacopoeial standard). The content uniformity test was also carried out as per official method and it was found that different batches shown good content uniformity. It was found that all batches shown percent drug content more than 98 %. The tablet hardness of all the formulations was determined and it was found sufficient in the range 7.5-8.1 kg/cm^2. Another measure of tablet hardness was the friability. A compressed tablet that loses less than 1% of their weight is generally considered acceptable. For all formulation tried here the weight loss was less than 1% hence acceptable.

In vitro bioadhesion time

Adhesion time of formulations was shown in table 3. Formulation 2 and 3 shows adhesion time up to 12 hours. Mucus turnover in humans is 12 hours. So formulations were designed to adhered mucosa up to 12 hours.

Swelling study and matrix erosion

The percentage water uptake of the formulations (F1–F6) at 12 hr ranged from 47 to 61 %, shown in table 4.

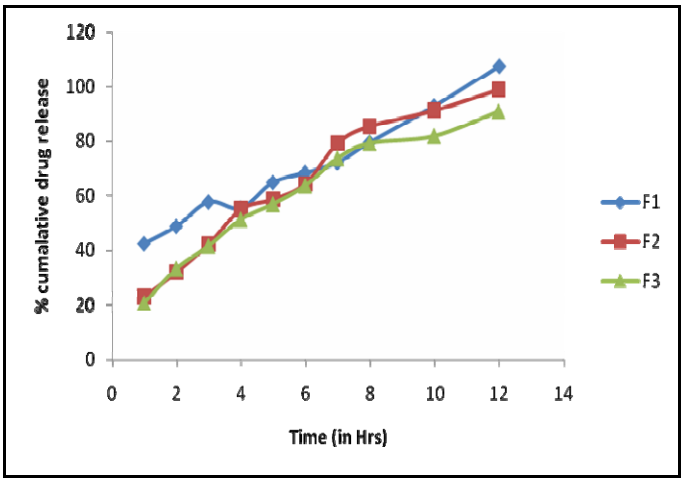

Figure 1. Drug release profile of formulation F1, F2 and F3.

Because of hydrophilic nature of carbopol the percentage water uptake was found to be increased on increasing the concentration of carbopol. While the percentage matrix erosion was found to be increased with increasing the concentration of carbopol in the formulations because carbopol get dissolve in water giving stable colloidal dispersion and thereby eroded to a greater extent; and was found to be decreased on increasing the concentration of eudragit RSPO and

ethyl cellulose because hydrophobic nature of polymer forming barrier for swelling of carbopol. The drug release rate decreases with increasing the concentration of carbopol and ethyl cellulose.

***In vitro* drug release study**

The drug release profile of formulation F1-F6 was shown in table 5. As the concentration of carbopol increases the drug release rate decreases due to high matrix gel formation. The drug release rate of formulation containing ethyl cellulose was less than formulation containing eudragit RSPO due to high hydrophobic nature of ethyl cellulose than eudragit RSPO which form strong barrier to restrict the swelling of carbopol and decrease the drug release rate.

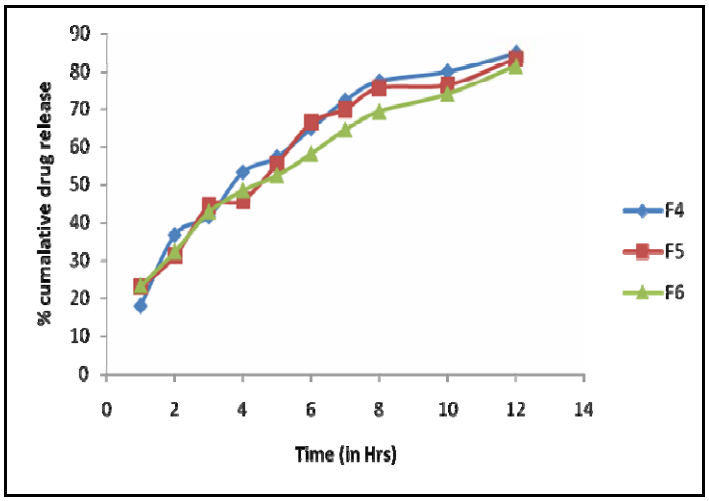

Figure 2. Drug release profile of F4, F5 and F6.

Conclusion

The prepared mucoadhesive tablets of Venlafaxine hydrochloride prepared and evaluated. The adhesion time of the batch F2, F3 and F6 are up to 12hours which increases its GI residence. As the concentration of carbopol 971P increased, the adhesion time is increase. The swelling index of the batch F3 and F6 is higher as compared to other batches. Drug release was found to be decreased as level of ethyl cellulose is increase and batch F2 having considerable swelling index and release of drug up to 12 hrs (98.85%). So it was concluded that Batch F2 can be taken as an ideal or optimized formulation of sustained release tablets for 12 hour release as it fulfills all the requirements for sustained release tablet.

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