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Quality by Design (Qbd) Assisted Development of Extended Release Pellets of Venlafaxine HCL

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ABSTRACT

The present study was aimed to develop extended release pellet of Venlafaxine HCL (VEN) employing different tools of Quality by Design (QbD). VEN pellets were prepared by extrusion spheronization technique with the help of L-HPC LH-31 and Hypromellose 15 cps. The pellets were further coated by extended release coating using different ratio of EC 45 cps and Hypromellose 6 cps by fluidized bed process. Based on former knowledge and preliminary experimental data, risk based assessment was done by FMEA and RPN score. For further optimization, 3^2 full factorial design (FFD) was used for choosing % EC and % coating as independent variables and % drug release at 2, 4, 8, 12 and 20 hrs as dependent variables. Results of DSC study revealed compatibility of VEN with proposed excipients. Statistical analysis and SEG revealed suitability of applied FFD. Results of physicochemical characterization of VEN pellets were in accordance with pharmacopoeia. Drug release from VEN pellets followed Weibull model. Final coating composition of VEN pellets was 8% coat and 84% EC in coating. SEM analysis showed spherical structure of pellets. Short term stability study exhibited stable features of VEN pellets. So, optimized VEN pellets were the promising approach for achieving desirable constant release upto 24 hrs and so choices of design for once a therapy.

Keywords: Venlafaxine HCL; Quality by design; Risk assessment; Extended release pellets

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INTRODUCTION

Venlafaxine Hydrochloride (VEN) is a unique antidepressant bicyclic phenyl ethylamine derivative which is structurally varies from other available antidepressants [1]. It is efficacious and tolerable as it inhibits neuronal reuptake of serotonin and norepinephrine with a less affinity for alpha-adrenergic adrenergic, muscarinic cholinergic or histaminergic receptors [2]. The steady state half-life ($t_{1/2}$) of VEN is 5 h and its prescribed daily dose is 75-225 mg/day. Thus, need of twice or thrice dosing per day cause missing of a dose and also not suitable to patients due to high dosing frequency [3]. VEN belongs to BCS class I, bearing high solubility and high permeability and freely soluble in water (572 mg/ml). These biopharmaceutical and physicochemical belongingness reveal that VEN is an idealistic candidate to formulate into ER formulation. Due to higher solubility, if VEN is not formulated judiciously, it may promptly release the drug at a quicker rate and produce a toxic concentration upon oral administration. So, it is a challenging task to develop a suitable dosage form for extended delivery of highly water soluble drug (VEN) [4].

Multi particulate drug delivery systems are the most recognized and extensively used system offering ample advantages over single unit dosage forms. Advantages include better bioavailability because of enhanced surface area, less inter subject variation, more uniform and inevitable distribution and transportation with less chances of dose dumping [5-7].

Additionally, film coating is a vernacular operation to change drug release pattern. When this approach it applied to pellets, they further show well control on drug release and also assist to deliver drug in predetermined way and accordingly meliorate therapeutic effects. In case of coated pellets, drug release pattern can be tailored by optimizing thickness of coat and composition [8].

Therefore, design of pellets necessitates many processing steps and quality of pellets also relies on process and formulation variables causing the entire process complex. So, the traditional approach of formulation development (trial and error) is hopeless and faulty when preparation of ER pellet of highly water soluble drug is concerned. To defeat traditional approach, now a days Quality by Design (QbD) approach is widely used which helps to optimize formulation make-up, design process and to infer the route cause and effect relationship. Therefore, present work was aimed to develop VEN ER pellets with objectives of patient compliance, streamline drug release and errorless quality using principles of QBD [risk assessment (RM) and Design of Experiments (DoE)] [9].

MATERIALS AND METHODS

Drug-Excipient Interaction Studies

The possibility of drug-excipient interactions was studied by differential scanning calorimetry (DSC; TA-60WS, Shimadzu, Japan). The results of compatibility of pure drug (VEN) with proposed excipients (EC, Hypromellose, L-HPC LH-31) were graphically recorded by DSC thermographs. The samples were individually locked in aluminium cells and put in a thermal analyzer. The thermal analysis was carried out in a nitrogen atmosphere across a temperature range of 30°C to 300°C.

Formulation and Optimization of VEN Pellets

Application of QbD principles:

To acquire formulation of VEN pellets with desired quality various tools of QbD were applied in the development phase. In the following section QbD application is elaborated.

Risk assessment:

Fish-bone diagram (Ishikawa diagram) was used to find the possible risks and important causes. Failure mode and effect analysis (FMEA) was applied considering pre information and initial experimental data. Individual significant failure component was ranked based on probability (P), severity (S), and detectability (D). The product of R, P and N is known as Risk Priority Number (RPN) and it was accounted which showed overall risk magnitude. The ranking of RPN terms were assigned with proper justification. The rank of severity was allotted as, no impact (1), low impact (2), moderate impact (3) and high impact (4). The rank of detectability was allotted as ever time detection (1), almost time detection (2), sometimes detection (3), rare case detection (4) and no detection (5). Similarly, the rank of probability was assigned as no failure (1), rare failure (2), sometimes failure (3), almost failure (4) and each time failure (5). The possibility of high RPN rank is 100, showing all three terms at extreme level and that was considered as significant critical factor affecting the quality of VEN pellets.

Optimization of VEN pellets employing DoE (3^2full factorial design; FFD):

Following multilinear regression model representing main, interactive and polynomial term was wont to estimate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the response and b_0 is the arithmetic average of adjudicated runs, and b_i is the counted coefficient for the factor X_i. The individual effects independent variables (X_1 and X2) illustrate the arbitrate result of altering one factor at a time amongst range of minimum to maximum. The fundamental interaction term (product of independent variables; X_1X_2) exposes how the response changes when some variables are altered at the same time. The multinomial terms (exponential relation; X_1^2 and X_2^2) are accommodated in equation to look into non-linearity. A 3^2 full factorial design was fitted to optimize the variables. Experimental runs were executed at all nine potential combinations for two factors and individually at 3 levels. Independent variables include percentage coating (X_1) and % of EC in coating component (X_2) whereas accumulative % drug release after 2, 4, 8, 12 and 20 hrs were defined as responses.

$$(Y_1\ (Q_{2hrs}\text{-}\%),\ Y_2\ (Q_{4hrs}\text{-}\%),\ Y_3\ (Q_{8hrs}\text{-}\%),\ Y_4\ (Q_{12\text{-}hrs}\text{-}\%) \text{ and } Y_5(Q_{20hrs}\text{-}\%))$$

The FFD layout (composition of FFD batches V1 to V9) is exposed in Table 1.

Table 1: Layout of 3^2 full factorial designs

Batch	Independent Variables	
	% Coating (X_1)	**% EC in coating (X_2)**
V1	6 (-1)	80 (-1)
V2	8 (0)	80 (-1)
V3	10 (+1)	80 (-1)
V4	6 (-1)	85 (0)
V5	8 (0)	85 (0)
V6	10 (+1)	85 (0)
V7	6 (-1)	90 (+1)
V8	8 (0)	90 (+1)
V9	10 (+1)	90 (+1)
	Dependent variable/Response	**Constraints**
Y_1	% Release at 2 hrs (Q_{2hrs})	Not more than 10%
Y_2	% Release at 4 hrs (Q_{4hrs})	Not more than 30%
Y_3	% Release at 8 hrs (Q_{8hrs})	40% to 70%
Y_4	% Release at 12 hrs (Q_{12hrs})	60% to 90%
Y_5	% Release at 20 hrs (Q_{20hrs})	Not Less than 80%

Validation of FFD:

The imposed factorial design was corroborated by standard error graph (SEG), which is a plot manifesting the error of prediction for areas in the design space (DS). For satisfactory criterion this plots to have comparatively low standard error (about 1.0 or less) across the region in DS. [10].

Verification tests of model:

To assert the accuracy and robustness of the developed model, two unlike combinations were preferred at different levels of the chose factors within DS. These batches (check point) were examined and further equated the found responses with the expected [11].

Preparation of VEN pellets:

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 Dibutyl sebacate as a plasticizer by Fluid bed equipment. The detail composition of VEN pellets is shown in Table 2.

Table 2: Composition of VEN pellets

Sr. No.	Ingredients	Quantity per capsule (mg)
Core pellet		
1	Venlafaxine HCL eq. to Venlafaxine 150 mg	169.71
2	Low Substituted HPC (L-HPC LH-31)	159.53
3	Hypromellose 15 cps	10.18
4	Purified Water	q.s.
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	Dichloro Methane	q.s
9	Methyl Alcohol	q.s.
Lubrication		
10	Talc	1%

Characterization of VEN Pellets

Physicochemical characterization [12]:

Density and filling of pellets into capsules: The final batch of VEN pellets were submitted for checking bulk density and finally packed into HGC (size 0) using automated capsule filling machine.

Weight variation: Capsules (10) containing pellets were weighed and the pellets were removed. The capsule body and cap were singly weighed and weight variation was found.

Lock length: The lock length was found using digital Vernier calipers and average of 10 capsules was noted.

Friability and spherocity: Friability tester (CS-2, Tianjin, China) was used to find friability. The % weight of loss was computed using following formula.

$$F\ (\%) = \frac{Wo - W}{Wo} * \ 100$$

Where, Wo is the initial weight of pellets and W is the weight of pellets remained after testing (n=3).

The sphericity of the pellets was reckoned using one-plane-critical-stability (OPCS) [13]. OPCS is the angle encased between a horizontal plane and a slanted plane producing maximum stability staying on that plane.

***In vitro* Drug Release Study [14]**

Calibrated USP dissolution test apparatus I (Electrolab, Model TDT 06-T, India) was used for *in vitro* dissolution study in purified water for 24 hrs at 100 rpm at a temperature of 37 ± 0.5°C throughout the study. Samples (10 mL) were drawn back. Quantification of drug was done by UV spectrophotometric method at 226 nm. Fresh dissolution medium (10 mL) was added after each sampling to conserve the fixed volume of dissolution media (900 mL) (n=3).

Drug Release Kinetics

In vitro drug release data were charged into DD Solver software to understand the mechanism of drug release from developed pellets. The model showing least SSR and Fisher's ratio (F) with maximum R^2 was considered as best fit [15].

Surface Morphology

VEN pellets were sputtered with gold palladium and then observed with a scanning electron microscope (SEM) Philips ESEM XL 30 FEG at a voltage of 5 and 10 KV.

Stability Studies

Accelerated stability studies as per ICH guidelines for developed pellets was carried out in stability chambers for (40 ± 2°C and 75 ± 5% RH; 3 months). Samples were taken out at 1, 2 and 3 months and evaluated [16].

RESULTS AND DISCUSSION

Drug Excipients Study

Figure 1 indicates the DSC thermograms of VEN and VEN + excipients. This showed intense endothermic peak at 217-219°C representing to melting of the VEN. Thus, VEN is compatible with the proposed excipients and so for further study these excipients were enrolled.

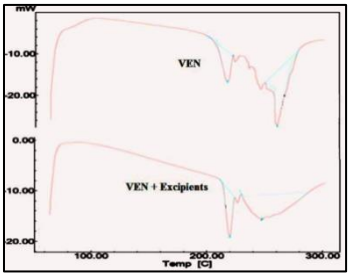


Figure 1: DSC spectra of VEN and VEN + Excipients

Defining QTPP and CQAs for VEN Pellets

QTPP for VEN pellets are depicted in Table 3. The CQAs for pellets were confirmed from prior art and preliminary experiments i.e. % drug release at different time interval (i.e. 2, 4, 8, 12 and 20 hrs) [17].

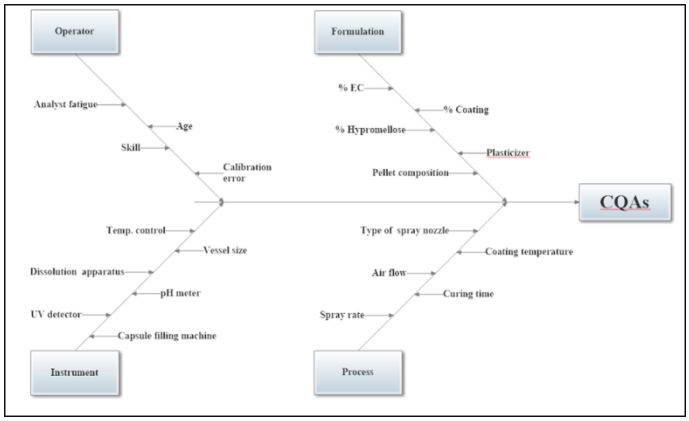
Table 3: QTPP for VEN pellets

Attribute	QTPP
Final Dosage form	Capsule
Type of core content	Pellets (ER)
Route of administration	Oral
Appearance	Spherical shape
Strength	150 mg
In vitro release	% drug release at 2, 4, 8, 12 and 20 hrs: NMT 10%, 30%, 40-70%, 60-90% and NLT 80% respectively
Friability	<1.0%
Impurity	Below safety threshold
Assay	Acceptable limit
Content uniformity	Acceptable limit

Risk Assessment

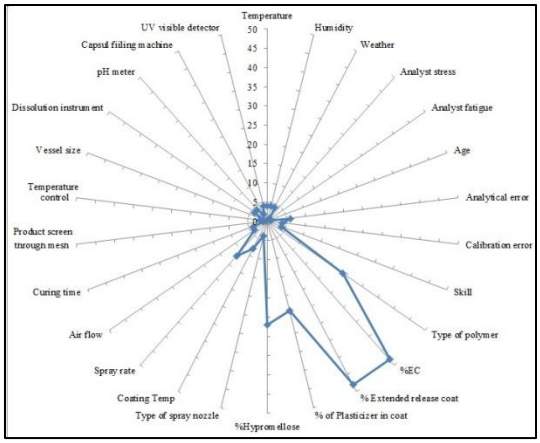
To distinguish likely high risk factors looking quality of the pellets, a fish bone diagram (Ishikawa diagram) was constructed as per ICH Q8 R2 guideline (Figure 2). From detail analysis of entire manufacturing process of VEN pellets, four main causes as shown in Figure 2 were listed.

Figure 2: Ishikawa diagram portraying factors that may effect on the CQAs of VEN pellets



High risk variables were considered those having RPN>35 and form Figure 3 they were screened i.e. % coating and % EC in coat composition. Further, FFD was enforced for detail study on selected factors.

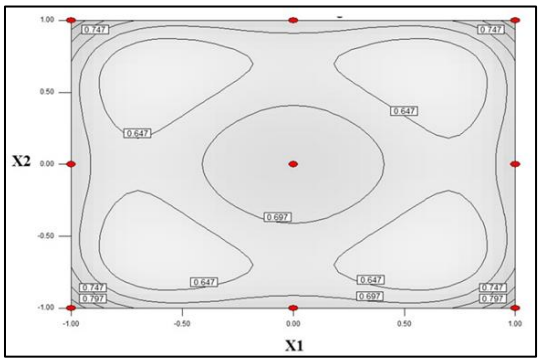
Figure 3: SeDeM diagram showing RPN score



Validation of FFD

The standard error graph (SSG) of applied FFD in shown in Figure 4. From Figure 4 it can be easily read out that standard error is 0.697 speculating efficacious anticipation power of employed FFD.

Figure 4: Standard error graph of applied FFD



Application of FFD

The ANOVA analysis of selected dependent and independent variables is shown in Table 4. Further investigation was not done on non-significant terms. The interaction effect (X_1X_2) was found significant for Y5 only out of selected five responses; this is attributed due to strong effect of both factors on dissolution at last hrs.

Table 4: ANOVA analysis of applied FFD

Source	Sum of square	D.f.	Mean square	F value	P-value	Comment
For Y_1 (Q_{2hrs} - %)						
Model	166.13	5	33.23	35.94	0.007	S
X_1	76.33	1	76.33	82.56	0.0028	S
X_2	63.38	1	63.38	68.55	0.0037	S
X_1X_2	1	1	1	1.08	0.3748	NS
X_1^2	21.78	1	21.78	23.56	0.0167	S
X_2^2	3.65	1	3.65	3.94	0.1413	NS
Residual	2.77	3	0.92	-	-	-
For Y_2 (Q_{4hrs} - %)						
Model	1808.78	2	904.39	22.91	0.0016	S
X_1	1238.41	1	1238.41	31.37	0.0014	S
X_2	570.38	1	570.38	14.45	0.009	S
Residual	236.88	6	39.48	-	-	-
For Y3 (Q8hrs - %)						
Model	3434.96	2	1717.48	23.86	0.0014	S
X_1	1911.74	1	1911.74	26.56	0.0021	S
X_2	1523.23	1	1523.23	21.16	0.0037	S
Residual	431.92	6	71.99	-	-	-
For Y_4 (Q_{12hrs} - %)						
Model	2597.86	2	1298.93	13.76	0.0057	S
X_1	1229.8	1	1229.8	13.03	0.0112	S
X_2	1368.06	1	1368.06	14.49	0.0089	S
Residual	566.36	6	94.39	-	-	-
For Y_5 (Q_{20hrs} - %)						
Model	2112.93	5	422.59	30.01	0.0092	S
X_1	669.93	1	669.93	47.57	0.0062	S
X_2	945.02	1	945.02	67.1	0.0038	S
X_1X_2	186.32	1	186.32	13.23	0.0358	S
X_1^2	8.27	1	8.27	0.59	0.4993	NS
X_2^2	303.4	1	303.4	21.54	0.0188	S
Residual	42.25	3	14.08	-	-	-

Note: S = Significant; NS = Non-Significant

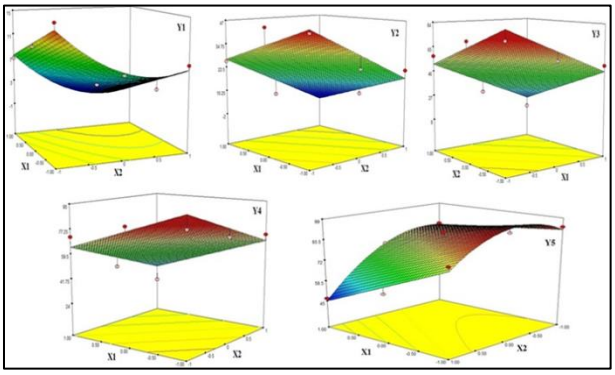
Moreover, based on the significant terms in selected model, MLR equations were evolved. In Table 5, reduced model equations are shown which may assist to predict the response based on linear relation.

Table 5: MLR equation (reduced model)

Responses	MLR equation (reduced model)
Y1	+2.93 - 3.57X1 - 3.25X2 + 3.30X12
Y2	+22.23 - 14.37X1 - 9.75X2
Y3	+49.70 - 17.85X1 - 15.93X2
Y4	+65.37 - 14.32X1 - 15.10X2
Y5	+86.11 -10.57X1 -12.55X2 -6.83X1X2 - 12.32X22

So, from MLR equations (Y_1-Y_5), it can be expected that selection of X_1 and X_2 is appropriate as they are present in all reduced MLR equations. The interactive term (X_1X_2) is present only in Y_5 in showing significant effect at later stages. Polynomial terms were present in MLR equation of Y_1 and Y_2 showing effect in first and last hrs of dissolution. The relation of dependent and independent variables is presented in Figure 5 (response surface plots). They indicate decrease in percentage drug release with increasing percentage coating and percentage of EC and increase in percentage drug release with decreasing percentage coating and percentage of EC.

Figure 5: Response surface plots of selected responses



Confirmation Tests of Model

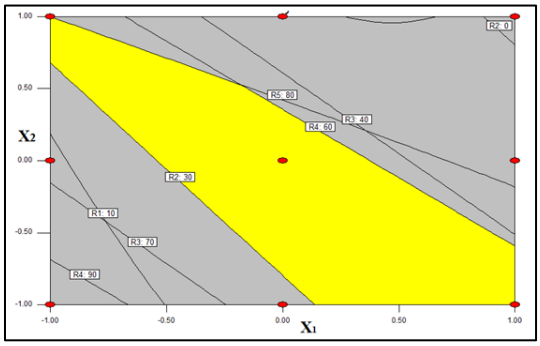
Check-point batches V10 and V11 (within design space) were formulated to confirm pertinence of acquired reduced MLR equations. The predicted and experimental responses of Y_1(%), Y_2(%), Y_3(%), Y_4(%) and Y_5(%) for batch V10 and V11 are depicted in Table 6. The percentage error value indicates that mathematical models obtained from 3^2 full factorial design was well fitted and hence the results affirmed predictive potency of the developed MLR equations. Based on the desirable results of *in vitro* drug release from batch V11 was finalized as an optimized batch comforting predetermined standards in terms of % drug release at 2, 4, 8, 12 and 20 hrs.

Table 6: Predicted and observed responses with % error (Check point batches)

Batch code	V10			V11		
Responses	**Predicted**	**observed**	**% Error**	**Predicted**	**observed**	**% Error**
Y_1 (Q_{2hrs}-%)	4.3	4.5	4.7	3.6	3.8	5.6
Y_2 (Q_{4hrs}-%)	20.9	21.8	4.3	24.2	25.2	4.1
Y_3 (Q_{8hrs}-%)	50.3	52.5	4.4	52.9	54.8	3.6
Y_4 (Q_{12hrs}-%)	67.3	70	4	68.4	71.3	4.2
Y_5 (Q_{20hrs}-%)	86.5	90.2	4.3	88.1	89.5	1.6

Overlay contour plot depicting dark region of interest is portrayed in Figure 6. The desirable range of the independent variable (factors) were restricted to 6 to 10% for X_1 and 80 to 90% for X_2, whereas desirable responses were restricted to NMT 10% for Y_1, NMT 30% for Y_2, 40 to 70% for Y_3, 60 to 90% for Y_4 and NLT 80% for Y_5.

Figure 6: Overlay plot



Characterization of VEN Pellets

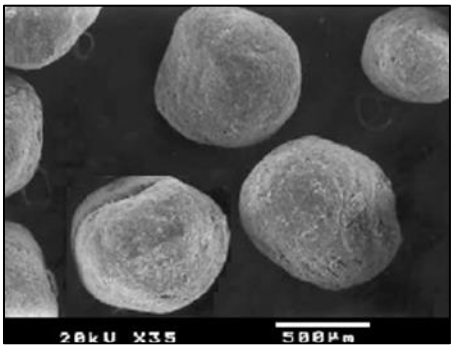
Physicochemical characterization:

Optimized VEN pellets showed bulk density (0.569 g/ml) and tapped density (0.621 g/ml). For size 0 capsule lock length value was 21.40 mm. The weight variation in optimized batch of VEN pellets was 372.15 ± 3.50 mg. The spherocity of developed VEN pellets was proximal to the 1.

Surface morphology:

Figure 7 shows SEM image of VEN pellets which indicates spherical shape and smooth surface. This affirms the intactness of coating over pellets which help to prevent dose dumping.

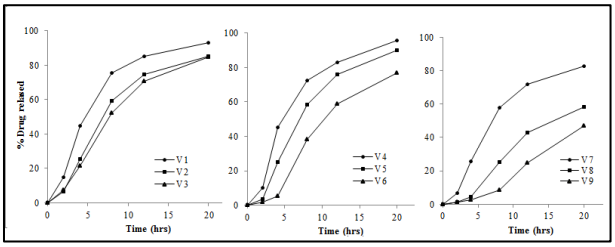
Figure 7: SEM image of VEN pellets



In vitro drug release:

Figure 8 indicates dissolution profiles of VEN pellets. Independent variables have strong effect on drug release as all profiles were significantly differ amongst each other.

Figure 8: Drug release profiles of FFD batches of VEN pellets



To compliance with recent FDA guideline, dissolution profile of developed pellet was also executed in dissolution media in presence of 10% alcohol. The similarity of these profiles was confirmed as f_2 value was 80.34±1.06. This infers that pellets success is not deviated in presence of alcohol.

Drug release kinetics study:

Table 7 depicts drug release kinetics model data. Out of selected model, Weibull model was best fitted to the drug release data of VEN pellets as it shows highest R^2 and least SSR and F value. The mechanism of drug release is anomalous transport as the value of drug release exponent (n) is 0.695.

Table 7: Results of drug release kinetics

Model	V11		
	R^2	SSR	F value
Zero Order	0.983	220.81	22.01
First Order	0.9713	373.06	37.31
Higuchi	0.9127	1137.39	113.44
Korsmeyer-Peppas	0.9492	593.52	65.95
Hixson-Crowell	0.983	220.81	22.08
Weibull	0.9985	15.524	1.94

Stability Study

Stable characteristics after specified stability testing time was observed in developed formulation of VEN pellets (V11). Table 8 presents the results of the stability study.

Table 8: Results of stability study (V11)

Parameters	V11			
	Initial	1 month	2 months	3 months
Assay (%)	98.12 ± 0.056	99.41 ± 0.022	101.35 ± 0.022	98.77 ± 0.034
Physical degradation	No	No	No	No
% Drug release after 2 hrs	3.8 ± 0.23	3.9 ± 0.15	3.7 ± 0.31	3.3 ± 0.28
% Drug release after 4 hrs	25.2 ± 1.32	25.0 ± 1.26	24.3 ± 1.14	24.7 ± 2.04
% Drug release after 8 hrs	54.8 ± 2.12	54.3 ± 3.14	53.9 ± 2.61	53.7 ± 2.48
% Drug release after 12 hrs	71.3 ± 2.57	71.6 ± 2.41	72.4 ± 3.17	72.5 ± 2.19
% Drug release after 20 hrs	89.50 ± 3.05	84.12 ± 2.11	80.64 ± 2.04	86.37 ± 2.47

CONCLUSION

In a nutshell, it can be concluded that, QbD approach have aided development of VEN pellets. FMEA analysis riddled two significant factors (% Extended release coat and % EC) affecting quality of VEN pellets. 3^2 full factorial design has outstandingly given detail information about linearity between selected variables. The physical intactness of developed pellets was witnessed by SEM study. Role of hydrophilic polymer (EC) into extended release coat was found important as per as extended release of highly water soluble drug is concerned.

REFERENCES

[1] MW Mandoki; MR Tapia; MA Tapia; GS Sumner; JL Parker. *Psychopharmacol Bull*. **1997,** 33(1), 149.
[2] EA Muth; JA Moyer; JT Haskins; TH Andree; G Husbands. *Drug Dev Res*. **1991,** 23(2), 191-199.
[3] K Tripathi: Essentials of medical pharmacology, JP Medical Ltd; **2013**.
[4] SN Makhija; PR Vavia. *Eur J Pharm Biopharm*. **2002,** 54(1), 9-15.
[5] N Follonier; E Doelker. *STP Pharma Sci.* **1992,** 2(2), 141-158.
[6] A Vial-Bernasconi; E Doelker; P Buri. *STP Pharma Sci.* **1988**, 4, 397-409.
[7] N Dey; S Majumdar; M Rao. *Trop J Pharm Res*. **2008**, 7(3), 1067-1075.
[8] Y Liu; Y Sun; J Sun; N Zhao; M Sun; Z He. *Int J Pharm*. **2012**, 426(1), 21-28.
[9] XY Lawrence. *Pharm Res*. **2008**, 25(4), 781-791.
[10] PB Parejiya; BS Barot; HK Patel; PK Shelat; A Shukla. *Drug Dev Ind Pharm*. **2013**, 39(11), 1851-1863.
[11] AS Rathore; A Saleki-Gerhardt; SH Montgomery; SM Tyler. *Bio Pharm Int*. **2009**, 26(8).
[12] I Pharmacopoeia. *Worldwide Book Service*, **2014.**
[13] AM Bouwman; JC Bosma; P Vonk; JHA Wesselingh; HW Frijlink. *Powder Technol*. **2004,** 146(1), 66-72.
[14] UP XXII; N XVII. *Rockville Md.* **1990,** 1788-1789.
[15] PB Parejiya; BS Barot; HK Patel; PK Shelat; AK Shukla. *Drug Deliv Lett*. **2012,** 2(1), 35-45.
[16] S Bajaj; D Singla; N Sakhuja. *J Appl Pharm Sci*. **2012,** 2(3), 129-138.
[17] S Kan; J Lu; J Liu; J Wang; Y Zhao. *Asian J Pharmaceut Sci Tech.* **2014,** 9(5), 268-278.