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FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAIN RELEASE TABLET OF VANLAFAXINE

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ABSTRACT
Highly water soluble compounds found in antidepressants like Venlafaxine must be packaged into delivery systems in the form of pellets in order to provide a constant and prolonged release. Self-observation, FTIR analysis, and DSC drug profiling were used in the prefformulation investigation of the drug excipients. Both medications had an analytical method (UV) established for them in various media. Extrusion and spheronization were regulated processes used to create drug-loaded pellets, which were then covered in a controlled-release coating and compacted into tablets. For the created system, physicochemical, functional, and structural characterisation were carried out. Results of prefformulation tests showed that particular medications were suitable for oral solid dosage forms. New UV techniques demonstrated required linearity with little noise. Drugs and a few excipients were discovered to be compatible. Pellet optimization was aided by the use of QbD tools such as risk assessment, screening design, and DoE. 3.3%, 26.8%, 51.9%, 74.1%, and 91.4% of the drug was released at 2, 4, 8, 12, and 20 hours from an optimised pallet filled with VEN, and 4.3%, 26.5%, 57.2%, 78.7%, and 93.3% from compressed tablets loaded with VEN, respectively. The created multiparticulate pellets compressed as tablet system for the chosen medicament yielded the desired drug release profile. So, if BCS class I medicines are added to a designed system, consistent blood plasma concentration can be anticipated.
Keywords: Sustain release, Antidepresent drugs, pettel, multiparticulate drug delivery system

INTRODUCTION
The most conventional oral drug products are as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile.[1]
The term *modified-release drug product* is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized".[2]

MATERIALS AND METHOD
The drug Venlafaxine Hydrochloride was a gift sample from Cadila Healthcare Ltd, India and all excipients were obtained from RPCL Limited.

Composition of VEN pellets ad tablets

Sr.No.	Ingredients	Quantity per Tablet (mg)
	CORE PELLET	
1.	Venlafaxine HCl eq. to Venlafaxine 150 mg	169.71(1:3 IR to SR)
2.	microcrystalline cellulose	149.53
3.	polyethylene gly-col	12.18
4.	Crospovidone	18
	Total weight of IR pellets	339.42
	POLYMER COATING	
5.	Ethyl Cellulose (45 cps)	Optimized by FFD
6.	Hypromellose (6 cps)	
7.	Dibutyl Sebacate	10% of polymer blend
8.	Dichloromethane	q.s
9.	Methyl Alcohol	q.s.
	LUBRICATION	
10.	Talc	1%

Derived properties

The results of derived properties are shown in Table 5 There is no any significant distinct between experimental and reference value which suggest the less instability or any other fformulation problems.

Table 5 Result of prefformulation study (Derived properties) of VEN

No.	Parameter	Experimental value	Reference value
1	D(90)	51.11µm	56.30 µm (D90 <100 mµ)
2	Bulk density	0.254 (gm/cm3)	0.26 (gm/cm3)
3	Taped density	0.416 (gm/cm3)	0.42 (gm/cm3)
4	Compressibility Index	38.94%	38.10%
5	Haussner's ratio	1.64	1.62
6	Angle of repose	27.09	29.15
7	Loss on drying (at 105 C)	0.37% w/w	0.18% w/w (NMT 0.5% w/w)
8	Melting Point	215.8 C-216.4 C	215 C-219 C

Identification of drug

The FTIR spectrum of VEN is shown in Fig.1 and their interpretation is explained inTable 6

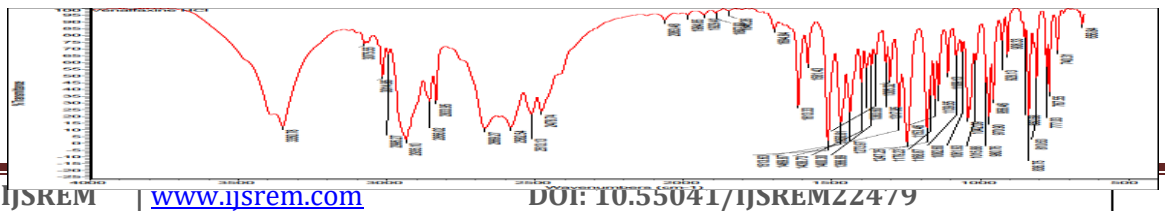

Figure 1: FTIR spectrum of Venlafaxine Pure drug

Interpretation of FTIR Spectrum

Major functional groups methoxy, amine and alcohol groups Present in Venlafaxine Hydrochloride were showed at 2935 cm^{-1}, 1317.95 cm^{-1} and 1153.46 cm^{-1} respectively. These peaks were identical to functional group of Venlafaxine Hydrochloride. Hence, the sample was confirmed as Venlafaxine Hydrochloride.

Drug excipients compatibility study by visual inspection (VEN)

The study was carried out by mixing the drugs with excipients used in fformulation in different ratio and charging them at accelerated conditions as per ICH for four weeks. The results of this study indicated stable characteristics of drugs with proposed excipients. Moreover, the results were confirmed by FTIR and DSC peak profiles as there were non-significant changes in the characteristics peaks of drugs. The results arepresented in Table 7 for VEN.

Table 8 Various DSC thermogram parameters

S. No.	DSC thermogram	Onset temperature (°C)	Peak temperature (°C)	Endset temperature (°C)
1	Venlafaxine HCL	209.88	216.23	222.10
2	Venlafaxine HCL IR VEN Pallet	210.77	215.45	220.65
3	Venlafaxine HCL ERVEN Pallet	211.01	213.31	221.93
4	Venlafaxine HCL Tablets	202.81	214.36	221.81

From results of Appearance, FTIR and DSC study of drug samples (VEN) and physical mixture of drugs with selected excipients, it is suggested that there is no any remarkable change in appearance, characteristics peak of FTIR and endothermic peak of DSC thermogram. Hence, it indicates that there is no interaction with excipients and it is also supported by FTIR and DSC study of IR pellets and ER pellets as well as compressed tablets.

Analytical methods

The absorption maximum for Venlafaxine Hydrochloride in purified water was found to be 225 nm and absorption maximum was shown in Figure.

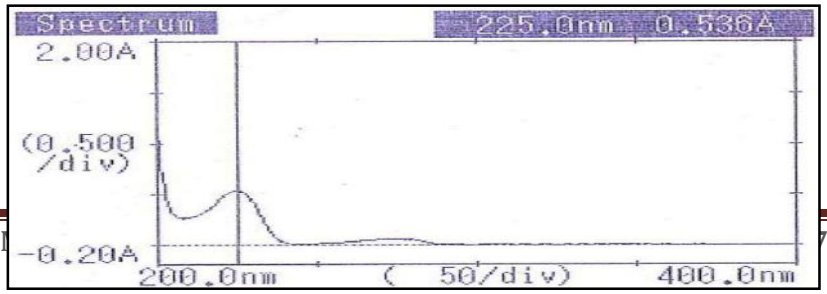

Figure 2 Wavelength maxima of VEN (15.0 µg/ml) in purified water

Preparation of standard graph of Venlafaxine Hydrochloride in 0.1NHCl:

The absorbance of each solution was measured at 225 nm using UV-visible double beam against purified water as a blank. Observations for standard calibration curve (in triplicate) shown in Table 9 and graphically shown in Figure

Table 9 Absorbance of VEN in purified water (225 nm)

Sr. No.	Conc. (µg/ml)	Absorbance				
		1	2	3	Mean	SD (±)
1	2.5	0.102	0.101	0.103	0.102	0.002
2	5.0	0.194	0.198	0.193	0.195	0.002
3	7.5	0.277	0.279	0.288	0.282	0.005
4	10.0	0.352	0.364	0.367	0.361	0.005
5	12.5	0.456	0.467	0.464	0.464	0.006
6	15.0	0.539	0.541	0.546	0.548	0.007
7	17.5	0.620	0.636	0.639	0.635	0.008
8	20.0	0.717	0.723	0.732	0.725	0.008
Slop of regression line : 0.0349 **Intercept of regression :** +0.0149 **R-square :** 0.9996						
Equation of the line: **Absorbance=0.0353 (Concentration) + 0.0149**						

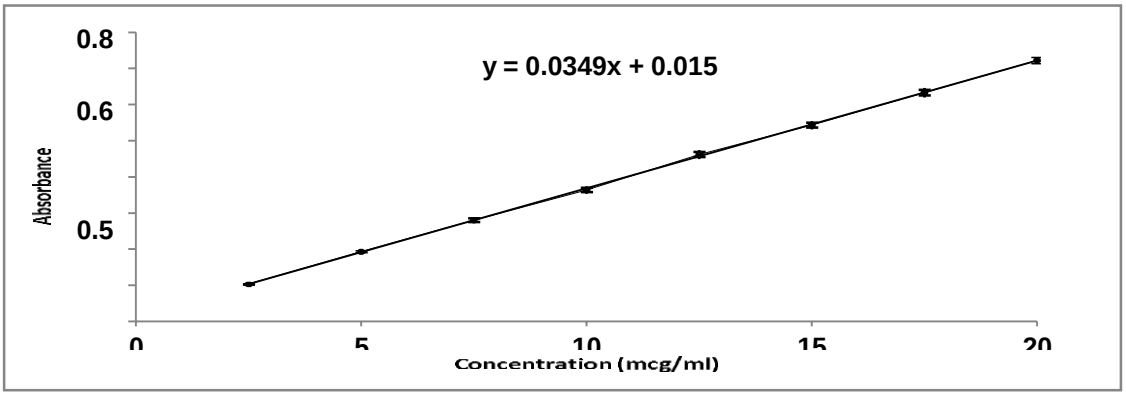

Figure 3 Standard calibration curve of VEN in Purified water at 225 nm

Development of VEN pellets

Development of VEN pellets

Table 10 Quantitative data for evaluation of core pellets (IR)

B. No.	SAR	Size by sieve analysis					Hardness (gm/cm^2)	Friability(% w/w)
		16#	18#	20#	25#	MPD (mm)		
IR1	1.28	10.53	45.38	31.32	12.77	1.00	450	0.09
IR2	1.35	18.25	52.97	22.00	6.78	1.06	507	0.04
IR3	1.23	8.95	43.20	33.80	14.05	0.99	423	0.07
IR4	1.05	16.50	67.10	15.73	0.67	1.09	508	0.05
IR5	1.15	18.90	70.30	9.95	0.85	1.11	515	0.04
IR6	1.17	17.30	65.83	15.90	0.97	1.09	535	0.04
IR7	1.08	11.80	54.32	26.30	7.58	1.04	495	0.08
IR8	1.09	5.53	45.38	33.90	15.19	0.98	465	0.10
IR9	1.03	16.33	63.67	19.33	0.67	1.08	526	0.03

(SAR=Shape Aspect ratio, MPD=Mean Pellets diameter)

The data for the pellets strength, low friability, spherical shape and size for pellets prepared with L-HPC LH-31 is the most suitable, hence pellets prepared using IR9 formula was best round pellet. So, composition of batch no. F9 was finalized for immediate release pellets.

Table 11 Drug release profile of ER prototype fformulations

Time (hr)	% DRUG RELEASE							
	ER1	ER2	ER3	ER4	ER5	ER6	ER7	ER8
0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	1.2	0.8	17.0	6.7	2.8	3.8	4.2	1.2
2	11.4	6.4	92.3	33.7	10.5	9.2	10.2	3.4
4	91.3	24.6	100.6	67.1	43.9	25.6	45.3	25.0
6	98.0	43.6	101.1	79.8	62.4	43.0	62.2	46.6
8	98.7	57.6	102.0	86.8	74.2	56.4	72.4	58.3
10	98.5	66.8	102.4	91.8	80.1	65.2	78.2	69.0
12	98.4	78.4	102.5	94.9	84.7	71.6	83.2	76.2
16	97.8	-	-	99.0	90.6	78.6	89.3	85.0
20	-	-	-	101	94.5	84.2	95.6	90.1
24	-	-	-	103.3	96.9	91.9	98.4	94.3
	Eudragit NE30D:Talc (21%)	EC 45 cps (9%)	EC 7 cps: HPMC 6 cps (90:10) (15%)	EC 45 cps: HPMC 6 cps (90:10) (8%)	EC 45 cps: HPMC 6 cps (90:10) (10%)	EC 45 cps: HPMC 6 cps:DBS (90:10:10) (6%)	EC 45 cps: HPMC 6 cps:DBS (85:15:10) (6%)	EC 45 cps: HPMC 6 cps:DBS (85:15:10) (8%)

ER1 : Polymer coating with Eudragit NE30D show initial bursting.
ER2 : Polymer coating with Ethyl cellulose 45 cps show initial slower release.
ER3 : Polymer coating with Ethyl cellulose 7 cps and Hypromellose show initialbursting.
ER4, ER5: Polymer coating with Ethyl cellulose 45 cps and Hypromellose controlthe initial bursting and control release profile was achieved.
ER6 : Polymer coating with 6% w/w percentage coating of Ethyl cellulose 45 cps, Hypromellose 6 cps (90:10%) and plasticizer Dibutyl sebacate (10% of total polymer) control the initial bursting and control release profile was achieved.
ER7, ER8 : Polymer coating with 6% and 8% w/w coating of Ethyl cellulose 45 cps, Hypromellose 6 cps (85:15) with plasticizer Dibutyl sebacate (10% of total polymer) control the initial bursting and control release profile was achieved.
% coating and Ratio of EC: HPMC are identified as critical quality attributes foroptimization of fformulation.
In brief, pellets prepared using 47% of L-HPC LH-31 (spheronizing agent) and 3% of Hypromellose 15 cps binder solution using extruder fitted with 1.0 mm die roller and spheronizer with 3.25 mm chequered plate. Final weight of immediate release pellets (339.42 mg) was kept constant throughout the optimization study. Polymer coating of EC45 cps and Hypromellose 6 cps (varying ratio) was done using Dibutylsebacateas (kept constant) a plasticizer by Fluid bed equipment.

Characterization of VEN Pellets

Physicochemical characterization

The bulk density and tapped density of VEN pellets were 0.569 and 0.621 g/ml, respectively. The weight variation in optimized batch of VEN pellets was 372.00±3.50mg. The spherocity of developed VEN pellets was proximal to the 1.

Surface morphology

Figure shows SEM image of VEN pellets which indicates spherical shape and smooth surface. This confirms the intactness of coating over pellets which help to prevent dose dumping.

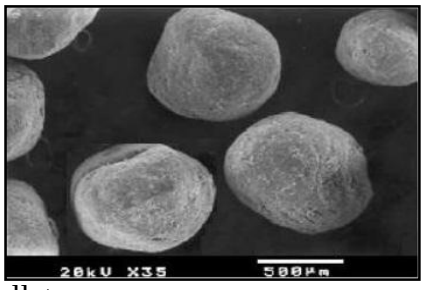

Figure 5 Morphology of VEN pellets

Hardness of VEN pellets

The result of hardness of VEN IR and ER pellets are summarized in Table.

Table 6.23 Hardness of VEN IR and ER pellets

Sample	Hardness (gm)	
	IR pellets	ER pellets

1	550	2813
2	587	3851
3	280	1928
4	910	3644
5	302	2649
Avg.	526	2977
SD	256	782
%RSD	49	26

The probe penetrates at a defined speed and measures the pellets resistance to movement in units of grams-force. Figure show the hardness data for a test that plots load on the Y-axis Vs distance traveled by the probe in a downward direction (X axis). The load increases as the probe moves downward. Figures indicate the distance between probe and base Vs Load to be applied. The downward linear curves reveals that as the distance shortens, the required load is increases. It can be clearly indicated by data that ER pellets (2977 gm) are harder than IR pellets (526 gm).

POST COMPRESSION STUDIES

VEN Pallet Tablet Evaluations

Uniformity of Weight:

The results for the uniformity of weight are tabulated in table.

Table 15. Uniformity of Weight

SSl. No.	Fformulationcode	Weight uniformity (mg)
1.	F1	341.3 ± 3.62
2.	F2	340.2 ± 3.32
3.	F3	341.9 ± 1.91
4.	F4	340.3 ± 2.16
5.	F5	343.1 ± 3.02
6.	F6	339.2 ± 2.81

Thickness of the VEN Pallet tablet

The results for the thickness of the VEN Pallet tablets are tabulated in table.

Table 16. Average thickness of the VEN Pallet tablets

SSl. No.	Fformulationcode	Thickness (mm)
1.	F1	5.98 ± 0.091
2.	F2	5.60 ± 0.067
3.	F3	5.081 ± 0.08
4.	F4	5.77 ± 0.051
5.	F5	5.75 ± 0.023
6.	F6	5.80 ± 0.053

Hardness of the VEN Pallet tablets

The results for the hardness of the VEN Pallet tablets are tabulated in Table.

Table 17. Average hardness of the VEN Pallet tablets

SSl. No.	Fformulationc	Avg.hardness (kg/cm^2)
1.	F1	8.24 ± 0.23
2.	F2	8.86 ± 0.18
3.	F3	8.63 ± 0.52
4.	F4	8.02 ± 0.09
5.	F5	8.52 ± 0.55
6.	F6	8.90 ± 0.11

Friability of the VEN Pallet tablets

The results for the friability test for the VEN Pallet tablets are tabulated in table 15.

Table 18. % Friability of the VEN Pallet tablets

SSl. No.	Fformulation code	Friability (%)
1.	F1	0.164±0.36
2.	F2	0.025±0.21
3.	F3	0.127±0.85
4.	F4	0.478±0.09
5.	F5	0.031±0.11
6.	F6	0.52±0.10

Surface pH

The results for the surface pH of the VEN Pallet tablets are tabulated in table.

Table 19.Surface pH of the VEN Pallet tablets

SSl. No.	Fformulation code	Surface pH
1	F1	6.78 ± 0.05
2	F2	6.88 ± 0.10
3	F3	7.01 ± 0.02
4	F4	6.90 ± 0.05
5	F5	6.83 ± 0.01
6	F6	6.99 ± 0.21

In vitro drug release study

The data obtained from the in vitro drug release study are represented in table for fformulations F1, F2, F3 and i table 18 for fformulation F4,F5,F6.

The in-vitro dissolution profile for the various VEN Pallet tablet fformulations is given below in Fig. 20 fo fformulation F1, F2 ,F3 and in Fig.. for fformulations F4, F5, F6**.**

Table 19 Cumulative percentage in-vitro drug release of VEN Pallet tabletfformulations F1,F2,F3

TTime (min)	F1	F2	F3
15	10.11±0.77	15.51±0.54	11.39±0.66
45	23.32±0.56	26.79±0.34	21.88±0.15
60	30.62±0.65	41.57±1.22	36.63±2.02
120	40.01±0.97	62.91±1.34	55.15±1.01
180	51.23±0.78	76.98±0.17	67.29±0.81
240	66.61±0.51	83.62±0.19	70.31±0.14
300	74.41±0.18	93.11±0.99	74.05±0.22
360	78.32±0.88	98.25±0.23	83.50± 0.12

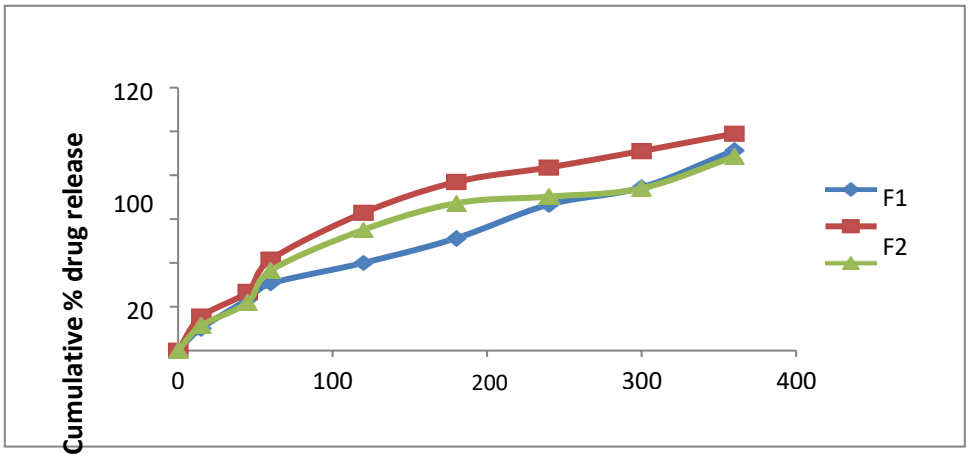

Fig. 6. In vitro dissolution profiles of VEN Pallet tablet fformulations F1 ,F2, F3

Table 20 Cumulative percentage in-vitro drug release of VEN Pallet tabletfformulations F4,F5,F6

Time (min)	F4	F5	F6
15	15.77±1.22	14.38±1.34	12.41±0.79
45	23.12±1.34	29.11±1.77	25.62±0.56
60	41.23±0.36	55.31±0.99	46.97±1.11
120	52.79±1.91	74.92±2.01	61.66±1.04
180	61.44±0.87	80.96±1.31	75.32±0.67
240	72.52±0.48	91.73±0.22	77.81±1.22
300	77.92±0.53	93.41±1.23	81.33±0.33
360	81.34±0.65	96.54±0.88	87.32±1.04

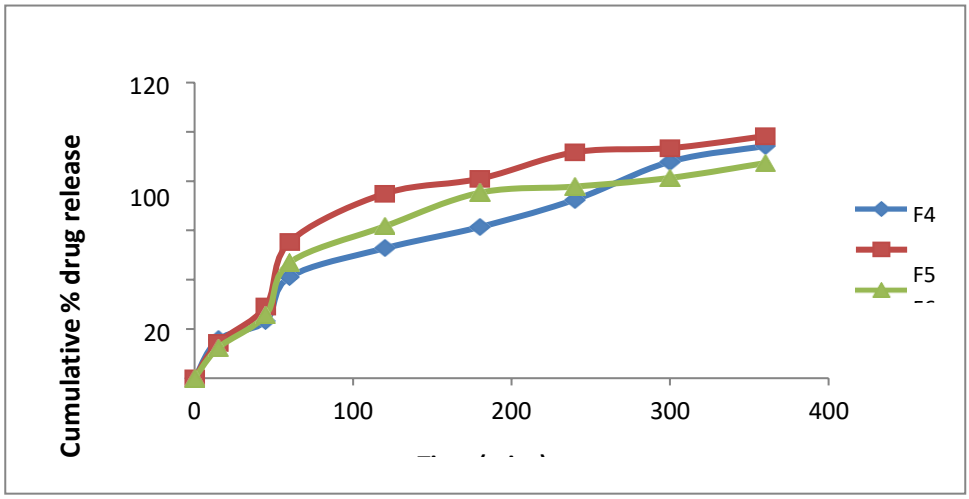

Fig. 8 In vitro dissolution profiles of VEN Pallet tablet fformulations F4, F5, F6

Ex vivo drug permeation study

The drug permeation data for the various VEN Pallet tablet fformulations is given below in table15 fo fformulation F1, F2, F3 and in table 20 for fformulations F4, F5, F6.

The ex vivo drug permeation profile for the various VEN Pallet tablet fformulations is given below in Fig for fformulation F1, F2, F3 and in Fig. for fformulations F4,F5,F6**.**

Table 21. Cumulative percentage drug permeation for VEN Pallet tabletfformulations F1, F2, F3

Time (min)	F1	F2	F3
15	8.93±1.28	11.2±1.22	7.32±1.24
45	20.13±1.45	25.42±0.56	21.01±0.63
60	29.86±1.71	31.3±0.34	30.51±1.05
120	36.23±2.04	49.71±2.01	40.13±1.12
180	47.51±2.11	66.32±1.73	56.91±0.89
240	56.31±0.66	79.52±0.77	60.91±0.67
300	68.92±0.79	83.08±0.225	79.70±0.35
360	72.63±0.71	96.63±0.23	83.55±0.78

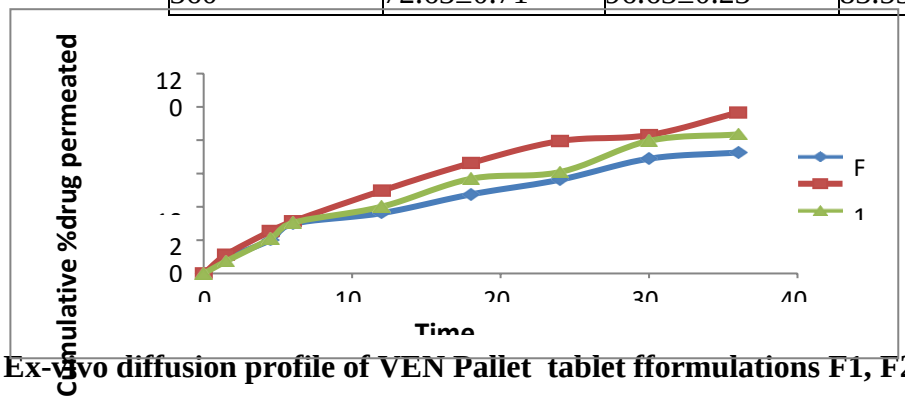

Fig. 9. Ex-vivo diffusion profile of VEN Pallet tablet fformulations F1, F2, F3

Table 22.Cumulative percentage drug permeation for tabletfformulations F4, F5,F6

Time (min)	F4	F5	F6
15	9.58±0.64	12.81±1.55	9.77±0.89
45	16.8±1.33	28.52±1.79	17.12±0.78
60	19.35±1.92	36.71±0.89	21.33±1.76
120	28.3±0.91	59.21±0.86	39.82±1.54
180	47.17±0.75	71.39±0.78	53.27±1.03
240	59.5±0.47	82.4±1.27	61.8±1.07
300	70.23±0.59	89.51±1.11	74.59±0.74
360	79.54±1.63	95.81±0.36	81.03±0.97

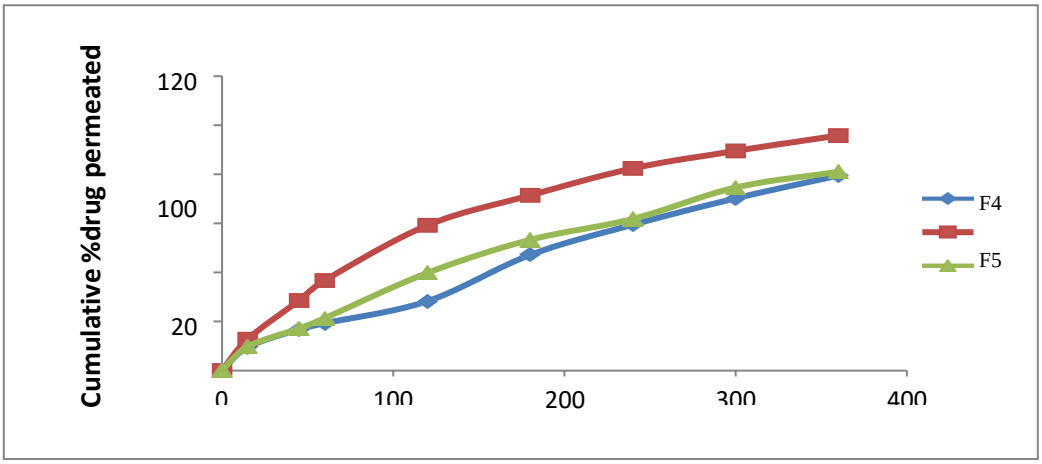

Fig. 10. Ex-vivo diffusion profile of VEN Pallet tablet fformulations F4,F5,F6

Drug release kinetics for the tablet fformulations

Out of all the prepared fformulation, F2 was selected as optimized fformulation as it gave the best results fo cumulative percentage drug release.

The drug release kinetics for the optimized fformulation (F2) was calculated and the results obtained ar represented in table 22. The zero order profile, first order profile, Higuchi profile and Korsmeyer-Peppas plot i represented in Fig. 25, 26,27 and 28 respectively.

Table 23. Release kinetics and mechanisms of VEN Pallet tablet of optimized fformulation (F4)

Fformulationc	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Hixon-Crowell (R^2)	Korsmeyer-Peppas	
					(R^2)	N
F4	0.9908	0.911	0.9835	0.799	0.9465	0.6798

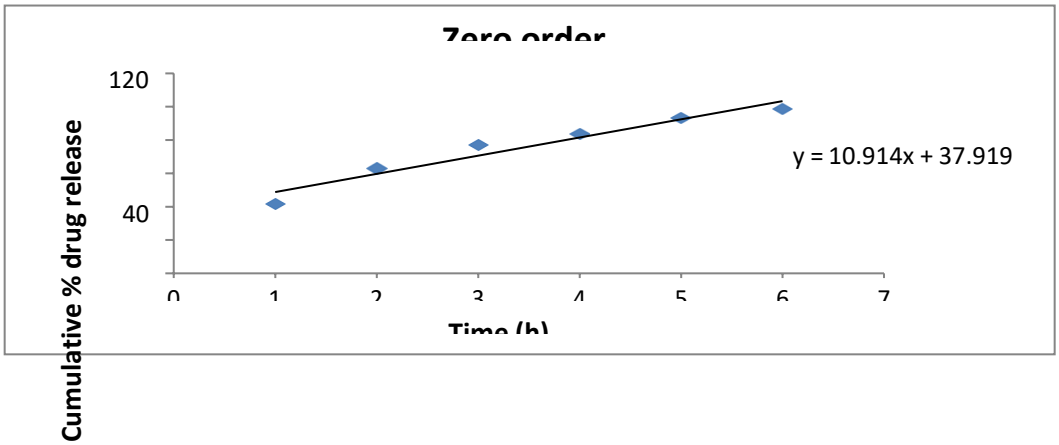

Fig. 11. Zero order profile for optimized fformulation F4

Fig. 12. First order profile for optimized fformulation F4

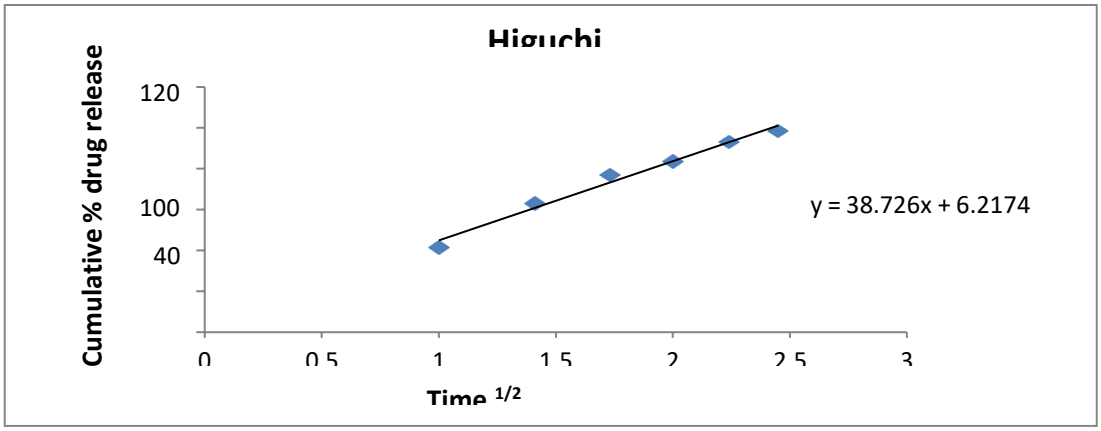

Fig. 13. Higuchi profile for optimized fformulation F4

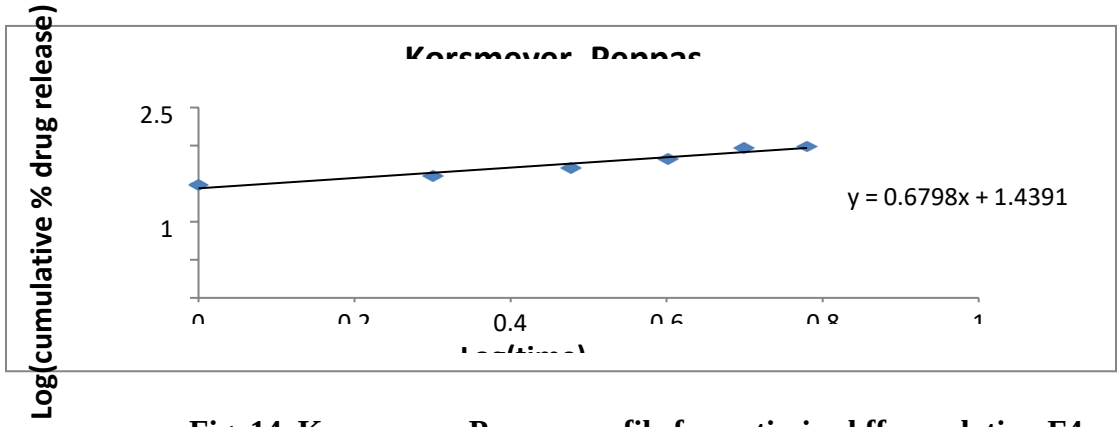

Fig. 14. Korsmeyer- Peppas profile for optimized fformulation F4

DISCUSSION

Precompressional fformulation parameters

The standard calibration of pure drug proved that VEN Pallet supplied was of pharmacopoeia standards.

From the obtained FTIR peaks it can be concluded that the physical mixture of the drug VEN Pallet does not show any major interactions with fformulation excipients.

Weight variation

Values of weight variation are found to be within the permissible limits of conventional oral tablets stated in the I.P.Weights of the tablets varied between 343.1-339.2 mg with deviation in the range of 1.91-3.62 The extreme variation could have been the result of mishandling of the tablet weights during punching process.

Thickness

The average thickness of VEN Pallet tablets is found to be quite uniform with minimum variation.

The thickness of various tablet preparation were observed in the range of 5.60mm to 5.98mm with standard deviation in the range 0.023 to 0.091.

Hardness and friability

The hardness of the prepared VEN Pallet tablet lies in the range of 5.24 to 5.02 g/cm^2 with the standard deviation in the range of 0.09 to 0.55.

Also the friability lies in the range of 0.025% to 0.520% Friability is not more than 1% for any fformulation. The hardness of VEN Pallet tablets is low, but the friability data suggests that the tablets are quite robust enough to withstand the normal handing.

Stability Studies

The stability studies of prepared fformulations revealed no significant changes in the physical parameters when stored at temperature and humidity conditions of 40 ± 2°C/75 ± 5% RH. Samples were withdrawn and retested for drug content after intervals of 7, 15, 30, 60, and 90 days. Percent drug content was found in all the prepared fformulations ranging from 95.21 ± 0.41 to 97.61 ± 0.37, indicating that no significant reduction in the content of the active drug was observed over a period of 3 months; the percent drug contained is found within a specified limit of USP. Therefore, there was no evidence of degradation of drug quantity.

SUMMARY AND CONCLUSION

From the study, it can be concluded that QbD tools have assisted development of VEN pellets. FMEA analysis screened two significant factors (% Extended release coat and % EC) affecting quality of VEN pellets. A 3^2 full factorial design has remarkably given detail information about linearity between selected variables. SEM study revealed spherical and intact shape of pellets. Role of hydrophobic polymer (EC) into extended release coat was found important as per as extended release of highly water soluble drug is concerned.

From the exhaustive study on fformulation and development of DVS pellets, it can be concluded that QbD and its tools assisted for proper development in systemic way. Role of EC was found superior than other factors for achieving desired release and coating composition was remained intact in dissolution media and also in the presence of 10% V/V alcohol. So, proposed drug delivery system can be suited best for once a day dosage regimen for DVS and similar drugs.

Moreover, drugs were found compatible with selected excipients and it was reflected in stability study as both fformulations were showed stale characteristics at the end of stability study.

So, overall it can be concluded that multiparticulate extended release delivery system (pellets with tailored release coat) is a promising design for consistent release of antidepressant drugs.

Highly water soluble compounds found in antidepressants like Venlafaxine must be packaged into delivery systems in the form of pellets in order to provide a constant and prolonged release. Self-observation, FTIR analysis, and DSC drug profiling were used in the prefformulation investigation of the drug excipients. Both medications had an analytical method (UV) established for them in various media. Extrusion and spheronization were regulated processes used to create drug-loaded pellets, which were then covered in a controlled-release coating and compacted into tablets. For the created system, physicochemical, functional, and structural characterisation were carried out. Results of prefformulation tests showed that particular medications were suitable for oral solid dosage forms. New UV techniques demonstrated required linearity with little noise. Drugs and a few excipients were discovered to be compatible. Pellet optimization was aided by the use of QbD tools such as risk assessment, screening design, and DoE. 3.3%, 26.8%, 51.9%, 74.1%, and 91.4% of the drug was released at 2, 4, 8, 12, and 20 hours from an optimised pallet filled with VEN, and 4.3%, 26.5%, 57.2%, 78.7%, and 93.3% from compressed tablets loaded with VEN, respectively. The created multiparticulate pellets compressed as tablet system for the chosen medicament yielded the desired drug release profile. So, if BCS class I medicines are added to a designed system, consistent blood plasma concentration can be anticipated.

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