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*Research Article*

# FORMULATION AND EVALUATION OF VENLAFAXINE HYDROCHLORIDE TABLETS AS CONTROLLED RELEASE MODULES

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**ABSTRACT**

Controlled release (CR) / Sustained release (SR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into the systemic circulation for a prolonged period at a predetermined rate. The main objective of the work is to develop a pharmaceutically equivalent. Antidepressant Venlafaxine Hydrochloride controlled release formulation were developed and compared to marketed formulation. Innovator and Prototype evaluation were performed to assess the release of branded product. Preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms. Preformulation testing is to done generate information useful to the formulation in developing stable and bioavailable dosage forms. Different formulae were developed by incorporating various polymers like HPMC K100M , Ethyl Cellulose and Cross Linked Polyvinyl Pyrrolidone 0.45% respectively. All the developed formulations were subjected to invitro dissolution testing and the data was fitted to various exponential equations in order to assess the exact release mechanism. Compatibility among the drug and polymers was checked by subjecting the samples to FTIR and DSC characterization.

**Keywords**: Venlafaxine hydrochloride, Controlled Release, Dissolution Testing, Analysis.

## INTRODUCTION

From time immemorial, drugs have been an inseparable part of mankind's history since they fulfill one of our most basic necessities[1]. To administer these drugs in an appealing and palatable form and in the required amount and rate, they have to be developed into an acceptable dosage form. Thus, the concept of formulation development was evolved, resulting in solid, liquid and semi-solid dosage form. Solid dosage forms are widely prevalent due to their age-old application. Especially, oral solid formulations hold a high potential as they serve to be most convenient for the administration of drugs[2]. These have been developed into a wide range of formulations from conventional dosage forms for immediate release of the drug to controlled release dosage forms for the constant rate of drug release. Oral rouse is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems[3].

Venlafaxine HCl is a bicyclic antidepressant, and is usually categorized as a serotonin-norepinephrine reuptake inhibitor (SNRI), but it has been referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor. It works by blocking the transporter "reuptake" proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse. The neurotransmitters affected are serotonin (5-hydroxytryptamine) and norepinephrine (noradrenaline).

## MATERIALS

Venlafaxine HCl was obtained as a gift sample obtained from Sashan Pharmaceutical Pvt.

Ltd, Coimbatore. HPMC K100 M, Polyvinyl pyrrolidine was obtained a generous gift from Colorcon Asia Private Ltd, India. Microcrystalline cellulose, Aerosil, Ethyl cellulose and Magnesium stearate was purchased from Rankem , India. All other solvents and reagents were of analytical grade.

**INNOVATOR AND PROTOTYPE EVALUATION**

Objective of the Innovator evaluation is to know dissolution of EFFEXOR XR extended release capsule 75mg, manufactured by Wyeth Ayerst, Philadelphia. Innovator evaluation is done to evaluate and generate the data of manufacturing parameters which are used for product manufacturing, so that the final product at pilot scale / test batch will produce consistent results[4]. The physico-chemical parameters with respect to EFFEXOR XR like thickness, hardness, dissolution rate were evaluated as per Standard Operating Procedures (SOP's) and Standard Testing Procedures (STP's).

Objective of the prototype evaluation is to monitor the manufacturing process of Venlafaxine hydrochloride 75mg in different granulation techniques during the developmental stage of the formulation[5]. In Prototype studies the different granulation batches are tested to which it is feasible. At first direct compression was processed but the tablets was failed to get with suitable parameters, then tested for dry granulation but approximately half of the batch got failed due to capping and lamination problems and later the alternative processing i.e. Wet granulation was tested for feasibility (Table 1 & 2).

**PREFORMULATION STUDIES**

The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms[6]. Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients[7]. It is the first in the rational development of dosage forms. Assessment of preformulation parameters maximizes the chances in formulating an acceptable, safe efficacious and stable product[8] (Table 3).

**Table 1: Innovator Product Evaluation – Dissolution Profile for Effexor XR**

| Time (hrs) | % Venlafaxine HCl released |
|---|---|
| 0 | 0 |
| 1 | 21 |
| 2 | 84 |
| 3 | 91 |
| 4 | 99 |
| 6 | |
| 8 | |
| 10 | |
| 12 | |

**Table 2: Results of Prototype Evaluation**

| Trail | Thickness (mm) | | Hardness (Kg/cm$^2$) | | Friability (% w/w) | | Dissolution | |
|---|---|---|---|---|---|---|---|---|
| | Min | Max | Min | Max | Min | Max | Min | Max |
| 1 | 3.89 | 4.11 | 67.8 | 80.1 | 0.52 | 0.98 | 35.28 | 97.68 |
| 2 | 3.99 | 4.33 | 70.4 | 75.3 | 0.43 | 0.86 | 49.61 | 98.45 |
| 3 | 3.87 | 4.12 | 61.3 | 78.6 | 0.48 | 0.92 | 40.36 | 98.09 |
| 4 | 3.95 | 4.23 | 64.5 | 79.3 | 0.55 | 0.91 | 41.51 | 94.86 |
| 5 | 3.95 | 2.14 | 69.9 | 77.6 | 0.41 | 0.89 | 35.10 | 95.17 |
| 6 | 3.96 | 4.21 | 68.8 | 76.9 | 0.53 | 0.85 | 30.23 | 99.17 |
| 7 | 3.88 | 4.28 | 72.4 | 79.9 | 0.42 | 0.88 | 31.88 | 98.34 |
| 8 | 3.84 | 4.17 | 74.8 | 78.3 | 0.49 | 0.94 | 46.27 | 95.34 |
| 9 | 3.87 | 4.10 | 71.2 | 76.4 | 0.44 | 0.91 | 45.37 | 98.6 |
| 10 | 3.91 | 4.29 | 63.4 | 75,2 | 0.59 | 0.92 | 42.61 | 97.33 |
| 11 | 3.93 | 4.20 | 69.5 | 76.5 | 0.57 | 0.90 | 39.67 | 97.84 |
| 12 | 3.81 | 4.22 | 63.4 | 77.1 | 0.51 | 0.81 | 28.91 | 99.57 |

**Table 3: Preformulation Characteristics of Blend of All Formulations**

| Trial | Bulk Density (g/cm³) | Tapped Density (g/cm³) | Hausner Ratio | Compressibility Index (%) (I=1-$V_0$/V) | Angle of Repose ( ° ) |
|---|---|---|---|---|---|
| 1 | 0.56 | 0.65 | 1.16 | 13.84 | 27.5 |
| 2 | 0.54 | 0.63 | 1.16 | 14.28 | 26.8 |
| 3 | 0.53 | 0.62 | 1.15 | 14.51 | 26.5 |
| 4 | 0.52 | 0.60 | 1.15 | 13.5 | 27.8 |
| 5 | 0.53 | 0.61 | 1.15 | 13.1 | 27.6 |
| 6 | 0.58 | 0.63 | 1.14 | 14.6 | 26.9 |
| 7 | 0.55 | 0.66 | 1.16 | 14.32 | 26.6 |
| 8 | 0.51 | 0.60 | 1.15 | 13.55 | 27.4 |
| 9 | 0.59 | 0.69 | 1.14 | 13.67 | 27.8 |
| 10 | 0.55 | 0.62 | 1.15 | 14.1 | 27.6 |
| 11 | 0.50 | 0.65 | 1.14 | 14.4 | 26.9 |
| 12 | 0.54 | 0.69 | 1.16 | 13.98 | 27.1 |

**Drug-Excipient Compatability Study**

The compatibility studies were carried out to study the possible interactions between the active pharmaceutical ingredients and several inactive ingredients used in the formulations physical mixtures were kept in 40°C / 75% RH and 60°C in a 2ml glass vial in exposed condition for 1 month. Excipients are mixed with drug and at the interval of 2 weeks and 4 weeks the samples were withdrawn and analyzed for moisture content and assay for drug content at various temperatures and humidity conditions[9]. Physical compatibility assessment was carried out by subjecting the samples to FTIR and DSC studies.

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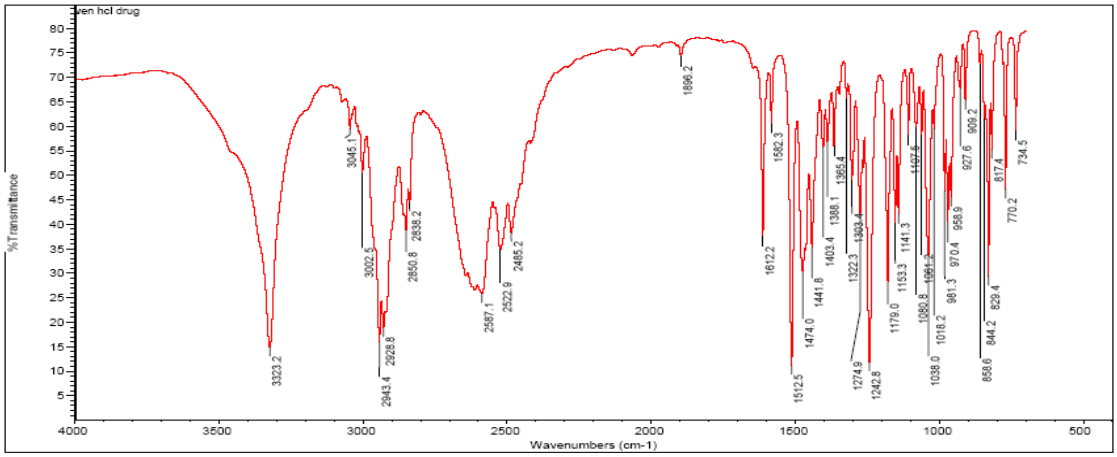


**Fig. 1: IR Report of Pure Venlafaxine Hydrochloride drug**

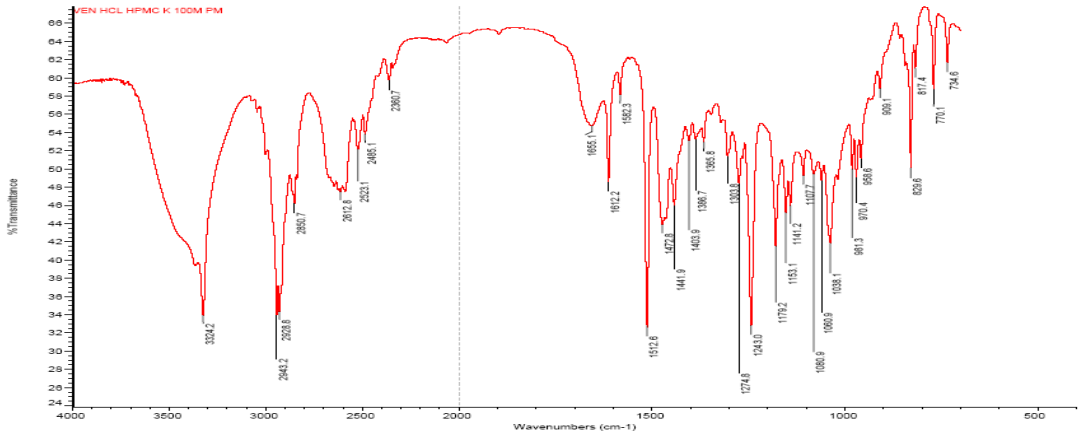


**Fig. 2: IR Report of Physical Mixture of Venlafaxine Hydrochloride and HPMC K 100M**

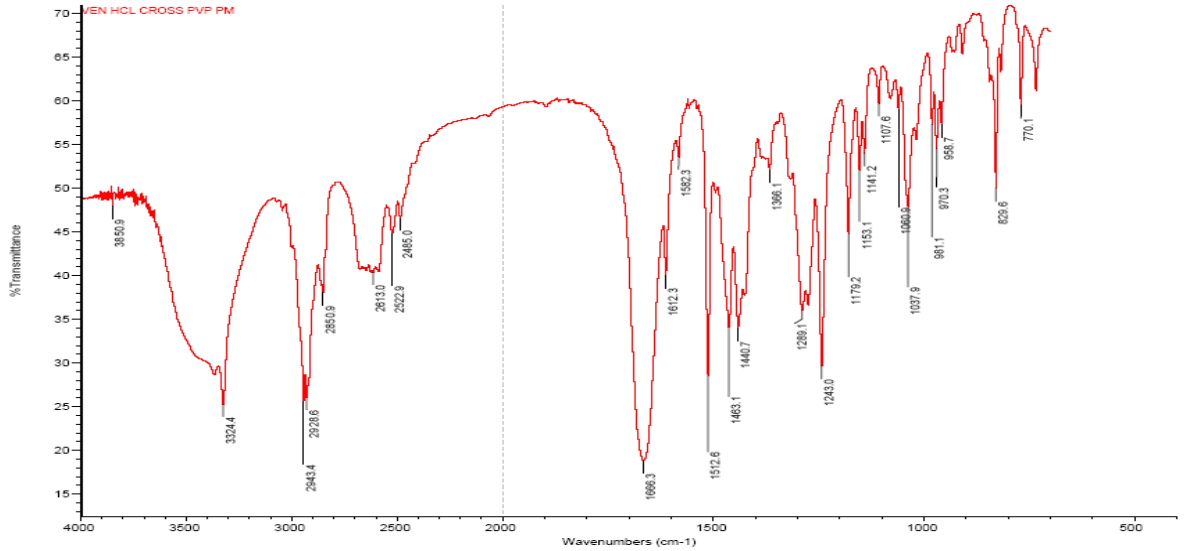


**Fig. 3: IR Report of Physical Mixture of Venlafaxine Hydrochloride and Cross linked PVP 0.45%**

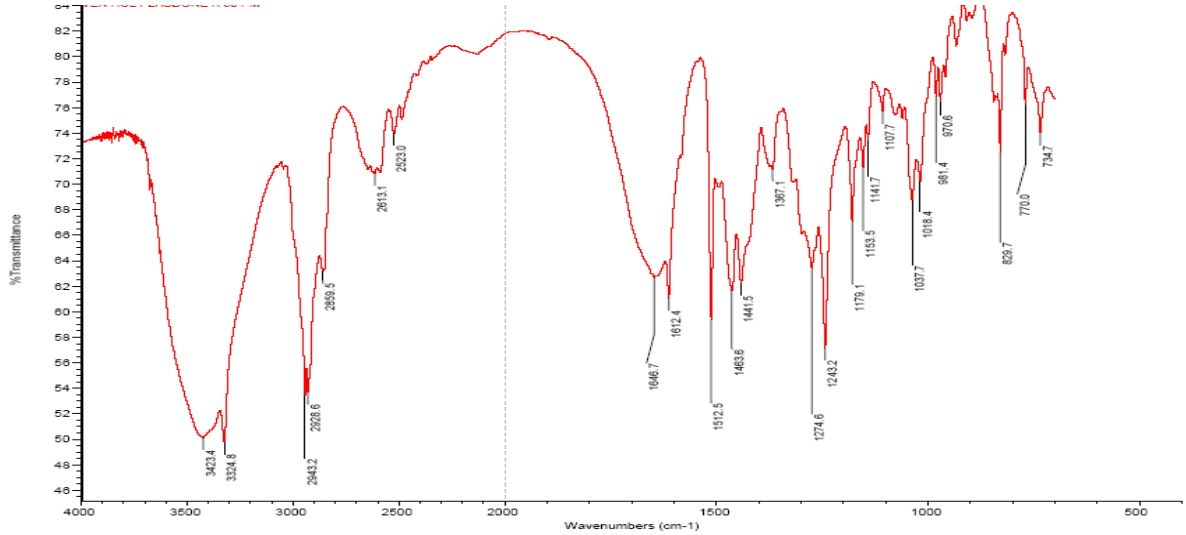


**Fig. 4: IR Report of Physical Mixture of Venlafaxine Hydrochloride and Ethyl cellulose 7 CPS**

**Table 4: Compatibility of Excipients**

| S. No. | Drug + Excipients | Parameter | Initial Value of Parameter | Condition | | | |
|---|---|---|---|---|---|---|---|
| | | | | 40°C+ 75% RH | | 60°C | |
| | | | | 2 weeks | 4 weeks | 2 weeks | 4 weeks |
| 1. | Venlafaxine hydrochloride | Moisture content | 2.38 | 3.68 | 4.42 | 1.69 | 1.54 |
| | | Assay | 100.8% | 99% | 98.6% | 100.9% | 99.9% |
| 2. | Venlafaxine hydrochloride + Cross linked poly vinyl pyrrolidone | Moisture content | 3.40 | 4.21 | 4.87 | 3.79 | 3.31 |
| | | Assay | 100.7% | 100.1% | 99.8% | 100.5% | 100.2% |
| 3. | Venlafaxine hydrochloride + HPMC K 100M | Moisture content | 4.69 | 5.19 | 5.75 | 4.79 | 4.50 |
| | | Assay | 99.8% | 99.1% | 98.2% | 98.9% | 98.1% |
| 4. | Venlafaxine hydrochloride + Ethyl cellulose 7 cps | Moisture content | 2.29 | 5.63 | 6.70 | 5.48 | 5.09 |
| | | Assay | 101% | 100.5% | 99.4% | 98.9% | 98.6% |
| 5. | Venlafaxine hydrochloride + Aerosil | Moisture content | 5.62 | 5.84 | 6.33 | 6.63 | 6.52 |
| | | Assay | 99.9% | 99.2% | 98.5% | 98.3% | 97.9% |
| 6 | Venlafaxine hydrochloride + Magnesium stearate | Moisture content | 1.55 | 4.48 | 4.63 | 1.57 | 0.82 |
| | | Assay | 100% | 101.7% | 100.9% | 99.8% | 99.3% |

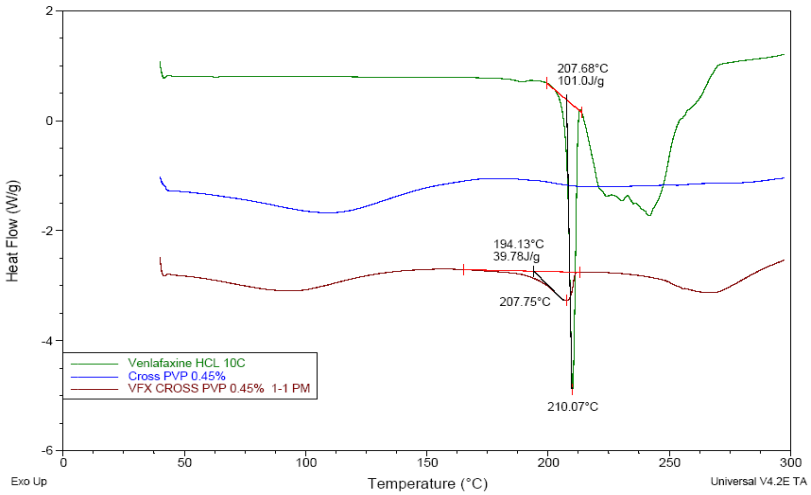


**Fig. 5: DSC Report of Physical Mixture of Venlafaxine Hydrochloride and Cross linked PVP 0.45%**

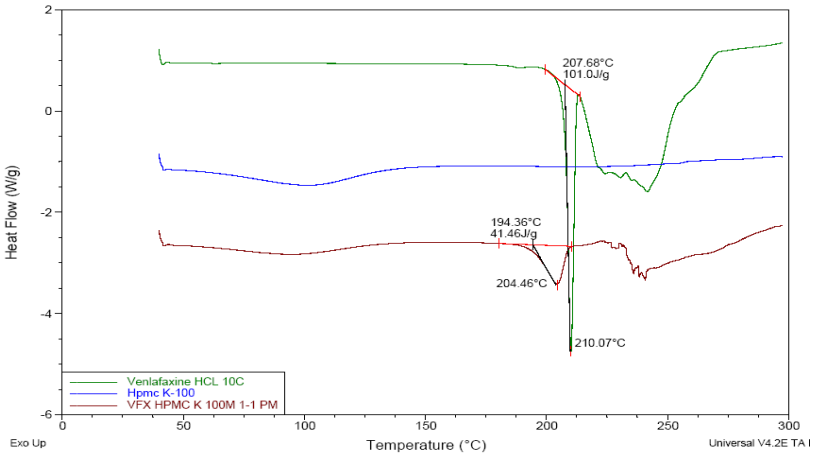


**Fig. 6: DSC Report of Physical Mixture of Venlafaxine Hydrochloride and HPMC K100M**

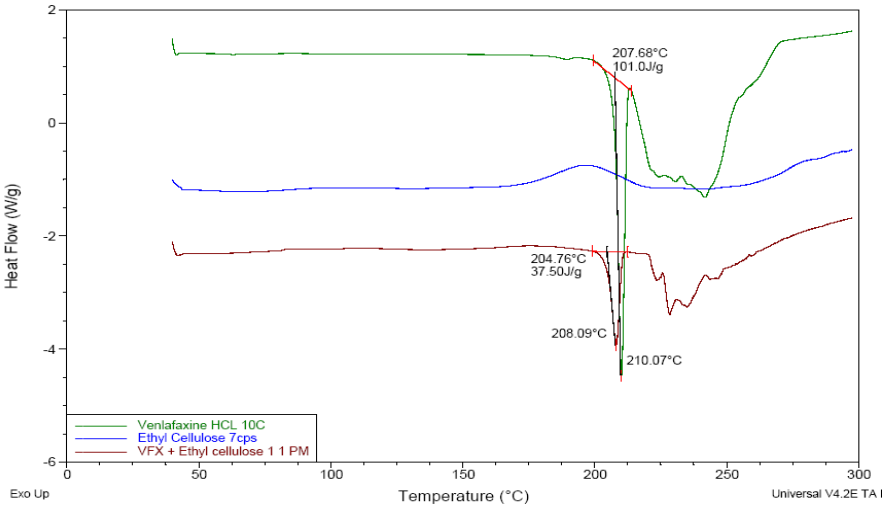


**Fig. 7: DSC Report of Physical Mixture of Venlafaxine Hydrochloride and Ethyl cellulose 7 CPS**

**FORMULATION DEVELOPMENT AND EVALUATION**

EFFEXOR XR" was selected as the reference product and the efforts were continued towards development with different polymers as a Primary choice that need to evaluate. Polymer controls drug release followed by dissolution, initiates the solubility process and its selection reflects the behavior of the drug *in vitro* and *in vivo*[11].

The most widely used polymers like HPMC K100M , ethyl cellulose were compared with that of the cross linked polyvinyl pyrrolidone and subjected to the present formulation development of Venlafaxine hydrochloride and the best opted polymer was identified on trial and error basis.

Different formulae were developed named as Trial 1, Trial 2, Trial 3, Trial 4, Trial 5, Trial, Trial 7, Trial 8, Trial 9, Trial 10, Trial 11, Trial 12 by incorporating various polymers like HPMC K100M, Ethyl Cellulose And Cross Linked Polyvinyl Pyrrolidone 0.45%respectively. The fed matter was compressed by following specifications (Table 5 & 6).

**Dissolution Studies**

"EFFEXOR XR" was selected as the reference product and the efforts were continued towards development with different polymers as a Primary choice that need to evaluate. Polymer controls drug release followed by dissolution, initiates the solubility process and its selection reflects the behavior of the drug *in vitro* and *in vivo*[12] (Table 7).

**Table 5: Compression Specifications**

| | |
|---|---|
| **Description** | White biconvex shaped tablets |
| **Tooling** | 8mm biconvex shaped |
| **Compression Force** | 6- 12 KN. |
| **Hardness** | 6-8kg/cm$^2$ |
| **Thickness** | 3.80-4.30mm |
| **Friability** | NMT 1% w/w |
| **Uniformity of Weight** | ± 5% of average weight |

**Table 6: Batches Done For Formulation Development**

| Ingredients | Trail 1 | Trail 2 | Trail 3 | Trail 4 | Trail 5 | Trail 6 | Trail 7 | Trail 8 | Trail 9 | Trail 10 | Trail 11 | Trail 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Venlafaxine hydrochloride | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| Cross linked PVP 0.45% | | | 75 | | | 10 | 25 | 10 | 25 | | | 12.5 |
| HPMC K 100M | 75 | | | 65 | 50 | 65 | 50 | | | 112.5 | | |
| Ethyl cellulose 7 CPS | | 75 | | 10 | 25 | | | 65 | 50 | | 112.5 | |
| MCC PH 101 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30.5 | 30.5 | 30.5 |
| Magnesium stearate | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Aerosil | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Total tablet weight | 184 | 184 | 184 | 184 | 184 | 184 | 184 | 184 | 184 | 222 | 222 | 222 |

**Note:** All the quantities of Inactive Ingredients are taken on the basis of Trial and Error.

**Table 7: *Invitro* Dissolution Data of Venlafaxine HCl Formulations**

| Time (hrs) | T1 | T2 | T3 | T 4 | T5 | T6 | T 7 | T 8 | T 9 | T10 | T 11 | T 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 35.28 ±0. 06 | 49.61± 0.02 | 40.36± 0.04 | 41.51± 0.11 | 35.10± 0.08 | 30.23± 0.09 | 31.88± 0.09 | 46.27± 0.09 | 45.37± 0.11 | 42.61± 0.06 | 39.67± 0.09 | 28.91± 0.02 |
| 2 | 53.11± 0.09 | 94.45± 0.13 | 59.93± 0.08 | 63.46± 0.09 | 46.64± 0.03 | 48.21± 0.12 | 48.43± 0.04 | 67.81± 0.07 | 67.65± 0.14 | 55.31± 0.09 | 53.21± 0.06 | 37.67± 0.12 |
| 3 | 76.94± 0.03 | 97.71± 0.12 | 73.63± 0.01 | 78.98± 0.07 | 58.34± 0.05 | 61.33± 0.03 | 64.61± 0.05 | 81.15± 0.09 | 93.41± 0.09 | 64.99± 0.06 | 71.41± 0.03 | 44.25± 0.14 |
| 4 | 87.31± 0.11 | 98.45± 0.14 | 84.91± 0.09 | 86.61± 0.05 | 71.17± 0.04 | 72.83± 0.08 | 76.15± 0.02 | 92.56± 0.13 | 94.45± 0.07 | 73.69± 0.04 | 84.23± 0.03 | 56.61± 0.09 |
| 6 | 97.68± 0.09 | --- | 97.63± 0.14 | 99.86± 0.11 | 84.61± 0.14 | 85.93± 0.09 | 90.91± 0.01 | 99.34± 0.14 | 95.56± 0.06 | 86.45± 0.08 | 99.84± 0.02 | 67.87± 0.08 |
| 8 | --- | --- | 98.09± 0.13 | --- | 99.17± 0.12 | 99.53± 0.14 | 94.16± 0.08 | --- | 97.45± 0.04 | 98.33± 0.06 | --- | 75.26± 0.05 |
| 10 | --- | --- | --- | --- | --- | --- | 97.57± 0.03 | --- | 98.60± 0.09 | --- | --- | 89.56± 0.09 |
| 12 | --- | --- | --- | --- | --- | --- | 98.34± 0.02 | --- | --- | --- | --- | 99.57± 0.07 |

Different formulae were developed named as Trial 1, Trial 2, Trial 3, Trial 4, Trial 5, Trial, Trial 7, Trial 8 , Trial 9, Trial 10, Trial 11, Trial 12 by incorporating various polymers like HPMC K100M , Ethyl Cellulose And Cross Linked Polyvinyl Pyrrolidone 0.45%respectively. Dissolution tests were carried for the above test formulations (trail 1 to trail 12) as per USP official procedure with water as medium.

The results of dissolution studies of the formulation were compared to the innovator product dissolution profile. From the dissolution data trail 7 and trial 12 formulations were optimized. Comparing the dissolution data of trial 7 and trial 12 the drug was retarded for 12hrs but not efficiently in controllable manner where as in trail 12 cross linked PVP 0.45% has retarded the drug release in a well controlled manner up to 12hrs. Hence trial 12 was considered as best optimized formulation.

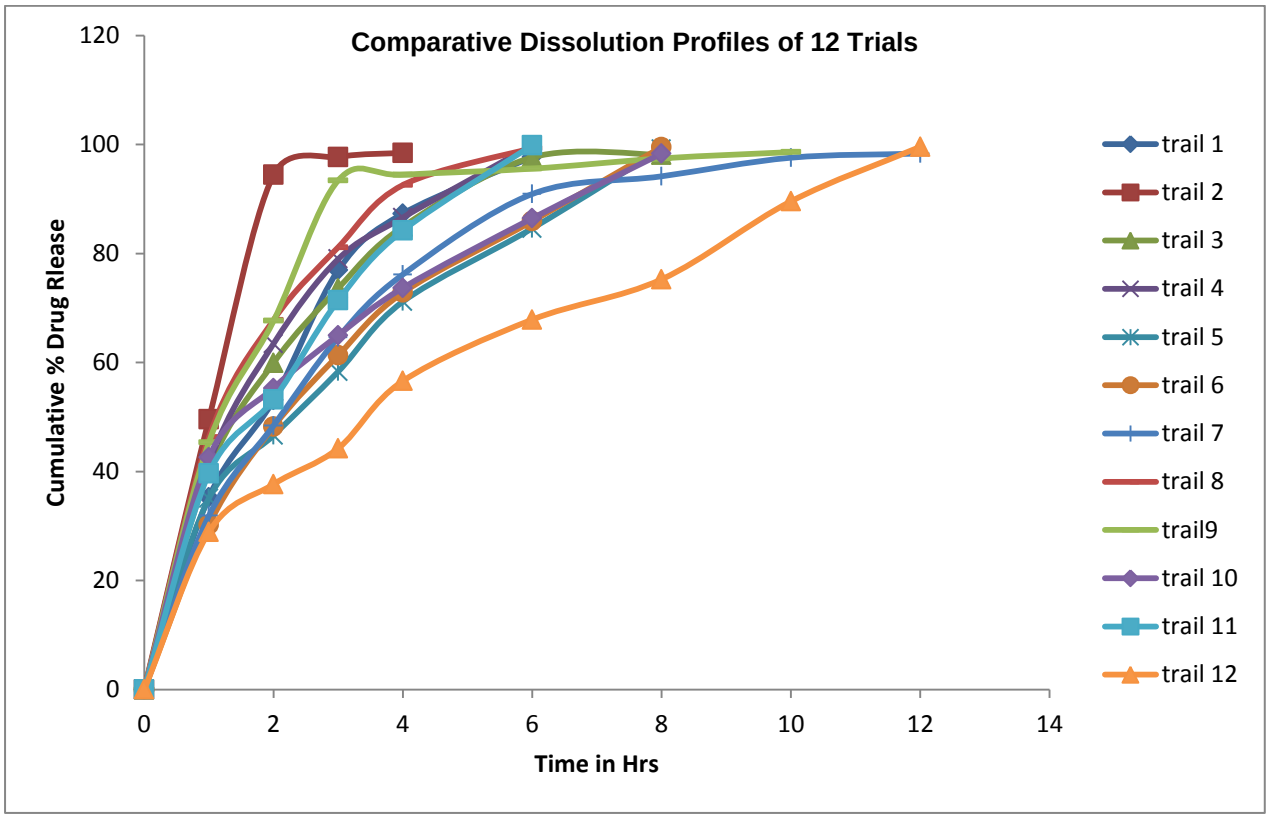


**Fig. 8: *Invitro* Dissolution Profiles of Venlafaxine HCl Formulations**

**Table 8: Dissolution Profile of Trial 12 and Innovator**

| Time (hrs) | Trail 12 | INNOVATOR- EFFEXOR XR |
|---|---|---|
| 0 | 0 | 0 |
| 1 | 28.91 | 21 |
| 2 | 37.67 | 84 |
| 3 | 44.25 | 91 |
| 4 | 56.61 | 99 |
| 6 | 67.87 | |
| 8 | 75.26 | |
| 10 | 89.56 | |
| 12 | 99.57 | |

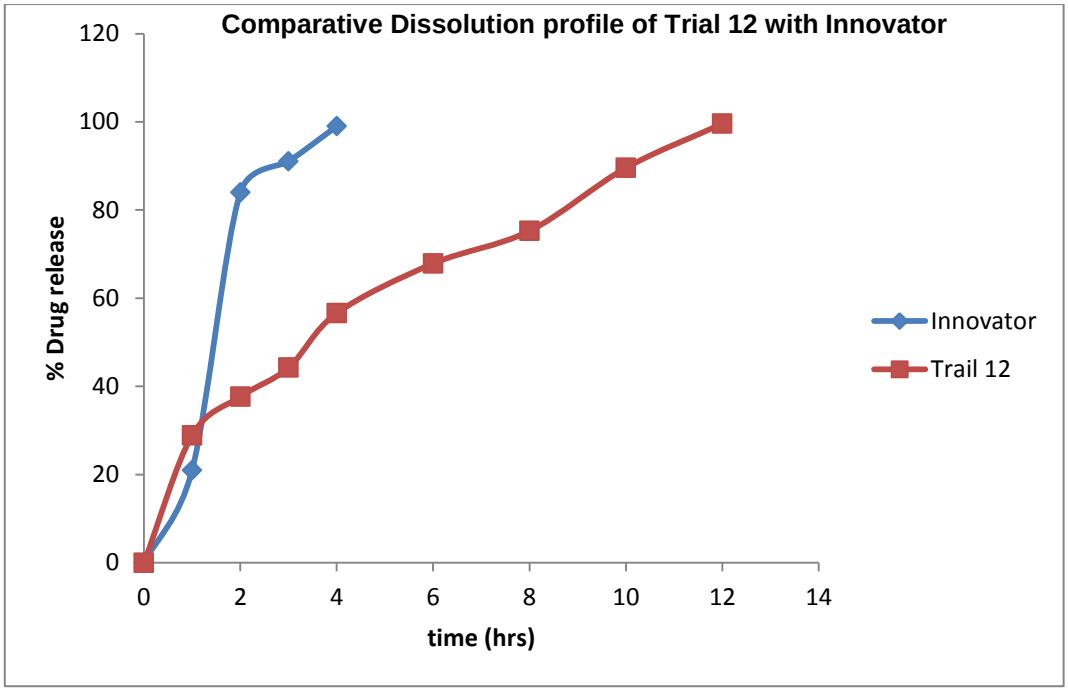


**Fig. 9: Comparative Dissolution Profile of Trial 12 and Innovator**

By comparing the dissolution profiles of innovator sample Effexor XR and optimized formulation trial 12 it was revealed that Effexor XR was retarded upto 4 hrs where as the current optimized formulation trial 12 ( with cross linked PVP 0.45% as polymer ) has retarded the drug release up to 12hrs successfully in a controlled manner.

**RELEASE KINETICS**

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model dependent approach, the dissolution data was fitted to five popular release models such as Zero order, First order, Diffusion and exponential equations. The order of drug release from matrix systems was described by using zero order or first order kinetics. The mechanism of drug release from matrix systems was studied by using higuchi equation and erosion equation and peppas-korsemeyer equation.

**Table 9: Correlation Coefficient Values ($R^2$)**

| Trials | Zero Order ($R^2$) | First Order ($R^2$) | Higuchi ($R^2$) | Erosion Equation ($R^2$) | Release Exponent (n in Peppas) |
|---|---|---|---|---|---|
| 1 | 0.980 | 0.892 | 0.981 | 0.994 | 0.599 |
| 2 | 0.882 | 0.803 | 0.941 | 0.793 | 0.504 |
| 3 | 0.952 | 0.894 | 0.969 | 0.951 | 0.443 |
| 4 | 0.948 | 0.825 | 0.981 | 0.979 | 0.472 |
| 5 | 0.959 | 0.897 | 0.997 | 0.993 | 0.497 |
| 6 | 0.916 | 0.904 | 0.995 | 0.967 | 0.568 |
| 7 | 0.971 | 0.774 | 0.948 | 0.953 | 0.460 |
| 8 | 0.955 | 0.787 | 0.968 | 0.928 | 0.421 |
| 9 | 0.843 | 0.581 | 0.857 | 0.736 | 0.320 |
| 10 | 0.930 | 0.837 | 0.990 | 0.984 | 0.398 |
| 11 | 0.944 | 0.902 | 0.995 | 0.990 | 0.526 |
| 12 | 0.992 | 0.930 | 0.994 | 0.915 | 0.505 |

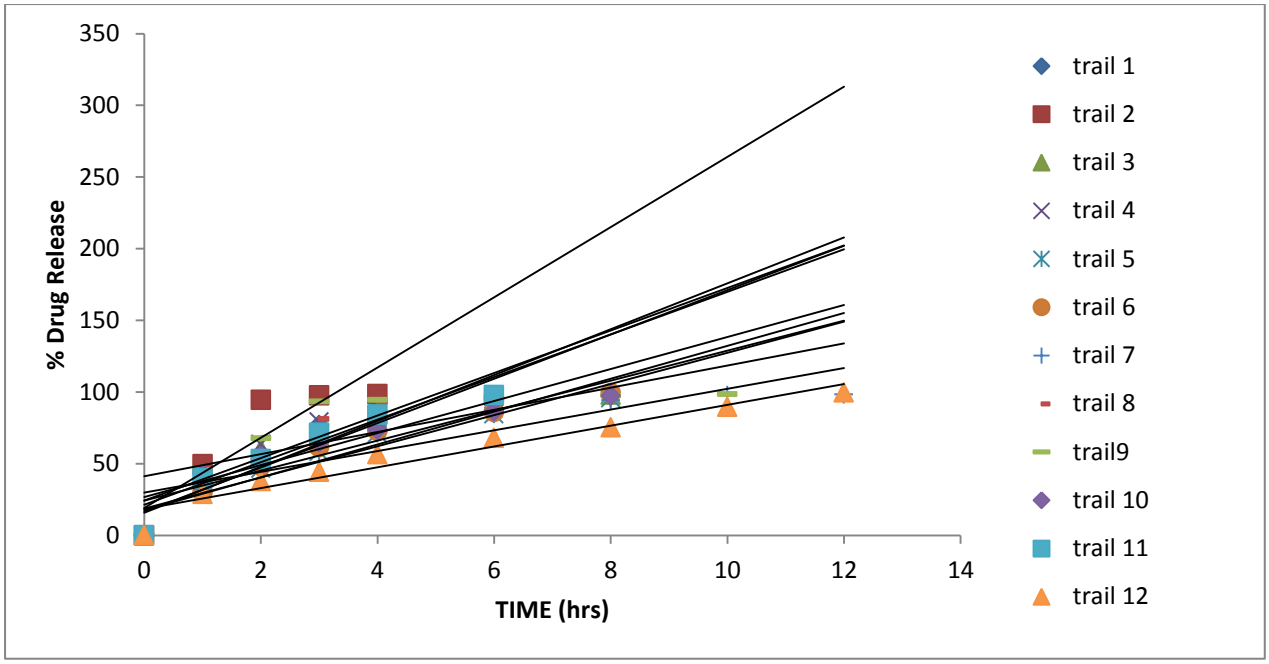


**Fig.10: Zero Order Linear Regression Plots for the Dissolution Profiles of Venlafaxine Hydrochloride**

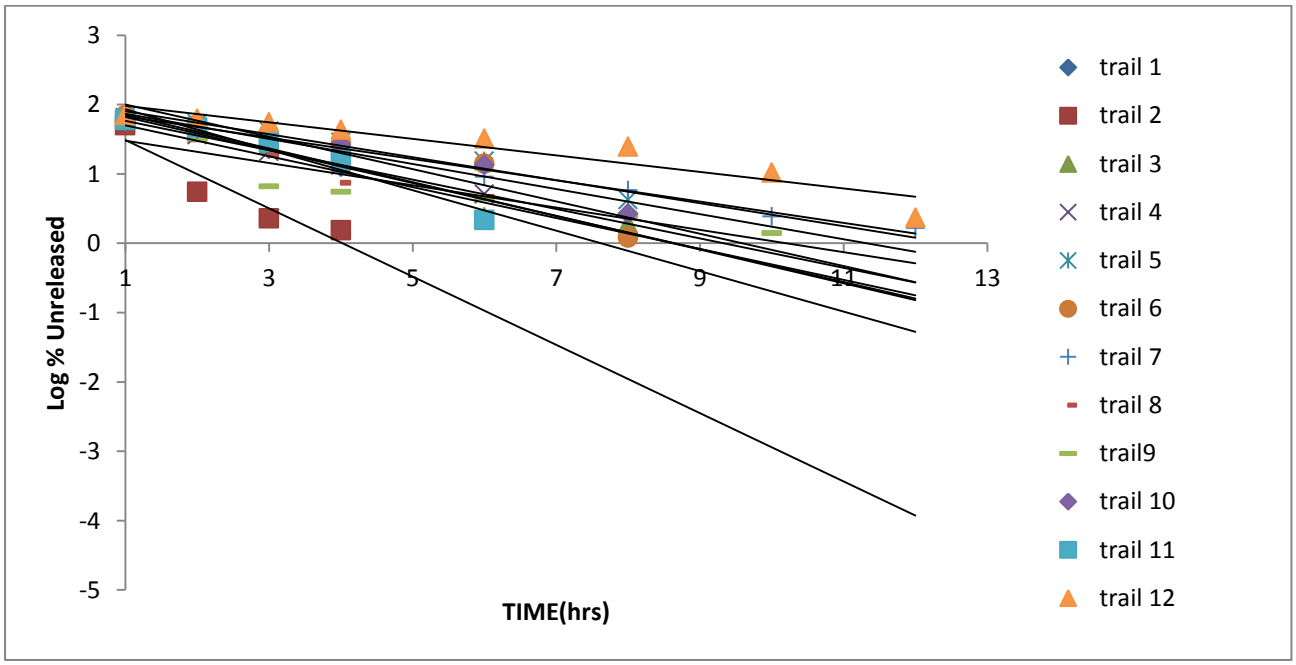


**Fig. 11: First Order Linear Regression Plots for the Dissolution Profiles of Venlafaxine Hydrochloride**

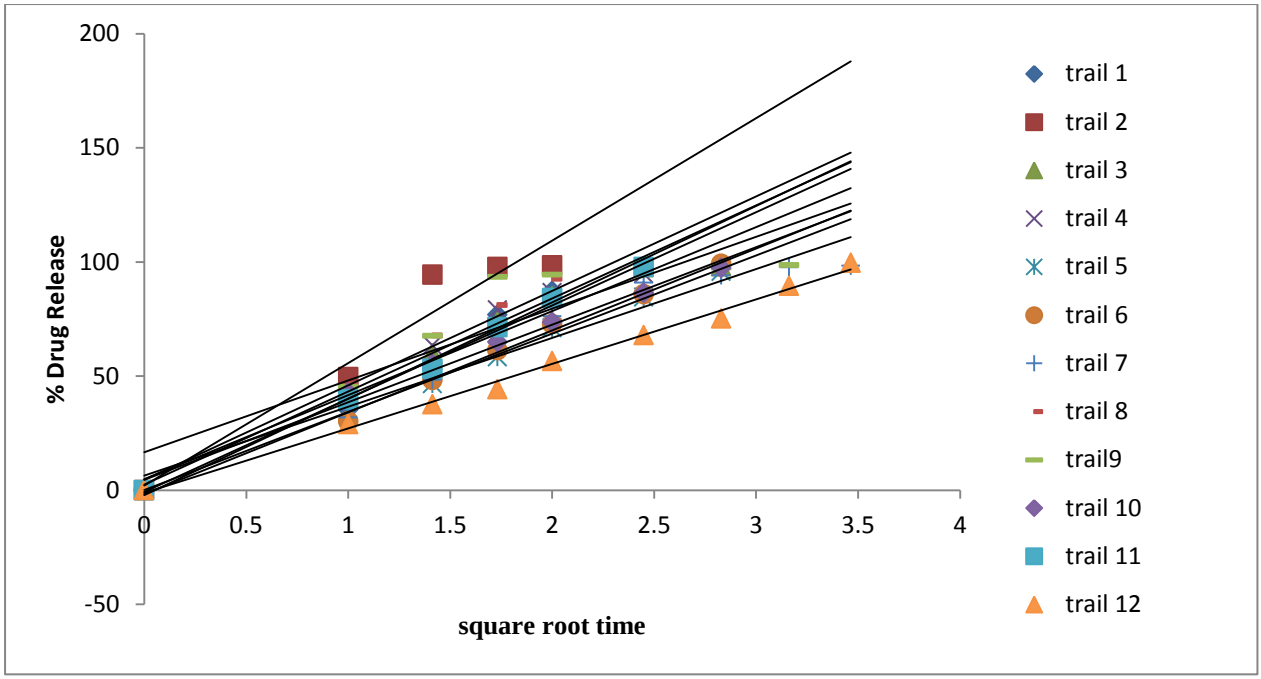


**Fig. 12: Higuchian Linear Regression plots for the Dissolution Profiles of Venlafaxine Hydrochloride**

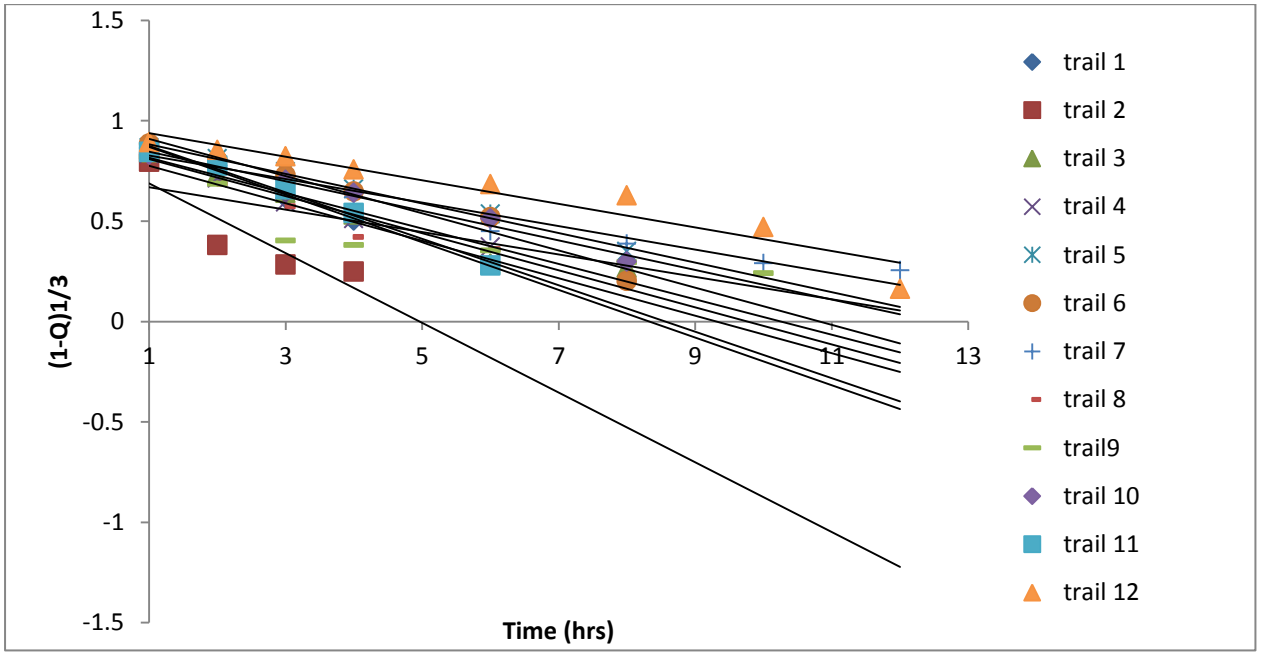


**Fig. 13: Erosion Linear Regression plots for the Dissolution Profiles of Venlafaxine Hydrochloride**

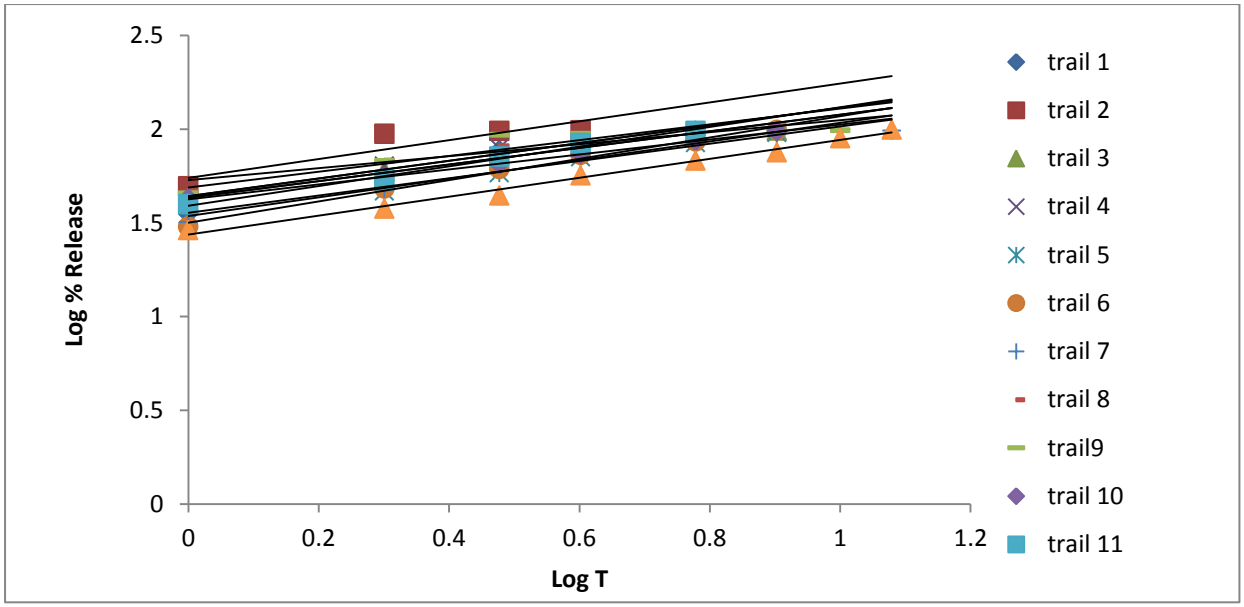


**Fig. 14: Power Law- Linear Regression plots for the Dissolution Profiles of Venlafaxine Hydrochloride**

In order to establish the mechanism of drug release the experimental data was fitted to 5 popular exponential equations. The drug release was found to be followed zero order kinetics which was indicated slightly by higher "r" values of zero order release model (0.843 to 0.992) when compared to those of first order release model(0.581 to 0.930).

The relative contribution of drug diffusion and matrix erosion to drug release was further confirmed by subjecting the dissolution data to Higuchi model and Erosion model. It was found that Ttrial 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 followed diffusion mechanism (0.857 to 0.994) and Trial 1, 6, 7 followed Erosion mechanism as indicated by their respective "**r**" values.

## CONCLUSION

The present work was aimed towards developing and oral dosage form having Venlafaxine Hydrochloride (Controlled Release) based on matrix system and the experimental results put forward cross linked PVP 0.45% as suitable rate retarding polymer for control release formulation of Venlafaxine HCl and the study recommends *invivo* evaluation of the best optimized formula towards assessment of various Pharmacokinetic parameters.

## ACKNOWLEDGEMENTS

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