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Research Article

Formulation Evaluation of Venlafaxine Hydrochloride Sustained Release Capsules

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ABSTRACT

In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities. There are so many oral delivery systems but one of the advance technique is Pellatization. Venlafaxine HCL sustained release capsules prepared by pellatization method that the Venlafaxine HCL is coated on inert sugar spheres by using PVPK-30 as a binder solutions and Plasidone S 630, Ethyl cellulose coating agents used for sustained release action. The prepared capsules were evaluated for content uniformity weight variation, in-vitro disintegration time, assay, and in-vitro drug release study. All the formulation exhibited assay, content uniformity with in the range given in E.P. Dissolution studies revealed that formulations containing PVPK-30 12.96 MG, coating agents ETHYL CELLULOSE 31.14 MG, PLASIDONE S -630 1.36 MG, Showed 100% of drug release, at the 24th hour. The concentration of coating agents Ethyl Cellulose , Plasidone S -630 had an effect on in-vitro drug release had the same release profile when compare with US dissolution parameters. Thus, the capsules apart from fulfilling all official and other specifications and exhibited higher rate of drug release.

INTRODUCTION

The development of novel drug delivery systems has revolutionized modern pharmaceutical formulation design, particularly sustained release (SR) systems that maintain therapeutic plasma concentrations over extended periods while minimizing dosing frequency and side effects [1]. Venlafaxine hydrochloride, a structurally novel antidepressant, acts as a potent serotonin and norepinephrine reuptake inhibitor and is indicated for major depressive disorder, generalized anxiety disorder, and panic disorder [2]. Conventional immediate-release formulations of venlafaxine require multiple daily dosing and are associated with fluctuations in plasma drug concentration that

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may lead to increased adverse effects or therapeutic failure [3].

Sustained release formulations aim to provide controlled and predictable drug release, achieving near-zero-order kinetics and improving patient compliance [4]. Among oral controlled release technologies, pelletization has emerged as a superior method due to its uniform drug distribution, smooth surface area, and reproducible dissolution characteristics. Sustained release pellets of venlafaxine hydrochloride encapsulated in hard gelatin capsules can offer consistent therapeutic response, minimize dose dumping, and reduce gastrointestinal irritation [5].

Previous studies demonstrated that venlafaxine besylate and hydrochloride salts could be effectively incorporated into matrix-based and coated systems for modified release applications [6]. Tian et al. developed a sustained-release pellet formulation using wax matrices and polymeric coatings, which significantly modulated drug release from highly water-soluble venlafaxine hydrochloride [7]. Similarly, Patel et al. prepared modified release pellets using a functional coating of polyvinyl acetate copolymer applied over non-pareil seeds. Gohel et al. optimized venlafaxine hydrochloride release using hydroxypropyl methylcellulose matrices to achieve 24-hour extended release profiles [8]. These studies collectively support the feasibility of producing once-daily sustained release venlafaxine formulations with improved therapeutic efficacy and stability.

Therefore, the present study aimed to design and evaluate a pharmaceutically equivalent, stable, and cost-effective sustained release capsule of venlafaxine hydrochloride using the pelletization technique and to compare its dissolution and assay profiles with those of marketed reference formulations [9,10].

2. MATERIALS AND METHODS

2.1 MATERIALS

2.1.1 Active Pharmaceutical Ingredient (API)

Venlafaxine hydrochloride (VEN HCl) was obtained as a gift sample from a certified pharmaceutical manufacturer. Venlafaxine hydrochloride is a white to off-white crystalline powder with high aqueous solubility (572 mg/mL) and a molecular weight of 313.87 g/mol [11].

2.1.2 Excipients and Chemicals

Inert non-pareil seeds (sugar spheres, 18–25 mesh) were used as pellet cores. Polyvinylpyrrolidone K-30 (PVP K-30) served as a binder, while ethyl cellulose (EC) and **Plasdone S-630** were used as sustained release coating agents.

Isopropyl alcohol and methylene chloride (1:1 v/v) were used as coating solvents.

All reagents and solvents were of analytical grade and used as received.

2.1.3 Instruments And Equipment

Fluid Bed Processor (Wurster Coater) – for drug layering and coating.

Rotary Tablet Press and Capsule Filling Machine – for encapsulation.

UV–Visible Spectrophotometer (Shimadzu UV-1800) – for drug content assay.

USP Dissolution Apparatus II (Paddle Type) – for in vitro release testing.

Analytical Balance (Shimadzu AUW-220D) – for accurate weighing.

Hot Air Oven (Lab India) – for drying operations.

Sieves (ASTM #18, #25, #40) – for particle size separation.

All equipment was calibrated prior to experimentation to ensure accuracy and reproducibility.

2.2 METHODS

2.2.1 Formulation Development

The formulation was designed using a pelletization technique that involved drug layering and polymer coating over inert sugar spheres. This approach ensured uniform drug distribution, improved flow properties, and reproducible drug release patterns.

2.2.2 Preparation of Venlafaxine Hydrochloride Sustained Release Pellets

The process comprised five steps: sieving and blending, drug layering, seal coating, sustained release coating, and drying.

a) Sieving and Blending

Venlafaxine hydrochloride and excipients were passed through sieve #40 to obtain uniform particle size distribution. The accurately weighed drug was geometrically mixed with PVP K-30 binder powder to ensure homogeneity.

b) Drug Layering

- A binder solution containing PVP K-30 (5% w/v in isopropyl alcohol) was prepared under continuous stirring.
- Non-pareil sugar spheres (18–25 mesh) were charged into a fluidized bed coater (Wurster), and the drug solution was sprayed at a controlled rate (8–12 mL/min).
- The inlet temperature was maintained at 38–42°C and the product temperature at 32–36°C, as per the parameters established by Tian et al. (2008).
- After completion, the pellets were dried at 40°C until the residual moisture content was below 2%.

c) Seal Coating

A thin protective coating of 5% HPMC in isopropyl alcohol was applied to prevent direct interaction between drug and polymer coating layers. This step also ensured mechanical integrity during subsequent processing.

d) Sustained Release Coating

Drug-loaded and seal-coated pellets were further coated with a solution of ethyl cellulose (31.14 mg) and Plasdone S-630 (1.36 mg) in an organic solvent mixture (isopropyl alcohol:methylene chloride = 1:1 v/v).

The coating process was carried out in a fluid bed processor using bottom spray (Wurster) configuration, ensuring uniform film deposition and reproducible release profiles.

The coating thickness was adjusted to achieve ~10% w/w polymer load, providing a controlled drug release up to 24 hours.

e) Drying and Sizing

The coated pellets were dried in a hot air oven at 28–32°C for 2 hours, then passed through sieves #18 and #25 to separate uniform-sized particles suitable for capsule filling.

2.2.3 Encapsulation

Optimized batches of coated pellets, equivalent to 75 mg of venlafaxine hydrochloride, were filled

into size '2' hard gelatin capsules using a manual capsule filling machine. Capsules were visually inspected for weight uniformity and sealing integrity.

2.2.4 Evaluation of Pellets

The prepared SR pellets were subjected to various pharmaceutical quality control tests, as per Indian Pharmacopoeia (IP 2020) and United States Pharmacopeia (USP 44) specifications.

a) Flow Properties

Bulk density, tapped density, Carr's Index, and Hausner's ratio were determined to evaluate the flowability of pellets.

b) Percentage Yield and Drug Content

The yield was calculated by comparing the final weight of coated pellets with theoretical weight.

Drug content uniformity was determined by dissolving accurately weighed samples in methanol and analyzing spectrophotometrically at λmax = 225 nm (Shimadzu UV-1800).

c) In-vitro Dissolution Study

- Dissolution testing was carried out using USP Apparatus II (paddle method) at 100 rpm in 900 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5°C.
- Samples (5 mL) were withdrawn at predetermined intervals up to 24 hours, filtered, and analyzed for drug content at 225 nm.
- The dissolution profile was compared with that of the marketed sustained release capsules of venlafaxine hydrochloride.

d) Stability Studies

Optimized formulations were stored at 40°C ± 2°C / 75% ± 5% RH for 60 days in accordance with ICH Q1A(R2) guidelines. Samples were evaluated periodically for appearance, drug content, and dissolution behavior to assess stability.[12-14]

2.2.5 Data Analysis

All experiments were performed in triplicate, and data were expressed as mean ± SD. Comparative release kinetics were evaluated using mathematical models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations to determine the mechanism of drug release.

3. RESULTS AND DISCUSSION

The present study was undertaken to formulate Venlafaxine HCL S.R pellets and pellets presented in the capsules. The study involves preformulation studies of drug and excipients, formulation and processing development along with evaluation of capsules and pellets made with the optimized formulation.

3.1 Pre Formulation Studies

Table no.1 Pre Formulation Studies

S.No.	Characteristics	Results
1.	Physical appearance	A white (or) almost white powder.
2.	Solubility	Freely soluble in water and in Methanol, soluble in Anhydrous ethanol and practically insoluble in Acetone.
3.	Bulk density	0.65gm/ml
4.	Tap density	0.79gm/ml
5.	Compressibility index	17.72%
6.	Melting point	217^0C
7.	Molecular weight	313.87.

3.2 Evaluation of Sustained Release Coated Pellets

Preformulation Characteristics of blend of all formulations.

3.2.1 Physical Evaluation

Table no.2 Physical Evaluation

S.No	Formulations	Angle of Repose (°)	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Compressibility Index (%)	Moisture Content (%)
1.	Trail 1	28.8	0.65	0.79	17.7	2.43
2.	Trail 2	25.6	0.69	0.81	14.8	2.44
3.	Trail 3	27.1	0.67	0.78	14.1	1.92
4.	Trail 4	28.6	0.70	0.88	20.5	2.63
5.	Trail 5	26.5	0.68	0.82	17.0	2.34
6.	Trail 6	24.4	0.66	0.77	14.2	2.35
7.	Trail 7	26.5	0.72	0.86	16.2	2.45
8.	Trail 8	25.7	0.69	0.80	13.7	2.22

3.3 Dissolution Studies

3.3.1 Trail-1 Dissolution Profile

The dissolution profile of this batch shows higher drug release than the reference capsules. In order to decrease the dissolution profile of the capsules, it was decided to increase the concentration of binder.

Table no.3 TRAIL-1 Dissolution profile

Product	% Drug release				
	2 hrs	4 hr	8 hr	12 hr	24 hr
Venlafaxine HCL Sustained Release Capsules 75mg (Innovator)	28	52	68	87	100
Venlafaxine HCL Sustained Release Capsules 75mg)	40	54	62	72	78

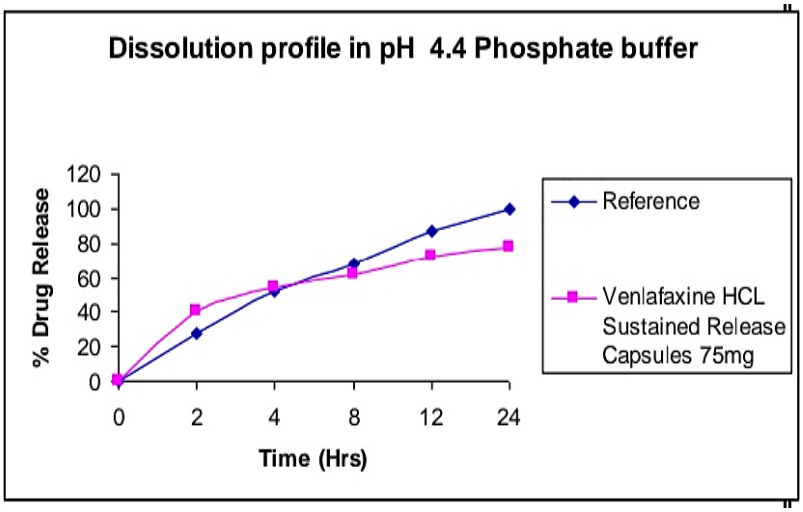

Figure no.1 TRAIL-1 Dissolution profile

3.3.2 Trail-2 Dissolution profile

The above dissolution data indicates the drug release of this batch releases the drug at higher rate at the 2'nd hour time points. But the dissolution profile was still higher than the reference capsules. Based on this observation it was decided to change the grade of Ethyl Cellulose 7CPS to Ethyl Cellulose 10 CPS.

Table no.4 Trail-2 Dissolution profile

Product	% Drug release				
	2 hrs	4 hr	8 hr	12 hr	24 hr
Venlafaxine HCL Sustained Release Capsules 75mg (Innovator)	28	52	68	87	100
Venlafaxine HCL Sustained Release Capsules 75mg)	35	52	63	67	78

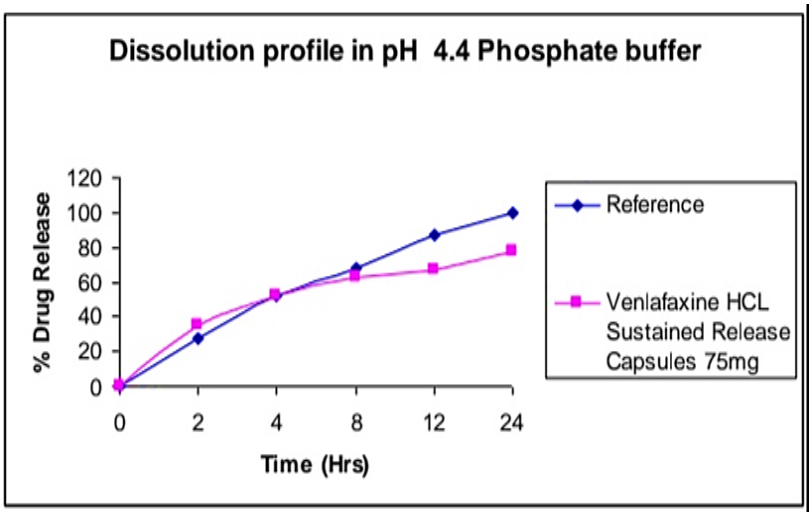

Figure no.2 TRAIL-2 Dissolution profile

3.3.3 TRAIL-3 Dissolution profile

Above dissolution data indicates that the increase of binder concentration and decrease of drug release. But the dissolution profile of present batch was still lower than the reference capsules. Based on this observation it was decided to decrease the binder and Coating Concentration is increasing.

Table no.5 TRAIL-3 Dissolution profile

Product	% Drug release				
	2 hrs	4 hr	8 hr	12 hr	24 hr
Venlafaxine HCL Sustained Release Capsules 75mg (Innovator)	28	52	68	87	100
Venlafaxine HCL Sustained Release Capsules 75mg)	32	38	46	58	68

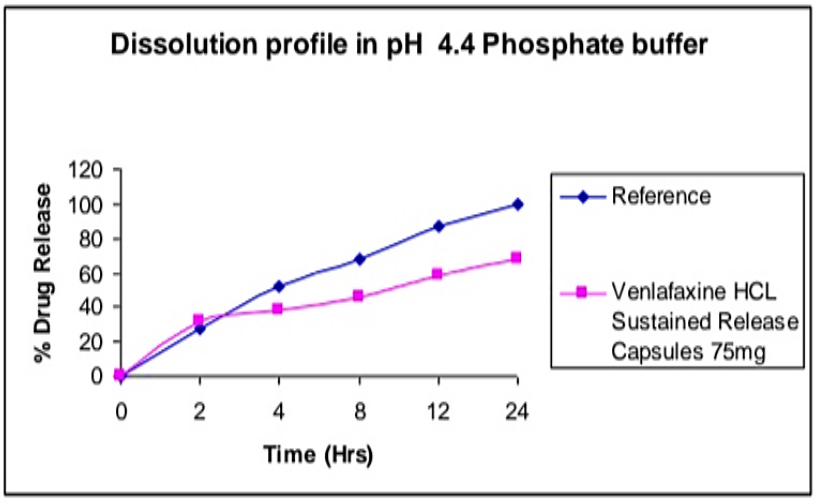

Figure no.3 TRAIL-3 Dissolution profile

3.3.4 TRAIL-4 Dissolution profile

The dissolution profile of this batch indicates drug release profile of the sample still lower than the

reference. Hence we are changing the binder and EthylCellulose and Plasidone-S-630 Concentration.

Table no.6 TRAIL-4 Dissolution profile

Product	% Drug release				
	2 hrs	4 hr	8 hr	12 hr	24 hr
Venlafaxine HCL Sustained Release Capsules 75mg (Innovator)	28	52	68	87	100
Venlafaxine HCL Sustained Release Capsules 75mg)	30	45	54	67	70

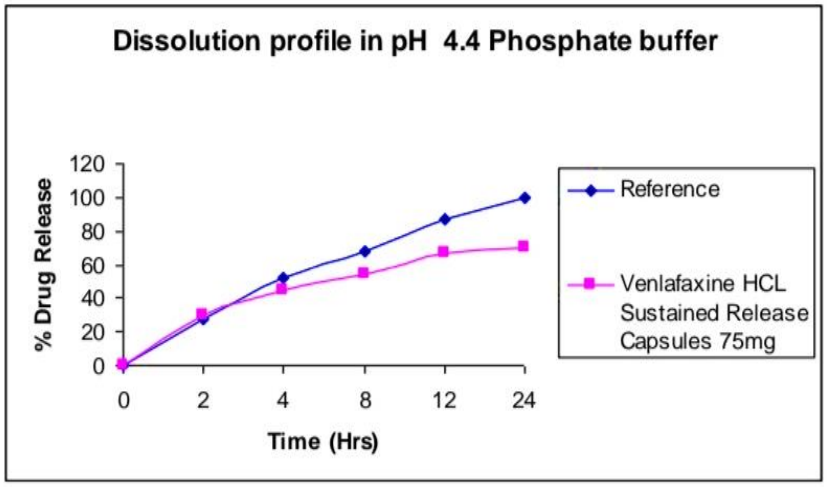

Figure no.4 TRAIL-4 Dissolution profile

3.3.5 TRAIL-5 Dissolution profile

The dissolution profile of this batch will not match with reference. Hence we are increasing the coating rate and decrease the binder concentration.

Table no.7 TRAIL-5 Dissolution profile

Product	% Drug release				
	2 hrs	4 hr	8 hr	12 hr	24 hr
Venlafaxine HCL Sustained Release Capsules 75mg (Innovator)	28	52	68	87	100
Venlafaxine HCL Sustained Release Capsules 75mg)	30	52	65	76	80

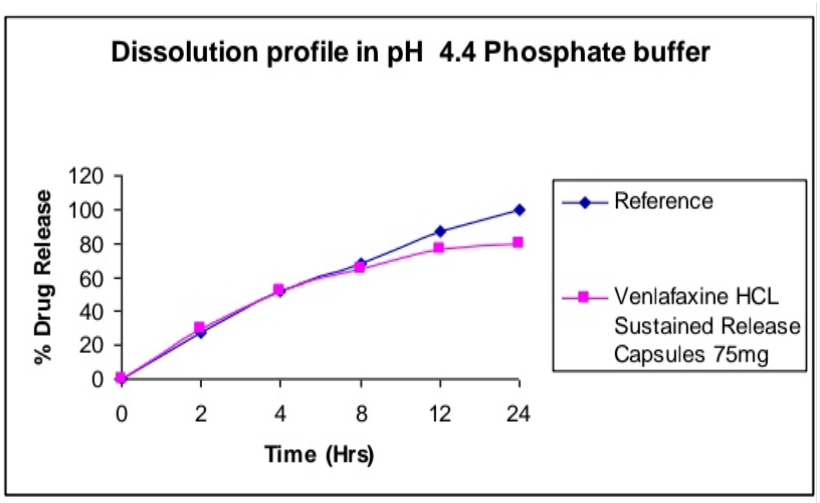

Figure no.5 TRAIL-5 Dissolution profile

3.3.6 TRAIL-6 Dissolution profile

The dissolution profile of this batch indicates drug release profile of the sample still lower than the reference. Hence we are decreasing the binder concentration and changing the grade of EthylCellulose 20 CPS to EthylCellulose 50 CPS to increase the coating rate.

Table no.8 TRAIL-6 Dissolution profile

Product	% Drug release				
	2 hrs	4 hr	8 hr	12 hr	24 hr
Venlafaxine HCL Sustained Release Capsules 75mg (Innovator)	28	52	68	87	100
Venlafaxine HCL Sustained Release Capsules 75mg)	30	46	62	72	82

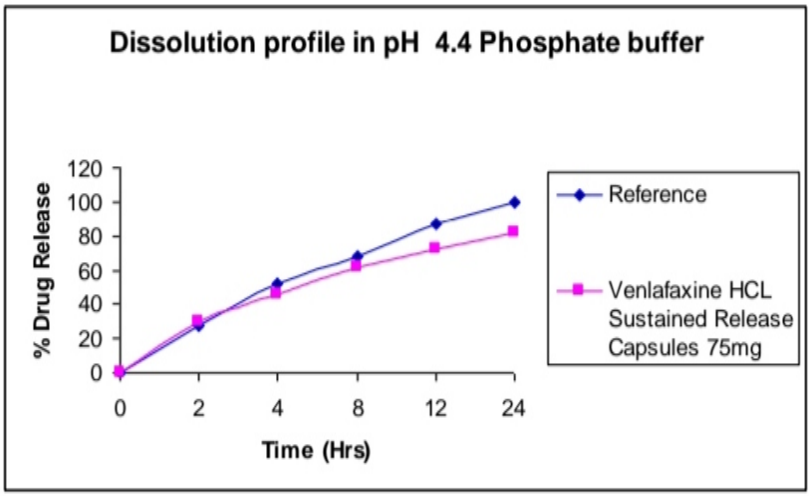

Figure no.6 TRAIL-6 Dissolution profile

3.3.7 TRAIL-7 Dissolution profile

The dissolution profile of this batch indicates drug release profile of the sample still lower than the

reference. Hence increasing the binder concentration and decreasing the coating rate.

Table no.9 TRAIL-7 Dissolution profile

Product	% Drug release				
	2 hrs	4 hr	8 hr	12 hr	24 hr
Venlafaxine HCL Sustained Release Capsules 75mg (Innovator)	28	52	68	87	100
Venlafaxine HCL Sustained Release Capsules 75mg)	28	50	73	89	96

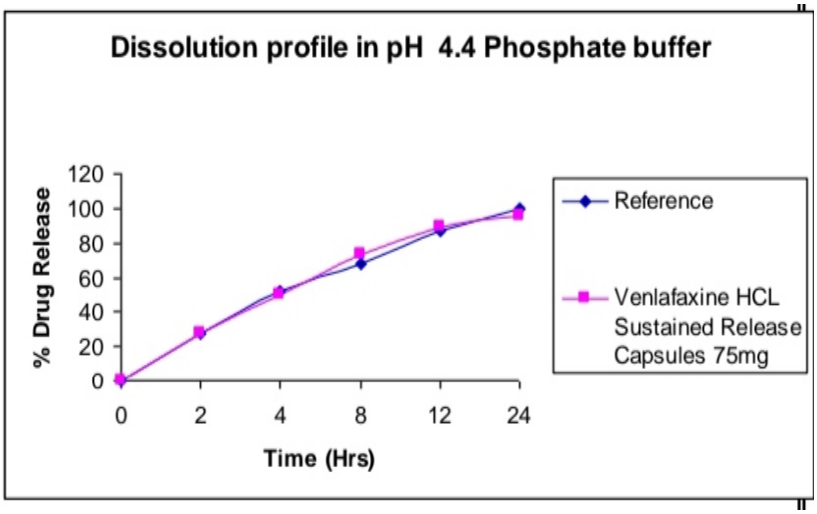

Figure no.7 TRAIL-7 Dissolution profile

3.3.8 TRAIL-8 Dissolution profile

The dissolution profile of this batch indicates drug release profile of the sample will have same release profile of the innovator.

Table no.10 TRAIL-8 Dissolution profile

Product	% Drug release				
	2 hrs	4 hr	8 hr	12 hr	24 hr
Venlafaxine HCL Sustained Release Capsules 75mg (Innovator)	28	52	68	87	100
Venlafaxine HCL Sustained Release Capsules 75mg)	28	54	70	90	99.7

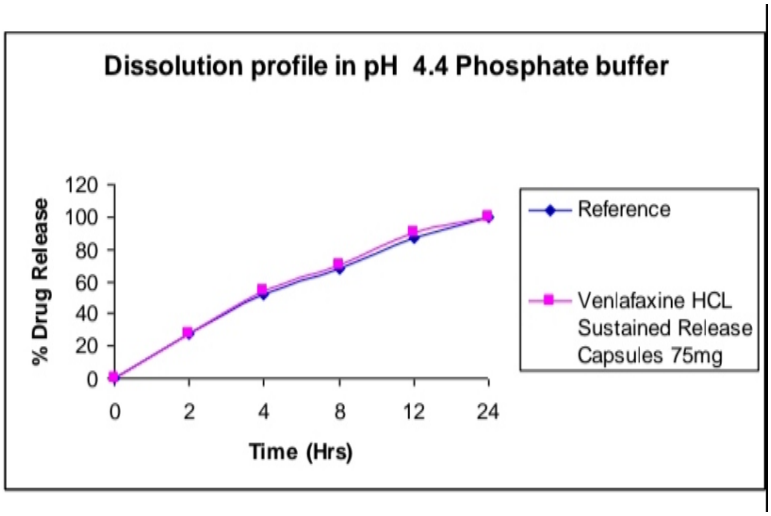

Figure no.8 TRAIL-8 Dissolution profile

3.4 Evaluation Of Capsules

Table no.11 Evaluation of Capsules

S.No	Formulation	Weight Variation	Maximum Deviation (+ve)	Minimum Deviation (-ve)	Disintegration Time
1	Trail 1	274.8	+8.07	-0.80	6.05
2	Trail 2	277.6	+7.70	-0.50	6.04
3	Trail 3	278.4	+7.75	-0.57	6.01
4	Trail 4	275.0	+8.36	-1.45	6.00
5	Trail 5	280.6	+5.84	-0.49	6.02
6	Trail 6	276.0	+7.95	-0.70	5.28
7	Trail 7	284.9	+4.94	-0.38	5.57
8	Trail 8	276.6	+8.45	-0.14	5.59

4. CONCLUSION

The active pharmaceutical ingredient Venlafaxine HCL was subjected to preformulation study, which encompasses the "Accelerated drug excipient compatibility study" and the results obtained with selected excipients showed good compatibility with Venlafaxine HCL. The Venlafaxine HCL SR pellets were loaded in size 2 capsules. It showed good results in formulation of stable dosage. The dissolution profile of the prepared Venlafaxine HCL SR release capsules were compared with that Venlafaxine HCL SR capsules (Wyeth) of the product. The release was found more in the case of pellets loaded in the capsules. And dissolution profile of Venlafaxine HCL SR capsules was compared with that of innovator (Wyeth). The release was found similar to that of Innovator. So the prepared product was

said to be equivalent with innovator. SR release pellets have minimum volume in size, greater surface area and more surface activity. The area of the drug loaded pellets release rate was also more. And also there was no need of disintegration time for pellets in capsules. Small volumes of pellets enter into the systemic circulation very fast. Moreover there was no accumulation of drug in the body. Drug release rate was more when compared with the innovator sample. In the case of Venlafaxine HCL SR capsules (Trail 8) meet the requirement for Invitro drug release were selected for stability studies. The capsules were stored in a bottle at 40°c / 75 % RH for 60 days. After 60 days samples were withdrawn and analyze. The results are reproducible and similar to theoretical set limits. Finally I conclude like Sustained Release Pellets in capsule have more drug release rate.

5. Conflict Of Interest Statement

We declare that we have no conflict of interest.

6. ACKNOWLEDGMENTS

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