RESEARCH ARTICLE

In-vivo Pharmacokinetic Evaluation of Venlafaxine HCl Sustained Release Tablet Formulation

Nilesh Sureshrao Mhaske, S. Sathesh Kumar*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science and Technology Advanced Studies (VISTAS), Chennai, India.

Received: 05th March, 2024; Revised: 26th May, 2024; Accepted: 03rd July, 2024; Available Online: 31st August, 2024

ABSTRACT

An optimized Venlafaxine SR tablets formulation, was chosen for *in-vivo* study against the commercial marketed Venlafaxine SR formulation. The non-compartmental pharmacokinetic specifications of both reference and standard were determined, after dosing via oral route. The peak plasma concentration (C_{max}) of optimized Venlafaxine SR tablets was found as 964.66 ± 53.15ng/ml in 5 hr, while C_{max} of marketed Venlafaxine SR tablets formulation was found as 872.33 ± 28.43 ng/ml in same time i.e. 5 hr. The C_{max} data suggests that absorption of drug in plasma from was in sustained manner from both the formulations, showing typical absorption pattern of SR product. The AUC_0-t for optimized and marketed Venlafaxine SR tablets was found to be 12981.63 ± 505.25 and 12023.83 ± 668.29 ng/ml*h, while AUC_0-∞ was found to be 13921.51 ± 417.40 and 13099.63 ± 742.21 ng/ml*h, respectively. The PK parameter showed the T_{max} and AUC for optimized Venlafaxine SR tablets as compared to its marketed product formulation. Pharmacokinetic parameter clearly suggested prolong release and availability of Venlafaxine in plasma from SR tablets formulation. Overall, the results suggest that the optimized SR formulation of Venlafaxine provides effective extended and controlled drug delivery, highlighting its potential clinical relevance in the treatment of depression and anxiety disorders.

Keywords: Pharmacokinetic; Sustained release; Tablet formulation; HPLC; Cmax; Tmax

International Journal of Pharmaceutical Quality Assurance (2024); DOI: 10.25258/ijpqa.15.3.09

How to cite this article: Mhaske NS, Kumar SS. *In-vivo* Pharmacokinetic Evaluation of Venlafaxine HCl Sustained Release Tablet Formulation. International Journal of Pharmaceutical Quality Assurance. 2024;15(3):1158-1163.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Venlafaxine hydrochloride is the well-known pharmaceutical product from the set of serotonin-norepinephrine reuptake inhibitors (SNRIs). Its main use as medication includes treating MDD which is a mood disorder, GAD which is an anxiety disorder, SAD which is a social anxiety disorder, and panic disorder(1). Venlafaxine functions by enhancing the amount of serotonin and norepinephrine which are the two neurotransmitters found inside the brain and they regulate mood, emotions and anxiety. It is needed to note that serotonin and norepinephrine play a major role in the regulation of mood and anxiety. The dual way of acting features above the selective serotonin reuptake inhibitors (SSRIs) and thereof it is less specific and has a bigger potential of effective solving mental disorders(2). Venlafaxine has two release forms, the immediate and the extended-release ones that equal to the choice of the dosage regimen while guaranteeing better tolerance to the medication. Notwithstanding the otherwise generally well-tolerated outcome, the most commonly reported side effects may include nausea and stomache, headache, sleeplessness, and erectile and sexual dysfunction. Venlafaxine hydrochloride has been shown to be the an excellent drug of choice in treating many mood and anxiety disorders. Patients are quite relieved of the symptoms of melancholy and anxiety(3,4).

An important point about controlled release tablet formulations that is they are needed for delivering drugs to the brain is that they generate the administration and the maintenance of medicines through a program(5). The combination of the sustained release mechanism and the maintenance of therapeutic medication concentrations in the circulation for a prolonged duration helps this treatment manage CNS conditions adequately as the drug cannot cross the blood-brain barrier through it. Continuous release forms provide the advantage of sustained release which guarantees drug delivery in a controlled manner and with a steady pattern. This method allows to limit the probability of adverse reactions and complications including toxicity or no efficiency of treatment that can be cause due to different drug level(6). Additionally, by utilizing a sustained a release tablet, patients have a less complicated medication regimen

*Author for Correspondence: sathesh2000@gmail.com

and therefore adhere to the necessary drug doses more and are more convenient to administer, which is crucial for smaller pharmaceuticals. In the scenario of long-term drug delivery systems, there is a high possibility to improve the delivery process of medication to the brain with the brain diseases like Alzheimer's, Parkinson's or epilepsy. Such an addition benefits primarily with patients' treatment effects, including the life quality(7). Along as well, nanomedicines can be designed to employ the pharmacokinetics of several low bioavailability drugs so as to extend the action of the drugs for a longer time(8). In summary, sustained release tablet formulations are a beneficial approach to deliver drugs to the brain in a controlled manner, effectively addressing the obstacles associated with central nervous system illnesses and enhancing treatment results for patients. In present study, we have formulated sustained release tablet formulation of Venlafaxine for the enhanced treatment of neurodegeneration and here we have performed it's *in vivo* pharmacokinetic studies.

MATERIAL AND METHODS

Determination of λmax of Venlafaxine

The calculation of the λ-max is vital for the identification of drugs since it is a characteristic of the wavelength that is mostly absorbed in the spectrum of light. This selective absorption band is specific of every substance, part of which is a fine molecular pattern giving an identity for the substance and to confirm the purity of the substance. The λMax info is used by researchers to improve the parameters of analysis methods such as UV-VIS spectroscopy, which helps them to obtain high sensitive and accurate concentrations of the drug. Besides, measurements of λmax also become imperative at the instance of drug development and validation and during the course of constant monitoring of stability and quality during formulation and storage. This is fundamental of making medicines and following the rules of regulations. The same Methanol content Methanol of Venlafaxine stock solution was obtained by dissolving 10 mg of drug in 10 ml of Methanol. Houn the original stocks, the stanches of Methanol were diluted also with this, such that we have now a concentration which is 10 µg/ml in a solution. The wavelength (λmax) was determined by application of Shimadzu UV-Visible spectrophotometer (Model UV-1800) in the range 200–400 nm. Methanol was used as blank. The observed maximum of colour characteristic of the particular solution was observed at about 235 nm.

HPLC Method Development

The stock solution and working solution preparation was done in methanol (10 mg/ml of venlafaxine) as per the reported literature(9). The process of methanol equilibration was over when the stationary phase approached the stabilized baseline. In the standard solution venlafaxine was measured and then different individual solvents mixtures were tried to have the required separation of peaks and be steady. The filtration of every mobile phase was performed on Whatman filter paper number. 42. Going to the column, peaks should be well developed, symmetric within limits and with okay resolutions. Based on experimental data and solubility, interaction of sample solubility and interaction of sample and the mobile phase composition was determined to obtain eligible separation. Instability of the mobile phase is the greatest challenge in development of HPLC methods which must lead to the good separation, resolution,and peak shape of analytes. Through trial-and-error procedures of testing various solvents mix-composition, pH rates and the flow paces, researchers attain the mobile phase that equips with the better selectivity and sensitivity of the analysis. This process leads to the determination of the best conditions of extracting lots of complex liquid, reducing the distribution process of peak tailing and minimizing the analysis time needed for the process. In general, this establishes unwavering reliability and repetition of the HPLC technique required for impeccable quantitative and qualitative standardization(9). The mobile phases tried are as follows:

- MEOH: H_2O (90:10)
- MEOH: H_2O (90:20)
- MEOH: KH_2PO_4 Buffer (0.05M):(90:10 pH 5.0)
- MEOH: KH_2PO_4 Buffer (0.05M):(80:20 pH 5.5)
- MEOH: KH_2PO_4 Buffer (0.05M):(70:30 pH 5.8)
- MEOH: KH_2PO_4 Buffer (0.05M):(65: 35pH 6.1)

Since mobile phase has been the tried numerous times, mobile phase made by using. MEOH: KH2PO4 Buffer (0. 05M):(65:35 pH 6. 1) was determined to be ideal due to the choice of a pH factor that helps to obtain not only a sharp, but also a reproducible retention time for Venlafaxine.

Chromatographic Conditions

The chromatographic conditions were determined via a process of trial and error and were maintained consistently throughout the technique.

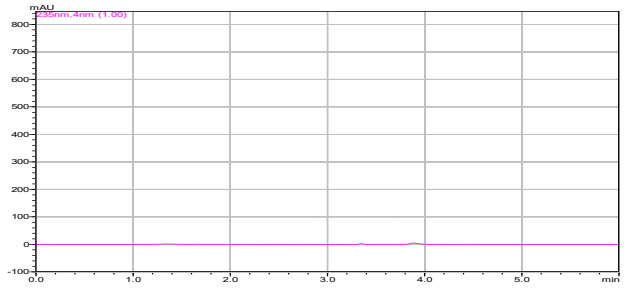

Figure 1: Blank chromatogram obtained by using MEOH: KH_2PO_4 Buffer (0.05M):(65:35 pH 6.1) as mobile phase

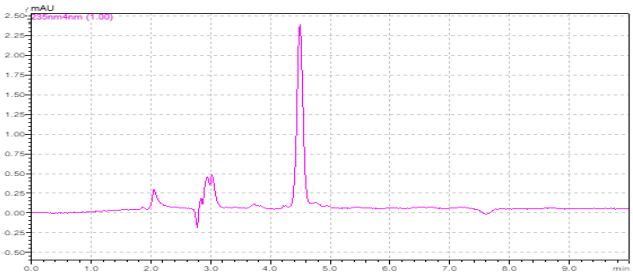

Figure 2: Trial chromatogram obtained by using MEOH: Water (90:10) as mobile phase

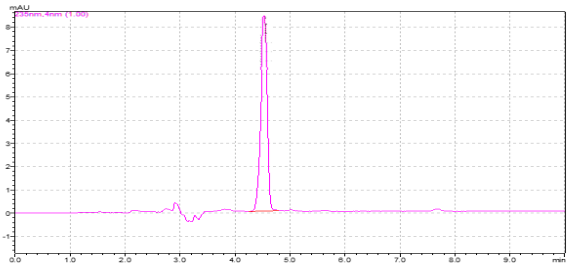

Figure 3: Trial chromatogram obtained by using MEOH: KH_2PO_4 Buffer (0.05M):(80:20 pH 5.5) as mobile phase

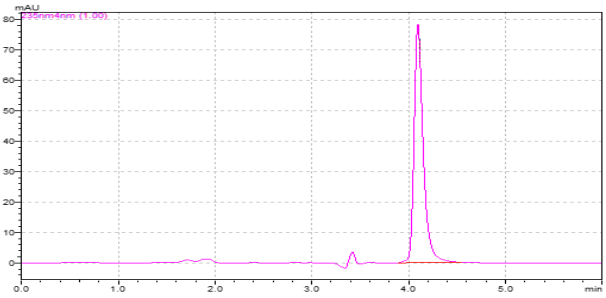

Figure 4: Trial chromatogram obtained by using MEOH: KH_2PO_4 Buffer (0.05M):(70:30 pH 5.8) as mobile phase

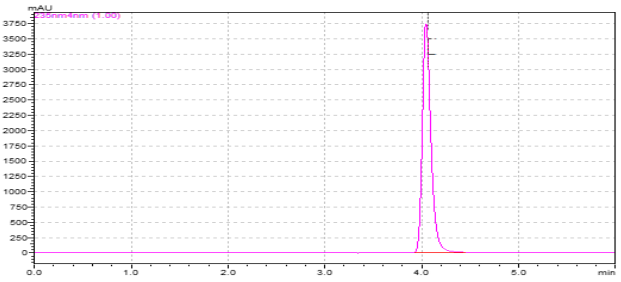

Figure 5: Trial chromatogram obtained by using MEOH: KH_2PO_4 Buffer (0.05M) (65: 35 pH 6.1) as mobile phase

Column	:Cosmosil 4.6 (id) x 250 mm
Particle size packing	:5 µm
Stationary phases	:C_{18} Grace
Mobile phase	:MEOH: KH_2PO_4 Buffer (0.05M):(65: 35pH 6.1)
Detection wavelength	:235 nm
Flow rate	:1 mL/min.
Temperature	:Ambient
Sample size	:20 µL

Preparation of Calibration curve

Venlafaxine standard stock solution

For calibration, preparing the standard solution is vital for obtaining coherent and precise readings in analytical measurements. A stock solution provides a highly, steady and identical reference that can be dilute with accuracy for the purposes of generating various calibration standards of different concentrations. The reduction of errors and varieties employs the strategy signifying that the calibration curve

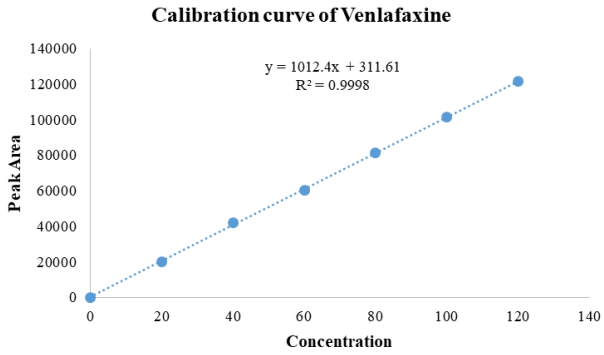

Figure 6: Standard calibration curve for venlafaxine

Table 1: Observation of standard curves of Venlafaxine

S. No.	*Conc. (µg/mL) Venlafaxine*	*Peak Area*
1	0	0
2	20	20345
3	40	41984
4	60	60313
5	80	81534
6	100	101567
7	120	121653

reproduces the true interaction of concentration and the result correctly. Besides that, following the stock solution method simplifies the steps toward the final completion of the analysis, therefore saving time and resources as long as accuracy and reliability of the method can be maintained. The venlafaxine (100 mg/mL) stock solution was further diluted with the mobile phase to obtain different concentrations.

Procedure

The mobile phase was allowed to reach equilibrium with the stationary phase until a stable baseline was achieved. The concentrations of Venlafaxine ranging from 20 to 120 µg/mL were injected and the peak area was observed. Figure 6 illustrates the relationship between the drug concentration and the corresponding peak area on the graph.

In-Vivo Pharmacokinetic study

The formulation that demonstrated favourable physical features and in vitro drug release, as determined by the evaluation parameter, was selected for the in-vivo investigation. It was then compared with commercially available Venlafaxine HCl SR tablets. An in vivo pharmacokinetic research was conducted on male albino rabbits in accordance with the requirements of the CPCSEA, following study permission (CPCSEA/IAEC/JLS/20/11/23/062).

Study design

The study was conducted on randomly selected healthy male albino rabbits weighing between 2.5 and 3 kg. The rabbits were randomly separated into two groups, each with six

Table 2: *In vivo* animal study design

Animal Used	Albino Rabbit (Male)											
Drug Dose	75 mg											
No. of animals	12 (Each group contain 6 animals)											
Wt. of animals (kg)	Group I (Test) Optimized Venlafaxine SR Tablets						Group II (Reference) Marketed Venlafaxine SR Tablets					
	2.78	2.92	2.98	3.00	2.84	2.90	2.75	2.88	2.94	2.87	2.80	3.00
Dose of Drug (mL)	75	75	75	75	75	75	75	75	75	75	75	75

rabbits (n=6). Marketed Venlafaxine HCl sustained released formulation (Venlor XR, Cipla Ltd) was administered orally to one set of animals, which was treated as a reference. The second group received optimized Venlafaxine HCl SR tablets formulation. Tablets were kept behind the tongue in order to avoid biting of formulation by animal and given sufficient water for easy swallowing. At predetermined time interval (1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h.), blood samples (1 mL) were collected from orbital sinus, before dosing from each animal. Collected sample was then transferred in to micro centrifuge tubes containing EDTA as an anticoagulant.

The mobile phase utilized in the study was made up of acetonitrile, methanol, and water in a 60:20:20 (v/v) ratio. 50µL of plasma were combined with 0.5 ml of mobile phase, from which a 20 ml sample was manually injected into a column at a flow rate of 0.7 mL/min and the response at 226 nm were noted by HPLC method(9).

Pharmacokinetic Parameters and Statistical Analysis

T_{max}, C_{max}, and AUC are the crucial target indices of the pharmacokinetic research work. Tmax helps in establishing the time required to reach the maximum concentration of plasma which helps to evaluate the drug's absorption rate. Cmax is the peak value of plasma concentration, thus it expresses the highest level of the drug's concentration in the bloodstream speculative of the drug's efficacy and toxicity in most cases. The AUC (area under the curve) is used to evaluate the drug concentration during the entire AUC time, making a holistic perspective about the drug's bioavailability and systemic exposure. As a whole, they make up the profile in which the major ADME characteristics of the drug are revealed, including the process of absorption, distribution, metabolism, and excretion (ADME). A graph illustrating the relationship between the concentration of the medication in the plasma and time was generated through the use of HPLC analysis(9).

RESULTS AND DISCUSSION

In-vivo Pharmacokinetic study

Finding pharmacokinetics attributes for a drug formulation that is already developed is crucial in estimating how the drug works in a human body. These parameters give consequential information on the ADME which indicate whether the formulation produced effectively treats the disease. The combination drugs typically see improvements in maintaining targeted dosing strengths, improving therapeutic efficacy, and reducing side effects(10). Also, drug disposition profiles are relevant for the sake of clinical trial/approval processes and the future direction of clinical development. Based on the optimization study, an optimized Venlafaxine SR tablets formulation, was chosen for *in-vivo* study against the commercial marketed Venlafaxine SR formulation. The non-compartmental pharmacokinetic specifications of both reference and standard were determined, after dosing via oral route.

The peak plasma concentration (C_{max}) of optimized Venlafaxine SR tablets was found as 964.66 ± 53.15ng/ml in 5 hr, while C_{max} of marketed Venlafaxine SR tablets formulation was found as 872.33 ± 28.43 ng/ml in same time i.e. 5 hr. The Cmax data suggests that absorption of drug in plasma from was in sustained manner from both the formulations, showing typical absorption pattern of SR product. The AUC_0-t for optimized and marketed Venlafaxine SR tablets was found to be 12981.63 ± 505.25 and 12023.83 ± 668.29 ng/ml*h, while AUC_0-∞ was found to be 13921.51 ± 417.40 and 13099.63 ± 742.21 ng/ml*h, respectively. The PK parameter showed the Tmax and AUC for optimized Venlafaxine SR tablets as compared to its marketed product formulation. Pharmacokinetic parameter clearly suggested prolong release and availability of Venlafaxine in plasma from SR tablets formulation. Results revealed that the optimized SR formulation of venlafaxine provided effective sustained and prolonged release of drug, having potential of extended/controlled drug delivery. The table 2 displays the *in vivo* Cmx for Test and Reference, whereas table 3 shows the different pharmacokinetic properties of Optimized Venlafaxine SR tablets and Marketed SR Venlafaxine formulation. Total solubility is considered to be the most important constituent of the absorption of drugs from the gastrointestinal tract, one of the key factors controlling the bioavailability of drugs, mainly the fact that bioavailability is often limited by the poor solubility of drugs. Solubility is also an important factor as drugs with poor solubility have their therapeutic price depressed because they will have their capacity to dissolve in the intestine reduced, thus limiting their ability to absorb in the bloodstream. As an example, the methods of solid dispersion, nano-particles formation or the application of surfactants or co-solvents would help to improve solubility by an order of magnitude. Better dissolution rates is means that more of the drug will become soluble therefore with increased availability for absorption a greater concentration will reach the blood stream which may improve treatment efficacy. This

Table 3: Plasma drug concentration in rats during *in-vivo* testing and comparison

Time (hr)	*Concentration in ng/ml*	
	Test (Optimized Venlafaxine SR Tablets)	*Reference (Marketed Venlafaxine SR Tablets)*
0	0 ± 0.0	0 ± 0.0
1	176.21 ± 33.32	198.67 ± 42.91
2	260.30 ± 32.47	354.30 ± 40.08
3	480.00 ± 54.58	566.23 ± 42.03
4	818.33 ± 32.13	780.67 ± 50.33
5	964.34 ± 53.15	872.20 ± 28.43
6	834.53 ± 59.02	771.67 ± 46.61
8	771.24 ± 70.26	696.15 ± 34.70
10	708.66 ± 27.15	658.56 ± 29.40
12	666.10 ± 52.46	602.13 ± 42.03
14	602.13 ± 63.76	544.40 ± 34.77
16	534.23 ± 29.90	486.31 ± 34.53
18	545.30 ± 41.47	410.63 ± 20.40
20	423.14 ± 70.58	324.67 ± 45.08
22	364.42 ± 37.00	241.67 ± 32.13
24	187.33 ± 23.86	166.41± 22.19

Values are mean ± SD (n=6)

Table 3: PK Parameters of Optimized Venlafaxine SR tablets and Marketed Venlafaxine SR Tablets

Pharmacokinetic Parameter	*Optimized Venlafaxine SR tablets*	*Marketed Venlafaxine SR Tablets*
T_{max} (h)	5 ± 0.00	5 ± 0.00
C_{max} (ng/ml)	964.66 ± 53.15	872.33 ± 28.43
$t_{1/2}$ (h)	3.46 ± 0.54	4.50 ± 0.35
AUC $_{0\text{-}t}$ (ng/ml*h)	12981.63 ± 505.25	12023.83 ± 668.29
AUC $_{0\text{-}inf.}$ (ng/ml*h)	13921.51 ± 417.40	13099.63 ± 742.21
MRT (hr)	12.28 ± 0.46	12.34 ± 0.026

Mean ± SD (n=6)

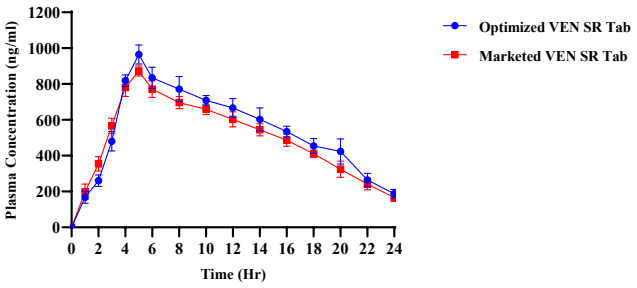

Figure 7: Plasma drug concentration profile of Optimized Venlafaxine SR tablets and Marketed Venlafaxine SR tablets

refinement makes sure that the drug is capable of reaching to its target site of action in sufficient amount leading to more appropriate and desirable therapeutic effects. However, the solubility improvement conclusion is not the only one. The solubility improves pharmaceutical formulations should be created efficiently(11).

CONCLUSION

Venlafaxine is available in both immediate-release and extended-release formulations, offering flexibility in dosing and improved patient adherence. The study aimed to compare the pharmacokinetic parameters of an optimized sustained-release (SR) formulation of Venlafaxine hydrochloride tablets with a marketed Venlafaxine SR formulation. Healthy male albino rabbits were divided into two groups and administered either the optimized or the marketed formulation. Blood samples were collected at predetermined intervals, and plasma concentrations of Venlafaxine were determined using HPLC. The results indicated that the optimized Venlafaxine SR tablets exhibited a higher Cmax and AUC compared to the marketed formulation, suggesting sustained and prolonged drug release. These findings demonstrate the potential of the optimized formulation for extended and controlled drug delivery. The statistical analysis confirmed the significance of the observed differences, highlighting the superiority of the optimized SR formulation in providing sustained release of Venlafaxine. Overall, the study concludes that the optimized Venlafaxine SR tablets offer enhanced pharmacokinetic profiles and may represent a promising alternative for the treatment of depression and anxiety disorders.

REFERENCES

1. Freeman R, Raskin P, Hewitt DJ, Vorsanger GJ, Jordan DM, Xiang J, et al. Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. Curr Med Res Opin. 2007;23(1):147–61.
2. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: Systematic review, meta-analysis and updated NeuPSig recommendations. Lancet Neurol. 2015;14(2):162–73.
3. He Y, Yu Y, Zhang L, Fang Z, Wu Z. Pharmacokinetics and bioequivalence of Venlafaxine hydrochloride sustained release tablets in Beagle dogs. Drug Eval Res. 2019;42(7):1314–7.
4. Jain A, Chauhan R, Singh S, Kulkarni S, Jain S. Optimization of coating material for sustained release venlafaxine hydrochloride tablet. Int J Life Sci Pharma Res. 2015;5(3):P1–12.
5. Butani SB. Development and Optimization of Venlafaxine Hydrochloride Sustained Release Triple Layer Tablets Adopting Quality by Design Approach. Pharmacol & Pharm. 2013;04(03):9–16.
6. Mahesh PG, Jeganath S. Formulation and evaluation of venlafaxine hydrochloride sustained release matrix tablet. Asian J Pharm Clin Res. 2018;11(Special Issue 4):170–4.
7. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: A double-blind, placebo-controlled study. Pain. 2004;110(3):697–706.
8. Bhandwalkar MJ, Avachat AM. Thermoreversible nasal in situ gel of venlafaxine hydrochloride: Formulation, characterization,

and pharmacodynamic evaluation. AAPS PharmSciTech. 2013;14(1):101–10.
9. Nemade LS, Patil MP. In vivo Pharmacokinetic evaluation of Lansoprazole-loaded Nanosuspension : As a proof of Enhanced Solubility and. Adv Biores. 2023;14(March):124–32.
10. Baig MS, Haque MA, Konatham TKR, Mohammad BD, Yahya BA, Saffiruddin SS, et al. Recent Advancements in Hyperthermia-Driven Controlled Drug Delivery from Nanotherapeutics. Recent Adv Drug Deliv Formul [Internet]. 2022;16(4):270–86. Available from: https://pubmed.ncbi.nlm.nih.gov/36056855/
11. Ďurišová M. Computational Analysis of Pharmacokinetic Behavior of Ampicillin. J Appl Bioanal. 2016;2(3):84–9.