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Formulation and Evaluation of Sustained release tablets of Venlafaxine HCl

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ABSTRACT

The aim of the present study was to develop a tablet formulation for sustained release of venlafaxine HCl. Control or sustained release formulations have great applications in improving the physicochemical properties and the pharmacokinetic profile of the drugs. Carbopol tablets containing venlafaxine HCl were developed successfully by wet granulation technique. The tablets were evaluated for matrix integrity and drug release in 0.1 N HCl using USP II dissolution apparatus maintained at optimum conditions. The developed tablets were robust and possessed excellent physicochemical properties. The tablets showed great matrix integrity and withstood the hydrodynamic environment of the dissolution medium for > 12 hours. The hydration and swelling behaviour of the tablets was excellent. It was found that the swelling characteristics of the tablets depended on the amount of the polymer used in the tablets as well as the polymer/drug ratio. The tablets provided more than 90% drug release over a period of 12 hours. The drug release data was subjected to kinetic dissolution modelling. It was found that the drug release from the tablets followed Korsmeyer-Peppas model of drug release. This suggests that the mechanism of the drug release from the formulations may be both diffusion as well as polymer erosion.

Keywords: Sustained release, Carbopol, Venlafaxine HCl

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INTRODUCTION

Drug treatment via the oral route is the most common and convenient way to administer medications (1). Due to its non-invasive nature, it can be regarded as cost efficient, highly acceptable to patients and thus compliance enhancing (2, 3). Sustained release (SR) drug delivery systems are developed to modulate the apparent absorption and/or alter the site of release of drugs, in order to achieve specific clinical objectives that cannot be achieved with conventional dosage forms (4, 5). Possible therapeutic benefits of a properly designed SR dosage form include improved efficacy and reduced adverse effects, increased convenience and patient compliance, optimized performance, a greater selectivity of activity or new indications. Drug release modification is a technique or approach by which the delivery pattern of a therapeutic agent is altered via engineering of physical, chemical and/or biological components into delivery systems for achieving desired/target plasma drug levels defined by the clinical pharmacology.

Different polymers are used to impart sustained release characteristics to the formulations (6-8) e.g. hydroxypropyl methyl cellulose (HPMC), Eudragit, ethyl cellulose, carbopol etc. In the present study carbopol has been used a sustained release polymer for formulation development (9-11). Carbopol, a polyacrylic acid is a synthetic, high molecular weight, crosslinked polymer (12). It is readily absorbs water, hydrates and swells (13, 14). In addition, its hydrophilic and crosslinked nature makes it a potential candidate in controlled release drug delivery systems (15). In case of tablets formulated with carbopol polymer, the drug is trapped in the glassy core in dry state. It forms a gelatinous layer upon hydration. However, this gelatinous layer is significantly different structurally from the traditional matrix tablets. The hydrogel is not entangled chains of polymer, but discrete microgel made up of many polymer particles in which the drug is dispersed. The crosslinked network enables the entrapment of drug in the hydrogel domains. Since these hydrogels are not water soluble they do not dissolve, and erosion in the manner of linear polymer does not occur. Rather, when the hydrogel is fully hydrated, osmotic pressure from within works to break up the structure, essentially by sloughing off discrete pieces of the hydrogel. This hydrogel remains intact, and the drug continues to diffuse through the gel layer at a uniform rate.

Venlafaxine HCl is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class first introduced by Wyeth in 1993 (16-19). Steady-state concentrations of venlafaxine and O-desmethylvenlafaxine

(20) in plasma are attained within 3 days of oral multiple dose therapy. Venlafaxine and O-desmethylvenlafaxine exhibited linear kinetics over the dose range of 75 to 450 mg/day. Mean +/-SD steady-state plasma clearance of venlafaxine and O-desmethylvenlafaxine is 1.3 +/- 0.6 and 0.4+/-0.2 L/hr/kg, respectively; apparent elimination half-life is 5 +/- 2 and 11 +/- 2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5 +/- 3.7 and 5.7 +/- 1.8 L/kg, respectively. Venlafaxine and O-desmethylvenlafaxine are minimally bound at therapeutic concentrations to plasma proteins (27% and 30%, respectively).

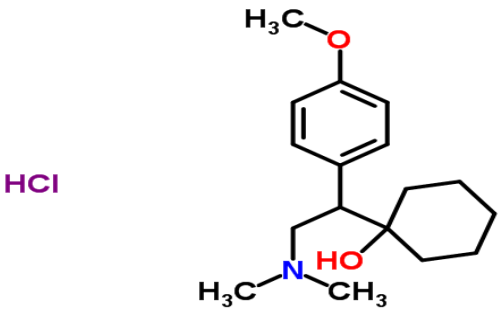

Figure 1: Structure of Venlafaxine HCl

MATERIALS AND METHODS

Venlafaxine HCl was a kind gift from Sun Pharma India. Carbopol was kindly provided by Lubrizol India. All the other chemicals were of analytical grade.

Preparation of Matrix Tablets

Matrix tablets of venlafaxine HCl were prepared by wet granulation technique. All the ingredients were accurately weighed and thoroughly blended. The powder mixture of all the ingredients was then fed into the die cavity of the tablet machine which was compressed by 8 mm punch. The tablets were collected and stored in air tight polythene bags. The composition of various matrix tablets prepared is shown in **table 1.**

Table 1: Composition of various sustained release tablets of Venlafaxine HCl

Formulation	Drug (mg)	Polymer (mg)
F1	50	400
F2	50	300
F3	50	200
F4	50	100
F5	50	50

Weight variation and content uniformity

Weight variation test was done on a batch of 20 tablets. The tablets were weighed individually and average weight of all the tablets was determined. The difference in the weight of all the tablets from the average weighed was calculated. Then the mean deviation of each tablet from the average weight was determined.

Content uniformity test was conducted on 10 tablets. The tablets were dissolved in 0.1N HCl and the solution was filtered through Whtaman filter paper. Amount of drug in the solution was determined by UV spectrophotometric method at λ_{max} 274 nm.

Swelling Studies

The tablets were immersed in 0.1 N HCl using USP II dissolution apparatus for 12 hours. The dimensions of the tablets at different intervals of time were measured using a Vernier caliper. Also the amount of water intake was determined by taking the difference of the initial and the final weights of the tablets at the start and the end of the experiment.

Dissolution studies

In vitro drug release was performed for the manufactured tablets of venlafaxine HCl according to the USP 30 "Dissolution procedure" <711>, over a 12 hour period, using an automated dissolution system. A minimum of 6 tablets per batch were tested (N = 6). USP apparatus II (paddle) was used at 50 rpm, with 900 ml dissolution medium (0.1N HCl) at 37°C; the UV absorbance of the dissolution medium was measured at different sampling time points. The release was calculated using a standard solution. The parameters set of in vitro dissolution testing of venlafaxine HCl and indomethacin matrix tablets is given in table 5 – 21. The conditions for dissolution studies of venlafaxine tablets are summarized in **table 2**.

Table 2: Conditions for dissolution testing of carbopol tablets

Parameter	Venlafaxine HCl Matrix Tablets
Condition	37 °C
N	6
Test period	12 hours
Agitation rate	50 rpm
Dissolution media	0.1N HCl
Sampling time points	1, 2, 4, 6, 8, 12 hours
Sinker	JP basket sinker

RESULTS AND DISCUSSION

Polymer screening

Before selecting a proper polymer for the development of matrix tablets of venlafaxine HCl a number of polymers possessing rate controlling properties were screened for best physicochemical properties. The polymers were screened on the basis of matrix integrity of the tablets and the drug release from the tablets. After evaluating a number of polymers like, HPMC, ethyl cellulose, eudragit etc. carbopol was found to impart the optimum properties to the sustained release tablets of venlafaxine HCl.

Swelling Behaviour of Matrix Tablets

The tablets of venlafaxine were placed in 900 ml of 0.1 N HCl in USP II dissolution apparatus stirring at a speed of 50 rpm and maintained at 37± 0.5 ºC. At different intervals of time the tablets were taken out and the dimensions of the tablets measured using a Vernier caliper. It was found that with time, the volume of the tablets increased largely **(fig 2)**. It was found that the volume of the tablets was increased to more than double of the initial volume of the tablets. This may be attributed to the fact that carbopol undergoes rapid hydration when it comes in contact with water. As the water penetrates into the polymer matrix, it surrounds the individual polymeric chains, hydrates them and forms gel like structures. These gel like structures increase the dimensions of each polymer chain and hence the bulk of the tablet matrix increases.

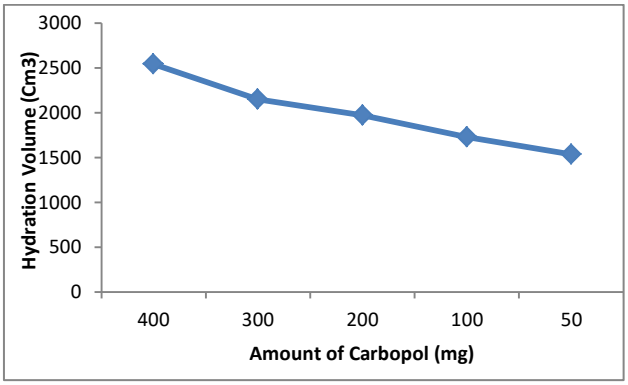

Figure 2: Effect of amount of carbopol on swelling behaviour of tablets. With decrease in the amount of carbopol the swelling behaviour of tablets decreased

Effect of Drug on Swelling Properties of Matrix Tablets

Figure 3 shows the effect of drug on the swelling behaviour of the matrix tablets. It can be clearly seen from the graph shown that as the amount of the drug in the matrix tablets increases the hydration volume of the tablets decreases. This may be attributed to the fact that as the amount of the drug in the tablets increases a large proportion of the polymer is replaced by the drug. Hence the decrease in the amount of the polymer decreased the volume of hydration and the amount of swelling. Further, since the drug dissolution results in the leaching out of the drug from the polymer matrix, which results in incorporation of voids inside the matrix and hence decreases the net contents of the tablet resulting in decreased swelling.

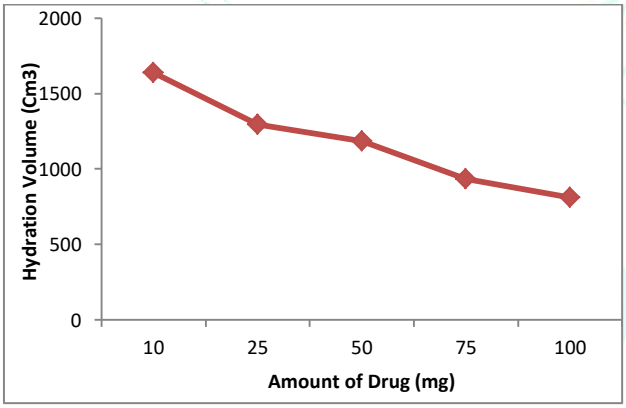

Figure 3: Effect of amount of drug on hydration volume of carbopol tablets. With increase in the amount odrug the hydration volume decreased

Polymer:Drug Ratio and Integrity of Tablets

Tablets containing different amounts of polymer and drug were evaluated for matrix integrity. The tablets were placed in 900 ml of 0.1N HCl in USP II apparatus stirring at a speed of 50 rpm and maintained at 37± 0.5 ºC for 12 hours and the effect on the matrix integrity was observed up to 12 hours. It was found that that as the polymer to drug ratio decreased the matrix integrity of the tablets also decreased. This is because of the fact that the polymeric chains in the carbopol matrices are chemically crosslinked and as the amount of the polymer in the tablets decreases the amount of crosslinking also decrease resulting in lowered matrix integrity. **Figure 4** shows the effect of the polymer:drug ratio on the matrix integrity of the tablets.

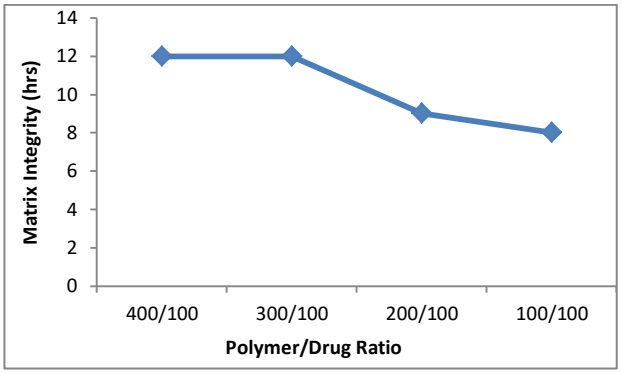

Figure 4: Effect of Polymer/Drug Ratio on matrix integrity of carbopol tablets. With decrease in polymer/drug ratio, matrix integrity of carbopol tablets decreased.

Drug Release Studies

The carbopol tablets were evaluated for drug release studies using a USP II apparatus. The tablets were placed in 900 ml of 0.1 N HCl maintained at 37± 0.5 ºC and with the paddles stirring at a rate of 50 rpm. The drug release profile of the carbopol tablets containing venlafaxine is shown in **table 3** and **Figure 5**. Among the various formulations prepared, F2 and F3 showed the better results. The matrix integrity as well as the drug release was excellent. The tablets withstood the hydrodynamic conditions of the dissolution medium up to 12 hours and the drug release from the formulation was > 90%.

Table 3: %Cumulative drug release from carbopol tablets

Time (hrs)	F2	F3
1	18.65	19.32
2	27.89	29.75
3	37.49	37.95
4	43.5	44.37
5	50.46	55.74
6	59.72	63.41
7	64.13	68.58
8	68.83	76.03
9	75.4	81.63
10	82.73	87.44
11	87.55	92.89
12	92.51	96.77

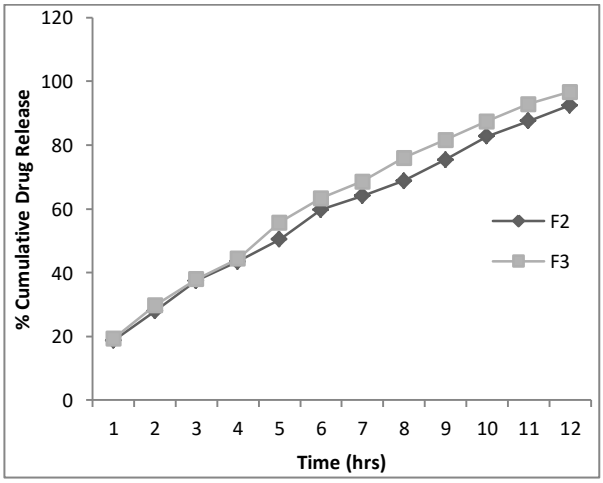

Figure 5: Graphical representation of the drug release profile of carbopol tablets

Dissolution Data Modelling

Dissolution modelling is very important in providing the idea about the kinetics of the drug release from a dosage form. The drug release obtained from the formulations F2 and F3 were subjected to dissolution data modelling in order to derive the basic underlying mechanism of drug release from the tablets. The outlook of the various models applied to the drug release is provided in **table 4** below.

Table 4: Regression values obtained from various dissolution data models

Model		Zero Order	First Order	Higuchi	Korsmeyer-Peppas
R^2 Value	F1	0.9916	0.9385	0.9624	0.9983
	F2	0.9871	0.9105	0.9683	0.9975

It was found that the tablet formulations mentioned above followed Korsmeyer-Peppas model of drug release since the regression values for the model among the all other models was highest close to 1 (R^2=0. 9983). Hence it can be concluded that according to the given model the drug from the tablet formulations is released by a combination of more than one mechanism, i.e. diffusion and polymer erosion. The various models are shown in **figure 6**.

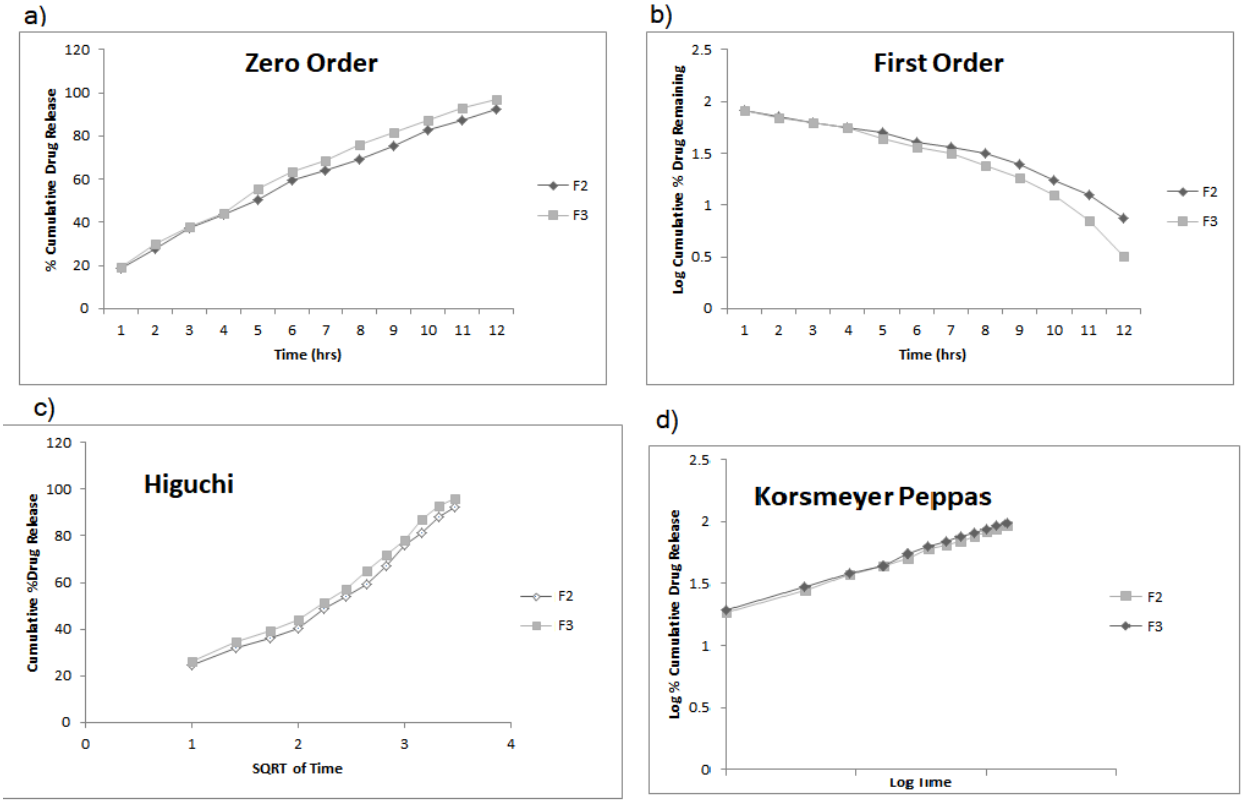

Figure 6: Various dissolution data models showing kinetics of drug release a) Zero Order model; b) First Order model; c) Higuchi model; d) Korsmeyer-Peppas model

Weight variation and content uniformity

The average weight of the formulations tested was found to be within the permissible limits as shown in **table 5**. The test was carried on 20 tablets and all the tablets passed the test.

Table 5: Weight variation of sustained release tablets

Formulation	Tablets	Average Wt.
F1	20	361 ± 8
F2	20	259 ± 9

The uniformity in the amount of drug in all the formulations prepared was evaluated by content uniformity test. This test was conducted on 10 tablets. The variation in the amount of the drug in different tablets of a batch was within the permissible limits. **Table 6** shows content uniformity of the tablet formulations.

Table 6: Drug content uniformity of sustained release tablets

Formulation	Tablets	Average Drug Content
F1	10	50 ± 2
F2	10	50 ± 3

CONCLUSION

A large number of polymers are being investigated for the development of sustained drug delivery systems. These dosage forms ensure constant delivery of drugs to the site of absorption and as a result improve the pharmacokinetics of drugs. In the present study sustained dosage form of venlafaxine HCl using carbopol as rate controlling polymer has been developed. It has been clearly shown that carbopol tablets of venlafaxine HCl can be efficiently prepared by wet granulation technique. The developed tablets possessed excellent physicochemical properties and provided drug release of >90% over a period of 12 hours at a constant rate. The tablets displayed great matrix integrity for the whole time of experiment (i.e. >12 hours). Hence the above developed tablets can be beneficial in providing constant drug to the site of absorption and thus increasing the bioavailability of the drug, venlafaxine HCl.

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