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DESIGN AND OPTIMIZATION OF CONTROLLED RELEASE MATRIX AND RESERVOIR BASED VENLAFAXINE HCL TABLETS USING DESIGN OF EXPERIMENTS

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ABSTRACT

Venlafaxine Hcl is one of the most widely used antidepressant drug. The exact mechanism of action of Venlafaxine hydrochloride is unknown, but appears to be associated with its potentiating of neurotransmitter activity in the CNS. Venlafaxine HCl inhibits the reuptake of both serotonin and nor epinephrine with a potency greater for the 5-HT than for the NE reuptake process. Due to its short half life it is formulated as a controlled release dosage form which allows for once a day drug administration. The innovator product available in the market is a reservoir system based on the MUPS platform. This system typically involves a complex process of loading of the drug onto non peril pellets followed by solvent based coating of the pellets with ethyl cellulose and pore former. The processing times may be as high as 36 to 60 hours and involve multiple stage sampling and analysis. The current work focuses on developing a simple tablets system based on swellable hydrophilic matrix and reservoir based coating systems in order to give a release profile similar to the innovator product. Our Aim is to design and optimize the controlled release matrix and reservoir based tablets of Venlafaxin hydrochloride (antidepressant drug) by using design of experiments. Our objective is to study the effect of concentration of polymers on the rate of drug release. In order to establish the controlled release we planned to use the polymers of 3 different grades (HPMC-K4M,K15M,K100M) at 3 different levels. Another 3^3 factorial design will be introduced to optimize the formulation of Venlafaxin hydrochloride loaded with PVP, Aerosil and with 3 different grades (k4M,k15M,k100M) of HPMC in 3 different levels(10%,15%,20%.). For the reservoir based system, core tablets of Venlafaxin HCl shall be formulate and then coated with Ethyl cellulose and pore former. The coating weight gain,

and the level of Ethyl cellulose and pore former shall be optimized using design of experiments (DOE).

KEYWORDS: Venlafaxine Hcl, antidepressant, 3 different grade polymers (HPMC-K4M,K15M,K100M), 3^3 factorial design method, PVP,Aerosil, 3 different grades of HPMC (k4M,k15M,k100M), Ethyl cellulose, DOE.

1. INTRODUCTION

The diseases affecting the CNS are becoming increasingly common especially in the area of schizophrenia and depression. Even though a large number of drugs are extant, there is a huge gap in therapeutics since all the drugs available only treat to the symptoms and do not necessarily address the under laying cause. One of the major reasons for failure of therapy with even the most potent drug is noncompliance and non-adherence to therapeutic regimen. Hence, the focus of global pharmaceutical companies is to modify the delivery of existing drugs in such a way that frequency of dosing can be significantly reduced.

The present work focuses on evaluating the effect of hydrophilic sustained release polymers on two widely used drugs affecting the CNS in order to control drug delivery and thereby reducing the dosing frequency.

Venlafaxinehydrochloride is a unique antidepressant, according to Vaughan Williams Classification it comes under class I. The exact mechanism of action of Venlafaxine Hydrochlorideis unknown, but appears to be associated with itspotentiating of neurotransmitter activity in the CNS.Venlafaxine inhibit the reuptake of both serotonin and nor epinephrine with a potency greater for the 5-HT than for the NE reuptake process.

In order to retard the drug release and to release it over 24 hours at a required rate, matrix and reservoir type of controlled drug delivery system has been utilized. In present work, we are getting the data base platform for oral controlled release matrix based system for oral control release reservoir based system for Venlafaxine hydrochloride has also been targeted to achieve. A design space has been formulated within which hydrophilic polymers can successfully achieve a fixed targeted in vitro dissolution profile for controlled delivery over 24 hours for the model drugs selected. The hydrophilic polymers used in this study are HPMC K4M, K15M and K100M. The reason behind selection of these polymers is they are well characterized and most widely used.

In a matrix system the drug is dispersed as particles within a porous matrix. In this sense, the term "matrix" indicates the three dimensional network containing the drug and other substances such as solvents and excipients required for the specific preparation. Matrix drug delivery systems release the drug in continuous manner either by dissolution controlled or diffusion controlled mechanisms or both. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer.[5]

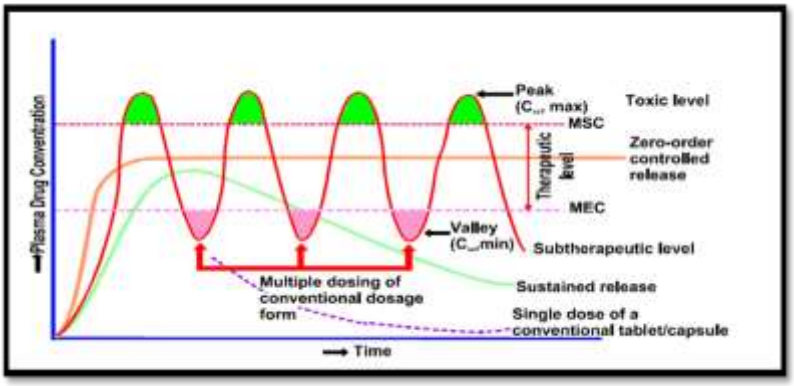

Figure 1.1: A Hypothetical Plasma Concentration-Time Profile From Conventional Multiple Dosing and Single Doses of Sustained and Controlled Delivery System.[6]

1.1 Drug delivery systems[7]

a) **Diffusion-controlled DDS:** Oral matrix-type systems, hydrophobic matrix systems, Hydrophilic Matrix systems, Reservoir-type systems, Transdermal, Drug in Adhesive systems, Monolithic adhesive systems, Multilaminate Adhesive systems, inert matrix systems, Semisolid matrix systems Reservoir matrix systems, other diffusion controlled systems, Intrauterine devices and intra vaginal rings, Intraocular inserts Subcutaneous implants.

b) **Dissolution-controlled DDS**: Based on dissolution-controlled release of solid particles. Based on dissolution-controlled release coated technologies, Based on dissolution-controlled release matrix technology.

c) **Osmotic controlled DDS**: Osmotic delivery systems for solids and liquids.

d) **Biodégradable Polymeric DDS**: Microparticles, Nanoparticles, Implants

e) **Programmable DDS**: Pulsatile systems, Feedback-controlled systems.

f) **Stimulus responsive**: Physically modulated.

g) **Chemically modulated**: pH dependent.

1.2 Matrix systems

Matrix forming material can be of hydrophilic, lipid, inert and biodegradable type. In a matrix system the drug is dispersed as particles within a porous matrix. The release of the drug is by dissolution controlled as well as diffusion controlled mechanisms. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer.[7]

Mechanism of Drug Release

The diffusion – controlled release are split into two types: reservoir system and matrix or monolithic system. In the matrix or monolithic system, drug is distributed through a polymer that serves as the diffusion barrier. Though diffusion release is the major mechanism of drug release for inert matrices, matrix swelling and erosion can also have significant impact on release rate for other matrix material.

Various mathematical models have been studied to predict the delivery performance as a function of material properties and device fabrication process of drug delivery system.

i. *Higuchi Model*[10]

The release behavior for such systems can be mathematically described by the following equation:

$Q = D\varepsilon / T [2 A - \varepsilon Cs] Cst^{½}$ (1)

Where

Q = weight in grams of drug released per unit area of surface at time t

D = Diffusion coefficient of drug in the release medium

ε = porosity of the matrix

Cs = solubility of drug in release medium

T= Tortuosity of the matrix

A = concentration of drug in the tablet, as gm/ ml

ii. *Korsmeyer and Peppas Model*

The simple Empirical equation is as follows-

$M_t/M_\infty = Kt^n$ (2)

Where

Mt is the amount of drug released at time t;

M∞ is the amount of drug released at infinite time;

n is the diffusion constant indicating the release mechanisms

And k is the kinetic constant.

1.3 Experimental Design Objectives[17]

Types of designs are listed here according to the experimental objective they meet.

- **Comparative objective**: If you have one or several factors under investigation, but the primary goal of your experiment is to make a conclusion about one a-priori important factor, (in the presence of, and/or in spite of the existence of the other factors), and the question of interest is whether or not that factor is "significant".
- **Screening objective**: The primary purpose of the experiment is to select or screen out the few important main effects from the many less important ones.
- **Response Surface (method) objective**: The experiment is designed to allow us to estimate interaction and even quadratic effects, and therefore give us an idea of the (local) shape of the response surface we are investigating. RSM designs are used to:
  - Find improved or optimal process settings
  - Troubleshoot process problems and weak points.
- **Optimizing responses when factors are proportions of a mixture objective**: If you have factors that are proportions of a mixture and you want to know what the "best" proportions of the factors are so as to maximize (or minimize) a response, then you need a mixture design.
- **Optimal fitting of a regression model objective**: If you want to model a response as a mathematical function (either known or empirical) of a few continuous factors and you desire "good" model parameter estimates (i.e., unbiased and minimum variance), then you need a regression design.

1.4 Choosing an experimental design

1. Three-level full factorial designs[19]
2. The 3^2 design
3. The 3^3 design

2. LITERATURE REVIEW

1. ***Samuel R et al.***[20] (2009)have reported the effects of alkalizing buffers in HPMC matrices. These agents are incorporated to provide micro-environmental buffering, protection of acid-labile ingredients, or pH-independent release of weak acid drugs. In this study, the influence of sodium citrate on the release kinetics, gel layer formation,

internal gel pH and drug release mechanism was investigated in HPMC 2910 and 2208 (Methocel E4M and K4M) matrices containing 10% felbinac 39% HPMC, dextrose and sodium citrate. Matrix dissolution at pH 1.2 and pH 7.5 resulted in complex release profiles. HPMC 2910 matrices exhibited biphasic release, with citrate increasing the immediate release phase (<60min) and reducing the extended release. HPMC 2208 matrices were accelerated, but without the loss of extended release characteristics. Studies of early gel layer formation suggested gel barrier disruption and enhanced liquid penetration. PH modification of the gel layer was transitory (<2h) and corresponded temporally with the immediate release phase. Results suggest that in HPMC 2910 matrices, high initial citrate concentrations within the gel layer suppress particle swelling, interfere with diffusion barrier integrity, but are lost rapidly whereupon drug solubility reduces and the diffusion barrier recovers. These Hofmeister or osmotic-mediated effects are better resisted by the less methoxylated HPMC 2208.

2. ***Wilding& Pendleton***[21] **Patent Application no: US20100004262, ZYSIS LIMITED.** Zysis is a privately –owned pharmaceutical company optimizing therapies for disorders of the central nervous system. Zysis has formulated Aripiprazole-an effective anti-psychotic molecule, to provide a patent protected, controlled release, once-weekly maintenance phase therapy in oral tablet form to improve clinical outcomes in schizophrenia.
3. ***Tiwari S.B et al.***[22] (2003) have studied the effect of concentration of hydrophilic (Hydroxypropyl methylcellulose [HPMC]) and hydrophobic polymers (hydrogenated castor oil [HCO], ethyl cellulose) on the release rate of Tramadol. Hydrophilic matrix tablets were prepared by wet granulation technique, while hydrophobic (wax) matrix tablets were prepared by melt granulation technique and in vitro dissolution studies were performed using United States Pharmacopeia (USP) apparatus type II. Hydrophobic matrix tablets resulted in sustained in vitro drug release (>20 hours) as compared with hydrophilic matrix tablets (<14 hours). The presence of ethyl cellulose in either of the matrix systems prolonged the release rate of the drug. Tablets prepared by combination of hydrophilic and hydrophobic polymers failed to prolong the drug release beyond 12 hours. The effect of ethyl cellulose coating (Surelease) and the presence of lactose and HPMC in the coating composition on the drug release was also investigated. Hydrophobic matrix tablets prepared using HCO were found to be best suited for modulating the delivery of the highly water-soluble drug, tramadol hydrochloride.

4. ***Sarmila Sahoo et al.***[23] (2010)have taken chitosan, that has been blended with different amounts of polycaprolactone (PCL) (80:20, 75:25, 60:40 and 50:50) for control delivery of ofloxacin. The blends were characterized by Fourier transmission infra-red spectroscopy (FTIR), UV–visible spectroscopy (UV), scanning electron microscopy (SEM), and X-ray diffraction (XRD) analysis. From the FTIR spectra the various groups present in chitosan and PCL blend were monitored. The homogeneity, morphology and crystallinity of the blends were ascertained from SEM and XRD data, respectively. The swelling studies have been measured at different drug loading. The kinetics of the drug delivery system has been systematically studied. Drug release kinetics was analyzed by plotting the cumulative release data vs. time by fitting to an exponential equation which indicated the non-Fickian type of kinetics. The drug release was investigated at different pH medium and it was found that the drug release depends upon the pH medium as well as the nature of matrix.
5. ***Lu .Z., et al.*** (2010)[23] worked with Ketoprofen and Hydrochlorthiazidefor making their release sustained using Chitosan and Polycarbophill.The inter polyelectrolyte complex matrices showed good swelling with low erosion and slower drug release approaching nearly zero order release.
6. ***Bravo-Osuna.I. et al.***[25] (2008)investigated the effect of the initial moisture content of the polymer on the tabletting and drug release behaviour of controlled release inert matrices elaborated with methyl methacrylate (MMA)-starch copolymers. The copolymers, obtained by free radical polymerization and dried by two different methods (oven-drying or freeze-drying), were equilibrated at different relative humidities (0%, 25%, 50% and 75% RH) at room temperature. From these copolymers, matrix systems were directly compressed containing either a slightly water-soluble drug (anhydrous theophylline) or a freely water-soluble drug (salbutamol sulphate), and their compaction properties and in vitro dissolution profiles were evaluated. The release profiles were compared following model-independent methods, such as the Qt parameter and the similarity factor f2. Moreover, several kinetic models were employed to evaluate the possible changes in the release mechanism. For anhydrous theophylline, the initial moisture content of the copolymers did not affect the release characteristics from the inert matrices under study, and a typical Fickian diffusion mechanism was observed for the different formulations. However, in case of salbutamol sulphate, the presence of moisture might induce a fast drug dissolution, promoting the weakness of the matrix structure and hence, its partial

disintegration. So, an "anomalous" mixed phenomenon of diffusion and erosion was found, influenced by the initial moisture content of the copolymer.

3. EXPERIMENTAL METHOD

3.1 Formulation development

Venlafaxine HClDelayed Release Pellets (MUPS): In this work, the method used for preparing Venlafaxine HCl layered release pellets was solution/suspension- layering technique.

Solution/suspension-layering technique: The two main steps followed in solution/suspension layering technique to prepare controlled release pellets of Venlafaxine HCl were,

1. Drug coating
2. Functional coating

Drug coating/ loading: A coating solution containing appropriate concentration of drug, binder, and other excipients was prepared. Then, the solution was sprayed on to the non-peril sugar seeds by using Wurster bottom spray (FBP), by maintaining all appropriate parameters like spray rate, bed temperature, inlet temperature, and exhaust RPM, dried form of coated pellets were obtained.

Functional coating: After drugloading, this step plays the most important role in controlling the drug release. This step is also called as polymer coating, where a coating solution containing appropriate concentration of polymer was prepared and sprayed on the seal coated pellets. The coating solution was sprayed on the pellets using same mechanism and by maintaining the appropriate parameters.

Table 3.1: Fluidized bed processor parameters maintained during coating of NPS.

Parameters	Lot-1		Lot-2	
	Set valve	Process valve	Set valve	Process valve
Inlet air temperature °c	48-48.5	48.4-49.6	50-52	50-54.3
Bed temperature °c	36-37	36.9-38	40-42	40-43.1
Exhaust temperature °c	-	25.7-28.7	-	28.6-37.9
Blower RPM	1200-1500	1200-1500	1200-1600	1200-1600
Blower CFM	-	1275-1807	-	1488-2019
Atomizing air pressure Kg/cm²	1	1	1	1
Peristaltic pump RPM ml/min	0.8-1	0.8-1	0.8	0.8

Table 3.2: Fluidized bed processor parameters maintained during Functional coating.

Parameters	Set valve	Process valve
Inlet air temperature °c	48	46.5-49.7
Bed temperature °c	36	37.2-39.7
Exhaust temperature °c	-	29.4-34.3
Blower RPM	1800	1500
Blower CFM	-	1594-1700
Atomizing air pressure Kg/cm²	1.5-1.8	1
Peristaltic pump RPM ml/min	0.8	0.8

4. RESULTS AND DISCUSSION

4.1 Dissolution Profile Studies

Dissolution profile for VenlafaxineHCl 100mg sustained release pellets in 0.1N HCL

Table 4.1: Dissolution profile studies for venlafaxine HCl 100mg sustained release pellets in 0.1N HCl.

Polymer	Concentration (%)	
	L	H
PEG	5	15
PVP	5	15

Table 4.2: Dissolution profile of Venlafaxine HCl pellets using ethyl cellulose.

Time (Inhrs.)	Tpp		Ethyl cellulose(%weight gain)							
	Low	High	5%	10%	15%	20%	25%	30%	35%	40%
O	0	0	0	0	0	0	0	0	0	0
2	0	5	25.48	10.09	7.08	8.78	2.98	0	0	0
4	10	30	56.09	44.28	16.88	22.76	4.07	0	0	0
8	25	55	88.09	65.78	37.89	30.09	10.76	5.76	2.45	0
12	50	75	90.26	82.27	46.67	35.77	12.85	8.54	5.76	1.54
16	65	85	92.17	90.08	60.98	42.56	22.65	10.44	8.97	3.07
24	80	100	98.09	92.09	74.78	55.88	30.28	12.77	10.09	5.48

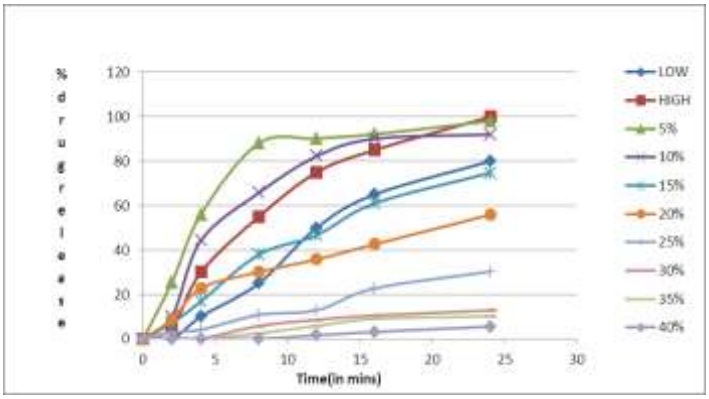

Figure 4.1: Dissolution profile of Venlafaxine HCL pellets using polyethylene glycol-4000 at 0.1N HCl0.1N HCL.

Table 4.3: Dissolution profile of VenlafaxineHCl pellets using ethyl cellulose.

Time (in hrs)		Tpp	LL	LM	LH	ML	MM	MH	HL	HM	HH
	Low	High	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0	0
2	0	5	7.54	12.45	27.09	4.23	5.87	14.32	0	0.37	3.29
4	10	30	28.87	38.45	54.98	17.89	20.61	29.45	1.29	7.58	12.76
8	25	55	30.79	62.67	67.78	28.44	37.45	43.08	5.35	13.49	25.48
12	50	75	55.32	75.34	80.97	53.87	62.07	78.12	14.48	26.55	44.07
16	65	85	75.29	84.35	85.67	72.64	68.34	80.16	34.08	42.78	67.57
24	80	100	84.28	87.28	87.54	83.24	85.28	87.54	55.87	66.08	78.09

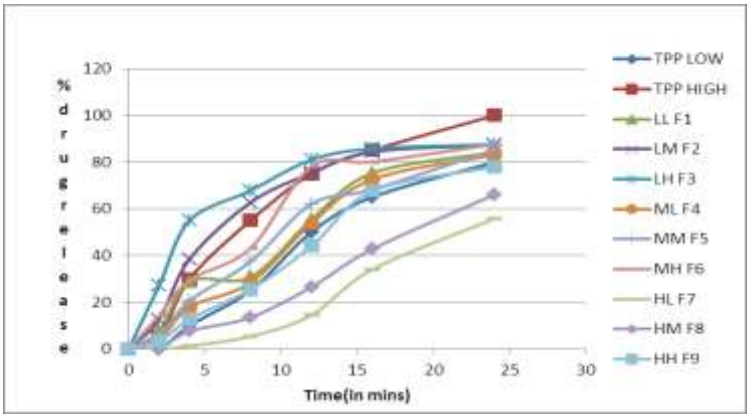

Figure 4.2: Dissolution profile of Venlafaxine HCL pellets using polyethylene glycol-4000 at 0.1N HCl.

PEG as pore former only formulation medium/lower that is medium level of ethyl cellulose (20%), low level of PEG (5%) alone is able to give dissolution profile matching to the target product profiles.

The dissolution values of 2hrs, 8hrs and 24hrs were fed into the DOE pro-excel software surface plots and interaction plots are shown in Fig-3, 5And 8.

DOE for 2 hrs. in 0.1N HCl

Table 4.4: DOE for 2 hrs. in 0.1N HCl.

Factor	A	B	%drug release
Row#	Ethyl cellulose	PEG-4000	Y1 bar
1	15	5	84.28
2	15	10	87.28
3	15	15	87.54
4	20	5	83.24
5	20	10	85.28
6	20	15	87.54
7	25	5	55.87
8	25	10	66.08
9	25	15	78.09

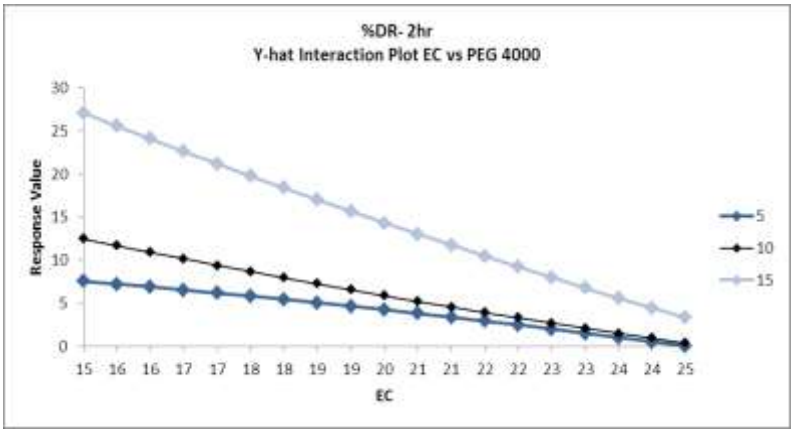

Figure-4.3.

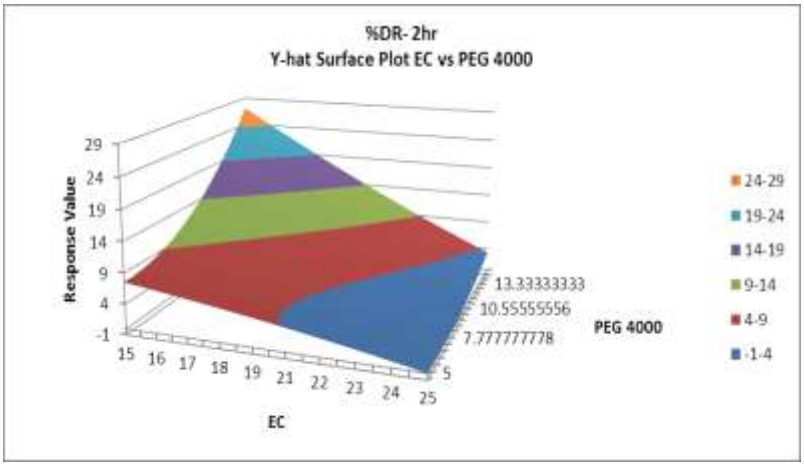

Figure- 4.4.

DOE for 8 hrs. release in 0.1N HCl

Table-4.5.

Factor	A	B	%drug release
Row	Ethyl cellulose	PEG-4000	Y1 bar
1	15	5	30.79
2	15	10	62.67
3	15	15	67.78
4	20	5	28.44
5	20	10	37.45
6	20	15	43.08
7	25	5	5.35
8	25	10	13.49
9	25	15	25.48

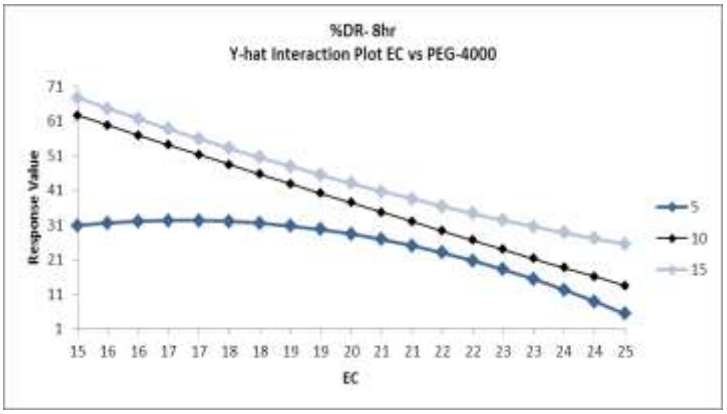

Figure-4.5.

Table 4.6: DOE for 24 hrs. release in 0.1N HCl0.1N HCl.

Factor	A	B	%drug release
Row	Ethylcellulose	PEG-4000	Y1 bar
1	15	5	84.28
2	15	10	87.28
3	15	15	87.54
4	20	5	83.24
5	20	10	85.28
6	20	15	87.54
7	25	5	55.87
8	25	10	66.08
9	25	15	78.09

5. CONCLUSION

The current work focused on the development and optimization of modified release Venlafaxine Hydrochloride tablets. The dissolution profile was targeted to match with the innovator product Effexor ER. The effect of the concentration and viscosity grades of combination of HPMC polymers K4M, K15M and K100M on the release profile was studied in DOE environment, And VenlafaxineHCl controlled release product was also developed using the MUPS platform, and ethyl cellulose as the semi permeable membrane. The role of two water soluble polymers in modulating the drug release was evaluated using full factorial design of experiments. Full factorial 3^2 design of experiments was conducted by varying the levels of EC and PEG 4000 and PVP as pore former. The dissolution profile was conducted for all 9 batches and the values at 2, 8 and 24 hours were fed into DOE Pro XL software.

Based on the results of the study, the following conclusions can be drawn:

(1) The dissolution profile with 30% K4M was matching to that of Effexor ER (f2 = 62).

(2) The 27 experiments (3^3) which were designed by the DOE software throws up a narrow optimum range for each of these 3 polymers within which the formulation may always match the innovator product. The three formulation fabricated within the design space prove the claim made in point**.**

(3) Based on the DOE experiments, it was established that PVP is a better pore former for VenlafaxineHCl controlled release pellets as compared to PEG. This may be due the fact that PVP acts as a solubilizer for the practically insoluble VenlafaxineHCl.

(4) The reproducibility and stability experiments indicate that it is possible to develop a controlled release product of VenlafaxineHCl using the micro porous film platform and the MUPS platform with the product matching to the target product profile and having excellent reproducibility and stability.

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