Research Article

Design and Development of Extended Release Pellets Delivery of Desvenlafaxine by Employing Principles of Quality by Design

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ABSTRACT

Desvenlafaxine succinate (DV) is one of several serotonin-norepinephrine reuptake inhibitors (SNRIs). Present study was attempted to formulate extended release pellets of DV. The pellets were prepared by extrusion spheronization technique and appropriate extended release coating was applied by fluidized bed coater. Various principles of QbD (i.e. QTPP assessment, Risk estimation matrix, screening design, factorial design) were applied for optimization. In coating composition, % weight gain and % EC were selected as independent variables and % drug release at 2, 4, 8, 12 and 20 hrs were constrained as responses. The drug was found compatible with proposed excipients and proved by FTIR and DSC study. Quantification of DV was done at 224 nm by UV spectrophotometry method. Results of physicochemical study revealed pharmacopoeial compliance of DV pellets. Drug release kinetics study revealed that drug release profile fitted best to Weibull model. The intactness of coating on pellets was checked by SEM and found appropriate. Results of short term stability study of DV pellets confirmed physical and chemical stability. Thus, it can be concluded that developed formulation of ER pellets can be established for prognosticating approach for once a day dosing of DV for continuous release in treatment of depression.

Keywords: Desvenlafaxine, Pellets, QbD, Placket burman design.

INTRODUCTION

Desvenlafaxine (DV) is the major active metabolite of the third generation anti-depressant venlafaxine, which is comparable to venlafaxine in efficacy, but arouses lesser side effects (Coleman et al., 2012). DV was approved by the Food and Drug Administration (FDA) in 2008 for use in major depressive disorder (MDD). Its efficacy has been found for other conditions also including anxiety, neuropathic pain and menopause symptoms. Looking to its mechanism of action, it acts like SNRI but reveals a differential serotonergic and noradrenergic activity profile. DV has proven efficacy for the treatment of MDD in clinical trials with doses ranging from 50 to 400 mg/day. DV is advantageous over other SNRIs due to its simple metabolism, less chances of interaction with drugs and no need for dose titration.[1]

Due to weakly basic moiety, DV freely dissolves in gastric media fluids and is remarkably absorbed upon oral administration. Subsequently, this overdraws its side effects. Indeed, this highlights the need to prepare extended release of DV formulations to increase the compliance of patients suffering from depressive disorder and decrease side effects compared to the immediate release formulation.[2]

DV has low plasma protein binding (30%) and is independent of drug plasma concentration. It is mainly metabolized by conjugation and to a minor extent via through oxidative pathway. The single-dose PK of DV is linear and proportional to dose in the ranging from 50 to 600 mg per day.[3]

Many scientists have contributed in development of extended release formulations of DV. In similar line, Wael Samy et al have designed hybrid polymeric matrices and achieved a controllable release profile of DV employing Methocel, Maltodextrin and Sodium carboxy methylcellulose (SCMC).[2] Payghan et al developed extended release controlled release matrix tablet of DV by melt granulation technique employing lipidic excipients (Compritol 888 ATO, Precirol ATO 5 and Hydrogenated castor oil).[4]

Currently, in pharmaceutical industries, pellets have been extensively looked into to develop modified release oral formulations that release the drug in GIT at desired rates. Comparative to single unit dosage from, pellets are technically more complicated to manufacture, but it possess a significant advantages including the better drug absorption, low plasma fluctuation due to even distribution at the site. Pellets are more insusceptible to dose dumping and can be tailored to obtain customized release profiles varying coating, composition and combination. Moreover, availability of sophisticated technology including fluidized bed coater, extrusion spheronization and other automated versions of equipment made formulation of pellets based preparations easy.[5]

The complexity of pharmaceutical operations can be simplified if carried out in scientifically and rationalized way. Application of Quality by Design (QbD) approach to

the development of pharmaceutical formulation returns lot many advantages including minimum trials, assured quality, minimum risk, consistent reproducibility and less rejection and recall of batch.[6-8] So, in the present study extended release pellets are prepared using different principles of QbD tools.

MATERIALS AND METHODS

Materials

Desvenlafaxine was obtained from Zydus Cadila Healthcare Ltd (Gujarat, India). Ethyl cellulose was obtained from The Dow Chemical's Co. Ltd (Europe). Low Substituted HPC (L-HPC LH-31) and Hypromellose 15 cps were received from Shin-Etsu Chemical Co. Ltd. (Japan). Dibutyl Sebacate was received from Vertellus Performance Materials Inc (USA) and Dichloro Methane was purchased from Finar Chemical Ltd (India). Empty hard gelatin capsules (size 0) were used as received from ACG (India). All other chemicals used in experiments were of analytical grade and were used as such. Ultrapure water (Milli-Q® Integral system, Billerica, MA) was used wherever needed.

Methods

Quantification of DV

Double-beam UV spectrophotometer (Shimadzu-1800, Kyoto, Japan) was utilized for drug analysis. A known amount of DV was taken and dissolved in the dissolution media (0.9% NaCl in water) and analyzed at 224 nm. Standard concentrations in the Beer-Lambert's range of 5-40 µg/mL were prepared and used further for study. Linearity test was applied to attest the standard curve.[9]

Drug excipients compatibility study [10, 11]

Differential scanning calorimetry (DSC; TA-60WS, Shimadzu, Japan) was employed to assess the possibility of interaction of drug (DV) with selected excipients (EC, Hypromellose, L-HPC LH-31) and DSC thermographs were recorded to ascertain the significance of interaction. The samples were singly sealed in aluminium cells and placed in a thermal analyzer. The study was executed in the temperature range of 30°C to 300°C (heating rate of 10°C/minute). FTIR study was performed for drug and physical mixture of drug with above said excipients. The study was run in the range of 4000-400 cm^{-1} wave numbers.

Application of QbD tools

To achieve extended release formulation of DV in the form of pellets with predetermined specification, different QbD principles including defining QTPP and CQAs, risk estimation matrix, screening design and factorial design were employed and are discussed in following section.

Specifying the QTPP and CQAs

Specifying QTPP is the initiative for QbD assisted formulation development of DV ER pellets which delineates the succinct of prime characteristics of the drug product to accomplish safe, efficacious and regulatory compliance dosage form for desired administration. For specifying QTPP, various critical quality attributes (CQAs) were distinguished. The summary of elements of QTPP for development of DV ER pellets is presented in Table 1, whereas Table 2 reveals the justification of individual CQA.

Table 1: Quality Target Product Profile (QTPP) for DV ER pellets

No.	QTPP Elements	Target	Justification
1	Dosage form	Capsule	Suitable dosage form to carry pellets
2	Dosage design	Sustained release	Necessary for desired plasma concentration
3	Route of administration	Oral	Patient compliance route and mode for best action
4	Dosage strength	100 mg	Pharmaceutical equivalence requirement
5	Stability	Minimum 24-month shelf-life at room temperature	For better action till shelf life
6	Assay	In acceptable limit	To compliance under regulatory authority
7	Content Uniformity	In acceptable limit	To compliance under regulatory authority
8	Dissolution	% release at 2 hrs NMT 10% % release at 4 hrs NMT 30% % release at 8 hrs: 40% - 70% % release at 12 hrs: 60% - 90% % release at 20 hrs: NLT 80%	To achieve desired *in vivo* performance
9	Degradation Products	Below safety threshold	To compliance under regulatory authority
10	Microbial Limits	Under limit	For microbial stability
11	Residual Solvents	Below safety threshold	For better safety to patient
12	Packaging	Strip	To attain wanted shelf-life and promising stability
13	Alternative methods of administration	None	Not practicable other than oral

Drafting of Risk Estimation Matrix (REM)

The risk assessment studies were carried out to identify the critical material attributes (CMAs) and/or critical process parameters (CPPs). Preliminary studies were carried out to find out CMAs/ CPPs with high risk by constructing the risk estimation matrix (REM) for

qualitative analysis of risk by assigning low, medium and high risk levels to each material attributes and/or process parameters.[8]

Table 2: Critical Quality Attributes (CQAs) of DV ER pellets (100 mg)

No.	Quality Attributes of the Drug Product	Target	Is this a CQA?	Justification
1	Appearance	Color and shape acceptable to the patient.	No	General appearance is not directly linked with safety and efficacy profile of drug. So, it is not critical. It is only for patient acceptance.
2	Odor	No unpleasant odor	No	Odor is not directly related with efficacy and safety but it has great impact on patient acceptance.
3	Friability	Less than 1.0% w/w	No	It is routine parameter which may affect the rigidity of pellet structure and not directly related with safety and efficacy.
4	Assay	100% w/w of label claim	Yes*	Dose fluctuation in formulation may affect efficacy of drug. Should be monitored at IPQC level of formulation.
5	Content Uniformity (CU)	Comply compendia limit	Yes*	Each pellet should have even drug content to prevent fluctuation in recommended dosing.
6	Dissolution	% release at 2 hrs: NMT 10% % release at 4 hrs: NMT 30% % release at 8 hrs: 40% -70% % release at 12 hrs: 60% - 90% % release at 20 hrs: NLT 80%	Yes	Compliance to dissolution specification can impact bioavailability. The dissolution profile of RLD should be matched with developed formulation for approval of product. This can be affected by formulation and process variables. So, this CQA is considered as important factor for quality and efficacy point of view.
7	Degradation Products	Below threshold limit and no any unknown impurity (As per RLD)	Yes*	Impurity due to degradation pathway may affect safety of product which should be similar to RLD and thus the level should be monitored through F&D.
8	Residual Solvents	Not beyond permissible limit	Yes*	No toxic solvent should be present in the final formulation considering safety. Stringent monitoring should be done during F&D.
9	Water Content	Under permissible limit	No	In general, water content may promote instability and bacterial growth in formulation. Though DV is not water sensitive this is not a CQA.
10	Microbial Limits	Meets relevant pharmacopoeia criteria	Yes*	To prevent further microbial growth and final stability of formulation.

Screening of factors by Plackett Burman design (PBD)

Considering the outcome of risk estimation matrix, Plackett Burman design (PBD) was employed further to screen important factors influencing CQAs. The screening design was applied with each factor evaluated at high (+1) and low (-1) levels. The low and high level was arbitrary selected as per the prior knowledge and preliminary study.[12] (Variables: - A: % coating, B: % EC in coat, C: % of plasticizer, D: Spray rate, E: Curing time, F: Atomizing pressure, Responses:-% drug released at 20 hrs,-1: Low level, +1: High level)

Application of full factorial design (FFD)

Based on the outcome of PBD, significant factors were further exhaustively studied by applying full factorial design. The detail of independent variables, level of selected independent variables, dependents variables (responses) with desired criteria (constrains) are summarized in Table 3.[13]

Validation of model

The imposed FFD was validated by standard error graph (SEG). Standard error graph is a contour plot showing the standard error of expectation for areas in the design space (DS). For acceptable measure this plots to have

relatively low standard error (approximately 1.0 or lower) intersections the region of concern.[14]

Confirmation of model

To assert the truth and cogency of the model, two unlike combinations were preferred at different levels of the picked out factors inside design space (DS). These trials (check point) were examined and further compared the observed responses with the expected.

Table 3: Effect of Independent variable on dependent variable by 3^2 full factorial design

Formulation Batch code	Independent variable	
	X_1-% coating	X_2- % of EC in EC/Hypromellose
D1	6 (-1)	80 (-1)
D2	8 (0)	80 (-1)
D3	10 (+1)	80 (-1)
D4	6 (-1)	85 (0)
D5	8 (0)	85 (0)
D6	10 (+1)	85 (0)
D7	6 (-1)	90 (+1)
D8	8 (0)	90 (+1)
D9	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%

Table 4: Composition of DV pellets

Sr. No.	Ingredients	Quantity per capsule (mg)	Quantity (%w/w)
Core Pellets			
1.	Desvenlafaxine succinate eq. to Desvenlafaxine 100 mg	144.840	41.38
2.	Low Substituted HPC (L-HPC LH-31)	170.590	48.74
3.	Hypromellose 15 cps	6.437	1.84
4.	Purified Water	q.s.	-
total Weight of IR pellets		321.867	-
POLYMER COATING			
5.	Ethyl Cellulose 45 cps	19.897	5.68
6.	Hypromellose 6 cps	3.511	1.00
7.	Dibutyl Sebacate	2.341	0.67
8.	Dichloro Methane*	q.s	-
9.	Methyl Alcohol*	q.s.	-
Total Weight of ER pellets		347.616	-
LUBRICATION			
10.	Talc	2.384	0.68
Total Weight of ER pellets (Lubricated)		350.00	100.00

(* Loss during processing does not remain in final product except in traces)

Formulation of pellets

DV pellets were prepared by 53% of L-HPC LH-31 (spheronizing agent) and 2% of Hypromellose 15 cps (binder) solution using extruder fitted with 1.0 mm die roller and spheronizer with 3.25 mm chequered plate equipped in fluidized bed processor. Final weight of immediate release pellets (321.867 mg) was kept constant throughout the optimization study. Polymer coating of EC45 cps and Hypromellose 6 cps (85:15) was done using Dibutyl sebacate (plasticizer; 10% of total polymer). The proto type composition of DV pellets are presented in Table 4.

Characterization of DV pellets [15]

Physicochemical characterization

(a) Loading of pellets into capsules

The optimized DV pellets were assessed for the bulk density and were filled into hard gelatin capsules (HGC) size 0 automatically.

(b) Weight variation test

Ten capsules comprising of DV pellets were singly weighed and the powder mass were transferred in butter paper. The emptied capsules were individually weighed and the net weight of the mass was calculated using following formula.

$$Weight\ variation = \frac{(Wt\ of\ Capsule - Average\ weight)}{Average\ wt\ of\ capsule} * 100$$

(c) Lock length

Capsules were taken and lock length was measured by vernier calipers and average was recorded. (n=10)

(d) Friability and Spherocity

The friability of DV pellets was found using friability tester (CS-2, Tianjin, China) and pellets content (10 g) was crumbled for 100 rpm. The DV pellets were sieved by sieve after testing. The % weight of loss (F %) was found using following equation. The sphericity of the DV pellets was estimated by one-plane-critical-stability (OPCS) [16].

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

(e) **Scanning electron microscopy**

The surface property of developed DV pellets was studied by scanning electron microscope (SEM) using sputtering with gold palladium.

***In vitro* drug release study**

In vitro drug release from DV pellets was studied by calibrated basket apparatus (USP dissolution test apparatus I). The medium for dissolution was 0.9%w/v NaCl in purified water and the dissolution was studied for 24 hrs. The rotation of baskets was kept at 100 rpm. The study was carried out at a constant temperature of 37 ± 0.5°C. Aliquots (10 ml) were sampled with addition of fresh 10 ml dissolution medium and drug content was determined by corroborated UV spectrophotometric method at 224 nm. The volume of dissolution media was kept 900 mL and study was replicated (n=3).[17]

***In vitro* drug release kinetics**

DD Solver® software was employed to understand the drug release mechanism from developed DV pellets. *In vitro* drug release data were charged into software as input data and best model fitting was considered as per output data (adjusted R^2, SS and F).[18, 19]

Stability study

Short term stability study (3 months) was conducted for DV pellets as per ICH guidelines. Tre condition in stability study chamber was kept at 40 ± 2°C and 75 ± 5% RH. The sampling interval was one month for three months and the samples were evaluated for different parameters.[20]

RESULT AND DISCUSSION

Quantification of DV

The quantification of DV was done at 224 nm by UV spectroscopy method and Beer's Lambert law was satisfied in the range of 10-35 µg/mL with absorption range of 0.135±0.0022 to 0.920±0.023. The linearity was equated in the equation Y= 0.0229X + 0.0102 with R^2 value 0.999.

Drug excipients study

The results of physical appearance, FTIR and DSC study of DV and physical mixture of DV with proposed excipients declares that there are no significant changes in physical appearance, characteristics peak of FTIR and endothermic peak of DSC thermograph. The characteristics IR peaks due to different groups present in DV [C-H stretch (2850-2960), C-H bending (675-870), C=C bending (1500-1600), C-O stretch (1080-1300), C=O stretch (1690-1760), O-H stretch (3200-3600) and C-N stretch (1180-1360)] were retained in FTIR spectra of drug and physical mixture (Figure 1).

Similarly, the DSC thermograph of DV was shown at 102.42°C corresponding to its melting point was also retained at 105.28°C in DSC spectra of DV with excipients (Figure 2). [21]

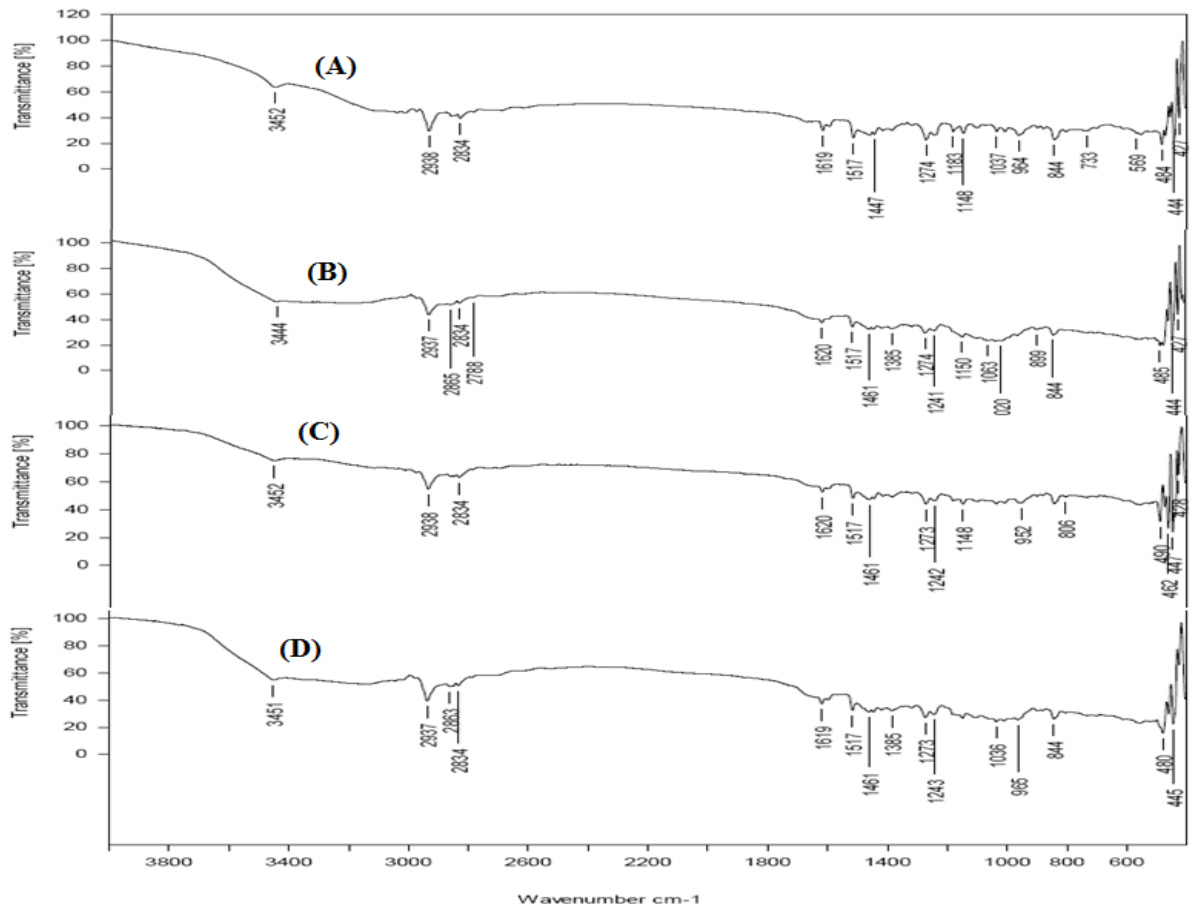

Figure 1: FTIR spectra of drug (A) and physical mixture of drug with proposed excipients L-HPC LH-31 (B), Hypromellose (C), MCC (D)

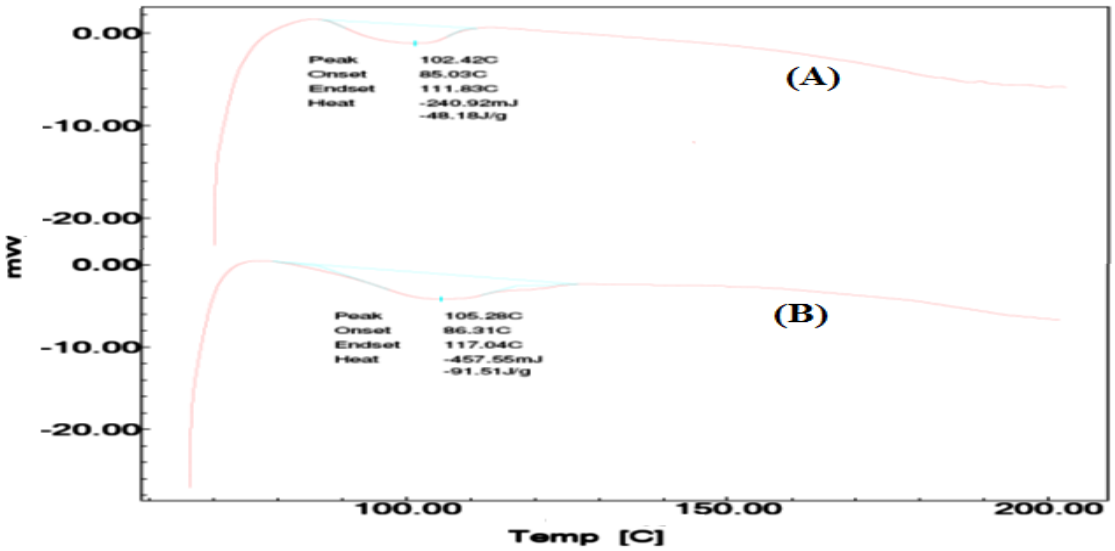

Figure 2: DSC thermograpm of DV (A) and DV with excipients (B)

Application of QbD

Risk assessment

As per the results of risk assessment study it can be concluded that at pilot level dissolution profiles at different intervals have high risk while assay, content uniformity, degradation product have low risk. The risky factors were further studied by PBD to understand the intensity of their influence on selected CQAs.

Screening of factors by Placket Burmann design (PBD)

The outcome of PBD can be inferred by Pareto chart, half normal plot and normal plot. The pareto chart reveals comparative highest standardized effect by factor B and factor A. The level was far away from the 2.571

(Threshold standardized effect). Moreover, Factor B has 2 degree more effect than factor A, which indicates that factor B has more significant effect than factor A on selected CQAs. Factors C, D, E and F have non-significant effect on selected responses. Also, inter variation between non-significant factors (C-F) was negligible. The inference of Pareto chart was further strengthened by half normal plot and normal plot where location of factor B and A reveals strong effect on selected factors. Also factor B and A are located in the same direction proving its similar effect on responses. The drug release after 20 hrs was found to be 86.52, 87.23, 81.54, 48.36, 81.90, 96.52, 97.82, 99.34, 49.56, 81.30, 86.51, and 53.47 respectively for P1-P12.

Validation of FFD

The standard error graph (SEG) of applied FFD was derived from Design expert software. It can be easily stated from the SEG that applied FFD has a significant prediction power as the standard error value is 0.697.

Application of FFD

The best suited model was confirmed by R^2 value from linear, 2FI and Quadratic for each selected response (Y_1-Y_5). Additionally, non-significant terms were omitted (NS; P>0.05) to strength the predictive power of model. An interactive term (X_1X_2) and one polynomial term (X_2^2) was found significant for Y_3, Y_4 and Y_5 only out of selected responses. This infers that in later stages of dissolution, independent factors behave differently than initial hours. Moreover, based on the significant terms in selected model, reduced MLR equations were evolved. The response surface plots (3D) for selected dependent variables and overlay plot are presented in Figure 3. The dark region highlighted in the overlay plot is the region of interest.

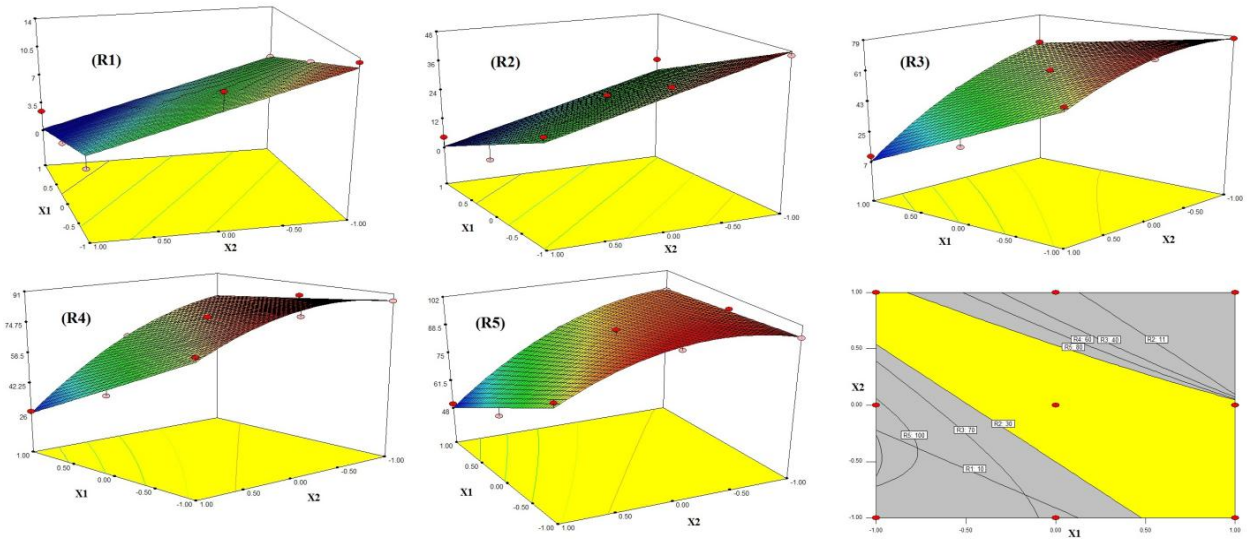

Figure 3: Contour plots and overlay plot of selected responses (Y1-Y5)

The MLR equation obtained after ANOVA analysis (FFD) is summarized as below:

$Y1 = +6.57 - 2.60X_1 - 3.77X_2$

$Y2 = +24.18 - 12.08X_1 - 11.60X_2$

$Y3 = +58.57 - 16.62X_1 - 18.35X_2 - 8.12X_1X_2 - 7.72X_{22}$

$Y4 = +74.97 - 13.48X_1 - 17.20X_2 - 8.85X_1X_2 - 9.33X_{22}$

$Y5 = +90.77 - 9.68X_1 - 14.63X_2 - 7.70X1X_2 - 10.53X_{22}$

Confirmation Tests of Model

To confirm the predictive power of equated MLR model, three batches (check point batches; D10, D11 and D12) were chosen within the periphery of design space. The %E value reveals that equated models generated from FFD are quite predictive with negligible variation. Check point batch D11 was considered as an optimized batch satisfying preset standards in fulfilling constrains for % drug release at 2, 4, 8, 12 and 20 hrs (selected responses, %E (D11) for Y_1:6.3,Y_2:5.9, Y_3:4.1, Y_4:2.4, Y_5:3.6)

Characterization

Physicochemical characterization

The DV pellets were successfully loaded into capsule (size 0) and the lock length value was found to be 21.35 mm. the DV pellets based capsule passed the test of weight variation. The friability was negligible was 0.05%. The value of spherocity for developed DV pellets was close to unity.

Surface morphology

The SEM image of pellets indicates orbicular shape and polish surface. This reasserts the perfection of coating over pellets. The intactness of coating is supporting for no chance of dose dumping.

Drug release study

Dissolution profiles of factorial batches of DV ER pellets (D1-D12) are presented in following Figure 4.

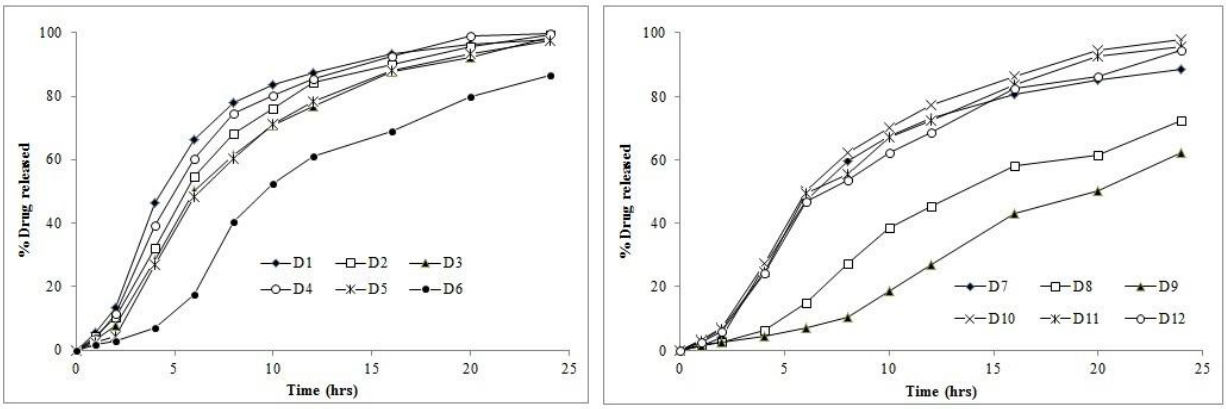

Figure 4: Dissolution profiles of DV pellets (D1-D12)

It is self-explanatory from the drug release curve that the dissolution behaviors of all batches are different. This further proves that selected independent factors have strong impact on drug release from pellets. According to the recent guideline published by FDA dissolution behavior of optimized batch (D11) was assessed in the presence of alcohol (10%) in media. There was insignificant difference in drug release profiles (f_2 value: 85.24±2.17). This further suggest that there formulation performance is not deviated in presence of alcohol.

Drug release kinetics

From the drug release kinetics model data of optimized DV pellets it can be inferred that Weibull was best suited drug release mathematical model due to maximum R^2 (0.995) and minimum SS (56.09) and F values (5.10).

Stability study

An optimized formulation of DV pellets (V11) showed non-significant changes in physical, chemical and performance behaviors after stipulated stability testing time.

CONCLUSION

From the exhaustive study on formulation and development of DV ER 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 DV and similar drugs and depression alike conditions.

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