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PREPARATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF VENLAFAXINE HYDROCHLORIDE

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Abstract:

The present investigation is aimed at formulating and evaluating Extended release tablets of Venlafaxine Hcl using different polymers such as HPMC K4M, Eudragit RL-100.Venlafaxine Hydrochloride used for the management of major depressive disorder. Different concentrations of the polymers were taken. The physical mixture was evaluated prior to compression for determining the flow properties. These tablets were evaluated for weight variation, hardness, thickness, friability, content uniformity and in-vitro drug release profile. It was found that the formulation F3 containing HPMC K4M Polymer release 99% of drug In 24 hours time period and it is selected as a optimized formulation. Drug –Excipient interactions of pure drug and optimized formulations was carried out by using FTIR Study.

Key words: *Venlafaxine HCl, HPMC K4M,Eudragit RL-100.*

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INTRODUCTION:

Oral route still remains the most popular for drug administration by virtue of its convenience to the patient.frequent drug administration is necessary especially,particularly when drug has a short biological half life.This result inwide fluctuation in drug levels [1-5].

In the recent years considerable attention has been focused on the development of new drug delivery systems. Pharmaceutical research since 1950 turned to a new era towards optimizing the efficacy of the drug by designing the drug in different dosage forms posing challenges to the pharmaceutical technologists. For many decades treatment of acute diseases or chronic illness have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, suppositories, creams, ointments, liquids, aerosols, and injectables [6,7]. The oral conventional types of drug delivery systems are known to provide a prompt release of drug [8,9].

Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery systems several times a day. This results in a significant fluctuation in drug levels often with sub-therapeutic and/or toxic levels and wastage of drug. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release [10-13].

The term modified-release product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional and immediate-release dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized".

An ideal drug delivery system involves two pre requisites. It should deliver the drug at a rate desired by the needs of the body, over the period of the treatment. This necessitates steady state blood levels or a tissue level that is therapeutically effective and non toxic for an extended period of time. It should channel the active entity to the site of action. Advanced research in pharmaceutical technology would find several controlled release dosage forms in the market. These products have been identified by various names as “sustained release”, “prolonged release”, “controlled release”, “timed release”, and “delayed release”.

Extended release dosage forms are formulated in such a manner to make contained drug available over an extended period of time following administration. Extended release oral formulations used since 1960s to enhance performance and patient compliance. By incorporating the dose for 24 hours into one tablet from which the drug is slowly released peaks of high plasma concentration and troughs of low concentration can be prevented. This helps to avoid side effects associated with high concentrations [14,15].

Many current oral extended release systems of matrix type, based on hydrophilic polymers. With these technologies, drug and excipients are mixed with polymers such as hydroxy propyl methyl cellulose (HPMC) and Hydroxy propyl cellulose (HPC) then formed as a tablet by conventional compression.

Advantages of Extended Release Drug Delivery Systems:

1. Total dose is low
2. Reduced dosing frequency
3. Improved efficacy
4. Better patient acceptance and compliance
5. More uniform drug effect

Disadvantages of Extended Release Drug Delivery Systems:

1. Dose dumping
2. Stability Problem
3. Reduced potential for accurate dose adjustment

METHODOLOGY:

Table 1: Composition of Venlafaxine HCl Tablets:

Code	Venlafaxine HCl	HPMC K4M	Eudragit RL100	Lactose	Talc	Mg.stearate
F1	75	200	-	110	5	10
F2	75	240	-	70	5	10
F3	75	280	-	30	5	10
F4	75	-	200	110	5	10
F5	75	-	240	70	5	10
F6	75	-	280	30	5	10

Evaluation of Precompression Blend:

Angle of Repose:

The angle of repose of granules was determined by the fixed funnel-method. The accurately weighed physical mixture (powder) was taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation (Raghuram et al., 2003).

$$\mathbf{Tan\ \theta = h/r}$$

Where h and r are the height and radius of the powder cone, θ is the angle of repose.

Determination of Bulk Density and Tapped Density:

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal . The bulk density and the tapped density were calculated using the following formulae.

Bulk density = W/V_0, Tapped density = W/V_f

Where, W= Weight of the powder, V_0 = Initial volume, V_f = final volume.

Compressibility Index (Carr's Index):

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the moreflowable it is.

CI = (TD-BD) x 100/TD.

Where, TD is the tapped density and BD is the bulk density.

Table 2: Carr's Index Values

S. No	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner's Ratio: It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index. And greater than 1.5 indicates that poor flow, in between these values passable.

Evaluation of Tablets:

Thickness:

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

Hardness:

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test:

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

% friability was calculated as follows

$$\mathbf{\%\ Friability = (W_1 - W_2) \times 100/W_1}$$

Weight Variation Test:

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\mathbf{\%\ weight\ variation = (W_A - W_I) \times 100/ W_A}$$

Drug Content Uniformity (Assay):

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount

In -Vitro Drug Release Characteristics:

Drug release was assessed by USP-II dissolution apparatus in O.1N HCL For First 2 hours then buffer PH-6.8 for remaining 22 hours. Absorbance observed at 224nm.

RESULTS AND DISCUSSION:

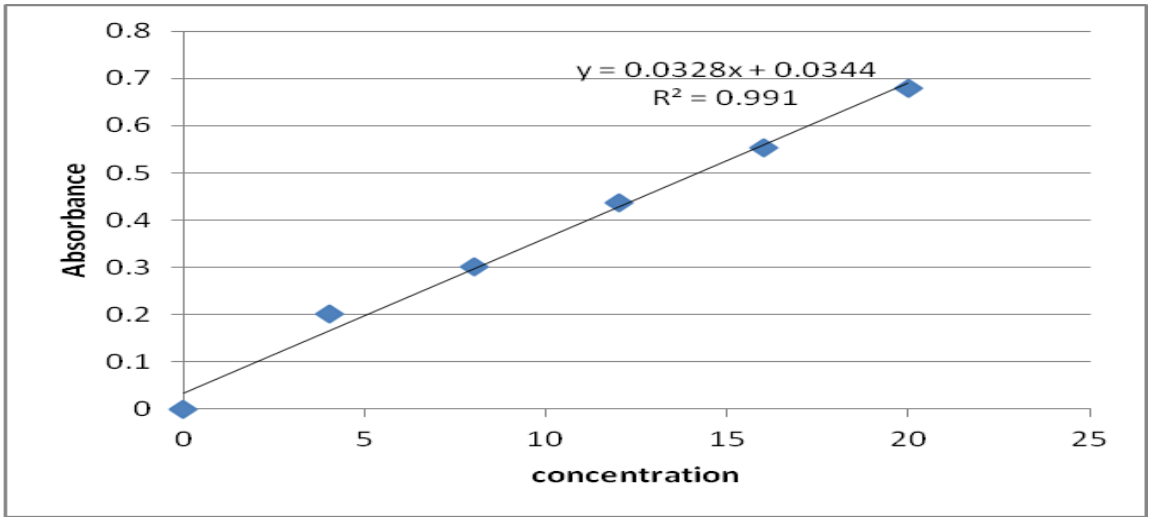

Fig 1: Standard graph of Venlafaxine HCl in 6.8 phasphate buffer

Table 3: Precompression evaluation of Venlafaxine HCl formulations:

Formulation code	Angle of repose(θ)	Hausner's ratio	Carr's index (%)
F1	27.45±0.14	1.07	13.4
F2	28.25±0.61	1.14	11.6
F3	27.23±0.91	1.17	14.6
F4	28.26±0.46	1.15	13.3
F5	28.26±0.15	1.17	12.9
F6	27.23±0.45	1.12	11.2

Table 4: Post compression evaluation studies for Venlafaxine HCl Tablets:

Formulation code	Hardness ±SD	Wt variation ±SD	Friability	Thickness ±SD	Assay ± SD
F1	6.4±0.4	354±2.42	0.28	4.12±0.13	98.23±0.64
F2	6.7±0.3	353±1.46	0.26	4.08±0.15	97.56±1.25
F3	6.5±0.2	352±2.01	0.34	4.09±1.14	98.36±0.71
F4	6.8±0.3	355±2.46	0.25	4.10±0.5	96.69±0.63
F5	6.5±0.5	352±2.79	0.36	4.12±0.5	96.45±1.03
F6	6.7±0.5	350±2.70	0.38	4.11±0.4	88.21±1.35

All values represent mean ± Standard Deviation (SD),n=3

FT-IR STUDY:

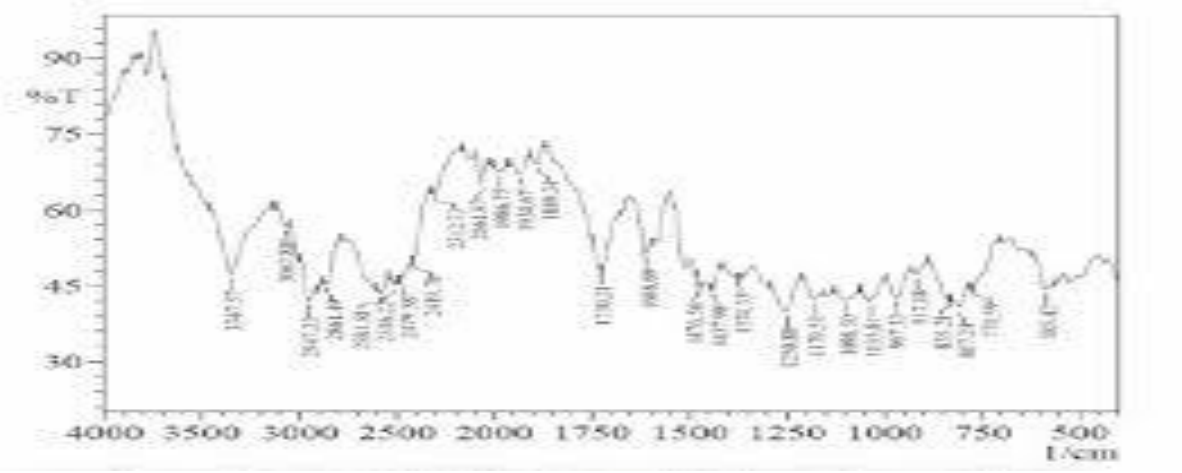

Fig 2: Optimized formulation

***In vitro* Drug Release Studies:**

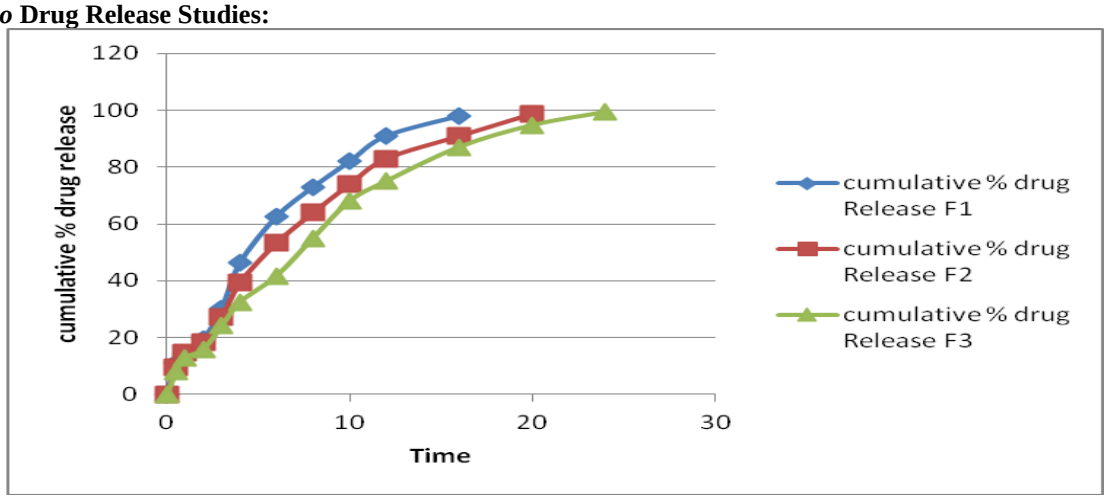

Fig 3: Drug Release from HPMC K4M:

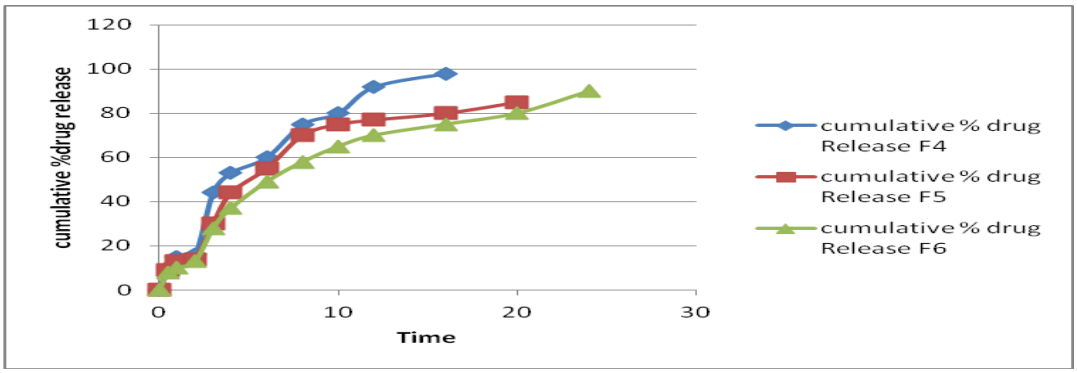

Fig 4: Drug Release From Eudragit RL 100:

Table 5: Drug Release kinetics of optimized formulation:

Optimized formulation	Zero order	First order	higuchi	Korsemeyer-peppas
R2	0.953	0.342	0.976	0.743

All the extended release tablets were found to extend the drug release24 hrs. The formulation F3 was extended the drug release more than 24 hours. Based on the dissolution data various dissolution parameters such as zero order, first order, higuchi constant and peppas constant were evaluated for all the tablet formulations along with HPMC K4M and Eudragit RL100 having micro orifice. Formulation F3 with micro-orifice exhibited zero order drug release, the correlation coefficient value obtained was 0.953. which indicates that the mechanism of drug release follows zero order which is achieved by drug diffusion from the micro orifice. The higuchi values for the formulation were linear with a R^2 value of 0.976.

The spectra of Optimized F3 tablet formulation exhibited all the principle peaks present in the pure drug. The results revealed that there were be no major interaction between drug and excipients used in the formulation of osmotic tablets. The IR spectra of optimized formulation were shown in figure 2.

CONCLUSION:

The present work is on the preparation of extended release tablets of venlafaxine HCl uses release retarding ability of HPMC K4M and Eudragit RL100 to extend the release of drug over 24 hrs period. Formulation F3 showed better drug release. It was selected as optimized formulation release 99.12% of drug within 24 hrs. Other polymer eudragit RL100 has shown less drug release. Drug release from optimized formulation Follows Higuchi and zero order model mechanism.

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