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# Formulation And Evaluation of Venlafaxine Hydrochloride Superporous Hydrogels Using Factorial Design Method

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**Abstract**

The purpose of this study was to develop formulations and systematically evaluate in vitro performances of the Superporous hydrogel of Venlafaxine HCl. Venlafaxine Hydrochloride-based Hydrogels were prepared by using a factorial design. A 3-factor three-level Box–Behnken design was employed to study the effect of independent variables on dependent variables. The selected independent variables considered were the concentration of HPMC K4M (g) (X1); HPMC K100M (g) (X2); and Stirring time (seconds) (X3). Mechanical strength, Porosity, and Dissolution were selected as the dependent variables. FT-IR spectra revealed that there was no variation in the properties of the drug and polymers in the formulation. The response Mechanical strength and Porosity followed interactive (3FI) model and the summary of Analysis of variance (ANOVA) and Optimization was performed with constraints of Mechanical strength in the range of 130 – 1000 g/sq.cm, Q4h in the range of 35-55%, and Q8h in the range of 65 - 90%, to get optimized formula solutions with higher desirability function.

**Keywords:** Venlafaxine Hydrochloride, 3-factor three-level Box–Behnken, ANOVA, Porosity.

## Introduction

Drug delivery technologies are as important as new chemical entities entering into the pharmaceutical industries, allowing more effective use of existing drugs and successful development of the new drug candidates (1). Hydrogels have long been established in this field to control the release of a drug from a conventional solid dose formulation (2). Hydrogel is a three-dimensional network of cross-linked polymers which are bonded physically (or) chemically (3) these are used widely in drug delivery and immobilization of enzymes. Super porous hydrogel has numerous pore sizes inside them SPHS possess an average pore size of greater than 100 these are a three-dimension network of hydrophilic polymers that are not soluble (4). They absorb a large amount of water in a short period due to porous structure SPHS has a greater surface area and shorter diffusion (5). Because of these unique properties, SPHC was initially proposed to develop gastric retention devices for extending the gastric residence time of drugs for achieving long-term, oral-controlled drug delivery (6,7).

Venlafaxine HCl is a novel white, crystalline, water-soluble ([500 mg/ml) third generation 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 (8,9). Venlafaxine is an effective therapy in moderate and severe conditions of depression, social anxiety disorder, and generalized anxiety disorder. To maintain the therapeutic window, venlafaxine has to be administered 2 or 3 times a day because of a short steady-state half-life (3–4 h for venlafaxine and 8–10 h for its active metabolite, O-desmethylvenlafaxine) (10).

The present study was designed to prepare new Superporous hydrogels by using Acryl amide, acrylic acid, BIS, Span 80, Ammonium per sulfate, TEMED Solutions in the presence of HPMC grades to prepare the most suitable hybrid hydrogels for sustained release of model hydrophilic drug over long periods.

## Materials

Venlafaxine Hydrochloride was obtained as a gift sample from APL India (Pvt. Ltd), Hyderabad.
Acrylic acid, Acrylamide, Chitosan, IS and TEMED were purchased from SRL Chem (Pvt. Ltd),

Maharashtra., India. HPMC K4M and HPMC K100M were purchased from Colorcon Asia Pvt Ltd, Goa. Span 80, Ammonium persulphate and Sodium bicarbonate were purchased from S.D. Fine Chem.Ltd. Mumbai. All additional chemicals, reagents, and solvents used were of analytical grade.

**Methods**

**ANALYTICAL METHOD**

UV spectroscopy method was used for Venlafaxine Hydrochloride estimation. A 1 mg/ml standard solution of Venlafaxine Hydrochloride in 0.1N HCL was scanned on a double beam UV spectrophotometer. From a UV-Visible spectrophotometer, Venlafaxine Hydrochloride λ max was obtained.

Preparation of Standard Stock solution: Stock solution-I: 100 mg of Venlafaxine Hydrochloride was dissolved in 100ml of 0.1N HCL in the volumetric flask to obtain 100ml. Stock solution-II: From stock solution-I, 10 ml solution was transferred in 100ml volumetric flask, and volume was made up to 100ml with 0.1N HCL to obtain 100 µg/ml. From stock solution-II aliquots of 0.5, 1, 1.5, 2 and 2.5ml were taken and volume was made adjusted to 10ml with 0.1N HCL to get 0,5,10,15,20,25µg/ml solution. The absorbances of solutions were determined against blank. A standard graph showing the absorbance vs. different concentrations was plotted and the correlation coefficient (R2) was also calculated.

**COMPATIBILITY STUDIES**

**Compatibility study of drug and polymer using FTIR:** The compatibility between the pure drug and excipients were detected by FTIR spectra obtained on Bruker Alpha II. The potassium bromide pellet method was used for solid samples and for liquids, samples were transferred to Liquid cell followed by recording the spectra's over the wavenumber of 4000 to 500cm-1(11).

**EXPERIMENTAL DESIGN**

Venlafaxine Hydrochloride based Hydrogels were prepared by using factorial design. A 3-factor three-level Box–Behnken design was employed to study the effect of independent variables on dependent variables as shown in Table 1. A total of 8 formulations was prepared according to the experimental design. chitosan solution was prepared by taking 6 g of chitosan and dissolved in 5% Glacial acetic acid solution under stirring (12). To 100ml beaker Acryl amide, acrylic acid, BIS, Span 80, Ammonium per sulphate, TEMED Solutions was taken and kept under mechanical stirrer, to the above solution polymer HPMC was added while stirring. To the prepared solution Drug (Venlafaxine Hydrochloride) was added under stirring 10 minutes from the addition of TEMED for the polymerization reaction to take place and Sodium bicarbonate was added quickly while stirring. After completion of stirring time, stirring was stopped and left for the formation of a hydrogel. Finally Synthesized Superporous Hydrogels were removed and dried in an oven at 50 $^{o}$C for 48 hours and stored for further characterizations shown in Figure 1(13).

Response surface graphs were used to appraise the factor association between the variables. The selected independent variables considered were the concentration of HPMC K4M (g) (X1); HPMC K100M (g) (X2); and Stirring time (seconds) (X3), while the two factorial levels for these variables were coded as −1, and +1 for low and high levels, correspondingly (14).

**Figure 1: Venlafaxine Hydrochloride Superporous Hydrogels**

**Table 1: Venlafaxine Hydrochloride SPH formulations**

| S.No | Ingredient | F1 | Fa | Fb | Fab | Fc | Fac | Fbc | Fabc |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Acrylic acid 50%v/v (ml) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 2 | Acrylamide 50%w/v (ml) | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 3 | Chitosan 6%w/v (ml) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 4 | BIS 2.5%w/v (ml) | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 |
| 5 | Span 80 10%v/v (ml) | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| 6 | Ammonium persulphate 20%w/v (ml) | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |
| 7 | TEMED 16.7%w/v (ml) | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |
| 8 | HPMC K4M (g) | 0 | 0.240 | 0 | 0.240 | 0 | 0.240 | 0 | 0.240 |
| 9 | HPMC K100M (g) | 0 | 0 | 0.240 | 0.240 | 0 | 0 | 0.240 | 0.240 |
| 10 | Venlafaxine HCl (g) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 11 | Sodium bicarbonate (g) | 2.9 | 2.9 | 2.9 | 2.9 | 2.9 | 2.9 | 2.9 | 2.9 |
| 12 | Stirring time (sec) | 20 | 20 | 20 | 20 | 30 | 30 | 30 | 30 |

| Independent Variables | | -1 | +1 |
|---|---|---|---|
| a | HPMC K4M (g) | 0 | 0.240 |
| b | HPMC K100M (g) | 0 | 0.240 |
| c | Stirring time (seconds) | 20 | 30 |

Mechanical strength, Porosity, and Dissolution were selected as the dependent variables. Eight formulations were required to analyze the interaction of each level on formulation characters. ANOVA was used to establish the statistical validity of the polynomial equations generated. All responses observed were fitted concurrently to different models.

**Characterization of Superporous**

**hydrogels:** Final drug-loaded formulation was evaluated for Drug content, Swelling studies, Porosity, Mechanical strength, and In-vitro Drug Release.

**Drug content analysis**

Two tests were performed to determine the amount of Venlafaxine Hydrochloride loaded in the hydrogels. Three hydrogels were selected from each sample and the mean was calculated (15).

**Determination of swelling ratio:**

At the beginning of each experiment, the dried gel was measured gravimetrically to obtain Md, and then it was immersed more than the medium for swelling. At various time intervals, the hydrogel was removed from the medium and weighed when excess hexane on the surface was blotted to determine MS (16).

The equilibrium swelling ratio can be calculated as follows.

$Q = (Ms - Md) / Md$

Where Q is the equilibrium swelling ratio, Ms is the mass in the swollen state Md is the mass in the dried state.

**Porosity:**

For Measurement of porosity, the dried SPHC was submerged in hexane overnight and weighed after excess hexane on the surface was blotted. The porosity was calculated by Porosity = $(M_2 – M_1) / \rho V$ where M1 and M2 are the mass of the hydrogel before and after immersion in absolute ethanol, respectively; ρ is the density of absolute ethanol and V is the volume of the hydrogel.

The total volume of SPHC can be measured from its dimensions as it is cylindrical. VT was calculated as VT = πr2h (17).

**Mechanical Strength:**

A bench comparator was used to test the mechanical properties of the Superporous hydrogels and their composites. A sample swollen in the simulated gastric fluid was placed longitudinally under the lower touch of the bench comparator that was connected to a micrometer gauge. The Superporous hydrogel was supported by a lab jack. Weight was applied to the upper touch of the bench comparator in incremental intervals. The swelling height of the Superporous hydrogels under pressure was read from the gauge. The pressure applied to the Superporous hydrogels was calculated from the weights and the contact area of the lower touch. Two parameters swelling height under 100cm water pressure and ultimate compression pressure were determined to characterize the mechanical properties of the Superporous hydrogels (18).

**In-vitro Drug Release studies:**

The in vitro release of Venlafaxine Hydrochloride from the prepared formulations was carried out using the USP type II dissolution apparatus, at a rotational speed of 100 rpm in 900 ml 0.1 N HCl (pH 1.2) at 37°C ± 0.5°C. Aliquots of 5 ml sample were withdrawn at predetermined intervals and replenished with fresh dissolution medium to maintain a constant volume. The samples were filtered and analyzed spectrophotometrically at 225 nm. All experiments were done in triplicate (19).

**Drug release kinetics:**

Kinetic studies of drug release for selected SPH formulation were carried out concerning different kinetic models viz; Zero-order kinetics, first-order kinetics, Hixon and Crowell, Higuchi and Korsmeyer Peppas model. After that regression analysis (R2) was determined and the diffusion coefficient (n) was also calculated. The drug diffusion coefficient or release exponent (n) of the given controlled release formulation understudy was calculated by comparing with the value of ‘n’ from the given Table and the drug release mechanism was determined (20).

**RESULTS**

**Standard Graph of Venlafaxine HCl:**

Standard graph of Venlafaxine HCl was constructed using concentration 5,10,15,20,25(µg/ml) in 0.1N HCL. It is evident from the figure 2 & 3 that the graph is linear with regression coefficient value of $R^2$ = 0.9990 and slope = 0.03698 at λ max of 225.0nm.

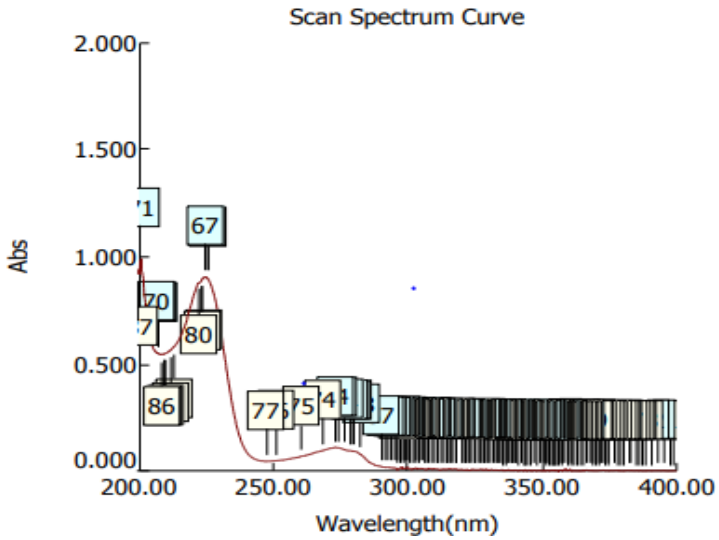



**Figure 2: Spectrum Scan of Venlafaxine Hydrochloride (µg/ml)**

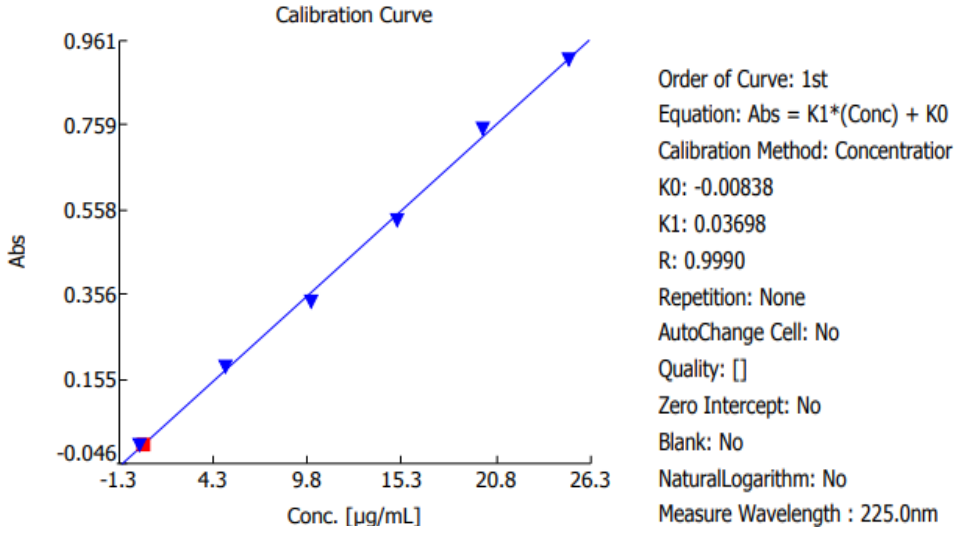



**Figure 3. Calibration Curve for Venlafaxine Hydrochloride**

**Compatibility study of drug and polymer using FTIR:**

The FT-IR spectrophotometer was used to identify as well as determine the possibilities of any interaction between the formulation components at the optimized composition. As shown in the Figure 4 and 5, there was no substantial differentiation in the FT-IR spectra of the drug when compared to the spectra of the physical mixture of drug and polymers. The FT-IR spectra of the drug and polymer showed that there was no shift in the major peaks. This further revealed that there was no variation in the properties of the drug and polymers in the formulation. Hence, the drug and polymers were compatible with each other.

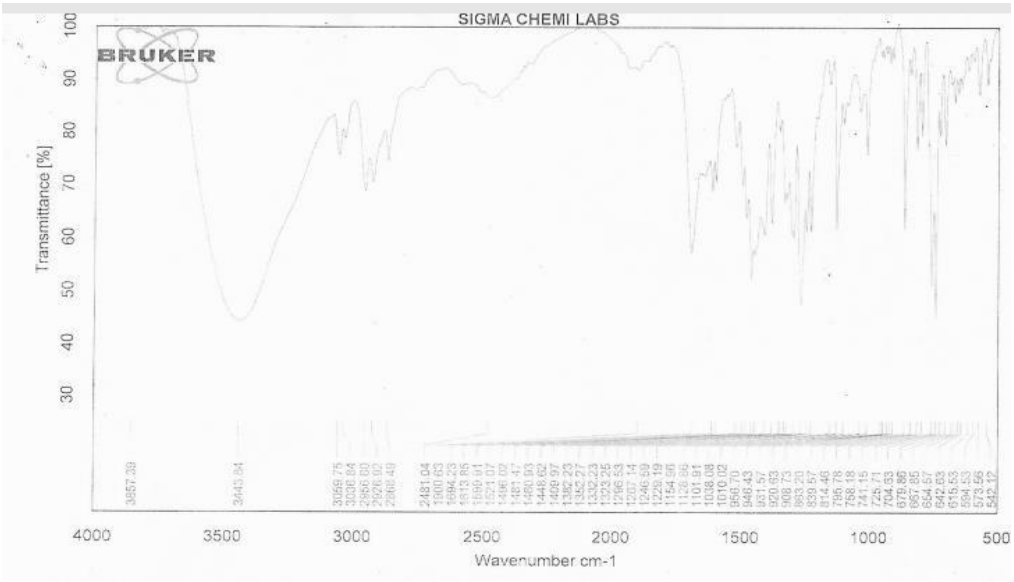



**Figure 4: FTIR Spectrum of Sample Venlafaxine Hydrochloride**

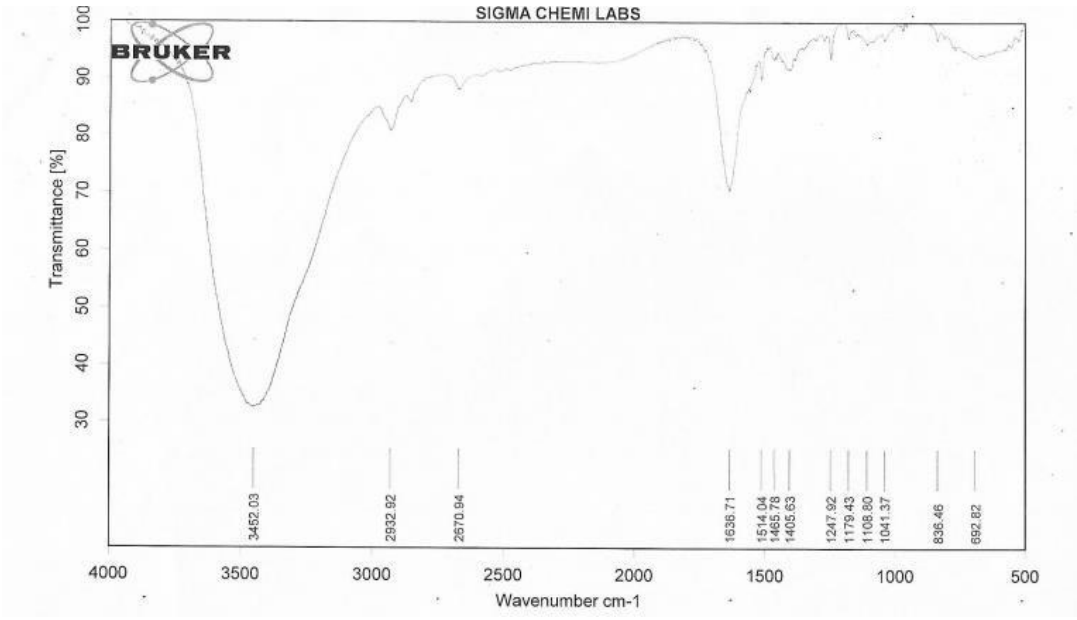



**Figure 5: FTIR Spectrum of Venlafaxine Hydrochloride and SPH Mixture**

**Preparation of Superporous Hydrogels:**

From the Box–Behnken factorial design, a total of 24 runs were projected by the design expert for three factors: HPMC K4M (%) (X1); HPMC K100M (%) (X2); and stirring time (%) (X3), which were varied at two different levels (coded as −1 and +1). Mechanical strength, Porosity, and Dissolution were studied for responses. The observed values of the responses are shown in Table 2. The obtained Mechanical strength was found to be in the range of 363 g/ sq.cm to 905.63 g/ sq.cm, the calculated porosity was about 50.07% to 78.33%, while the dissolution was estimated at 2 different time periods Q4h and Q8h and results are found around 45 to 100%. Statistical analysis of the selected variables on the responses was studied using the Design Expert. Calculated F values, p values, and estimated effects for the Mechanical strength, Porosity, and Dissolution are given in Table 4.

**Table 2: Selected variables on the responses of Mechanical strength, Porosity and Dissolution**

| | | Factor 1 | Factor 2 | Factor 3 | Response 1 | Response 2 | Response 3 | Response 4 |
|---|---|---|---|---|---|---|---|---|
| Std | Run | A:HPMC K4M | B:HPMC K100M | C:stirring time | Q4h | Q8h | Mechanical strength | Porosity |
| | | g | g | sec | % | % | g/ sq.cm | % |
| 1 | 16 | 0 | 0 | 20 | 79.95 | 87.23 | 545.79 | 68.10 |
| 2 | 23 | 0 | 0 | 20 | 67.73 | 82.67 | 546.67 | 68.91 |
| 3 | 7 | 0 | 0 | 20 | 64.01 | 81.26 | 545.86 | 74.09 |
| 4 | 13 | 0.24 | 0 | 20 | 65.69 | 77.60 | 363.53 | 67.94 |
| 5 | 20 | 0.24 | 0 | 20 | 76.85 | 86.54 | 463.53 | 69.46 |
| 6 | 8 | 0.24 | 0 | 20 | 74.82 | 85.96 | 421.53 | 67.17 |
| 7 | 10 | 0 | 0.24 | 20 | 100.96 | 99.71 | 536.47 | 74.37 |
| 8 | 21 | 0 | 0.24 | 20 | 98.42 | 100.82 | 483.53 | 72.96 |
| 9 | 11 | 0 | 0.24 | 20 | 99.78 | 100.55 | 583.53 | 76.60 |
| 10 | 3 | 0.24 | 0.24 | 20 | 80.47 | 91.25 | 710.64 | 64.07 |
| 11 | 24 | 0.24 | 0.24 | 20 | 75.91 | 87.90 | 636.54 | 75.82 |
| 12 | 17 | 0.24 | 0.24 | 20 | 86.55 | 95.44 | 675.53 | 64.38 |
| 13 | 5 | 0 | 0 | 30 | 67.96 | 76.55 | 646.70 | 68.09 |
| 14 | 2 | 0 | 0 | 30 | 66.55 | 75.57 | 717.85 | 72.59 |
| 15 | 9 | 0 | 0 | 30 | 56.54 | 73.46 | 683.54 | 65.14 |
| 16 | 4 | 0.24 | 0 | 30 | 70.89 | 76.59 | 472.59 | 76.24 |
| 17 | 19 | 0.24 | 0 | 30 | 70.11 | 80.36 | 546.35 | 72.08 |
| 18 | 6 | 0.24 | 0 | 30 | 72.25 | 81.20 | 510.53 | 79.03 |
| 19 | 18 | 0 | 0.24 | 30 | 63.67 | 74.57 | 616.26 | 78.95 |
| 20 | 15 | 0 | 0.24 | 30 | 62.45 | 73.22 | 570.79 | 72.82 |
| 21 | 1 | 0 | 0.24 | 30 | 64.81 | 73.48 | 676.08 | 78.33 |
| 22 | 12 | 0.24 | 0.24 | 30 | 52.05 | 61.57 | 899.99 | 54.89 |
| 23 | 14 | 0.24 | 0.24 | 30 | 51.54 | 59.32 | 905.63 | 50.07 |
| 24 | 22 | 0.24 | 0.24 | 30 | 47.26 | 59.57 | 879.54 | 59.03 |

**Table 3 : Independent factors for the estimated effects, F-ratio, and associated p-values for the SPH**

| Factor | Mechanical strength | | Porosity | | Dissolution Q4h | | Dissolution Q8h | |
|---|---|---|---|---|---|---|---|---|
| | F-Value | p-Value | F-Value | p-Value | F-Value | p-Value | F-Value | p-Value |
| **Model** | 42.32 | < 0.0001 | 9.97 | < 0.0001 | 27.36 | < 0.0001 | 58.42 | < 0.0001 |
| A-HPMC K4M | 3.08 | 0.0985 | 14.16 | 0.0017 | 8.52 | 0.0100 | 17.29 | 0.0007 |
| B-HPMC K100M | 81.21 | < 0.0001 | 1.99 | 0.1772 | 4.64 | 0.0468 | 0.8502 | 0.3702 |
| C-stirring time | 72.23 | < 0.0001 | 0.7766 | 0.3912 | 92.21 | < 0.0001 | 248.53 | < 0.0001 |
| AB | 128.32 | < 0.0001 | 28.69 | < 0.0001 | 28.06 | < 0.0001 | 34.52 | < 0.0001 |
| AC | 2.08 | 0.1681 | 0.9569 | 0.3425 | 1.94 | 0.1825 | 0.0024 | 0.9613 |
| BC | 1.49 | 0.2403 | 7.53 | 0.0144 | 56.11 | < 0.0001 | 103.39 | < 0.0001 |
| ABC | 7.85 | 0.0128 | 15.69 | 0.0011 | 0.0003 | 0.9869 | 4.34 | 0.0536 |

Table 3 gives Independent factors for the estimated effects, F-ratio, and associated p-values for the Superporous hydrogels

**Observed responses in the composite design for Venlafaxine hydrogels:**

The porosity of dried SPHC particles was determined from pore volume and bulk volume, by immersing a definite quantity of SPHC particles and the results were shown as

**Table 4: Observed responses for Porosity and Mechanical strength**

| **Formulation** | **F1** | **Fa** | **Fb** | **Fab** | **Fc** | **Fac** | **Fbc** | **Fabc** | **Optimized trial** |
|---|---|---|---|---|---|---|---|---|---|
| **Compression force** | 546.108 | 416.1997 | 534.5117 | 674.239 | 682.6963 | 509.8237 | 621.0467 | 895.0543 | 831.698 |
| **% Porosity** | 73.70001 | 68.18841 | 77.97534 | 68.09107 | 68.61071 | 75.785 | 73.36863 | 54.66442 | 58.993 |

**In Vitro Drug Release and Release kinetics:** The cumulative percentage drug release from Venlafaxine loaded Superporous hydrogels was studied as a function of time for 8hrs and the outcomes got are displayed in Table 5 and the drug release profile in Table 6 using 0.1 N hydrochloric acid at 37◦ C.

**Table 5: In Vitro Drug Release and Release kinetics**

| **Dissolution (in hrs.)** | **F1** | **Fa** | **Fb** | **Fab** | **Fc** | **Fac** | **Fbc** | **Fabc** |
|---|---|---|---|---|---|---|---|---|
| 0 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 0.5 | 47.906 | 27.369 | 37.905 | 29.646 | 40.163 | 26.484 | 34.434 | 22.100 |
| 1 | 54.662 | 39.838 | 62.998 | 58.788 | 48.951 | 38.832 | 43.823 | 31.344 |
| 2 | 63.043 | 55.699 | 86.821 | 69.806 | 56.987 | 54.898 | 54.888 | 39.900 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | 67.439 | 67.795 | 94.420 | 75.667 | 61.063 | 66.579 | 59.594 | 45.317 |
| 4 | 70.564 | 72.455 | 99.720 | 80.980 | 63.683 | 71.083 | 63.641 | 50.280 |
| 5 | 75.135 | 76.916 | 99.692 | 83.558 | 67.544 | 74.777 | 66.412 | 53.849 |
| 6 | 78.475 | 79.866 | 99.830 | 85.841 | 70.161 | 75.997 | 71.216 | 55.186 |
| 7 | 81.858 | 81.939 | 100.043 | 88.440 | 72.597 | 78.036 | 72.393 | 57.422 |
| 8 | 83.722 | 83.368 | 100.358 | 91.527 | 75.192 | 79.386 | 73.753 | 60.154 |

**Drug release kinetics:**

The in vitro drug release information of all formulations was exposed to numerical demonstrating. The estimations of Ko and r2 got were exhibited in Table 00. The best fit model with the most astounding relationship coefficient esteems or assurance coefficient (R2) for the definitions was observed to be zero request condition.

**Table 6. Different kinetic models for all formulations**

| **Model** | | **$F_1$** | **$F_a$** | **$F_b$** | **$F_{ab}$** | **$F_c$** | **$F_{ac}$** | **$F_{bc}$** | **$F_{abc}$** | **Optimized** |
|---|---|---|---|---|---|---|---|---|---|---|
| Zero order | $K_0$ | 4.124365 | 4.986703 | 4.468449 | 4.610458 | 3.738669 | 4.628683 | 3.960561 | 3.700408 | 4.485327 |
| | $r^2$ | 0.5537 | 0.6312 | 0.3763 | 0.5085 | 0.5571 | 0.6020 | 0.5928 | 0.6969 | 0.7701 |
| First order | $K_0$ | -0.067 | -0.081 | -0.134 | -0.089 | -0.043 | -0.059 | -0.044 | -0.031 | -0.049 |
| | $r^2$ | 0.9295 | 0.9594 | 0.378 | 0.9086 | 0.8329 | 0.8746 | 0.8469 | 0.8668 | 0.9667 |
| Peppas | $K_0$ | 0.1988 | 0.3668 | 0.2698 | 0.3068 | 0.2115 | 0.3573 | 0.2584 | 0.3360 | 0.3510 |
| | $r^2$ | 0.9972 | 0.9485 | 0.7658 | 0.8322 | 0.9938 | 0.9329 | 0.9830 | 0.9843 | 0.9991 |
| Higuchi | $K_0$ | 20.75 | 24.5 | 24.95 | 23.88 | 18.83 | 23.03 | 19.74 | 17.65 | 20.72 |
| | $r^2$ | 0.826 | 0.898 | 0.691 | 0.804 | 0.833 | 0.878 | 0.868 | 0.9354 | 0.9686 |

Experimental design matrix of Mechanical **strength**, **Porosity,** and Dissolution factors of venlafaxine hydrogel was given in the below equations and shown in the figure 6,7 and 8.

**Design expert Factor actual coding of Mechanical strength**

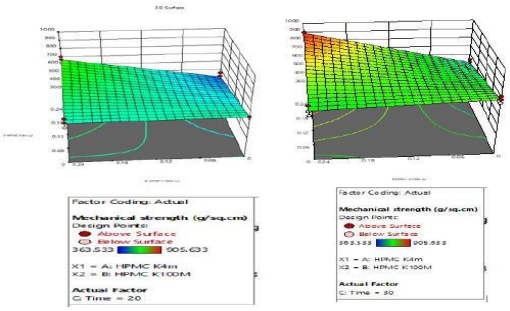



**Figure 6: Response surface plot of Mechanical strength at Stirring time 20sec and 30secs**

**DISCUSSION:**

IR spectrum of Venlafaxine Hydrochloride (Refer to the Attached Document for the Spectra) shows a broad peak at 3351.34 $cm^{-1}$ may be due to O-H stretching, 3076.58$cm^{-1}$ Aromatic C-H stretching, 2995.60 $cm^{-1}$ may be due to aliphatic C-H stretching, 1613.32 $cm^{-1}$ may be due to C-C Stretching, 1062.20 $cm^{-1}$ may be due to C-N Stretching, 1042.07 $cm^{-1}$ may be due to C-O stretching, 810.31 $cm^{-1}$ may be due to C-Cl stretching. The IR spectrum of the best formulation obtained the from the results,it is clear that, there is no appreciable change in the positions of the characteristic bands of the drug along with the IR spectrum of the formulation derived during the present investigation. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without going any chemical interaction with the polymers used.

**Mechanical strength:** The response Mechanical strength followed interactive (3FI) model and the summary of Analysis of variance (ANOVA) results with coefficient in terms of coded factors given by the Design-Expert®. The equation of Mechanical strength mentioned above (Eq.) suggests that factor A (% HPMC K4M), factor B (% HPMC K100M) and ABC have more negative dominant effect and factor C (stirring time), AB AC and BC have more positive dominant effect. This is further interpreted from ANOVA results and equation that increase in stirring time will result in significant ($p<0.05$) increase of Mechanical strength. This may be due to the formation a stronger gel when stirring time is increased.

**Porosity:** Porosity response also followed by interactive (3FI) model and summary by ANOVA, as per this model F-value is 4.27 and P-valve (0.0001) is less than 0.05. Further, the observed P values of model terms A and AB were less than 0.05. As per above mentioned equation) suggests that factor A (% HPMC K4M) and factor B (%HPMCK100M) have more positive dominant effect. Factor C (stirring time) has a negative dominant effect. There is negative interaction of AB. This is further interpreted from ANOVA results and equation that increase in HPMC K4M and HPMC K100M concentration and decrease in stirring time will result in significant ($p<0.05$) increase of porosity. This may be due to the swelling properties of polymers HPMC K4M and HPMC K100M due to which the formed gas bubbles after the addition of sodium bicarbonate will not be able to escape leading to the formation of large pores. When stirring time is the increased probability of escaping of gas bubbles is more due to which a compact porous structure will be formed.

**Dissolution Q4h and Q8h responses:**

The response Dissolution at 4h and 8h followed interactive (3FI) model and Design-Expert®. As per ANOVA results, interactive (3FI) model of response of Q4h and Q8h was significant as F-value are 27.36 & 58.42 and P-valve (<0.0001) is less than 0.05. Further, the observed P values of model terms A, B, C, AB, BC were less than 0.05 and A, C, AB, BC were less than 0.05 found to be significant and these results indicated that three independent selected variables individually and their interaction are significantly influencing the response Dissolution at 4h.

The response Mechanical strength and Porosity also followed interactive (3FI) model and the summary of Analysis of variance (ANOVA) results with coefficient in terms of coded factors given by the Design-Expert®. Response of mechanical strength was significant as F-value is 42.32 and P-valve (<0.0001) is less than 0.05 and porosity F-value is 9.97 and P-valve (0.0001) is less than 0.05.A multi-criteria decision optimization of approaches were employed for formulation optimization with desired responses. Optimization was performed with constraints of Mechanical strength in the range of 130 – 1000 g/sq.cm, Q4h in the range of 35-55% and Q8h in the range of 65 - 90%, to get optimized formula solutions with higher desirability function.

**Design expert Factor actual coding of Porosity:**

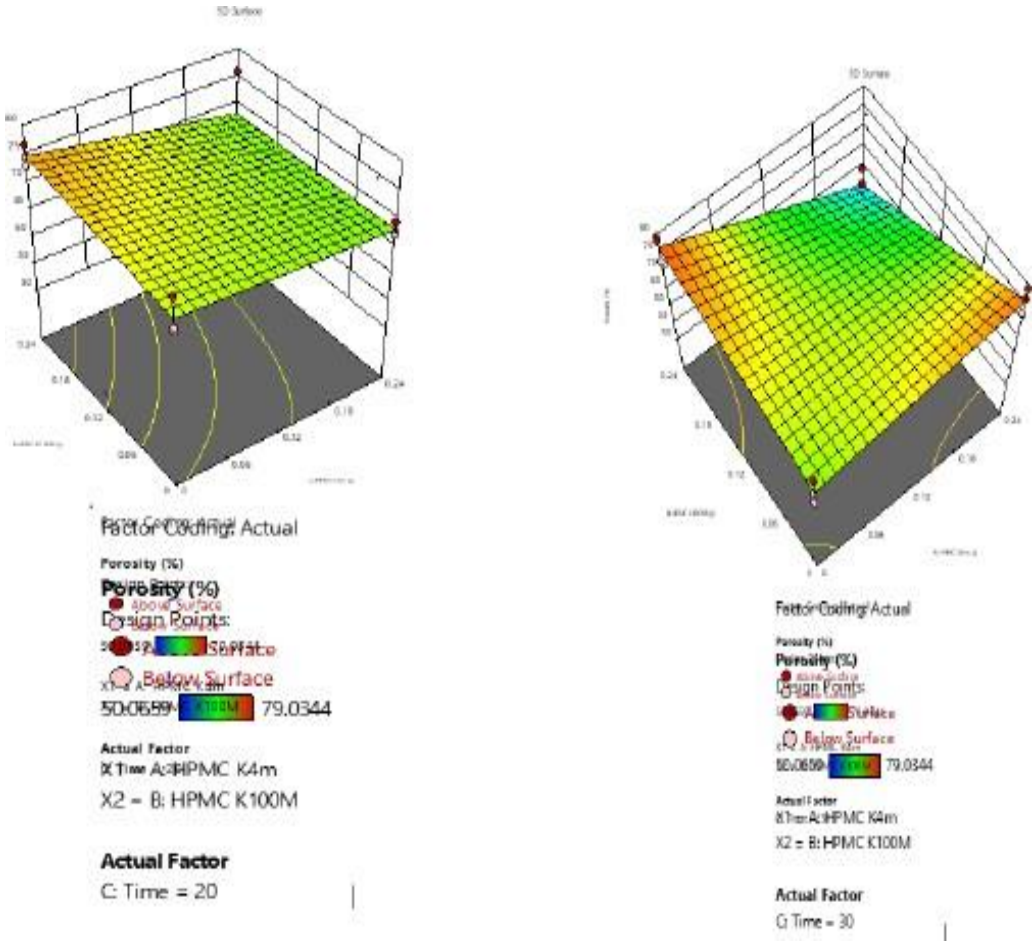
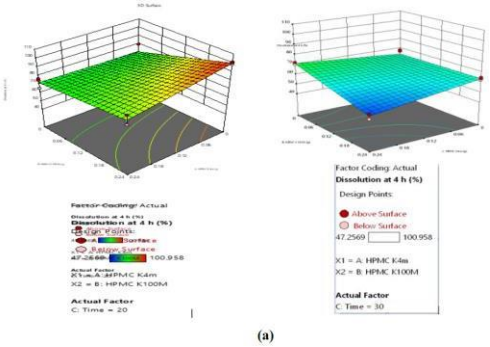
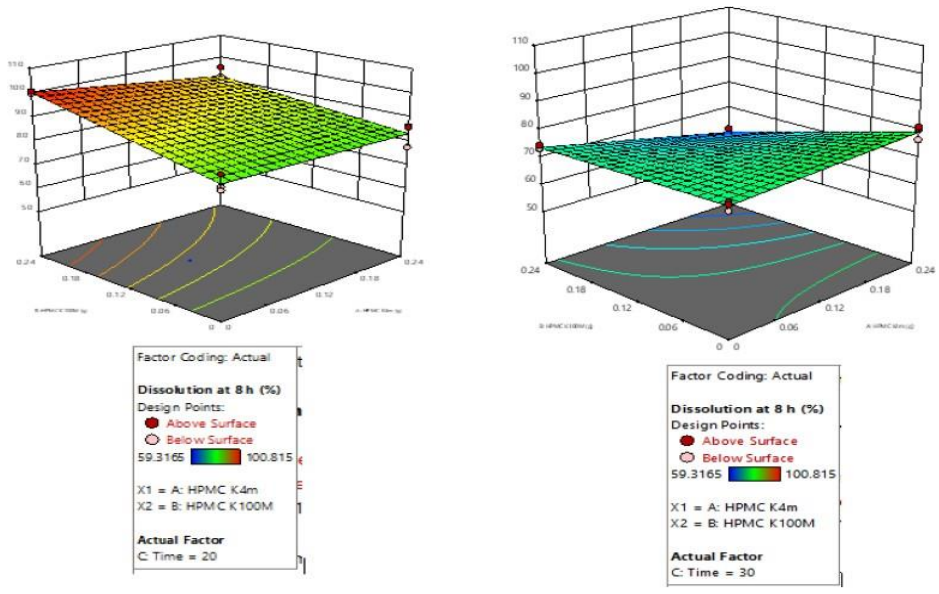



**Figure 7: Response surface plot of Porosity at Stirring time 30sec and 20secs**




(a)

**Design expert Factor actual coding of Dissolution:**




(b)

**Figure 8: Response surface plot of Drug release of (a) of Q4h at Stirring time 20sec and 30secs (b) of Q8h at Stirring time 20sec and 30secs**

**Optimization:**

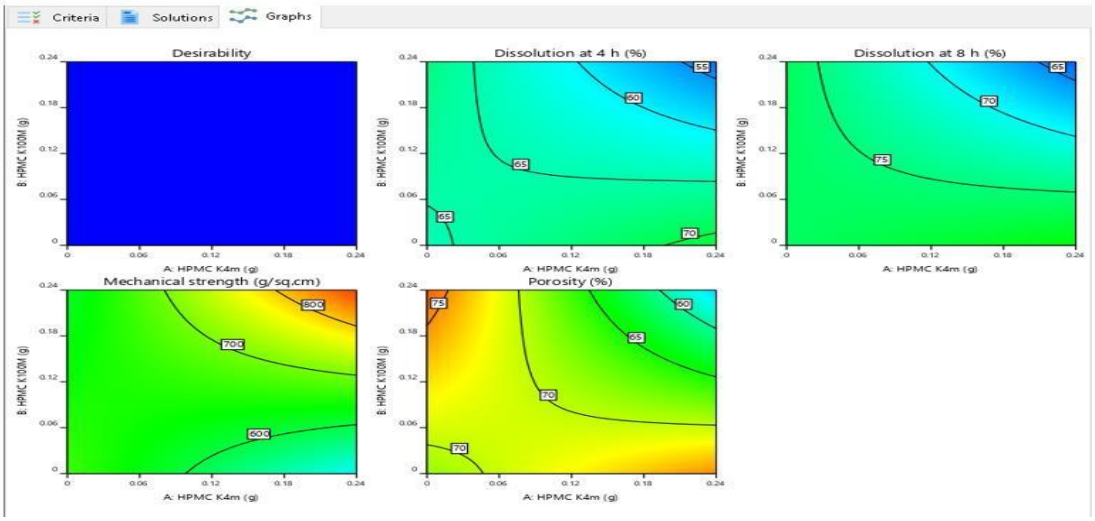



**Figure 9: Optimization formulations**

**Conclusion**

Chitosan and Acrylic acid-based hydrogel were prepared by stirring technique that showed good swelling in acidic media this was because chitosan swell at acidic pH. Mechanical strength, Porosity, and Dissolution were selected as the dependent variables. Mechanical strength was found to be in the range of 363 g/ sq.cm to 905.63 g/ sq.cm, the calculated porosity was about 50.07% to 78.33%, while the dissolution was estimated at 2 different time periods Q4h and Q8h and results are found around 45 to 100%. Optimization was performed with constraints of Mechanical strength in the range of 130 – 1000 g/sq.cm, Q4h in the range of 35-55% and Q8h in the range of 65 - 90%, to get optimized formula solutions with higher desirability function, further there is a scope to conduct the bioavailability studies.

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