Research Article

Available online through
www.ijrap.net

IJRAP
ISSN 2229-3566

FABRICATION OF SUSTAINED RELEASE MATRIX TABLETS OF VENLAFAXINE HYDROCHLORIDE USING EUDRAGITS

Radhika P.R*, Dedeepya Karanam, Sivakumar T
Nandha College of Pharmacy and Research Institute, Koorapalayam Pirivu, Erode, Tamilnadu, India

Received on: 05/06/2011 Revised on: 02/07/2011 Accepted on: 09/08/2011

ABSTRACT
The aim of the study was to design sustained release matrix tablets of Venlafaxine Hydrochloride using a high permeable Eudragit RLPO and low permeable Eudragit RSPO in different ratios. Tablet matrices were prepared by direct compression and were formulated as F_1, F_2 and. F_3 by using the above mentioned polymers. Technological characterizations like thickness, diameter, weight variation test, drug content, hardness, and friability were carried out with the formulated matrix tablet. The i*n-vitro* drug releases of the formulated tablets were measured using the USP - 24 types II dissolution apparatus. The formulations showed an optimum hardness, constant weight uniformity and low friability. The kinetic release treatment showed that the release of drug follows Zero order kinetic (r^2 = 0. 9965), Koresmeyer equation gave value of r^2= 0.9980 which was close to one indicating that the drug was released by Zero order kinetic. The *in- vitro* drug release data to Koresmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. The formulation F1 containing high quantity of Eudragit RSPO provided the slowest release profile and 90 % of the drug content was released after 18 hours than other formulations. The systematic formulation approach enabled to develop sustained release Venlafaxine Hydrochloride tablets.
Further investigations are needed to confirm the in vivo efficacy and this study demonstrated that Eudragit polymer can provide controlled release
KEY WORDS: Venlafaxine Hydrochloride, Sustained Release, Eudragit RLPO Eudragit RSPO, Matrix tablet.

***Author for Correspondence**
Dr. Radhika.P.R, Nandha College of Pharmacy and Research Institute, Koorapalayam Pirivu, Erode, Tamilnadu, India Email: radhi_kannan2005@yahoo.co.in

INTRODUCTION

Venlafaxine hydrochloride, novel antidepressants, is referred to as a serotonin-nor epinephrine-dopamine reuptake inhibitor[1, 2]**.** It works by blocking the transporter "reuptake" proteins for key neurotransmitter affecting mood, thereby leaving more active neurotransmitter in the synapse. The neurotransmitters affected are serotonin 15-hydroxy tryptamine and nor epinephrine (noradrenalin). It is widely prescribed for the treatment of depression, generalized anxiety disorder, and social anxiety disorder. The recommended oral dosages of Venlafaxine hydrochloride are typically in the range of 75 to 225mg per day. Because of its relatively short half-life of 5 hour, Venlafaxine should be administered in divided dosages throughout the day[3]**.** Its short biological half-life (5hr), calls for frequent daily dosing (2-3 times) and therapeutic use in antidepressant necessitates its formulation into sustained release dosage.

Plastic polymers examples acrylate and ethyl cellulose are capable of forming insoluble or skeleton matrices are widely used for controlled release of drugs due to their inertness and drug embedding ability. Liquid penetration into the matrix is the rate controlling step in such systems, unless channeling agents are used.[4.]
Acrylic polymers are widely used as tablet retardants and as coatings of drug release in sustained release formulation[5]. The most interested acrylic polymers are highly permeable Eudragit RLPO and low permeable Eudragit RSPO, both of which are neutral copolymers of poly (ethyl acrylate, methyl metha acrylate) and trimethyl amino ethyl methacrylate chloride. These are insoluble in water and digestive juices, but they swell and are permeable, which means that drugs embedded in their matrices can be released by diffusion [6]. Therefore, the permeability of drug through Eudragit RSPO and or RLPO is independent of the pH of the digestive tract. The degree of permeability depends on the relative

proportion of quaternary ammonium groups in Eudragit. The proportion of functional quaternary ammonium groups in Eudragit RL and Eudragit RS is 10% and 5% respectively. Eudragit RLPO and RSPO are fine, white powders with a slight amine like odour.

The present research was directed towards the development of sustained release dosage form of Venlafaxine hydrochloride tablets using Eudragit RSPO and Eudragit RLPO as plastic matrix to retard drug release.

MATERIALS AND METHODS

Venlafaxine hydrochloride was obtained from Orchid Pharmaceuticals, Chennai, Eudragit RSPO and Eudragit RLPO was procured from Rohm Pharma, Germany, Lactose, magnesium stearate and talc was of IP grades. All other ingredients used throughout the study are of analytical grade and were used as received.

Preparation of Sustained Release Venlafaxine Hydrochloride Matrix Tablets

Matrix tablet, each containing 37.5 mg Venlafaxine hydrochloride, was prepared by direct compression technique. The drug polymer ratios were developed to adjust drug release (Table-1) and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets were 400 mg with different drug polymer (Eudragit RSPO and Eudragit RLPO) ratios. A batch of 100 tablets was prepared in each formulation ($F1 - F_3$). The compositions of tablets are shown in the (Table-1) and the ingredients were passed through sieve no: 30 and thoroughly mixed. The powder blend was then lubricated with Aerosil, talc and magnesium stearate and compressed into tablets on a single punch 10 mm diameter tablet compression machine.

Evaluation of Tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of tablets was tested using Monsanto-tester, friability of the tablet was determined in a Roche Friabilator. The thickness of tablet was measured by using vernier calipers. Weight variation test was performed according to official method[7]. Drug content for Venlafaxine Hydrochloride was carried out by measuring the absorbance of samples at 224nm using UV-Visible spectrophotometer and comparing the content from the calibration curve prepared with standard curve of Venlafaxine hydrochloride (Table-2).

In-vitro Drug Release Studies

The i*n-vitro* dissolution studies were carried out using USP 24 dissolution Apparatus type- II [8] (paddle method at 100 rpm). Dissolution test was carried out for a total period of 24 hours using 0.1 HCl (pH1.2) solution with 900 ml as dissolution medium at 37 ± 0.5^{oc} for first 2 hours, and pH 7.2 phosphate buffer solution 900ml for the rest of the period .5ml of the sample was withdrawn at regular intervals and replaced with the same volume of pre warmed (37 ± 0.5) fresh dissolution medium. The samples withdrawn were filtered through 0.45 µ membrane filter and drug content in each sample was analyzed after suitable dilution by above mentioned spectrophotometer at 224 nm. The actual content in samples was read from a calibration curve prepared with standard Venlafaxine hydrochloride (Figure- 1).

Kinetic Analysis of Dissolution Data

The commonly adopted model of understanding release behavior of a drug from hydrophilic matrix is by a simple exponential equation[9]. The *in-vitro* drug release data were fitted in the experimental equation known as Korsmeyer - peppas equation $Mt/M_\infty = Kt^n$, where Mt corresponds to the amount of drug release in time t, M_∞ is the total amount of drug released after an infinite time, K is a constant related to the structural and geometric properties of the drug delivery system and 'n' is the release exponent related to the mechanism of the release. Table -3 shows an analysis of diffusional release mechanism obtained by various values of 'n'[10] The 'n' values used for elucidation of the drug release mechanisms from the tablets were determined from log cumulative percentages of drug released verses log time plots (ie, log Mt/M∞ ×100) verses log t.

Stability Studies

The selected fabricated tablet was kept at 45°c with 75% RH. Samples were withdrawn at 0, 15, 30 and 45 days for evaluation of appearance, drug content and *in-vitro* drug release.

RESULT AND DISCUSSION

For a freely soluble drug like Venlafaxine Hydrochloride, a rapid rate of hydration of matrix agent is necessary. A slow polymer hydration rate may lead to dose dumping due to quick penetration of dissolution fluid in the tablet core. Hence a rapidly permeable Eudragit RLPO and low permeable Eudragit RSPO were used as polymers, for preparing the sustained release matrix tablet of Venlafaxine Hydrochloride by direct compression.

The prepared tablets were subjected to different evaluation tests based on USP. The drug content of each tablet should be in the range of 85 % – 115%. According to the above said results, the drug content distribution of each formulation was uniform. All the formulations showed good uniformity in drug content.

Results of tablet hardness test showed that the hardness and friability of all formulations were in a range from 5 – 7 kg/cm^2 and 0.39% – 0.41% respectively. The tablet

hardness for all formulations was in the required limits. The hardness of the tablet increased proportionately with the amount of Eudragit RLPO and Eudragit RSPO. A small difference between formulations is related to the type and percentage of the retarding polymer. Since tablet hardness is not a perfect index to evaluate the strength of tablets, friability was also used to test the hardness of tablets. For all the prepared formulations, friability percentage was less than 1 %, which was in the acceptable range.

According to the pharmacopeial recommendation for tablets weighing more than 324 mg ± 5 % deviation from the mean weight is acceptable. The results show, the average weight deviation percentage of 20 tablets taken from each formulation was less than ± 0.5 %, and all the formulations met the official requirements (Table -2).

Drug Release Studies

When matrices containing swellable polymers are exposed to dissolution medium, tablet surface becomes wet and hydrated to form a gel layer. The initial release of drug from these matrices occurs by the drug dissolution in the water penetrated into the matrix. The overall drug release from these matrices is governed by hydration, gel layer formation, drug diffusion into the gel layer and to the dissolution media[11, 12]

Polymer erosion also plays a major role in release of drugs from these matrices[13]. These considerations indicate that hydrophilic polymers have the potential to sustain the release of drug from matrix tablets.

pH independent compressible Eudragit RSPO and RLPO were used for preparation of matrix tablets. Eudragit RSPO and RLPO are freely flowable powders which can be used for direct incorporation within the matrix.

The formulation F_1 containing high quantity of Eudragit RSPO provided the slowest release profile and 90 % of the drug content was released after 18 hrs. This in turn resulted in a delayed water penetration and gelling of the polymer, where as in the formulation F_3 the release of drug increased with increase in the proportion of Eudragit RLPO and decrease in the presence of Eudragit RSPO. This is due to the increase in the solubility of drug as a result of the presence of a more hydrophilic carrier surrounding the drug particles. This can be attributed to the hydrophilic nature of Eudragit RLPO. When exposed to the dissolution medium, the solvent penetrates into the free spaces between the macromolecular spaces of Eudragit RLPO.

In conclusion the formulation F_1 prepared with more quantity of Eudragit RSPO seems to produce a more appropriate sustained release profile than other formulations. As observed in Fig- 1, the release of F_1 Eudragit RSPO120 mg and Eudragit RLPO 80 mg sustained the release of the drug up to 18 hours i.e. up to 90 %, which indicates that by increasing the concentration of the Eudragit RSPO, drug release may be sustained more than 18 hours.

The formulation F_1 best suited with zero order release kinetics (0.9965) than the first order release kinetics. The Koresmeyer peppas drug release kinetics showed correlation coefficient (0.9980) and release exponent (n) 0.9272 which indicates that the drug release mechanism is Fickian diffusion (Table- 3)

CONCLUSION

Venlafaxine Hydrochloride tablets were prepared by direct compression using Eudragit RSPO and Eudragit RLPO in different ratios. These polymers have potentials for aiding the formulation of sustained release Venlafaxine Hydrochloride matrix tablets. The approach of the present study was to make a comparative evaluation among the methacrylic esters polymers and to find out factors involved on drug release profile. By using these polymers, sustained release dosage form of Venlafaxine Hydrochloride would not only increase the efficacy of treatment and patient compliance, but also produce desirable blood concentrations and decrease the incidence of adverse effects.

Finally it can be concluded that study have established a feasibility of formulating a sustained release matrix tablet of Venlafaxine Hydrochloride with different ratios of Eudragit RSPO and Eudragit RLPO and further studies could be carried out from these formulations.

REFERENCES

1. Holiday SM, Benfield P, Venlafaxine: A review of its pharmacology and therapeutic potential in depression, Drugs 1995: 49: 280-294

2. Haskins JT, Moyer JA, Muth EA, Sigg In hibition of Nor adrenergic neuronal activity by nivel bicyclic compounds, Wy – 45030 and Wy – 45881, SOC Neuro Sci Abstract 1984; 10:262.

3. Troy SM, Panker VD, Fruncillo RJ, Chiang ST. The Pharmaceutics of Venlafaxine when given in a twice daily regimen, J Clin Pharmacol 1993: 35: 404-409.

4. Reza MS, Quadir MA, Haider SS, Comparative evaluation of plastic, Hydrophilic and Hydrophobic polymer as matrices for controlled release drug delivery, J.Pharm Pharmaceutica , science 2003: 6: 282-291.

5. Mehta KA, Kislaloglu MS, Phuapradit W, Malick AW, Shah NH, Release performance of a poorly soluble drug from a novel Eudragit based multi unite erosion matrix, Int. J.Pharm ,2001: 213:7-12.

6. Kibbe AH 9th Ed Handbook of Pharmaceutical excipients, Washington DC, USA, American Pharmaceutical association 2000, 401-406.

7. Indian Pharmacopoeia, Vol-II, 4th Edn , The Controller of publications, New Delhi, 1996, 736.

8. The United States pharmacopoeia 24, the United States, Pharmacoepeial convention, Rockvillie, MD, 2000, 1942.

9. Korsmeyer RW, Gunny R and Peppas NA, Int.J.Pharm 1983; 15: 25.

10. Langer RS and Peppas NA, Biomaterials 1981; 2: 201.

11. Capany. Influence of technological factors on the formulation of sustained release tablets. Drug Dev. Ind. Pharm. 1988; 12:2337-2353
12. Kibbe AH (Ed). Handbook of pharmaceutical excipients, Washington D.C, USA, American pharmaceutical association 2000: 401-406.
13. Aulton ME. Editor Pharmaceutics, the science of dosage form design. Oxford. Churchill Livingstone 2005, 133-134.

Table- 1: Drug and polymer composition of different formulations

S.No	Ingredients	F_1(mg)	F_2(mg)	F_3(mg)
1.	Drug	37.5	37.5	37.5
2.	Eudragit RSPO	120	80	40
3.	Eudragit RLPO	80	120	160
4.	Lactose	140.5	140.5	140.5
5.	Talc	12	12	12
6.	Magnesium stearate	6	6	6
7.	Aerosil	4	4	4

Table: 2 Physical parameters of fabricated Venlafaxine Hydrochloride Matrix tablets

S.No.	Hardness (kg/cm^2)	Friability (%)	Weight Variation (%)	Drug Content (%)	Thickness (mm)
F_1	6.5±0.15	0.41	0.19	37.53±0.32	4.75 mm
F_2	7.0±0.10	0.39	0.14	37.50±0.31	4.74 mm
F_3	5.0±0.12	0.57	0.16	37.54±0.33	4.73 mm

Table: 3 Mathematical Modeling and Drug release kinetics of Venlafaxine Hydrochloride for the Formulated matrix tablets

FORMULATIONS	ZERO ORDER	PEPPAS PLOT	
	R	'n'	R
F_1	0.9965	0.9272	0.9980
F_2	0.9913	0.8031	0.9944
F_3	0.9810	0.6925	0.9876

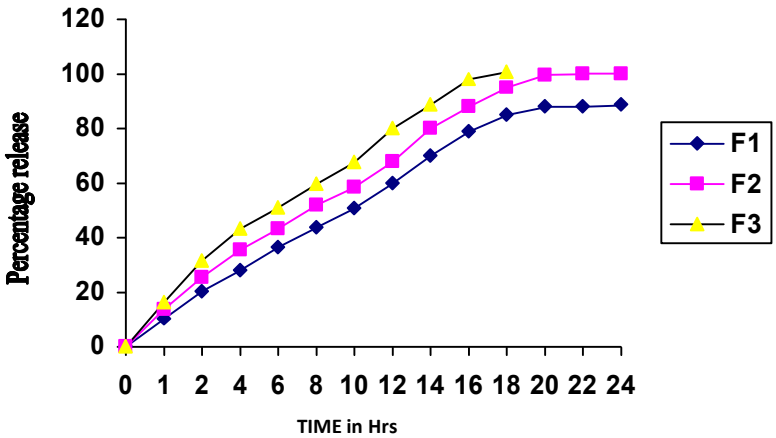

Figure: 1 Graph showing the *in-vitro* release profile of Venlafaxine Hydrochloride for the Formulated matrix tablets

Source of support: Nil, Conflict of interest: None Declared