RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Dosage Form of Venlafaxine Hydrochloride for Enhanced Treatment of Neurodisorders

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ABSTRACT

In the present study, we have designed and developed a sustained-release tablet formulation of Venlafaxine Hydrochloride. The optimized formulation was then subjected to various evaluation parameters. The formulation of venlafaxine hydrochloride sustained release tablets with a dosage of 500 mg included the utilization of several hydrophilic polymers, including jackfruit mucilage, HPMC K4, and PVPK30, as release retardants. This was done to extend the duration of drug release to 12 hours. The formulation features, including pre-compression and post-compression investigations, were conducted individually according to established protocols. The tablets were determined to be compliant in terms of weight uniformity, hardness, thickness, diameter, friability, and drug content. Separate in-vitro dissolution studies were done for both tablets. The venlafaxine hydrochloride SR formulation F18 was optimized to provide the desired release profile for up to 12 hours. The Venlafaxine Hydrochloride SR formulation was optimized and exhibited zero-order release kinetics. The stability studies conducted under accelerated conditions at a temperature of 40 ± 2°C and a relative humidity of 75 ± 5% yielded good results. The study indicated that the sustained release administration of Venlafaxine HCl is potentially efficacious. It reduces the frequency at which the patient has to take medication and improves patient adherence. Our objective is to conduct *in-vivo* pharmacokinetic studies of the formulation to verify the drug's entry into the systemic circulation.

Keywords: Venlafaxine HCl, Sustained release, tablet, *in-vitro*, release kinetics.

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INTRODUCTION

A sustained-release tablet formulation is a pharmaceutical preparation designed to release its active ingredients gradually over an extended period, providing controlled and prolonged drug delivery. Sustained-release tablets achieve controlled release through various mechanisms, such as matrix systems, osmotic pumps, or coated pellets, which dictate the rate at which the drug is released in the gastrointestinal tract.[1,2] Sustained-release tablets are commonly used in the treatment of chronic conditions where consistent drug levels are crucial, promoting a more steady and sustained therapeutic effect. Careful consideration of the pharmacokinetics of the drug and the desired therapeutic outcomes guides the formulation process, making sustained-release tablets a valuable option in modern pharmaceutical practice.[3] Venlafaxine is frequently used to treat numerous depressive disorders. In addition to its antidepressant properties, venlafaxine is known for its dual-action mechanism, impacting both serotonin and norepinephrine pathways.[4-7] The extended-release form of the medication allows for once-daily dosing, contributing to improved patient adherence. Like any medication, venlafaxine may have side effects, and healthcare professionals should carefully monitor its use. Adjustments to the dosage or alternative treatments may be considered based on individual patient response and tolerability.[8] In the present study, we have designed and developed a sustained-release tablet formulation of venlafaxine hydrochloride. The optimized formulation was then subjected to various evaluation parameters.

MATERIALS AND METHODS

Identification of Drug

The obtained drug sample was subjected to visual examination and observations.

Determination of Melting Point

The venlafaxine hydrochloride melting point was determined using the capillary fusion technique.

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FTIR Studies

The drug's infrared spectra were evaluated at a wave range of 4000 to 400 cm^{-1} using an FTIR spectrometer-430, resulting in the acquisition of spectra (Shimadzu 8400S, Japan).[9]

Differential Scanning Calorimetry (DSC) Studies

A thermogram for Venlafaxine hydrochloride was acquired using a DSC from Mettler-Toledo, Switzerland, specifically the Mettler DSC 1 star system.[10]

UV Spectroscopy Studies

The stock solution of a concentration of 100 µg/mL was prepared. The venlafaxine hydrochloride solution in methanol was subjected to UV spectroscopy, scanning the UV spectrum from 800 to 223 nm (λ max) as shown in Figure 1.[11]

Drug-Excipients Compatibility Studies

FTIR, DSC, and XRD

We examined the FTIR spectra of both pure Venlafaxine hydrochloride and a physical blend of polymers containing this drug. The FTIR spectra of the mixtures were compared to those of the pure drug and polymer to ensure that there were no alterations in the main peaks of the spectra. A thermogram for venlafaxine hydrochloride and physical mixtures (drug and polymers) was obtained using DSC. The XRD patterns of the pure drug and physical mixture (drug and polymers) were obtained. The measurement was conducted over a diffraction angle (2θ) range of 10 to 30º at a scanning rate of 10 minutes per minute.[12]

Powder characterization

The bulk density (BD), tapped density**,** Carr's index, Haussner's ratio, and the angle of repose (θ) of API powder were determined.

Experimental Factorial Design

Central composite design

Central composite design (RSM) was employed to optimize the formulation of sustained-release venlafaxine hydrochloride tablets using Design Expert® software (version 13, Stat-Ease Inc.). The study involved three formulation variables, denoted as X1 (Jackfruit mucilage, 15–25%), X2 (HPMCK4, 10–20%), and X3 (PVPK30, 9-15%), each having two levels, -1 (lower) and +1 (higher). The levels of MCC, Talc, and the drug remained constant throughout the experiment. The impact of these factors on response variables, namely Y1 (hardness) and Y2 (dissolution or %CDR), was assessed using RSM. The model's performance was further analyzed through regression coefficients, analysis of variance, and percent coefficient variance. A total of 20 experimental runs were generated, with varying levels of the specified variables as detailed in Table 1, and the experimental design factors are outlined in Table 2. For each formulation batch, precise measurements of the drug and other ingredients (as shown in Table 3) were taken using a digital balance (Mettler Toledo B204-S) and passed through a 60-mesh sieve to ensure uniformity.

Table 1: The optimization involves determining the optimal levels of variables

Batch code	*X1: Jackfruit*	*X2: HPMCK4*	*X3: PVPK30*
F1	20	23.4	12
F2	15	20	15
F3	25	10	9
F4	28.4	15	12
F5	20	15	12
F6	20	15	6.9
F7	15	20	9
F8	15	10	15
F9	20	15	17.0
F10	25	20	15
F11	25	20	9
F12	20	6.5	12
F13	20	15	12
F14	20	15	12
F15	25	10	15
F16	11.5	15	12
F17	20	15	12
F18	15	10	9
F19	20	15	12
F20	20	15	12

Table 2: Central composite design (RSM)

Batch code	*X1: Jackfruit*	*X2: HPMCK4*	*X3: PVPK30*	*Y1: Hardness*	*Y2: %CDR*
F1	100	75	85	5.1	96.89
F2	100	117	60	4.9	97.69
F3	100	32	60	4.7	97.78
F4	125	100	45	4.8	97.36
F5	100	75	60	5.3	96.28
F6	75	100	75	5.2	96.12
F7	100	75	60	5.3	96.38
F8	100	75	60	5.3	96.89
F9	57	75	60	4.8	97.36
F10	100	75	60	5.4	96.68
F11	75	50	45	5.1	96.52
F12	125	100	75	5.1	96.23
F13	142	75	60	4.9	98.38
F14	100	75	60	5.4	96.89
F15	125	50	75	4.7	97.32
F16	75	100	45	5.2	96.81
F17	75	50	75	5	96.2
F18	125	50	45	4.9	98.91
F19	100	75	60	5.3	96.29
F20	100	75	34	5.2	96.23

Table 3: Formulation table of venlafaxine hydrochloride tablets

S. No.	*Ingredients*	*Quantity (mg)*	*Category*
1	Venlafaxine hydrochloride	180	Antidepressant
2	Jackfruit mucilage	100	Sustained Release Polymer
3	HPMC K4	50	Sustained Release Polymer
4	PVPK30	45	Binder, Granulation agent
5	Lactose	65	Filler
6	Starch	25	Disintegration
7	Microcrystalline cellulose	23	Diluent
8	Magnesium stearate	7	Lubricant
9	Talc	5	Glidant
Total weight tablet		500 mg	

Method of Preparation of Venlafaxine Hydrochloride tablet

Direct compression method

Direct compression is used to design multiple sustained-release tablet formulations. An 80# sieve has been used to sieve all of the powders. Drug quantity required, as well as various polymer agents such as Jackfruit mucilage, HPMC K4, and PVP K30. Finally, talc and magnesium stearate were used as lubricants and glidants. A Rimek small press tablet machine was used to compress the mixture. Table 3 shows the composition of various batches.[13-16]

Evaluation of Tablets

General appearance

The tablets from each formulation batch were visually examined to assess their overall look. The visual evaluation assessed the general appearance characteristics, including form, color, and the presence or absence of odor and taste.

Uniformity of weight

A sample of twenty tablets was chosen at random, and each one was weighed independently. The mean weight was computed. The tablets' percentage deviation was computed and compared to the standard requirements.

Thickness, hardness, and friability

The thickness, hardness, and the determination of the friability of the produced formulations were conducted.

Drug content

During the tablet formulation process, it is essential to determine the drug content in order to guarantee that each tablet has the exact quantity of active pharmaceutical ingredient (API) that was previously defined. An accurate examination of the drug's content ensures that the dose is consistent, which is essential for the effectiveness of the treatment and the safety of the patient. Inconsistencies or variations in the manufacturing process may be identified with the assistance of this method, which enables modifications to be made in a timely manner in order to preserve product quality. Compliance with regulatory requirements and guidelines is required for market approval, and ensuring that the right medication content is present is also crucial. In the end, this assessment is an essential component in the process of providing patients with medicine that is both effective and dependable. Utilizing UV spectroscopy at 225 nm, the drug content was assessed after the calibration curve was prepared.

In-vitro drug release study and release kinetic parameters

The rate of venlafaxine hydrochloride release from sustained-release tablets was measured using the USP dissolution testing device II (paddle method). The method was used as per reported in the literature. It contributes to the development of efficient sustained-release tablets that are able to keep therapeutic medication levels stable for long periods of time. In order to examine the release kinetics of the sustained-release tablets in a laboratory setting, data collected from the dissolution research of the most effective formulation were analyzed using several mathematical models.

Accelerated stability study

The most promising formulations can be tested for short-term accelerated stability. The optimized formulation was placed at a temperature 40° ± 2°C and relative humidity (RH) 75 ± 5% for a period of 3 months as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn periodically and analyzed for thickness, uniformity of weight, and dissolution, as previously mentioned.

RESULT AND DISCUSSION

Identification of Drug

The obtained drug sample was then subjected to visual examination, and the observations were as follows: color: white; state: crystalline powder; solubility: Venlafaxine hydrochloride is soluble in water and methanol.

Melting Point Determination

The Venlafaxine hydrochloride sample exhibited melting point values within the range of 215 to 216ºC. The documented melting point of venlafaxine hydrochloride is 215.3ºC. Therefore, the experimental results closely matched the official ones.

FTIR

The presence of functional group peaks at specific wavelengths, as shown in Figure 2, matched exactly with the functional groups found in venlafaxine hydrochloride. As a result, it can be concluded that the sample is indeed venlafaxine hydrochloride.

Differential Scanning Calorimetry

The DSC analysis of venlafaxine hydrochloride provided valuable insights into its thermal behavior and stability. The melting point identified in this study is consistent with the literature, indicating the reliability of the analysis. The presence of an onset temperature suggests that the material is showing the starting of the melting point at 191.48°C, as shown in Figure 3. The onset of decomposition at around 234.29°C indicates that Venlafaxine Hydrochloride is thermally stable up to this temperature. This information is crucial for pharmaceutical manufacturers to establish appropriate storage conditions and ensure the drug's stability during transportation and storage.

UV Spectroscopy

The venlafaxine hydrochloride solution was subjected to scanning from 800 to 200 nm, and it exhibited peak absorption at 223 nm, as depicted in Figure 3. This observation was in agreement with the reported UV spectrum of venlafaxine hydrochloride, which also indicated a maximum absorption at 223 nm (λmax) as shown in Figure 1.

Drug-Excipients Compatibility Study

FTIR

FTIR spectral analysis demonstrated that there were no substantial interactions observed among the different rational combinations, including physical mixtures of the drug with polymers like HPMC K4 and Jackfruit mucilage. This lack of interaction is illustrated in the provided Figure 2. The FTIR spectra of the mixture containing the drug and polymer showed that there were no changes in the peak wavelengths or their intensities. This indicated the absence of any interaction between them.

DSC

DSC has been proposed as a rapid technique for evaluating the physical and chemical interactions between various components in a formulation. The process entails comparing the thermal characteristics of pure substances with those of a 1:1 physical combination in order to identify appropriate excipients for compatibility. When analyzing the DSC thermograms, it was seen that the drug exhibited a clear melting point at 219.68°C in this particular context. The melting values of HPMC K4 and Jackfruit mucilage were observed to be 93.09 and 92.10°C, respectively, in their DSC thermograms. When combined with venlafaxine HCl, there were no noticeable changes in these melting points. The absence of any change indicates that the drug is compatible with both HPMC K4 and Jackfruit mucilage. Additionally, in the DSC curve of the tablet, characteristic endothermic peaks were observed for the drug and both polymers, as well as an endothermic peak at 220.38 and 84.56°C, which corresponded to the dehydration of carbohydrates in jackfruit mucilage. Figure 3 displays a comparison of DSC thermograms for venlafaxine HCl, individual excipients, and physical combinations.

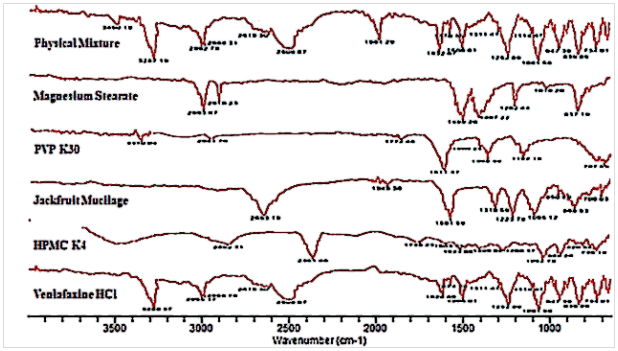

Figure 2: The FTIR spectrum of drug, excipients, and physical mixture

XRD

The XRD pattern of the pure drug displays distinct diffraction peaks at specific 2θ angles, which are indicative of its crystalline nature, as shown in Figure 4. These peaks correspond to the lattice planes within the crystal structure of the drug. The position and intensity of these peaks are unique to the drug's crystal lattice and can be used for its identification. Changes in the XRD pattern of the excipients in a compatibility study can also be informative. These changes might indicate interactions with the drug or other excipients, which can lead to alterations in the excipient's crystalline structure. This can result in shifts in peak positions, the appearance of new peaks, or the broadening of existing peaks. If the XRD patterns of the pure drug and excipients remain mostly unaltered when combined, it suggests the absence of substantial interactions between the drug and the excipients. This is a positive result, indicating good compatibility.

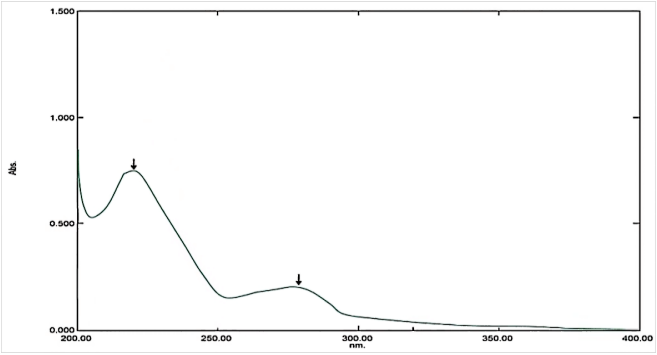

Figure 1: UV spectrum of venlafaxine hydrochloride

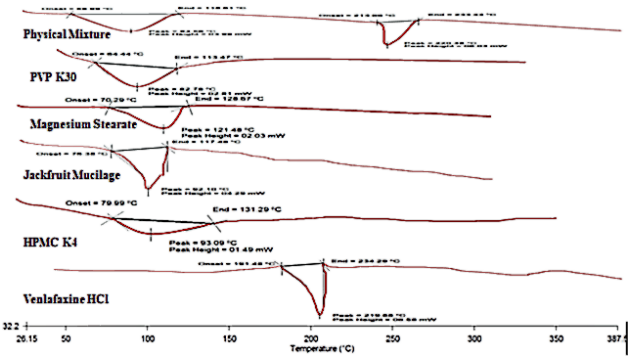

Figure 3: The DSC thermograms of venlafaxine HCl, individual excipients, and physical mixtures

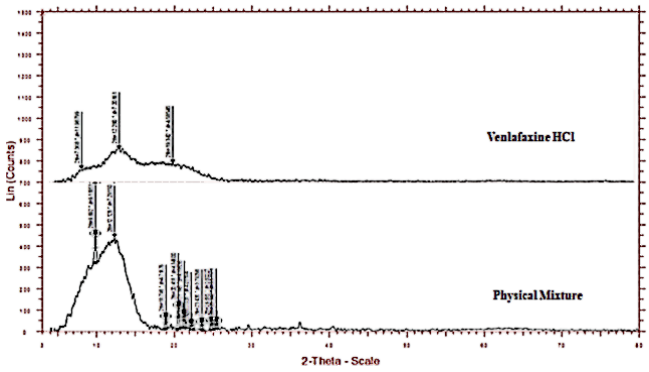

Figure 4: XRD graph of venlafaxine HCl and physical mixture

Powder characterization and pre-compression parameters

Powder characterization studies on the venlafaxine hydrochloride demonstrated that it has good flow and compressibility properties. It was advantageous to use immediately compressible grade components in the tablet formulation. All the determined parameters were within the acceptable range. Table 4 shows a preliminary study of sustained-release tablets. Pre-compression parameters of the sustained-release powder blend, such as the Carr's Index (CI), were reported in the range of 16-25. The F2, F4, F9, F13 and F18 had good flow properties, making them ideal for direct compression into matrix tablets. The Hausner's ratio (HR) was found to be between 1.18 and 1.33, with the angle of repose (AR) falling between 23 and 28 degrees. Other batches yielded decent and acceptable results, with F2, F4, F9, F13 and F18 exhibiting excellent flowability. All pre-compression parameters were found to be within acceptable limits.

Experimental Factorial Design

Central composite design

- *Response surface methodology*

RSM has been extensively employed in both developing new product formulations and enhancing existing ones. It involves creating polynomial equations and mapping responses across formulation variables to pinpoint the optimal formulation. In this study, RSM was also utilized to assess how the independent variables (X1-X3) influence various response variables (Y1-Y2). Quadratic models were used to explore the relationships between these factors and parameters such as weight, friability, disintegration, and dissolution. The statistical summaries of the response variables are provided in Table 5. The adjusted regression values (r2) for hardness and dissolution were found to be 0.74 and 0.72, respectively, indicating the suitability of the model for representing these variables.

- *RSM effect of excipients on the hardness*

The ANOVA findings for the hardness model that was used. F statistics revealed that the model probability was more than the F value of 7.08, indicating that the model is significant. The P-value of 0.0026, which is less than 0.0500, further validated the model's significance. X1, X2, X3, X1X2, X1X3, X2, and X3 are important model terms in this situation. Because the special cubic model was aliased, the outcome can be represented using the special quadratic model. It has a

Table 4: Powder blend pre-compression parameters

Batch code	*BD (gm/mL)*	*TD (gm/mL)*	*CI (%)*	*HR*	*AR*
F1	0.57 ± 0.03	0.72 ± 0.03	21.11 ± 0.02	1.22 ± 0.03	24.42 ± 0.11
F2	0.49 ± 0.03	0.57 ± 0.03	14.29 ± 0.02	1.19 ± 0.03	23.58 ± 0.23
F3	0.55 ± 0.02	0.69 ± 0.03	20.52 ± 0.02	1.29 ± 0.03	26.40 ± 0.21
F4	0.54 ± 0.03	0.65 ± 0.02	17.11 ± 0.03	1.28 ± 0.04	26.19 ± 0.21
F5	0.48 ± 0.04	0.60 ± 0.02	19.61 ± 0.04	1.29 ± 0.03	28.33 ± 0.22
F6	0.50 ± 0.04	0.67 ± 0.02	25.32 ± 0.03	1.38 ± 0.03	24.44 ± 0.21
F7	0.51 ± 0.03	0.65 ± 0.03	21.78 ± 0.03	1.31 ± 0.04	25.89 ± 0.18
F8	0.55 ± 0.03	0.70 ± 0.03	21.12 ± 0.02	1.24 ± 0.03	24.49 ± 0.11
F9	0.48 ± 0.03	0.56 ± 0.03	14.28 ± 0.02	1.16 ± 0.03	23.51 ± 0.23
F10	0.54 ± 0.02	0.68 ± 0.03	20.58 ± 0.02	1.25 ± 0.03	26.42 ± 0.21
F11	0.53 ± 0.03	0.64 ± 0.02	17.18 ± 0.03	1.20 ± 0.04	26.15 ± 0.21
F12	0.49 ± 0.04	0.61 ± 0.02	19.67 ± 0.04	1.24 ± 0.03	28.3 ± 0.22
F13	0.51 ± 0.04	0.68 ± 0.02	25 ± 0.03	1.33 ± 0.03	24.4 ± 0.21
F14	0.50 ± 0.03	0.64 ± 0.03	21.87 ± 0.03	1.28 ± 0.04	25.82 ± 0.18
F15	0.56 ± 0.03	0.71 ± 0.03	21.12 ± 0.02	1.26 ± 0.03	24.4 ± 0.11
F16	0.48 ± 0.03	0.56 ± 0.03	14.28 ± 0.02	1.16 ± 0.03	23.51 ± 0.23
F17	0.54 ± 0.02	0.68 ± 0.03	20.58 ± 0.02	1.25 ± 0.03	26.42 ± 0.21
F18	0.53 ± 0.03	0.64 ± 0.02	17.18 ± 0.03	1.20 ± 0.04	26.15 ± 0.21
F19	0.49 ± 0.04	0.62 ± 0.03	20.28 ± 0.02	1.21 ± 0.03	26.10 ± 0.21
F20	0.51 ± 0.04	0.66 ± 0.02	17.22 ± 0.03	1.26 ± 0.04	26.88 ± 0.21

Table 5: Brief overview of the response variables Y1 and Y2from the statistical model

Source of variation	*Sum of square*	*DF*	*Mean of square*	*F Value*	*p-value Prob> F*	*Summary*
(Y1:Hardness)	0.8575	9	0.0953	7.08	0.0026	
X1-Jackfruit (mg)	0.0541	1	0.0541	4.02	0.0728	
X2-HPMCK4 Press. (bar)	0.0592	1	0.0592	4.40	0.0624	
X3-PVPK30	0.0025	1	0.0025	0.1838	0.6772	
Residual	0.1345	10	0.0135	-	-	Model is Significant
Cor Total	0.9920	19	-	-	-	
Adequate Precision	7.4083					
Adjusted R^2	0.7423					
Mean	5.08					
%CV	2.28					
(Y2:Dissolution)	8.25	9	0.9166	2.93	0.0047	
X1-Jackfruit (mg)	2.59	1	2.59	8.27	0.0165	
X2-HPMCK4 Press. (bar)	0.4624	1	0.4624	1.48	0.0521	
X3-PVPK30	0.5173	1	0.5173	1.65	0.2276	
Residual	3.13	10	0.3130	-	-	Model is Significant
Cor Total	11.38	19	-	-	-	
Adequate Precision	6.5026					
Adjusted R^2	0.7249					
Mean	96.96					
%CV	0.577					

positive influence on hardness, according to the equation. The highest compressibility index was the most important factor. Between the independent components, a positive interaction effect was discovered. When the Jackfruit mucilage factor was adjusted at the same time, the effect was strongest. This provides information on the independent components' main and interaction effects. The concentration of Jackfruit mucilage in the tablet formulation can significantly affect tablet hardness. Higher concentrations of the mucilage can lead to harder tablets, while lower concentrations may result in softer tablets. The optimum concentration of mucilage shows a significant effect on the hardness of the tablet.

Dissolution testing is a crucial laboratory method used to predict how drugs will become available in the body. It becomes especially important when dealing with drugs that don't dissolve well in water, as the rate at which they dissolve can be a limiting factor for their absorption into the body. In our study, we found that the amount of drug released during dissolution testing fell within the officially accepted range of 92 to 105%, indicating that the drug formulation met the required standards. We also identified that Jackfruit mucilage and a combination of Jackfruit mucilage and HPMC K4 had a significant impact on the dissolution of the drug. Our analysis, using ANOVA (Analysis of Variance), showed that the data had a low standard deviation and an excellent %coefficient of variation of 0.55, suggesting high consistency and reliability in the results. We used Response Surface Methodology (RSM) to illustrate how these factors influenced drug dissolution. This method allowed us to visualize and understand the effects of different factors on the rate of drug release during dissolution testing.

All the response variables in our study displayed favorable regression coefficients, and there was a reasonable similarity between the predicted values (r-predicted) and the actual observed values (r-observed), indicating that our experimental design was well-suited for the research. Furthermore, the percentage coefficient of variation (%CV) and the adequate precision values fell within acceptable ranges, suggesting the reliability of our results. The model F-ratios were all below 0.05, which means that the statistical models we used were significant for all the response variables we measured. In terms of the formulation variables, we observed interactions in quadratic terms for all cases. However, when it came to disintegration, linear terms appeared to be more relevant for studying the response surfaces. The effect of the used sustained-release polymer showed the concentration-dependent release of the drug in dissolution. Sustained-release polymers are designed to release the drug at a controlled and often slower rate compared to immediate-release formulations. The polymer matrix or coating can act as a barrier that retards the diffusion or dissolution of the drug. This can result in a slower dissolution rate compared to conventional immediate-

Table 6: Tablet formulation's post-compression parameters

Batch Code	*Hardness (kg/cm^2)*	*Weight variation (mg)*	*Thickness (mm)*	*Friability (%)*	*% Drug content*
F1	5.1 ± 0.03	522 ± 2.01	3.2 ± 0.03	0.54 ± 0.02	98.51 ± 0.02
F2	5.5 ± 0.02	515 ± 3.21	3.3 ± 0.03	0.49 ± 0.03	99.22 ± 0.03
F3	4.1 ± 0.03	512 ± 2.54	3.6 ± 0.02	0.59 ± 0.03	99.41 ± 0.05
F4	5.1 ± 0.01	522 ± 2.31	3.4 ± 0.03	0.53 ± 0.02	99.80 ± 0.032
F5	5.7 ± 0.02	520 ± 2.45	3.6 ± 0.03	0.59 ± 0.03	101.3 ± 0.012
F6	4.2 ± 0.03	516 ± 2.63	3.5 ± 0.04	0.53 ± 0.04	99.62 ± 0.022
F7	4.7 ± 0.02	519 ± 3.01	3.1 ± 0.03	0.67 ± 0.02	98.14 ± 0.015
F8	5.2 ± 0.03	520 ± 2.01	3.3 ± 0.03	0.51 ± 0.02	98.56 ± 0.02
F9	5.2 ± 0.02	525 ± 3.21	3.1 ± 0.03	0.45 ± 0.03	99.65 ± 0.03
F10	4.3 ± 0.03	510 ± 2.54	3.4 ± 0.02	0.52 ± 0.03	99.47 ± 0.05
F11	4.9 ± 0.01	529 ± 2.31	3.1 ± 0.03	0.48 ± 0.02	99.19 ± 0.032
F12	5.8 ± 0.02	525 ± 2.45	3.1 ± 0.03	0.52 ± 0.03	101.3 ± 0.012
F13	4.2 ± 0.03	510 ± 2.63	3.1 ± 0.04	0.55 ± 0.04	99.69 ± 0.022
F14	4.8 ± 0.02	516 ± 3.01	3.3 ± 0.03	0.62 ± 0.02	98.10 ± 0.015
F15	5.2 ± 0.03	520 ± 2.01	3.3 ± 0.03	0.51 ± 0.02	98.56 ± 0.02
F16	5.5 ± 0.02	515 ± 3.21	3.3 ± 0.03	0.49 ± 0.03	99.22 ± 0.03
F17	4.3 ± 0.03	510 ± 2.54	3.4 ± 0.02	0.52 ± 0.03	99.47 ± 0.05
F18	4.9 ± 0.01	510 ± 2.31	3.1 ± 0.03	0.57 ± 0.02	99.85 ± 0.032
F19	5.8 ± 0.02	525 ± 2.45	3.1 ± 0.03	0.52 ± 0.03	101.3 ± 0.012
F20	4.5 ± 0.03	513 ± 2.63	3.0 ± 0.04	0.51 ± 0.04	99.6 ± 0.022

release formulations. Sustained-release polymers are tailored to provide drug release over an extended period, which can range from hours to days. The dissolution profile will reflect this prolonged release, showing a more gradual and sustained release curve.

Evaluation of Tablets

General appearance

Shape: circular; color: white to pale white; odor: odorless; taste: tasteless.

Post-compression parameters of tablets

The formulation is checked for its moisture content in order to prevent any possible deterioration or caking that may occur. Tablet producers are able to create tablets with the correct hardness, disintegration time, and dissolution profile by carefully monitoring and adjusting these pre-compression characteristics. This ensures both the effectiveness of the tablets and the safety of the patients. The results of post-compression parameters of sustained-release matrix tablets were computed and presented in Table 6. The hardness of batches F1-F20 ranged from 4.1 to 5.8 kg/cm^2, indicating good mechanical strength and the capacity to tolerate physical and mechanical stress during handling. The thickness ranged from 3.0 to 3.6 mm, with an average thickness variation of less than 5%. Each sample was tested three times. The overall weight of the tablets was reduced by 0.43 to 0.71 g. The %friability value in all formulations was less than 1%, ensuring that the formed tablets were mechanically stable. For all formulations, the maximum percent deviation was found to be 1.56%. F18 batch was selected as the optimized batch as per result obtained.

In-vitro drug release study

Conducting *in-vitro* drug release testing is an essential stage in evaluating the effectiveness of sustained-release tablet formulations. This testing entails quantifying the speed and degree of drug discharge from the tablet over a period of time in settings that mimic the human body. *In-vitro* drug release tests simulate the conditions of the gastrointestinal environment to assess the formulation's capacity to regulate drug release and sustain optimal levels in circulation for a prolonged duration. This information facilitates the process of optimizing the formulation and guarantees the creation of secure and efficient sustained-release drugs. The *in-vitro* dissolving study of SR tablets revealed that formulation F18, which included HPMC K15 and Jackfruit mucilage, exhibited optimal drug release over a 12-hour period. This is shown in Table 7 and Figure 5. The other formulations of SR are not meet the objective.

In-vitro release kinetic study

In-vitro release kinetic studies of tablet formulations include examining the pattern and rate at which the medication is released from the tablet over a period of time, using simulated physiological settings. These experiments provide clarity on the mechanism of drug release and ascertain the kinetics of drug dissolution from the formulation. Researchers may analyze experimental data by using mathematical models such as zero-order, first-order, or spelling errors. This allows them to understand the release behavior of drugs and fine-

Table 7: *In-vitro* drug release study of all formulation

Batch Code	*%CDR*						
	Time (Hours)						
	0	*2*	*4*	*6*	*8*	*10*	*12*
F1	0	12.9	38.18	49.03	57.39	67.59	96.89
F2	0	17.41	40.88	53	69.87	88.02	97.69
F3	0	18.5	39.56	64.05	84.23	87.23	97.78
F4	0	16.4	31.8	55.8	77.94	90.15	97.36
F5	0	8.16	26.35	48.17	89.54	92.36	96.28
F6	0	19.1	57.73	75.82	90.9	91.26	96.12
F7	0	24.6	43.13	58.94	80.51	91.78	96.38
F8	0	12.9	38.18	49.03	57.39	67.59	96.89
F9	0	25.4	56.8	69.8	81.94	91.71	97.36
F10	0	22.6	53.13	62.94	82.51	93.78	96.68
F11	0	19.1	57.73	75.82	90.9	92.36	96.52
F12	0	12.9	38.18	49.03	57.39	67.59	96.23
F13	0	16.4	41.8	55.8	67.94	81.1	98.38
F14	0	12.16	36.35	48.17	79.54	85.36	96.89
F15	0	19.1	47.73	79.82	87.9	91.26	97.32
F16	0	24.6	43.13	59.94	83.51	91.78	96.81
F17	0	12.9	38.18	59.03	77.39	87.59	96.2
F18	0	11.4	31.8	51.8	71.94	85.1	98.91
F19	0	18.6	43.13	62.94	85.51	91.78	96.29
F20	0	19.8	47.73	65.82	87.9	92.36	96.23

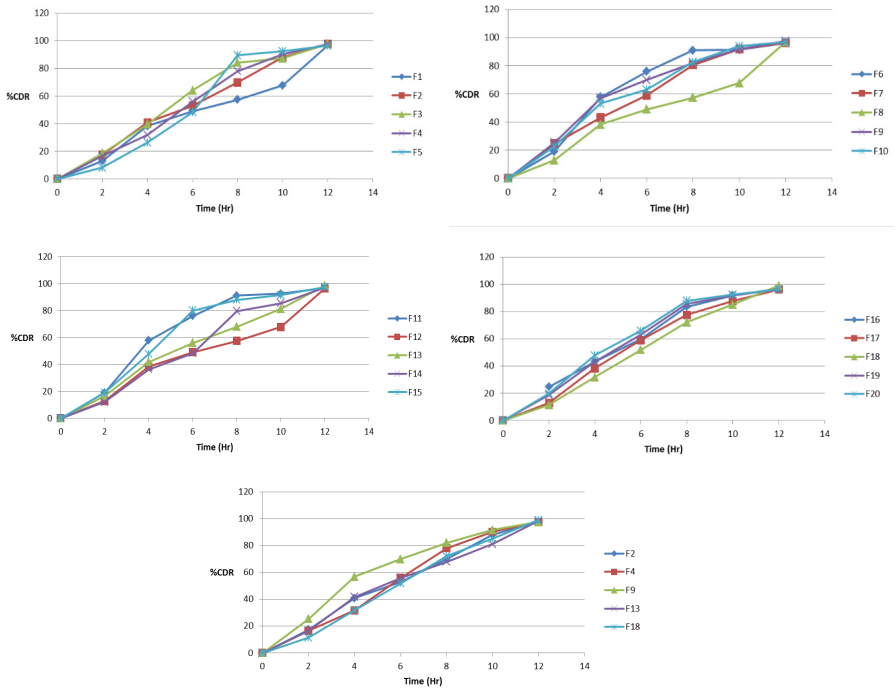

Figure 5: *In-vitro* dissolution study of F1-F20 formulations

Table 8: Kinetics of *in-vitro* release of venlafaxine hydrochloride SR tablets

Time (Hr.)	*%CDR*	*%Cumulative drug remaining*	*Log %CDR Remaining*	*Square root of time*	*Log time*	*Log of %CDR*	*Cube root of %drug remaining*
0	0	100 ± 0.09	2 ± 0.09	0	0	0	4.641 ± 0.09
2	11.4 ± 0.18	88.6 ± 0.11	1.947 ± 0.11	1.414	0.301	2.433 ± 0.18	4.458 ± 0.11
4	31.8 ± 0.22	68.2 ± 0.13	1.833 ± 0.13	2	0.602	3.45 ± 0.22	4.085 ± 0.13
6	51.8 ± 0.15	48.2 ± 0.15	1.683 ± 0.15	2.449	0.7781	3.94 ± 0.15	3.639 ± 0.15
8	71.94 ± 0.13	28.06 ± 0.14	1.448 ± 0.14	2.828	0.903	4.27 ± 0.13	3.038 ± 0.14
10	85.1 ± 0.11	14.9 ± 0.11	1.173 ± 0.11	3.162	1	4.44 ± 0.11	2.046 ± 0.11
12	98.91 ± 0.19	1.09 ± 0.13	0.037 ± 0.13	3.464	1.079	4.59 ± 0.19	1.019 ± 0.13

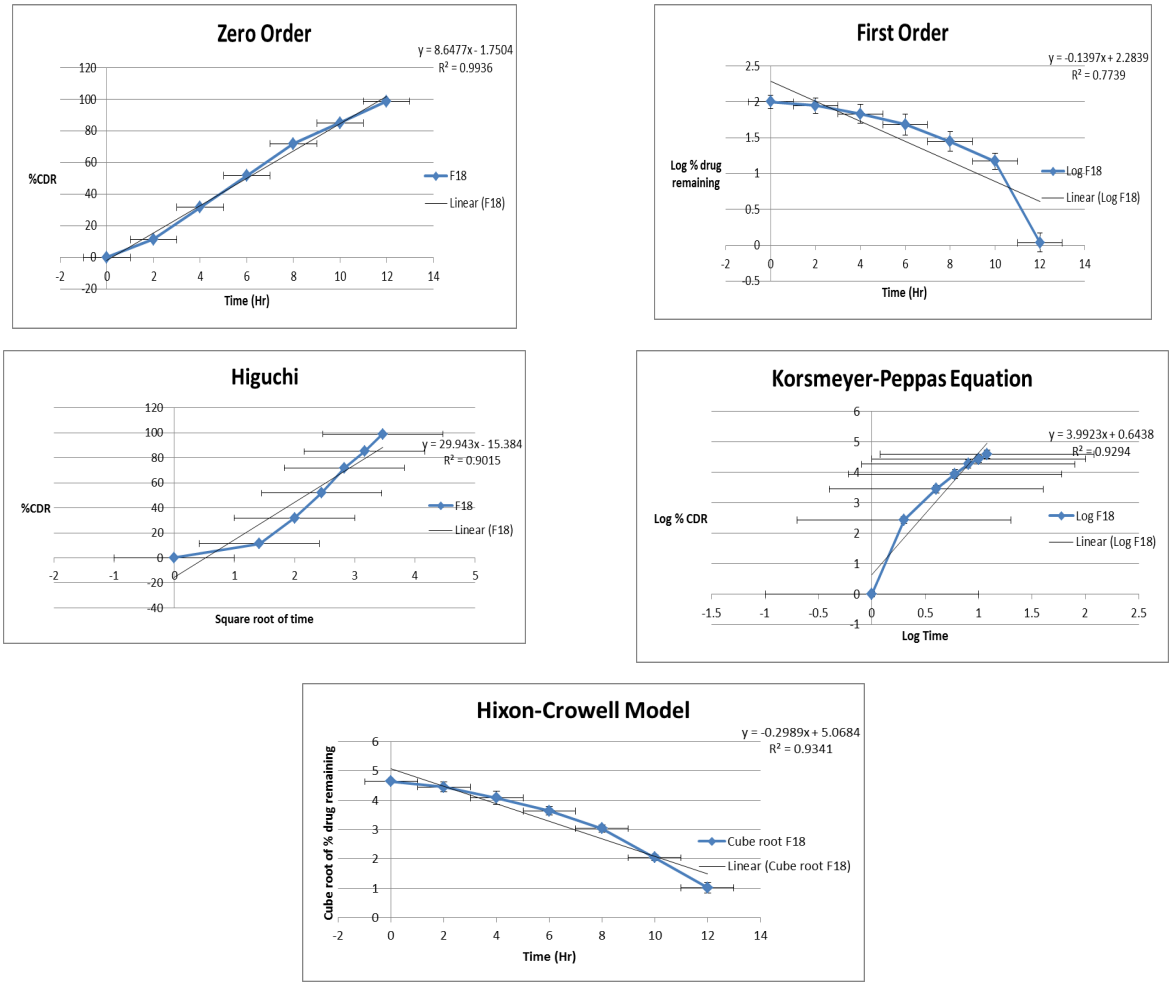

Figure 6: The *in-vitro* drug release pattern of optimized tablet formulation

Table 9: Parameters for stability assessment of the optimized formulation (F18)

Parameters	*Initial*	*1st Month*	*2nd Month*	*3rd Month*
Thickness (mm)	3.10 ± 0.03	3.15 ± 0.04	3.12 ± 0.02	3.13 ± 0.03
Uniformity of Weight (mg)	510 ± 2.31	518 ± 2.28	514 ± 2.33	512 ± 2.30
Dissolution (%)	99.85 ± 0.032	99.12 ± 0.035	99.78 ± 0.031	98.98 ± 0.039

tune formulation parameters in order to produce certain drug release patterns that are effective for therapeutic purposes. The results obtained from conducting *in-vitro* dissolving tests on Venlafaxine Hydrochloride sustained release tablets were fitted to several kinetic models. The findings are shown in Table 8 and Figure 6. The analysis of the kinetic parameters indicated that the release data of the optimized formula F18 exhibited an r^2 value of 0.9936, which is close to 1. All things considered, the data point to a drug release mechanism that is controlled by zero-order kinetics, meaning that the release rate is independent of drug concentration.

Accelerated stability study

Formulations undergo accelerated stability tests by exposing them to high temperatures and humidity levels for a brief duration, replicating the effects of long-term storage. These studies aid in forecasting the duration for which items may be stored by evaluating the changes in physical, chemical, and microbiological properties as time progresses. Researchers may obtain useful data to help product development, provide storage recommendations, and assure product quality and safety throughout its specified shelf life by speeding up degradation processes. A series of rigorous tests were conducted to evaluate the stability of the modified tablets, and the results are shown in Table 9. The findings indicate that Venlafaxine Hydrochloride sustained release tablets (Formulation batch F18) were stable under the specified temperature and humidity conditions.

CONCLUSION

The formulation of Venlafaxine HCl sustained release tablets at a dosage of 500 mg included the use of several hydrophilic polymers, including Jackfruit Mucilage, HPMC K4, and PVPK30, as release retardants. This was done to extend the release of the drug over a period of 12 hours. The formulation features, including pre-compression and post-compression investigations, were conducted individually according to established protocols. The tablets were determined to be within acceptable ranges in terms of weight uniformity, hardness, thickness, diameter, friability, and drug content. Separate *in-vitro* dissolution studies were done for both tablets. The venlafaxine hydrochloride SR formulation F18 was developed to provide the desired release duration of up to 12 hours. The venlafaxine hydrochloride SR formulation was improved and exhibited zero-order release kinetics. The stability experiments conducted at accelerated settings of 40 ± 2°C/75 ± 5% RH yielded good results. The present study concluded that sustained release delivery of venlafaxine HCl is possible and effective. It avoids the dosing frequency for the patient and increases patient compliance. We are aiming to perform the *in-vivo* pharmacokinetic studies of the formulation to ensure the drug reaches systemic circulation.

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