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RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Matrix Tablets of Venlafaxine Hydrochloride Using Natural and Synthetic Polymers

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ABSTRACT

The objective of the present work is to design sustained release matrix tablets of Venlafaxine Hydrochloride, evaluation of influence of natural, synthetic polymers on the release rate and *in vitro* drug release. The natural polymers like Ghatti gum, pectin and synthetic polymers like HPMC K- 100, SCMC were utilized in the formulation of matrix tablets. Matrix tablets were prepared by wet granulation technique. Granules were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The formulation was optimized by acceptable tablet properties (hardness, friability, drug content and weight variations), *in vitro* drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The *in vitro* release study of matrix tablets were carried out in pH 1.2 HCl for 2 hours and pH 6.8 phosphate buffer for the remaining 10 hours as dissolution medium. Among all the formulations, F-8 shows 98.89% of drug which was better-controlled release at the end of 12 hrs. It has been found that the optimized formulation F-8 containing a combination of HPMC and SCMC with each 75mg, as drug retarding polymers shows a better-sustained effect for 12 hrs, the results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of the drug release. The stability studies revealed that the selected formulation was stable.

KEYWORDS

Venlafaxine HCL, HPMC K 100, SCMC, Ghatti gum, Pectin, Matrix Tablets, Sustained release, Wet granulation.

INTRODUCTION

The drug may be administered by a variety of routes, but oral administration is adopted wherever possible. It is safest, easiest and most economical route of drug administration.[1] The term sustained release has been consistently used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed &/or prolonged & its plasma profile is sustained in duration[2]. Matrix diffusion sustained drug delivery system, the drug reservoir results from the homogeneous dispersion of the drug particles in either a lipophilic or a hydrophilic polymer matrix[3]. Antidepressants are the most prescribed therapy for depression. That antidepressants increase the concentration of one or more brain chemicals (neurotransmitters) that nerves in the brain use to communicate with one another[4]. On the basis of mass a balance study, at least 92% of a single dose of venlafaxine is absorbed. The relative bioavailability of venlafaxine from a tablet was 100% when compared to an oral solution. Plasma half-life is five hr. Venlafaxine is used primarily

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for the treatment of depression, general anxiety disorder, social phobia, panic disorder, and symptoms. At low doses (<150 mg/day), it acts only on serotonergic transmission, at high doses (>300 mg/day), it also affects dopaminergic neurotransmission[5]. The aim of this research work was to design and characterization of sustained release Venlafaxine hydrochloride matrix tablets containing synthetic, natural polymers and to improve patient compliance and therapeutic action.

MATERIAL AND METHOD

Venlafaxine hydrochloride was obtained as gift sample from Aarthi Industries Ltd, Pune; Ghatti gum was purchased from Loba Chemie, Thane. Pectin was acquired from yarrow Chem, Mumbai, HPMC K-100, Microcrystalline cellulose were purchased from Research- Lab Fine Chem Industries, Mumbai. SCMC, Magnesium Stearate, Talc, PVP K 30 were purchased from SD Fine Chemicals Ltd, Mumbai.

Formulation of Sustained Release Matrix Tablets

Tablet formulations were prepared by wet granulation method. Non-aqueous granulation process was adopted to prepare Venlafaxine HCL matrix tablets Proportion of excipients with the drug was as given in Table no 1. All ingredients were sifted through sieve no.60. The sifted ingredients were mixed thoroughly in a polybag for 15min. PVP K30 was dissolved in isopropyl alcohol and used for wet granulation of the final blend. To get the desired wet mass.

This wet mass was passed through Sieve # 16. The prepared granules were dried at 60^0C for 1 hour in a hot air oven; dried granules were sized by passing it through sieve no.20 and lubricated with magnesium stearate and Talc for 1 minutes. Finally, tablets were compressed at 500 mg weight on a ten station mini rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) with 8 mm flat-shaped punches.

Table 1: Composition of matrix tablet of Venlafaxine HCL (F1-F7)

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7
Venlafaxine HCL	75	75	75	75	75	75	75
HPMC	75	150	225	-	-	-	25
SCMC	-	-	-	75	150	225	50
MCC	310	235	160	310	235	160	310
PVP K 30 (5%)	25	25	25	25	25	25	25
Magnesium Stearate	10	10	10	10	10	10	10
Talc	05	05	05	05	05	05	05

Table 2: Composition of matrix tablet of Venlafaxine HCL (F8-F15)

Ingredients (mg/tablet)	F8	F9	F10	F11	F12	F13	F14	F15
Venlafaxine HCl	75	75	75	75	75	75	75	75
HPMC	75	150	-	-	-	-	-	-
SCMC	75	75	-	-	-	-	-	-
Pectin	-	-	75	150	225	-	-	-
Ghatti gum	-	-	-	-	-	75	150	225
MCC	235	160	310	235	160	310	235	160
PVP K 30 (5%)	25	25	25	25	25	25	25	25
Magnesium Stearate	10	10	10	10	10	10	10	10
Talc	05	05	05	05	05	05	05	05

Evaluation of Granules [6,7,8]

Angle of Repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured, and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where h and r are the height and radius of the powder cone.

Density

Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder/volume of the packing

TBD = weight of the powder / tapped volume of the packing

Carr's index (%) = [TBD-LBD] X 100 / TBD

Where TPD is Tapped bulk density

LBD is Loose bulk density

The physical properties of granules were shown in Table 3.

Evaluation of Tablets [6,7,8]

Post Compression Parameters

A. Thickness and Diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet were measured using Vernier calipers. It is measured in mm.

B. Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. The scale was adjusted to zero; load was gradually increased

until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. Hardness was expressed in Kg/cm^2.

C. Friability (F)

Tablet strength was tested by Roche friabilator. Pre-weighed tablets were allowed for 100 revolutions (4min), taken out and were deducted. The percentage weight loss was calculated by rewriting the tablets.

$$F = \frac{\text{(W initial) – (W final)}}{\text{(W initial)}} \times 100$$

D. Weight Variation

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet. All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability, and thickness according to suitable methods shown in Table 4.

E. Uniformity of Drug Content

Weigh and powder 20 tablets. Weigh a Quantity of the powder equivalent to 100 mg of voriconazole accurately, transfer to a 250 ml volumetric flask. Add about 150 ml of 6.8 Phosphate buffer. Shake well and sonicate it for 25-30 min. Make up the volume up to 250 ml with 6.8 Phosphate buffer Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 6.8 Phosphate buffer Measure the absorbance, of the resulting solution at the maxima at about 255 nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation:

$$Cu/Cs = Au/As * \text{dilution factor}$$

Cu = Concentration of unknown sample,

Cs = Concentration of Standard sample

Au = Absorbance of unknown sample

As = Absorbance of standard sample

F. *In-Vitro* Dissolution Study

Dissolution tests were performed in a USP Dissolution Test Apparatus II (Paddle method) at 37 ± 0.5°C. The Paddles were rotated at a speed of 100 rpm. The prepared tablets of Venlafaxine HCL tablets were placed in the dissolution vessel containing 0.1 N HCl solutions (pH 1.2) for 2 hrs. These were then transferred to phosphate buffer (pH 6.8) and continue dissolution. 5 ml of solution were withdrawn at different time intervals, filtered through 0.45 µm filter paper and the content of Venlafaxine HCL was determined spectrophotometrically at a wavelength of 225nm. At each (hour) time of Withdrawal, 5 ml of corresponding fresh medium was replaced into the dissolution flask. By release studies, the formulation which gave desired twice a day release of Venlafaxine HCL was chosen as the optimized formulation. The dissolution profiles of different formulations are shown in figure no 15 and 16. Among the various formulations F8 was found to be a better formulation.

Drug Release Kinetics

To determine the mechanism of drug release from this formulation, the drug release data of in-vitro dissolution study was analyzed with various kinetic equations.

Different kinetic equations. The data were treated according to:

1. Zero order kinetic model – Cumulative % drug released versus time.

2. First order kinetic model – Log cumulative percent drug remaining versus time.

3. Higuchi's model – Cumulative percent drug released versus square root of time.

4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

FT-IR Spectroscopy:

Compatibility between the drug and excipients assessed with an Agilent Technologies, Cary 630 FTIR by using KBR pellet to hold the sample

Thermal analysis:

Thermal analysis was carried out with a differential scanning calorimeter (DSC, Perkin-Elmer, and Pyris-1). Scanning was performed at a temperature ranging from to 227^{0}C at a heating rate of 5^{0}C/min under an atmosphere of nitrogen. The sample weight was 2 - 4 mg and it was sealed in a perforated aluminum pan.

Scanning electron microscopy (SEM) :

The surface morphology of the matrix tablets was examined with a scanning electron microscope (JEOL-JSM-840A, Japan)

Stability Study

The optimized formula was subjected to stability at 25ºC± 2ºC / 60% ± 5% RH, 30ºC ± 2ºC / 65% ±5% RH and 40ºC ± 2ºC/75% ± 5% RH for 90 days. The samples were withdrawn at intervals of 15 days and checked for physical changes, hardness, friability, drug content and percentage drug release.

RESULTS AND DISCUSSION

intervals of 15 days and checked for physical changes, hardness, friability, drug content and percentage drug release.

Preformulation Studies

Melting Point Determination: The melting point was found to be 215ºC, which complied with standards limits range 212^{0}C-220^{0}C, indicating purity of the drug sample.

Compatibility Study

Compatibility studies were performed using FTIR spectrophotometer and from DSC analysis.

FTIR Studies

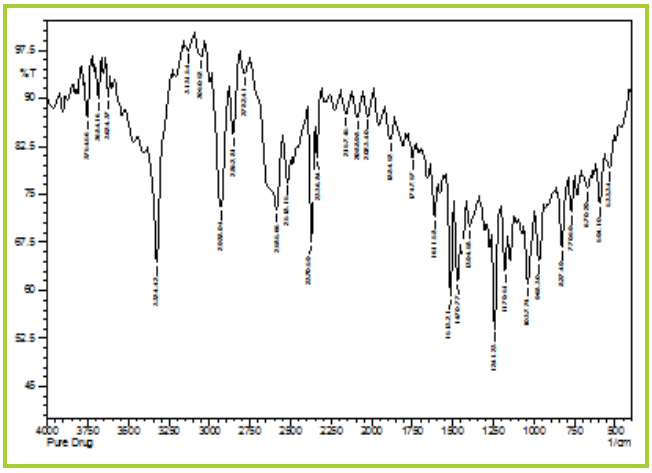

Figure 1: FTIR Spectroscopy of pure Drug

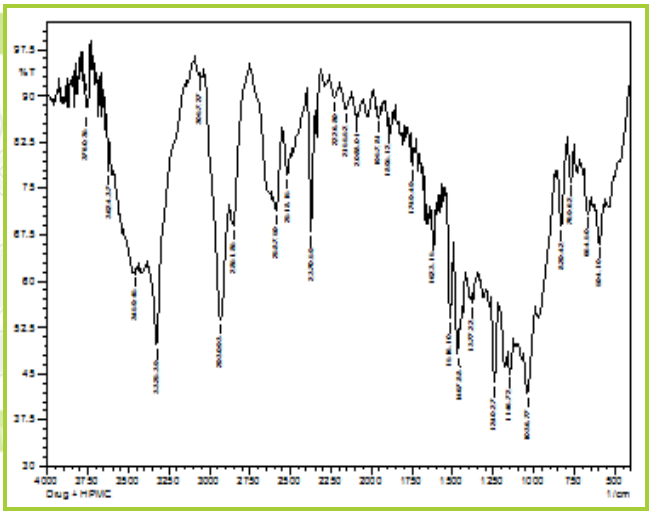

Figure2: FTIR Spectroscopy of Drug + HPMC

SR. No.	Functional Group	Reported Values	Venlafaxine HCL	Formulation F8
1	OH	3300-3400	3324	3323
2	C_6H_5	1500-1600	1513	1515
3	Aliphatic CH	2800-3000	2928	2931
4	C-O-C	1000-1200	1037	1035

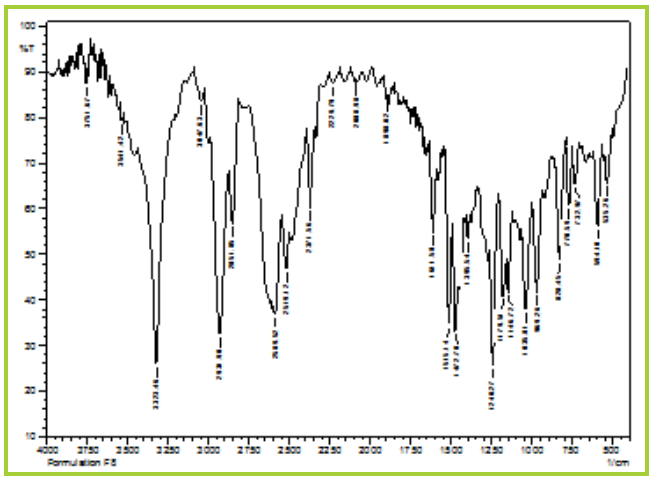

Figure 3: FTIR Spectroscopy of Drug + SCMC

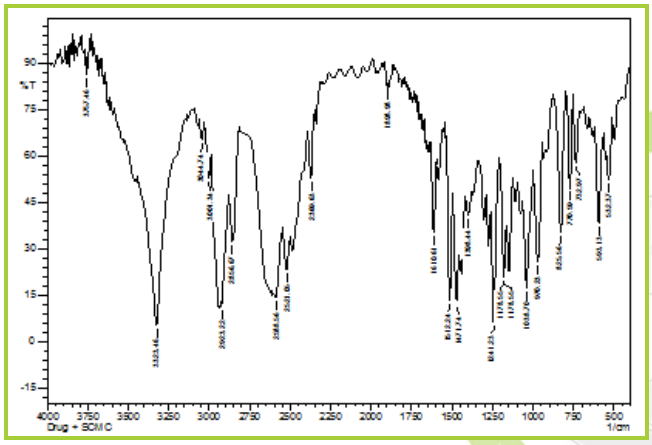

Figure 4: FTIR Spectroscopy of Formulation F8

Differential Scanning Calorimetry:

The DSC thermograms for pure drug sample and polymer were taken during the present study. The thermogram of venlafaxine hydrochloride is shown in figure 5.

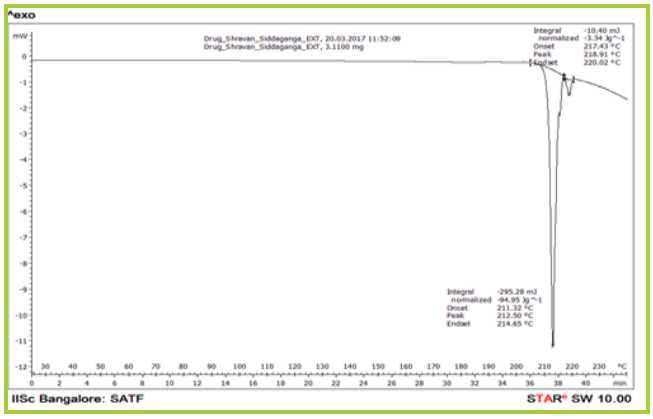

Figure 5: DSC of pure Venlafaxine HCl

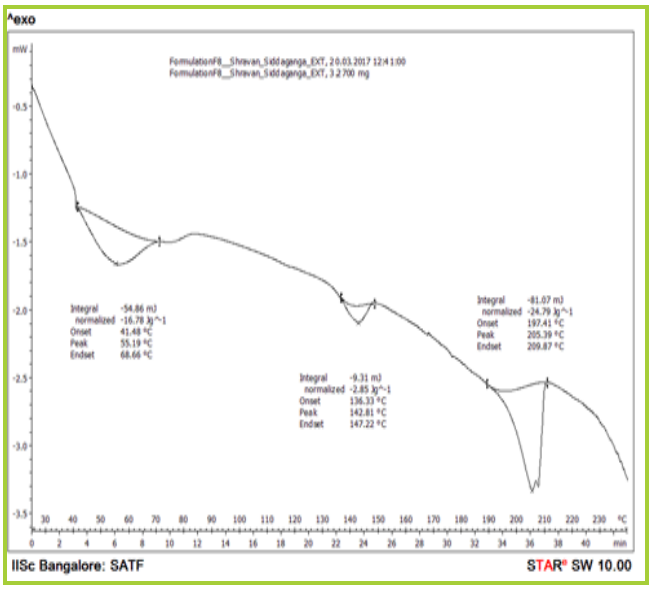

Figure 6: DSC of formulation F8

The drug and other excipients and also in optimized formulation was evaluated by FTIR and DSC. FTIR spectrum of pure drug was compared with that of formulations F-8. All peaks corresponding to the different functional groups of pure drug were present in the formulations which indicate there was no interaction between the drug and excipients as shown in figures 1 to 4 . DSC Studies review that, the peaks obtained from pure and optimized formulations of Venlafaxine HCL shows the peak range (205^0C - 212^0C) of its melting point (215^0C).

SEM STUDIES:

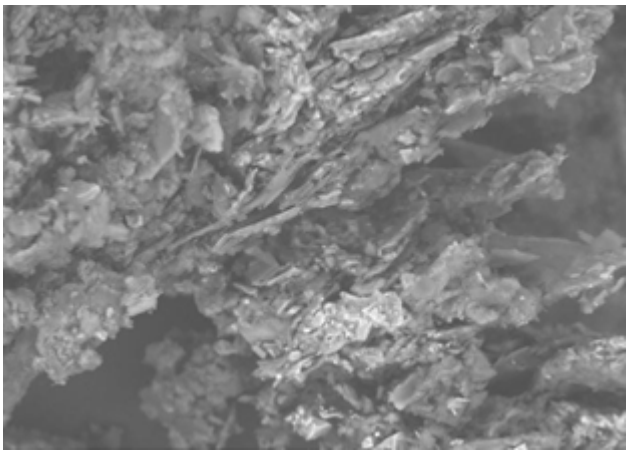

Figure 7: Before Dissolution

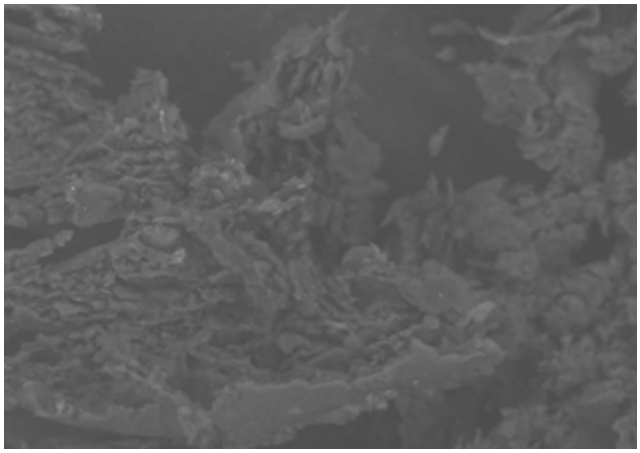

Figure 8: After Dissolution of 2 hours

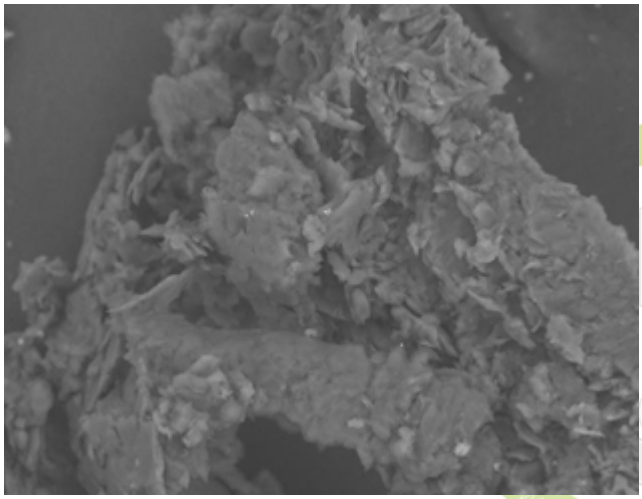

Figure 9: After Dissolution of 6 hours

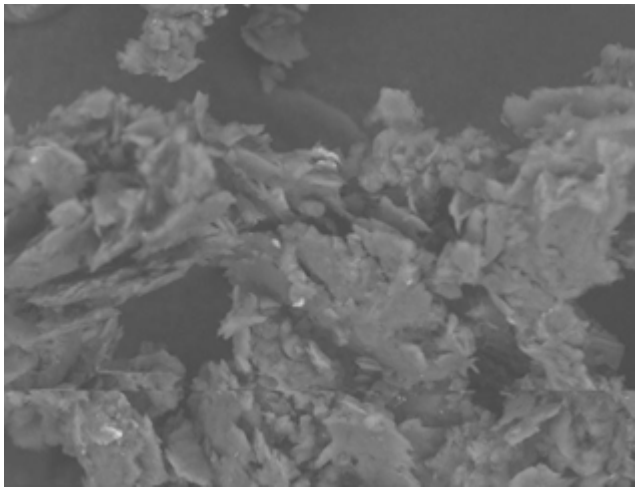

Figure 10: After Dissolution of 12 hours

Which indicates of pure drug shows peak value 215^0C and melting peak of optimized formulation F8 is 203^0C observed from figure 6. Change in temperature is due to various concentrations of drug and other excipients in the physical mixture compared to the pure drug this indicates that there is no interaction between drug and mixture materials.

SEM study further established both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet (F-8). SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact pores had formed throughout the matrix and also found formation of gelling structure.

Evaluation of Pre-Compression Parameters:

Pre-compressional parameters of Venlafaxine HCL blends were evaluated for bulk density, tapped density, angle of repose, compressibility index and hausner's ratio shows (Table 3). The Bulk densities were found to be in the range of 0.328 to 0.342 gm/cc, Tapped densities were in the range of 0.383 to 0.396 gm/cc, Compressibility index were in the range of 13.02% to 16.53 % and Angle of repose were found to be between 23.51 to 29.82 (Table 3)

Evaluation of Post Compression Parameters:

The punches used to compress the tablets were 11mm, standard cancave shaped. The shape and size of the tablets were found to be within the limit. Thicknesses of the tablets were found to be in the range of 4.07 to 4.15 mm. The results are given in the Table No.4. The hardness of the tablets was found to be in the range of 5.1 to 6.2 Kg/cm^2. It was within the range of monograph specification. The friability of the tablets was found to be less than 1% and it was within the range of standard specification. The drug content of the tablets was found to be in the region of 97.22% to 100.04%. It was within the range of monograph of specification. Weight variation is pass the limit and it found to be within the range of monograph of specification. (Table 4)

Table 3: Evaluation of Pre-Compression Parameters

Formulation Code	Paramet			
	Angle of repose	**Loose bulk density (LBD) (g/cc)**	**Tapped bulk density (TBD)**	**Compressibility index (%)**
F1	27.35 ±0.058	0.328±0.003	0.388±0.0023	15.46±0.01%
F2	27.27 ± 0.026	0.334±0.002	0.384±0.0026	13.02±0.01%
F3	26.27 ± 0.021	0.325±0.002	0.385±0.0032	15.58±0.02%
F4	28.46 ± 0.025	0.33±0.003	0.387±0.0022	14.72±0.02%
F5	28.34 ± 0.015	0.326±0.0015	0.383±0.0023	14.88±0.03%
F6	27.60±0.02	0.324±0.021	0.386±0.0012	16.06±0.03%
F7	26.14±1.22	0.342±0.03	0.396±0.0014	13.63±0.016%
F8	28.46 ± 0.025	0.33±0.003	0.387±0.0022	14.72±0.02%
F9	29.82 ± 1.42	0.328±0.015	0.393±0.0016	16.53±0.022%
F10	24.10 ± 1.6	0.338±0.01	0.395±0.0015	14.43±0.022%
F11	23.51 ± 1.31	0.338±0.02	0.392±0.0015 2	13.77±0.018%
F12	27.97 ± 1.58	0.328±0.01	0.388±0.0010	15.46±0.019%
F13	29.82 ± 1.42	0.328±0.015	0.393±0.0016	16.53±0.022%
F14	28.96 ± 1.57	0.324±0.012	0.394±0.0020	17.76±0.032%
F15	26.14±1.22	0.342±0.03	0.396±0.0014	13.63±0.016%

Drug Release Studies:

In-vitro release studies were carried out using electro lab dissolution apparatus. For 1st 2 hours 200 ml of 0.1N is used as dissolution medium and for later 10hours 700ml of phosphate buffer of pH 6.8 as dissolution medium at 50 RPM . The results were evaluated for 12hrs. As per the results of dissolution study formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14and F15 showed 97.01%, 94.97%, 85.96%, 95.60%, 96.09%, 84.84%, 96.59%, 98.89%, 91.50%, 96.11%, 94.97%, 96.11%, 95.51%, 96.40% and 92.0%, respectively and release at the end of 12 hours. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration. The dissolution studies were carried out for 12 hours. F-8 showed good drug release profile 98.89% they showed excellent matrix integrity during the period of study, when compare to other formulations. Based on all these results, formulation F-8 is selected as the optimized formulation with 98.89%, drug release. (Figures 15,16).

Kinetics Studies

Correlation coefficients of different mathematical models for formulations F-8

The release data fitted to various mathematical models to evaluate the kinetics and mechanism of

Table 4: Evaluation of Post-Compression Parameters

Formulation code	Parameters			
	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	4.12±0.02	5.6±0.43	0.38±0.01	98.52
F2	4.12±0.03	5.6±0.20	0.42±0.02	98.64
F3	4.10±0.01	5.2±0.56	0.44±0.01	97.25
F4	4.13±0.01	5.7±0.20	0.37±0.03	98.32
F5	4.12±0.01	5.9±0.15	0.39±0.01	99.80
F6	4.11±0.03	6.2±0.36	0.38±0.01	100.02
F7	4.11±0.03	5.8±0.45	0.41±0.02	98.47
F8	4.13±0.02	6.0±0.26	0.40±0.01	98.81
F9	4.10±0.02	6.0±0.37	0.36±0.01	99.28
F10	4.07±0.21	5.4±0.45	0.39±0.01	98.81
F11	4.11±0.01	5.2±0.40	0.42±0.02	100.04
F12	4.10±0.03	5.1±0.30	0.41±0.03	99.54
F13	4.12±0.01	5.2±0.30	0.37±0.01	97.22
F14	4.15±0.02	5.4±0.62	0.36±0.01	98.11
F15	4.13±0.01	5.6±0.45	0.38±0.03	97.51

Table 5: Correlation coefficients of different mathematical models for formulations F- 1 to F-15

Formulation Code	**Zero order kinetics**	**First order kinetics**	**Higuchi kinetics**	**Korsmeyer / Peppas kinetics**	
				R^2	**N value**
F1	0.997	0.830	0.979	0.986	0.661
F2	0.998	0.846	0.973	0.988	0.774
F3	0.994	0.899	0.951	0.984	0.839
F4	0.996	0.811	0.960	0.980	0.721
F5	0.987	0.786	0.938	0.981	0.828
F6	0.989	0.898	0.942	0.981	0.858
F7	0.992	0.879	0.972	0.991	0.848
F8	0.996	0.739	0.959	0.988	0.917
F9	0.982	0.844	0.929	0.981	0.954
F10	0.986	0.922	0.994	0.994	0.561
F11	0.988	0.901	0.993	0.994	0.633
F12	0.982	0.957	0.995	0.993	0.771
F13	0.990	0.920	0.988	0.987	0.632
F14	0.995	0.890	0.972	0.972	0.668
F15	0.988	0.950	0.981	0.989	0.714

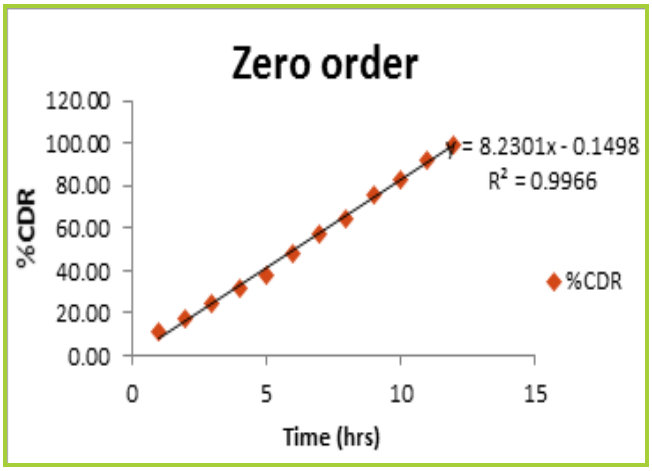

Figure 11: zero order equation for optimized F8 Formulation

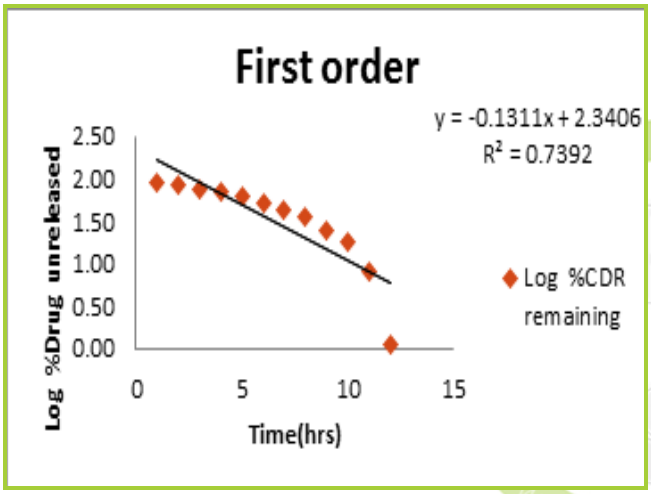

Figure 12: First order equation for optimized F8 Formulation

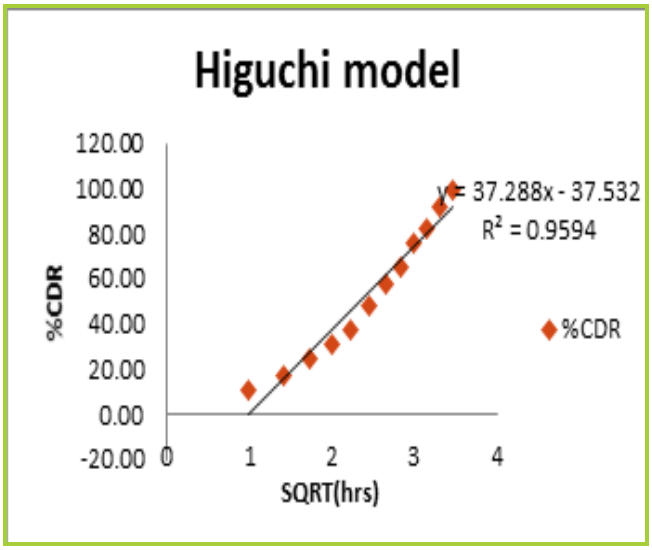

Figure 13: Higuchi Equation for optimized F8 Formulation

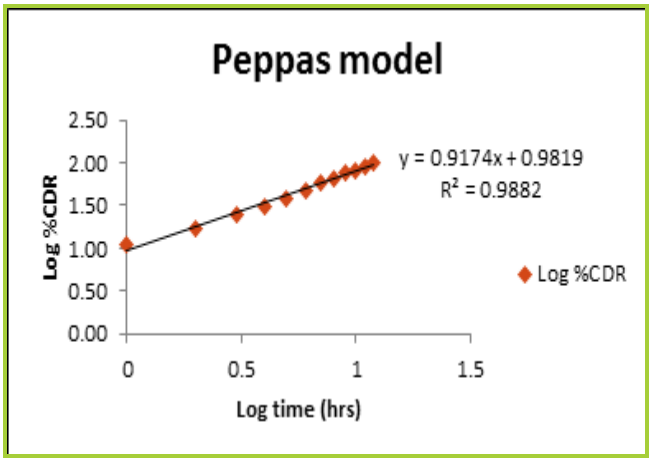

Figure 14: Peppas equation for optimized F8 Formulation

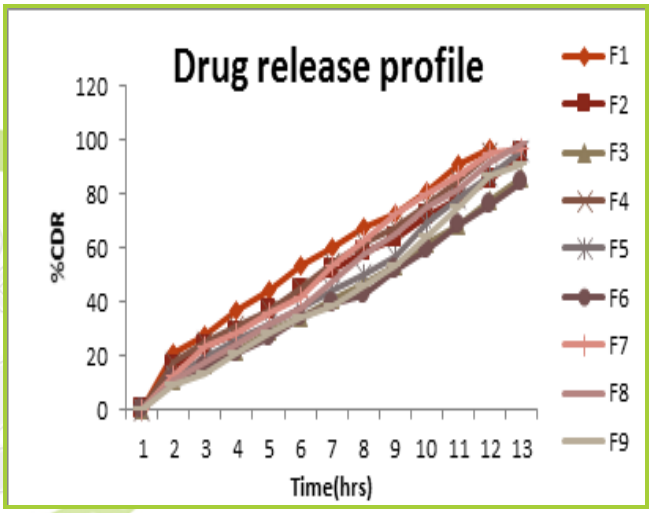

Figure 15: Drug release profile F1-F9

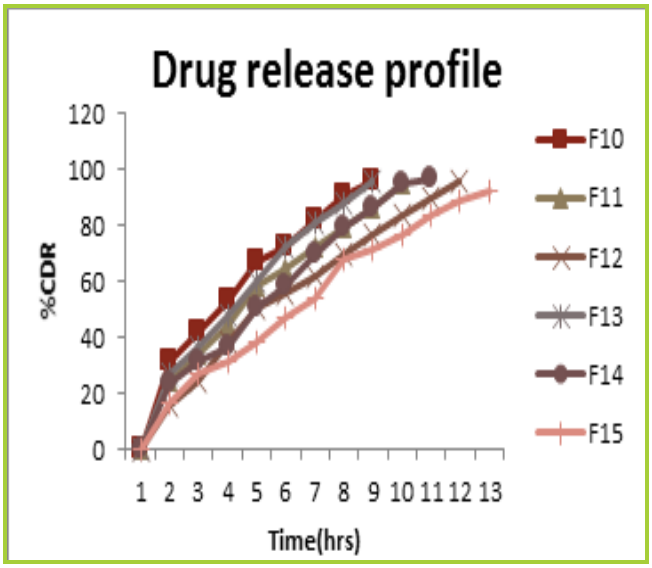

Figure 16: Drug release profile F10-F15

drug release. The kinetics data of all formulations F1-F15 could be best expressed by zero order equations as the plots shows highest linearity (0.982 to 0.998), than first order (0.739 to 0.957). The n values obtained from korsmeyer peppas plots range from (0.561 to 0.954) indicates that mechanism of release of formuations F1 to F15 was anomalous (non Fickian) diffusion. (Table 5).

STABILITY STUDIES :

The stability studies for optimized formulation F8 was carried out based accelerated stability conditions & study of various parameters carried out at 0, 15,30, 45,60, 75,90 days of intervals and the results found satisfactorily and that revealed that the optimized formulation was stable under accelerated condition.

Table 6: Physical appearance of optimized formulations after stability studies

Temperature and relative humidity	**F8**							**Parameters**
	Days							
	0	**15**	**30**	**45**	**60**	**75**	**90**	
$25^0C \pm 2^0C$ / 60% ± 5% RH	No change in physical appearance							
$35^0C \pm 2^0C$ / 60% ± 5% RH								
$40^0C \pm 2^0C$ / 60% ± 5% RH								

Table 7: Hardness of optimized formulations after stability studies

No. of days	F8		
	Hardness (Kg/cm2)*		
	25^0C / 60% RH	30^0C / 65% RH	40^0C / 75% RH
0	4.8	5.0	4.9
15	5.0	4.9	4.8
30	4.9	4.9	4.9
45	4.8	5.0	5.0
60	4.9	5.0	4.8
75	4.0	4.9	5.0
90	4.9	4.8	4.9

Table 8: Friability of optimized formulations after stability studies

No. of days	F8		
	Friability (%)		
	25^0C / 60% RH	30^0C / 65% RH	40^0C / 75% RH
0	0.423	0.425	0.466
15	0.435	0.431	0.482
30	0.473	0.442	0.429
45	0.451	0.419	0.429
60	0.440	0.467	0.434
75	0.420	0.432	0.429
90	0.423	0.451	0.436

Table 9: Drug content of optimized formulations after stability studies

No. of days	F8		
	Drug content (mg)		
	25^0C / 60% RH	30^0C / 65% RH	40^0C / 75% RH
0	99.10	99.15	99.18
15	99.15	99.20	98.13
30	99.22	99.17	99.20
45	99.18	99.15	98.18
60	99.11	98.10	99.08
75	99.08	99.12	98.02
90	99.10	99.08	98.91

Table 10: Percentage drug release from optimized formulations after stability studies

No. of days	F8		
	% Drug release		
	25^0C / 60% RH	30^0C / 65% RH	40^0C / 75% RH
0	98.07	98.45	98.20
15	98.16	98.09	98.16
30	98.19	98.05	98.75
45	98.04	98.07	98.17
60	98.17	98.01	98.09
75	98.05	98.17	98.13
90	98.05	98.18	98.05

CONCLUSION

In this study revealed that the formulation F8 showed good drug release and matrix integrity , it shows better sustained effect for 12 hrs and was most promising formulation it follows Peppas plot. F8 follows Anamolous (non-Fickian) diffusion mechanism. The regression coefficient (R2) values of zero order in the optimized formulation F8 had greater than First order. Thus, the drug release follows zero order kinetics. SEM study confirms diffusion and erosion mechanisms responsible for sustaining the release matrix tablets. Formulation F8 was found to be stable after 90 days and could perform better than conventional dosage form.

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